# Drug Dosing at the End of Life

*A Pharmacometric Approach*

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Layout and printed by: Optima Grafische Communicatie, Rotterdam, the Netherlands
ISBN: 978-94-6361-049-0

# Drug Dosing at the End of Life:
## *a Pharmacometric Approach*

### Dosering van geneesmiddelen bij het levenseinde:
*een farmacometrische aanpak*

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

woensdag 7 februari 2018 om 13:30 uur

door

Linda Goverdina Wilhelmina Franken
geboren te Etten-Leur

**Erasmus University Rotterdam**

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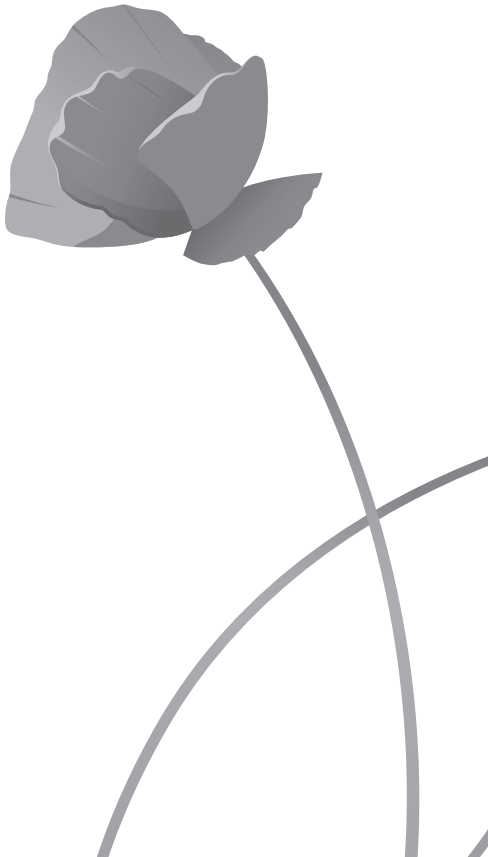

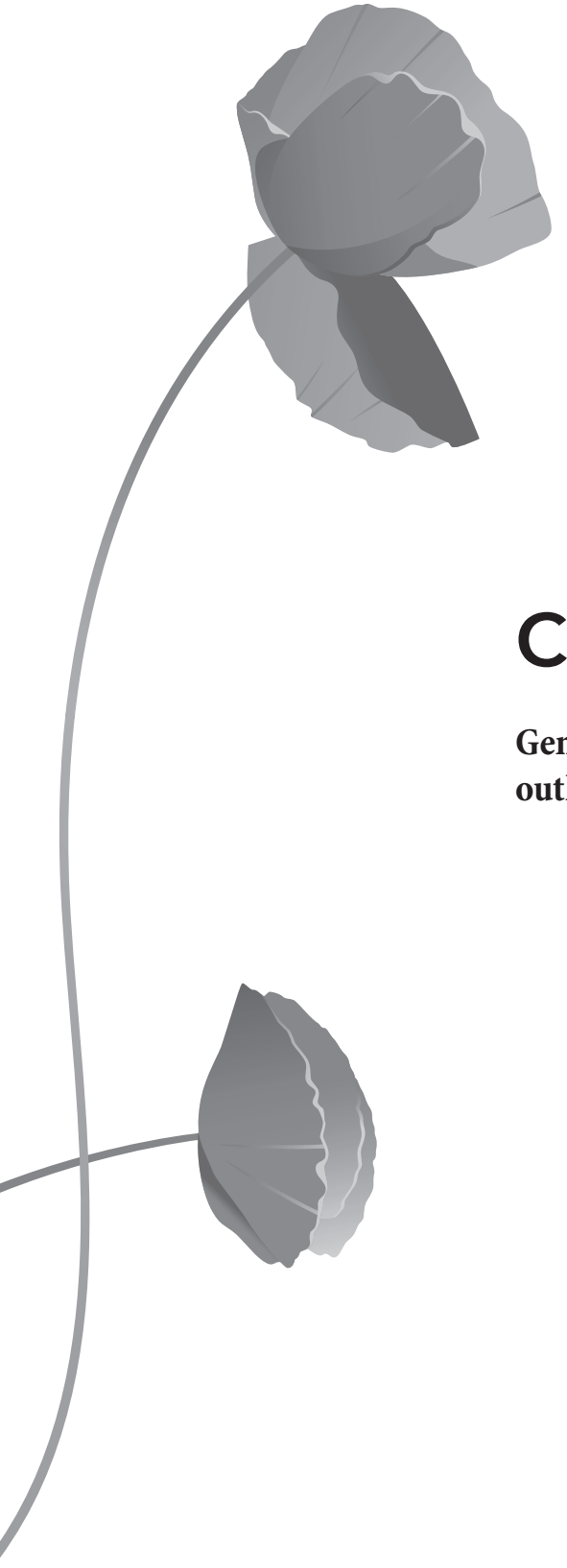

# CHAPTER 1

**General introduction and outline of this thesis**

## GENERAL INTRODUCTION

### Palliative care

Palliative care is defined by the world health organisation (WHO) as: "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" [1]. Palliative care is generally initiated in the case of terminal illness when cure is no longer possible and life expectancy is limited. There is however not always a clearly defined moment when palliative care replaces curative care. Instead this shift from cure to care is a gradual transition, described by the model of Lynn and Adamson (figure 1) [2]. This gradual transition makes it difficult to calculate prevalence numbers for patients in need of palliative care. The WHO estimates that worldwide, a total of 40 million people are in need of palliative care each year. Because of differences in medical care standards and disease prevalence, the number of patients in need of palliative care will differ between countries. For the Netherlands, an estimation is made on the basis of the total number of deaths each year. In 80% of these cases, the death of the patient did not come unexpectedly and it was therefore assumed that in these cases death was preceded by some form of palliative care [3]. Based on these data a total of 108.500 patients, annually, will receive palliative care in the Netherlands. This number will most likely increase in the upcoming years, due to the ageing population. As reflected by the WHO definition, the main goal of palliative care is symptom management. Since symptoms can be both physical, psychosocial and spiritual, symptom management is best performed in a multidisciplinary setting and consists of both pharmacological and non-pharmacological interventions.

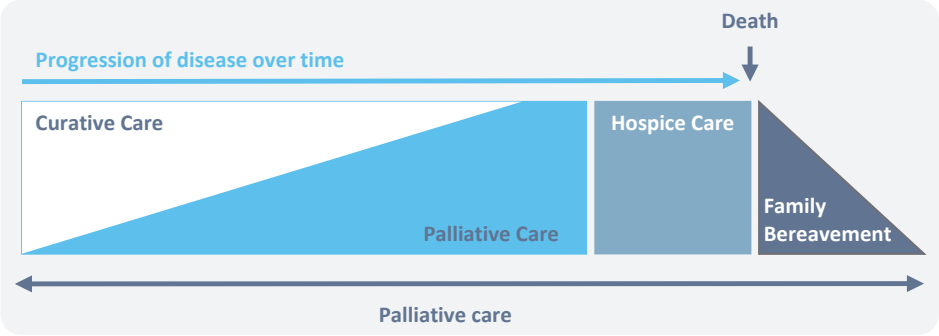


**Figure 1.** Trajectory Model adapted from Lynn et al [2].

## Symptom management

Palliative care patients can suffer from a variety of symptoms depending on their terminal illness as well as co-morbidities. In terminally ill cancer patients, which is the majority of the terminally ill population, patients suffer from an average of 12 symptoms in the last year of life [4]. Of these symptoms the five most common symptoms are fatigue (74%), pain (71%), lack of energy (69%), weakness (60%) and appetite loss (53%) [5]. They can have a severe impact on the quality of life and their burden will increase with decreasing life expectancy [6]. Relieving distress in these patients can be done either by treating the underlying cause or trigger, by symptomatic treatment (both with and without medication) and/or with supportive care. There are however circumstances in which symptoms cannot be adequately controlled with these measures alone. In the case of such refractory symptoms, palliative sedation can be initiated as an option of last resort.

By applying palliative sedation, a patient's consciousness is decreased, thereby taking away the perception of the symptoms. Palliative sedation is applied proportionally, guided by the symptoms of the patients without striving for deep coma, or shortening life. It is generally only used for limited amount of time as 47% of the patient die within 24 hours after sedation is started and another 47% within 1 to 7 days [7, 8]. In a hospice setting this form of symptom management is regularly applied, with an average of 46% (range 22 – 67%) of the terminally ill patients being sedated for refractory symptoms at the end of life [9-13]. The most common causes for palliative sedation are delirium or restlessness in the terminal phase (57%), dyspnoea (23%), pain (17%) and vomiting (4%) [7].

## Pharmacology

Pharmacological therapy plays an important role in symptom management, both in general symptom management as well as in palliative sedation. An overview of the pharmacological therapy in this population is given by the International Association for Hospice and Palliative Care (IAHPC) who provided a list of 33 essential medicines for palliative care [14]. As this list is an international consensus, not all drugs mentioned here are used in the Dutch palliative care setting. Looking specifically at the Dutch hospice setting the top 3 of most commonly used drugs at the end of life were morphine, midazolam and haloperidol [15]. Morphine is an analgesic of the opioid class. It is an antagonist of the μ-opioid receptor in the central nervous system and is used in palliative care to treat pain and dyspnoea. It was the most commonly used drug in the final days of life with over 80% of the terminally ill patients receiving it. Midazolam is a sedative of the benzodiazepine class and has a prominent role in the national guideline for palliative sedation and is being prescribed in approximately 50% of the terminally ill patients. Finally, haloperidol is a typical antipsychotic and the drug of choice according to the guidelines to treat (terminal) delirium. With delirium occurring in 85 to 90% of the terminally ill patients in the last hours or days before death it is also commonly subscribed. The fact that it is less commonly used than morphine or midazolam is due to the

fact that delirium in its agitated form only occurs in around 20% of the cases and in 22-50% of all cases delirious symptoms go unnoticed.

Despite the fact that these drugs are frequently used and have a prominent place in (inter)national guidelines, there are very few high quality clinical trials on their safety and efficacy in terminally ill patients. The efficacy and safety of palliative sedation has been studied by Morita et al in 2005 [16]. This study showed that if full symptom control was reached this took between 1 and 48 hours. It also showed that in 17% of the patient's symptom relief remained inadequate and that 49% of the patients awoke at least once from a deeply sedative state. In addition, this study also revealed that in 22% of the cases patients' experienced serious adverse events, such as aspiration, paradoxical reactions and respiratory suppression. This is of clinical concern as it causes severe distress for both the patients themselves as well as their loved ones.

Such a variability in response may be explained by several different factors. First of all, the fact that patients suffer from multiple symptoms and co-morbidities may lead to polypharmacy which increases the possibility of relevant drug-drug interactions [17-19]. In addition, pathophysiological changes and co-morbidities, like renal and hepatic impairment, are also likely to cause variability between and within patients by affecting the way the body processes these drugs (pharmacokinetics). In fact, such pharmacokinetic changes as well as pharmacodynamic ones have been shown before in elderly and critically ill patients [20-25]. Terminally ill patients do show some similarities with these populations however the terminally ill population is also a very heterogeneous so there will likely be large variability both between patients as well as within a single patient as their disease progresses. Unfortunately, most current guidelines lack individualised dosing recommendations. Instead dosing is often guided by clinical effect. These empirical dose adjustments however take time and this is disadvantageous in the case of severe symptoms and limited life expectancy. We therefore need to expand our knowledge on pharmacokinetics and pharmacodynamics in terminally ill patients, and aim to develop individualised dosing regimens that will help improve the care for these patients in their final months of life.

## THE AIMS OF THIS THESIS ARE

1. To give an overview of how the pharmacokinetic processes in terminally ill patients differ from the average population, and how this may affect drug exposure
2. To gain insight in the drugs used in palliative care and the relevance of drug-drug interactions in this population
3. To evaluate the pharmacokinetics and the inter-individual variability of morphine and its metabolites in terminally ill patients.

4. To evaluate the pharmacokinetics and the inter-individual variability of midazolam and its metabolites in terminally ill patients.
5. To investigate the effect of midazolam plasma concentrations on depth of sedation.
6. To evaluate the pharmacokinetics of haloperidol in terminally ill patients.

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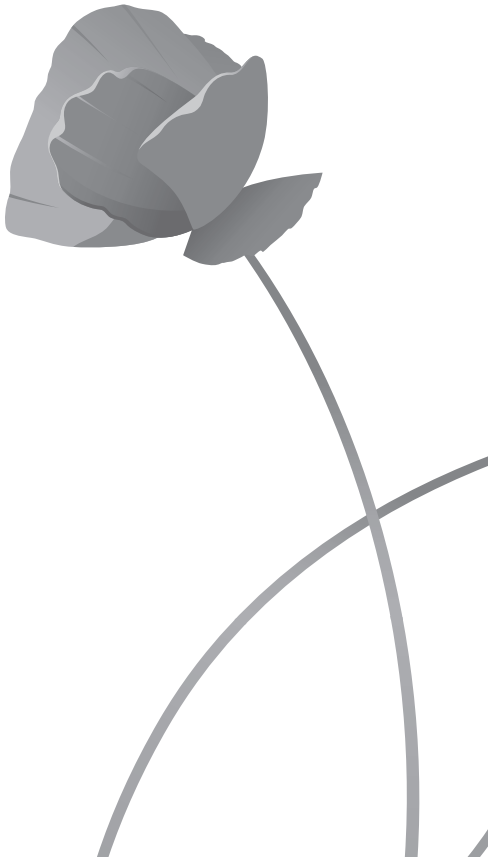

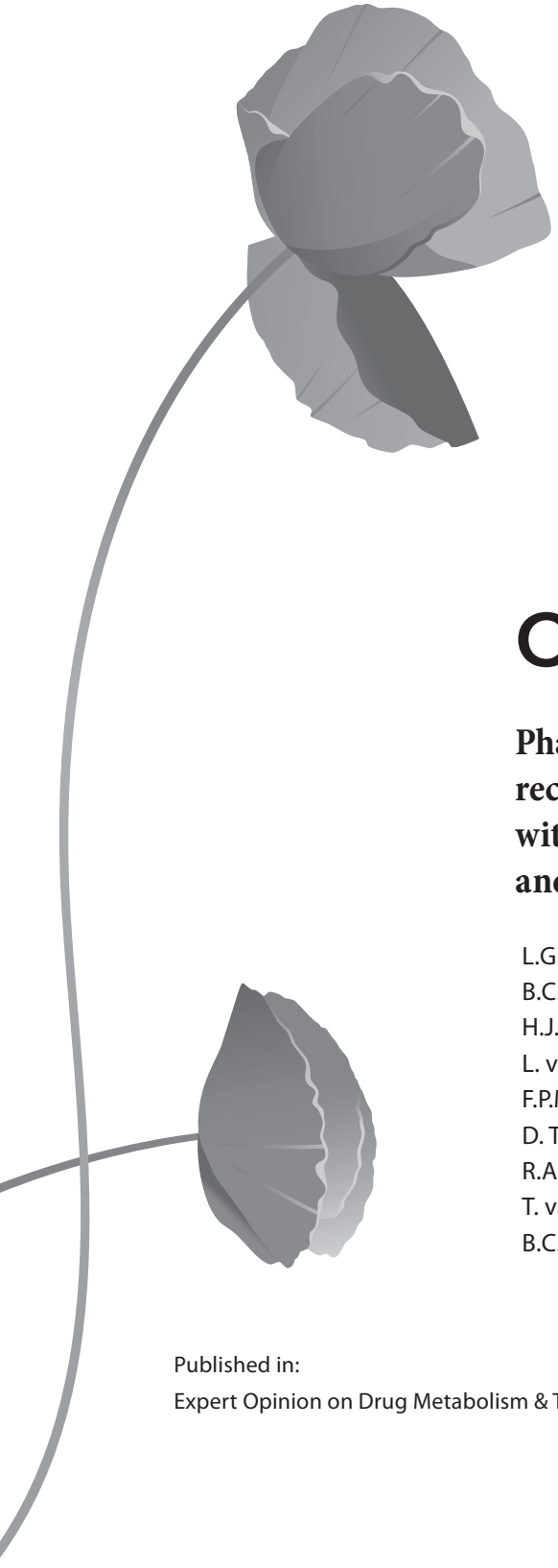

# CHAPTER 2

## Pharmacokinetic considerations and recommendations in palliative care, with focus on morphine, midazolam and haloperidol

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Published in:
Expert Opinion on Drug Metabolism & Toxicology. 2016 Jun; 12(6):669-80

## ABSTRACT

### Introduction

A variety of medications are used for symptom control in palliative care, such as morphine, midazolam and haloperidol. The pharmacokinetics of these drugs may be altered in these patients as a result of physiological changes that occur at the end stage of life.

### Areas covered

This review gives an overview of how the pharmacokinetics in terminally ill patients may differ from the average population and discusses the effect of terminal illness on each of the four pharmacokinetic processes absorption, distribution, metabolism, and elimination. Specific considerations are also given for three commonly prescribed drugs in palliative care: morphine, midazolam and haloperidol).

### Expert opinion

The pharmacokinetics of drugs in terminally ill patients can be complex and limited evidence exists on guided drug use in this population. To improve the quality of life of these patients, more knowledge and more pharmacokinetic/pharmacodynamics studies in terminally ill patients are needed to develop individualised dosing guidelines. Until then knowledge of pharmacokinetics and the physiological changes that occur in the final days of life can provide a base for dosing adjustments that will improve the quality of life of terminally ill patients. As the interaction of drugs with the physiology of dying is complex, pharmacological treatment is probably best assessed in a multi-disciplinary setting and the advice of a pharmacist, or clinical pharmacologist, is highly recommended.

## INTRODUCTION

In palliative care, when curation is no longer possible, the goal is to maintain or improve the quality of life. To achieve this, a variety of medications, such as morphine, midazolam, and haloperidol, are used for symptom control.[1] Changes in the pharmacokinetics of these drugs may cause increased or decreased drug blood concentrations, which can result in altered efficacy or increased risk of adverse drug reactions. To optimize the use of these drugs, an understanding of pharmacokinetics in this specific patient population is therefore essential.

Pharmacokinetic (Pk) parameters (e.g. drug clearance and volume of distribution) are subject to interpatient variability and may be altered in the palliative population, as patients with cancer are known to differ from healthy volunteers with regards to, for example, age, body weight, and plasma protein levels.[2] In addition, several physiological changes (e.g. decreased fluid intake, a catabolic state, inflammation, and cachexia) occur at the end of life, which can also influence pharmacokinetics.[3–5]

So far there is limited knowledge on how these changes affect the different drugs used in palliative care, in particular in the terminal phase, i.e. the last days before death in which a patient is bedridden, semi-comatose, and are no longer able to take oral medication. The aim of this review is to give an overview of how the pharmacokinetics in terminally ill patient differ from the average population, and how changes in the palliative, and especially the terminal phase, can affect drug exposure (Figure 1). We will discuss the effect of terminal illness on each of the four pharmacokinetic processes: absorption, distribution, metabolism, and elimination (ADME) and give some considerations for three drugs commonly prescribed in the terminal phase (i.e. morphine, midazolam, and haloperidol). [6]

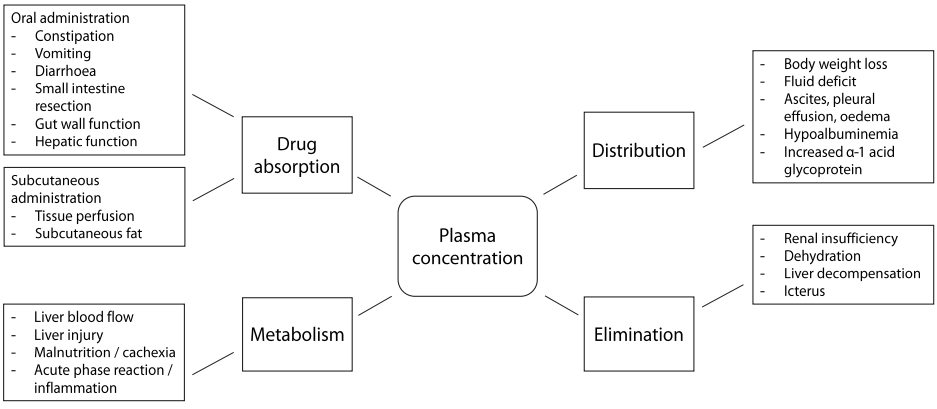


**Figure 1.** Physiological changes that can influence pharmacokinetics in the terminally ill adult patient.

## ABSORPTION

Terminally ill patients frequently suffer from gastro intestinal (GI) problems, such as constipation, nausea, vomiting, and diarrhoea. In the case of orally administered drugs, which are used in the palliative care setting when patients are still able to take oral medication, these symptoms can influence both the rate of absorption and bioavailability of a drug. Changes in the absorption rate will affect time-to-peak concentrations (Tmax), whereas changes in bioavailability will affect the initial peak concentration (Cmax) and total exposure, expressed as area under the curve (AUC). If and to what extent a drug is influenced by physiological changes will depend on the physicochemical properties of the drug and the pharmaceutical formulation (e.g. drug solubility and extended release formulations). An overview of the factors influencing absorption is given in Table 1. For this review, we will focus on the most commonly used routes of administration in palliative care, which are oral administration in the palliative phase and subcutaneous and transdermal administration in the terminal phase.

**Table 1.** Physiological changes affecting drug absorption

| Physiological change in palliative care | Potential pharmacokinetic change | Consequence | Example drugs |
|---|---|---|---|
| Decreased GI motility | Increase in Tmax | Drug concentration is unaffected yet the effect may be delayed | Morphine and tramadol |
| | Increase in F and AUC of sustained release formulations and drugs with enterohepatic cycling | Increase in drug concentration and effect | Oxycontin ® and lorazepam |
| Vomiting or administration via tube | Possible decrease in F and AUC depending on the moment of vomiting or declamping the tube | Possible decrease in drug concentration and effect | All oral drugs |
| Delayed gastric emptying | Increase in Tmax | Drug concentration is unaffected yet the effect may be delayed | Morphine and tramadol |
| | Increase in AUC for drugs in which dissolution is the rate limiting step | Increase in drug concentration and effect | Oral haloperidol |
| Diarrhoea | Increase in AUC of drugs with low F | Increase in drug concentration and effect | Domperidon |
| | Decrease in AUC of drugs with normal to high F | Decrease in drug concentration and effect | Haloperidol |
| Small intestine resections | Decrease in F and AUC | Decrease in drug concentration and effect | Morphine and tramadol |
| Alterations in gut wall function due to cachexia | Decrease in F and AUC | Decrease in drug concentration and effect | Morphine and tramadol |
| Decreased hepatic function or liver blood flow | Decrease in first-pass effect, resulting in increased AUC | Increase in drug concentration and effect | Morphine |
| Decreased tissue perfusion | Decrease in Tmax and possibly F of subcutaneously or transdermal administered drugs | Decrease in drug concentration and the effect may be delayed | Fentanyl patches and subcutaneous midazolam |
| Decreased subcutaneous fat | Increased Tmax of subcutaneously or transdermal administered drugs | Drug concentration is unaffected yet the effect may be accelerated | Fentanyl patches and subcutaneous midazolam |

Abbreviations: Tmax = time to peak concentration, AUC = area under the curve (i.e. total exposure to the drug), F = bioavailability

## Oral administration

The absorption of orally administered drugs is complex as a drug has to dissolve in the stomach, pass through either the stomach or gut wall, and pass the liver via the portal vein before they reach the systemic circulation. Whether the transportation of the dissolved drug into the bloodstream occurs in the stomach or gut is dependent on the drug's physicochemical properties. Drugs that are weakly acidic are best absorbed within the acid environment of the stomach. Though most drugs are weak bases (e.g. morphine, haloperidol, and midazolam) and are therefore absorbed in the alkaline environment of the small intestine.

*GI symptoms*

Absorption of oral drugs can be altered in terminally ill (cancer) patients as this population often suffers from GI symptoms, such as constipation, vomiting, diarrhoea, or a delayed gastric emptying due to cachexia. Constipation (i.e. decreases GI motility) occurs in around 50% of the terminal cancer patients and can be a result of dehydration, hypercalcaemia, a bedridden state, and medication use (e.g. opiates). [7, 8] Decreased GI motility can result in a reduced absorption rate as it takes longer for the drug to reach the site of absorption. [9–11] In the case of a sustained release formulation or drugs with an enterohepatic circulation, decreased GI motility can increase the absorption as there is more contact time with the GI mucosa.

Constipation can also cause nausea and vomiting. Vomiting can evidently decrease the bioavailability of oral medication. The same applies for unclamping the tube if medication is administered via this tube. To what extend the bioavailability is decreased will depend on the time between ingestion and vomiting or releasing the clamp of the tube. The time it takes for a drug to pass from the stomach to the intestine can range from 1 h, for healthy persons up to 4 h, for patients with delayed gastric emptying. As delayed gastric emptying is relevant in this patient population, it has to be taken into account that vomiting or unclamping the tube even several hours after intake of medication the bioavailability can be decreased.

Delayed gastric emptying by itself can also result in a decreased absorption rate for drugs that are absorbed through the small intestine. [11,12] In the case of a drug for which formulation dissolution in the stomach is the rate-limiting step in absorption, a decrease in gastric emptying time may increase the overall extent of absorption and, hence, systemic drug exposure.

Diarrhoea can also influence the bioavailability of oral drugs. It can cause a decrease in bioavailability due to increased elimination from the gastro intestinal tract. On the other hand, if the intestinal mucosa is damaged (for instance in the case of an inflammatory process) it can also lead to increased bioavailability. These concepts cause drugs with low bioavailability generally have increased absorption in patients with diarrhoea while drugs with

good intestinal absorption are more affected by the increased GI motility and, therefore, will have lower absorption. [13]

Furthermore, patients with a gastrointestinal malignancy may have some of their small intestine resected. Small intestine resections involving the loss of more than 100 cm of ileum frequently lead to malabsorption, which could also decrease drug absorption.[14] Absorption might also be decreased by alterations in gut wall function, which is caused by body wasting or cachexia, or decreased splanchnic perfusion. [13, 15]

*First-pass metabolism*

After absorption from the GI tract, the bioavailability of drugs may be altered in terminal patients due to changes in hepatic function or liver blood flow, which can occur in the case of hepatic cirrhosis or congestive heart failure. A decrease in hepatic blood flow can result in increased bioavailability of drugs with a high first-pass metabolism, as was shown for hydromorphone. [16]

## Subcutaneous/transdermal administration

Other common routes to administer drugs in palliative care are transdermal or by subcutaneous injection or infusion. These routes are advantageous in the case of GI problems as this route also bypasses the portal vein, first-pass metabolism does not occur. Factors that may influence absorption of subcutaneous or transdermal medication, however, are tissue blood perfusion and amount of subcutaneous fat. In terminally ill patients, reduced tissue blood perfusion, which can occur as a result of dehydration or old age, can result in a decrease in absorption rate or bioavailability after subcutaneous or transdermal administration. [9, 17, 18] Alternatively a decrease in subcutaneous fat mass, which is also commonly seen in terminally ill patients, can in theory lead to increased absorption rate and possibly higher peak concentrations. [19]

## Clinical considerations

For clinical practice, we recommend that in the palliative phase GI problems should be closely monitored, and that medication and doses should be reassessed if changes in GI motility occur. As the effect of alterations in GI motility will differ per drug, depending on their chemical properties, this needs to be evaluated on a case by case basis. This assessment is preferably performed in a multi-disciplinary setting and the advice of a pharmacist, or clinical pharmacologist, is recommended. In the presence of a nasogastric tube that decompresses the gut in case of an intestinal obstruction, the administration of drugs through the oral route, or via the tube, is not rational. In the terminal phase, switching to subcutaneous administration, if possible, is preferred not only for the prescribing physician but also for patient's comfort. In the case of subcutaneous or transdermal drug administration, changes will occur more gradually and monitoring of the clinical effect will probably

suffice. If therapy is switched from oral to subcutaneous administration, one should correct for a difference in bioavailability, in addition, it is advisable to look for signs of diminished tissue perfusion (cool extremities, cyanosis, oedema, and diminished or absent peripheral pulses) as this could result in a decreases absorption. Finally, in patients with an intestinal obstruction either anatomical or functional administering drugs via a tube followed by 1 or 2 h of clamping the tube will not likely lead to drug absorption, as most drugs are absorbed in the small intestine and in the case of delayed gastric emptying the drug may not have passed from the stomach yet. Therefore, in the case of intestinal obstruction drug administration via the subcutaneous route is preferred.

## DISTRIBUTION

The volume of distribution (Vd) of a drug is dependent on its chemical properties (e.g. its hydrophilicity and its affinity with plasma proteins). As a rule, hydrophilic drugs will diffuse into the intravascular, extracellular, and possibly intracellular water, and their Vd will not exceed the volume of total body water (around 42 L for an average adult of 70 kg). Whereas lipophilic drugs or drugs with high affinity to plasma proteins will have low free plasma concentrations and, therefore, a large volume of distribution. As the Vd is determined only by concentration and dose, the plasma concentrations of a drug can be influenced by body composition and amount of plasma protein. Both of these can be altered in terminally ill patients and can change over time, an overview of the factors influencing Vd is given in Table 2.

**Table 2.** Physiological changes affecting drug distribution

| Physiological change in palliative care | Potential pharmacokinetic change | Consequence | Example drugs |
|---|---|---|---|
| Loss of body weight and cachexia | Decrease in Vd for lipophilic drugs | Increase in drug concentration and effect | Midazolam |
| Fluid deficit | Decrease in Vd for hydrophilic drugs | Increase in drug concentration and effect | Morphine |
| Ascites, pleural effusion or generalised oedema | Increase in Vd for hydrophilic drugs | Decrease in drug concentration and effect | Morphine |
| Hypoalbuminemia | Increase in unbound fraction of weakly acidic drugs | No effect unless elimination is inhibited | Temazepam |
| Increased α-1 acid glycoprotein | Decrease in unbound fraction of weakly alkaline drugs | Prolonged effect due to decreased elimination and slow redistribution from tissues | Morphine |

Abbreviations: Vd = volume of distribution

### Body composition

The main factors that influence body composition are loss of body weight and fluid deficit. Loss of body weight and cachexia are common in terminally ill patients, especially in cancer patients. The incidence of weight loss however differs between cancer types with the highest incidence (83–87%) for pancreatic or gastric cancers and the lowest frequency (31– 40%) for favourable non-Hodgkin lymphoma, breast cancer, acute non-lymphocytic leukaemia, and sarcomas.[20] Fearon et al. showed that in cachectic patients the reduction in body weight is mainly caused by a reduction of adipose tissue (by 80%) and muscle protein (by 75%).[21] A reduction of adipose tissue will result in a lower Vd for lipophilic drugs which will result in higher peak concentrations (Cmax).

Fluid deficit, which is also common among terminally ill patients, can also affect the body composition as it results in loss of total body water. The loss of water can be both intracellular, in the case of dehydration, and extracellular in the case of volume depletion.[5,17] A loss of water will result in a lower Vd for hydrophilic drugs and, therefore, initially lead to higher concentrations. Alternatively, the volume of distribution of hydrophilic drugs can also be increased as a result of ascites, pleural effusion, or generalized oedema leading to a higher Vd and lower initial concentrations. [13, 22–24]

### Protein binding

Besides body composition, alterations in protein binding can also affect Vd. The two main drug binding proteins are albumin and α-1 acid glycoprotein (AAG). Albumin typically binds to weakly acidic drugs (e.g. temazepam and propofol), whereas AAG binds to weakly alkaline drugs (e.g. morphine and fentanyl). [2] Changes in binding proteins can be caused by inflammatory responses. A long-lasting inflammatory response occurs in almost all types of solid tumours and can also be the result of cachexia, infection, and degenerative diseases. [17, 25–27] As a result of the inflammatory response, albumin is downregulated and AAG is increased. [27] Hypoalbuminemia is, therefore, often seen in various types of cancer, cachectic patients, and hospitalized or institutionalized elderly patients. [14, 28–32] Increased plasma levels of AAG have also been shown in various types of cancer, acute illness, or chronic disease. [33, 34] As a result, highly AAG bound drugs will have decreased unbound concentrations while highly albumin bound drugs will have increased unbound concentration. A decreased unbound concentration can result in decreased elimination and due to slow redistribution from the tissues, the effect can be prolonged. The clinical relevance of increased amounts of unbound drug on the other hand is limited as the elimination of a drug increases when the unbound concentration increases. Still if the elimination is otherwise inhibited, for example, in the case of renal failure, this might lead to accumulation.

### Clinical considerations

As volume of distribution mainly affects the initial peak concentration (and also the time needed to reach steady-state concentrations), recommendations for clinical practice will primarily be relevant for drugs where an immediate response is desired. This is for instance the case in sedative or analgesic medication. For these drugs, a higher initial (loading) dose may be required if the volume of distribution in an individual is increased. For instance, to achieve adequate sedation, an obese patient will probably require a higher initial dose of midazolam (a lipophilic drug) than a cachectic patient. In addition, for pain management a patient with oedema may probably need a higher initial dose of morphine (a hydrophilic drug) than a dehydrated patient.

## METABOLISM

Conversion of drugs into metabolites primarily takes place in the liver and largely determines the duration of a drug's action, elimination, and toxicity. Hepatic clearance (ClH), the ability of the liver to remove drugs from the systemic circulation, is dependent on both liver blood flow and hepatic extraction ratio. The hepatic extraction ratio is the fraction of drug that is removed from the blood after a single passage through the liver. Drugs with a high extraction ratio will have a ClH that is primarily dependent on the liver blood flow. While for drugs with a low extraction ratio, this will be mainly dependent on intrinsic clearance (i.e. liver function). In patients with terminal illness, there are several factors that might influence drug metabolism, an overview is given in Table 3.

**Table 3.** Physiological changes affecting drug metabolism

| Physiological change in palliative care | Potential pharmacokinetic change | Consequence | Example drugs |
|---|---|---|---|
| Decreased liver blood flow | Decrease in $Cl_H$ of drugs with a high extraction ratio | Increase in drug concentration and effect | Morphine |
| Liver injury | Possible decrease in $Cl_H$ mainly for drugs metabolised by CYP450 enzymes | Possible increase in drug concentration and effect | Midazolam |
| Malnutrition or cachexia | Possible decrease in $Cl_H$, yet still inconclusive | Possible increase in drug concentration and effect | Midazolam |
| Acute phase reaction | Possible decrease in $Cl_H$, yet still inconclusive | Possible increase in drug concentration and effect | Midazolam |

Abbreviations: $Cl_H$ = hepatic clearance

### Liver blood flow

Liver blood flow reduces with age, and can also be decreased in dehydrated patients due to decreased cardiac output, in patients with liver cirrhosis due to intrahepatic and extrahepatic portal systemic shunting, or in patients with heart failure as a result of passive congestion or low cardiac output. [10, 17, 35, 36] These patients can, therefore, have a decreased metabolism of drugs with a high extraction ratio, such as fentanyl, morphine, and propofol. As a result, the effect of these drugs can be increased and prolonged.

### Intrinsic clearance

Intrinsic clearance is determined by the enzymatic capacity. There are two main enzymatic systems that are responsible for drug metabolism, i.e. phase I and phase II metabolism. Phase I metabolism includes oxidation, reduction, and hydrolysis and occurs predominantly by enzymes of the cytochrome P450 (CYP450) family. Phase II metabolism consists of conjugation with an endogenous substance (e.g. glucuronidation, acetylation, or sulfation). There are several factors that influence the metabolic capacity including genetic variability, enzyme induction, or inhibition (usually drug induced) and disease states including malignancies. [14] Liver injury in terminally ill cancer patients can be due to primary liver tumours or more often due to the presence of liver metastases or as a result of chemotherapy. In non-malignant terminally ill patients liver function can also be affected, for instance in the case of alcoholic liver cirrhosis or in Chronic Obstructive Pulmonary Disease (COPD) patients, who have been also shown to be more at risk for hepatobiliary diseases. [37]

The effect of liver pathology on metabolic capacity is, however, highly variable and difficult to predict. In fact, most liver functions can be maintained with some degree of liver injury, therefore liver pathology (including the presence of multiple liver metastases) can exist without affecting liver function. It is believed that unless liver cirrhosis is present, chronic liver diseases have little significant clinical impact on pharmacokinetics. In addition, phase II metabolism tends to be better preserved than phase I metabolism, only in advanced cirrhosis this pathway may also be impaired substantially. [18, 38]

As the metabolic capacity depends on nutrients and cofactors, it is probable that malnutrition can result in altered metabolism. Indeed, some studies showed that deficiency of specific nutrients (e.g. proteins, lipids, vitamin C, vitamin B6, and vitamin E) can result in a decrease in metabolic rate. However, some deficiencies, such as riboflavin and iron have also shown to increase CYP450 metabolism by a still unknown mechanism. [39] A reduction in the enzyme levels of some CYP450 enzymes (CYP2C8/10 and CYP2E1) have been shown, but this was not the case for some other CYP450 enzymes (CYP1A2 and CYP3A). [40] Studies on the direct effect of malnutrition/ cachexia on plasma drug levels are sparse and despite similar metabolic pathways, the influence of cachexia was divergent. Most of the drugs showed increased plasma levels after oral administration; however, with only plasma levels of the drug it is not possible to differentiate between changes in absorption, metabolism,

or elimination. One study on oxycodone in cachectic cancer patients also measured the metabolite, noroxycodone, formed via the CYP3A enzyme and did show higher plasma levels of oxycodone and a lower noroxycodone/oxycodone ratio in patients with a higher GPS score (a measurement for cachexia) indicating that cachexia decreases the hepatic metabolism of oxycodone. [41] This suggests a decrease in metabolic capacity, yet the overall effect of malnutrition and cachexia on metabolism is still unclear.

Another possible method by which CYP450 metabolism can be reduced in cancer patients is by inflammatory response. This is mediated largely through downregulation of gene transcription caused by pro-inflammatory cytokines. [27] This effect has not been studied extensively but it has been shown in some studies for the metabolism of CYP3A4 and CYP2C19. [42–44] In addition, there are also implications that inflammation may reduce the metabolic capacity of CYP1A2. [45–47] The clinical relevance of these reduction in metabolism, however, remains to be further investigated.

### Clinical considerations

For clinical practice, one should be aware that drug metabolism can be altered in patients with heart failure or those that suffer from decreased cardiac output due to dehydration (resulting in decreased hepatic blood flow) or patients with liver disease. In addition, drugs that are metabolized via the CYP450 enzyme system are likely to be affected more than drugs which are metabolized via phase II metabolism. As the effect of liver disease, dehydration, inflammation, and cachexia on liver metabolic capacity, is difficult to predict no specific recommendations can be made. Instead, care givers should be aware of the fact that patients with liver diseases can have a different reaction to medication, and they should look out for signs of altered efficacy and side effects in these patients, especially in the case of drugs with active metabolites.

## ELIMINATION

The elimination of drugs and metabolites can occur through a number of different routes (e.g. bile, sweat, and saliva); however, the main route of elimination is via the kidneys through glomerular filtration. Renal function, including glomerular filtration rate, decreases with increasing age. This alone means that most terminally ill patients will have a reduced elimination, as they are usually older (on average 63 years) than the healthy volunteers in which most pharmacokinetic studies are performed (on average 25–29 years).[2,48] Renal elimination can also be decreased in terminally ill patients as a result of renal insufficiency, which occurs in a large portion (50–60%) of the cancer patients.[49] Most terminally ill patients have a diminished fluid intake, which will cause prerenal kidney failure. Co-administration

Table 4. Physiological changes affecting drug elimination

| Physiological change in palliative care | Potential pharmacokinetic change | Consequence | Example drugs |
|---|---|---|---|
| Renal insufficiency or pre renal failure due to dehydration | Decrease in renal elimination | Increase in drug concentration and effect for renally eliminated drugs or metabolites | Morphine-metabolites |
| Liver decompensation | Possible decrease in hepatic elimination | Increase in drug concentration and effect for hepatic eliminated drugs or metabolites | Midazolam |
| Icterus | Possible decrease in elimination of drug that are excreted via bile | Increase in drug concentration and effect for drugs or metabolites that are excreted via bile | Lorazepam |

of non-steroidal anti-inflammatory drugs (NSAIDs) in this situation will severely compromise renal function. [24]

It is important to note that although renal insufficiency is common in this population, it might not be recognized using the standard blood chemistry tests. This is because glomular filtration is estimated using serum creatinine levels. In the case of terminally ill patients, this can be misleading as the production of creatinine is reduced as muscle mass is decreased. Therefore, glomular filtration rate can decrease without a change in serum creatinine concentrations. It is therefore important to realize that the eGFR provided by modification of diet in renal disease (MDRD) formula gives an overestimation of the renal function in patients with low muscle mass. For drugs that are not eliminated via kidneys but undergo hepatic elimination, accumulation can occur if the liver decompensates in the terminal phase. This can also happen if the bile is the primary route of elimination and the patient becomes icteric. [24] An overview of the factors affecting elimination is given in Table 4.

## Clinical considerations

In clinical practice, renal-eliminated drugs (or metabolites) will accumulate in the final days of life, if fluid intake is limited. Measuring renal function based on serum creatinine will not be very helpful in these patients. It is therefore recommended to either determine renal function using other parameters that correct for the loss of muscle for instance albumin or weight besides creatinine clearance or to measure drug concentrations. As both these interventions require blood sampling, it is probably of more practical value, to be aware of the fact that accumulation of certain drugs can occur and to monitor fluid intake and urinary output and look out for (increased) side effects in patients where these functions are diminished.

## CONCLUSION

In conclusion, there are numerous ways by which comorbidities and other physiological changes can alter pharmacokinetics in patients with terminal illness. The net effect of these alterations and the clinical relevance will be dependent on both the status of the individual patient and the properties of the drug in question. For clinical practice, we will discuss three commonly prescribed drugs in the terminal phase, i.e. morphine, midazolam, and haloperidol.



## MORPHINE

Morphine is widely used to treat pain and dyspnoea in terminally ill patients. [50] In a palliative setting, it is usually administered either orally (as normal release liquid or modified release tablets) or subcutaneously (as bolus injection or continuous infusion). Morphine is a relatively hydrophilic drug and is only partially bound (34–37.5%) to plasma proteins, predominantly albumin. [51] The metabolism of morphine takes place primarily in the liver. Morphine has a high extraction ratio and is metabolized mainly by Uridine 5' -diphosphoglucuronosyltransferase (UGT) enzymes into morphine-3-glucuronide (M3G) for 60%, and morphine-6-glucuorinide (M6G) for 10%. [52–54] The M6G metabolite is pharmacologically active and is 10–60 times as potent as morphine.[53–60] Its ability to cross the blood–brain barrier is, however, far less (1/57th) than that of morphine.[61] Nonetheless after chronic morphine administration, the gradual accumulation of M6G in the brain can account for increased potency compared to single administration. [53, 60, 62, 63] The M3G metabolite does not bind to the opioid receptors and, therefore, does not possess analgesic properties. [56, 64–67] Conversely, it has been suggested that M3G may be responsible for the side effects of morphine. [54, 68] Both glucuronide metabolites are eliminated through renal excretion. Overall, this pharmacokinetic profile of morphine means that its concentrations and effect may be influenced by changes in total body water (by influencing Vd), liver blood flow (by influencing metabolism and also via first pass absorption), and renal function (by influencing elimination of the metabolites).

The effect of total body water on the Vd of morphine have been shown by Baillie et al. [69]. Their results showed a decreased volume of distribution in elderly patients when compared to younger adults, which is in line with the fact that total body water declines with age. The clinical relevance of this will, however, be limited for terminally ill patients as the volume of distribution only determines the initial peak concentration and most patients will receive multiple doses of morphine.

An increased interpatient variability in morphine metabolism in terminally ill patients has been shown. This has been suggested to be due to reduced hepatic blood flow and

subsequent reduction in morphine clearance in these patients.[69] As a result of variability in metabolism, interpatient variability in oral bioavailability (between 15% and 49%) has also been shown.[70,71] The fact that this is caused by liver metabolism instead of absorption in the GI tract is supported by the fact that patients with icterus had an even higher oral bioavailability of 64%.[70] In addition, the fact that first-pass metabolism determines its bioavailability also means that the ratio of morphine to its metabolites will differ for different routes of administration.[72–74] This can be relevant as the metabolites of morphine can influence both its efficacy and side effects.

As the kidneys are responsible for the elimination of the glucuronide metabolites, renal function is an important aspect in morphine pharmacokinetics. This is especially relevant in terminally ill patients as renal insufficiency is common in this population. Accumulation of M3G and M6G in patients with renal insufficiency has been shown in several studies. [72, 73, 75–77] This can be advantageous due to the increased levels of the active M6G metabolite. It has indeed been shown that patients with renal insufficiency had an increased response to morphine and that they required lower doses. [77–80] Another advantage is that M6G has a lower risk of respiratory depression or hypoxia compared to morphine itself.[67,81–83] However, other side effects, such as delirium, myoclonus, and hyperalgesia/allodynia have been related to higher metabolite levels in terminally ill patients and are probably caused by accumulation of the M3G metabolite.[84–91]

In clinical practice, this means that physicians and nurses should be aware that if renal function declines (for instance if fluid intake ceases) delirium and myoclonus can occur. At the same time, the pain symptoms can both increase (hyperalgesia due to M3G accumulation) or decrease (due to M6G accumulation). If the pain is not increased, a reduction in morphine dose can be considered, otherwise switching to an analgesic without active metabolites (for instance fentanyl) may be an option. Furthermore, dosing forms that bypass the portal vein and, therefore, do not undergo first-pass metabolism (e.g. intravenous or subcutaneous injections) will probably have less side effects as the morphine–metabolites ratio is higher. This might therefore also be beneficial in patients with renal insufficiency.

## MIDAZOLAM

Midazolam can be used intermittently for the night times and is the drug of choice for palliative sedation in terminally ill patients. [6, 92–94] It is commonly administered via subcutaneous infusion but can also be administered orally to treat anxiety or insomnia. Midazolam is a highly permeable drug and is, therefore, believed to be completely absorbed through the GI tract, if given orally.[95] However, midazolam has limited bioavailability due to first-pass metabolism via CYP3A enzymes in the liver and gut wall. As midazolam is a highly permeable drug, the extent of first-pass metabolism can be influenced by variability

in intestinal blood flow. [95] In addition, it has also been proposed that midazolam bioavailability can be influenced by CYP3A metabolizing activity in the intestine. [96] Midazolam is highly lipophilic at physiological pH and is also highly bound to albumin (96–97%), resulting in a large volume of distribution.[97,98] It is metabolized in the liver, mainly by CYP3A into 1-hydroxymidazolam, which is then glucuronidated and excreted via the kidneys. 1-Hydroxymidazolam is pharmacologically active, although to a lesser extent than midazolam. [97] Midazolam has an intermediate extraction ratio its metabolism is, therefore, dependent on both liver blood flow and enzymatic activity.[99–101] Overall, this pharmacokinetic profile of midazolam means that its concentrations and effect may be influenced by changes in total body fat and albumin levels (by influencing Vd), liver blood flow, intestinal blood flow and CYP3A activity (by influencing metabolism and also via first-pass absorption) and renal function (by influencing elimination of the metabolites).

The effect of total body fat on the volume of distribution of midazolam has been studied primarily in obese patients. As expected, obese patient had a larger volume of distribution for midazolam. [96,102–104] We would therefore expect the opposite in terminally ill patients, and a study on cancer cachexia in rats did indeed show a decrease in Vd after the animals became cachectic. Increased plasma concentrations as a result of a decrease in Vd can be further enhanced as a result of hypoalbuminemia. Increased plasma concentrations as result of decreased Vd or hypoalbuminemia can have an impact on the onset of sedation after first administration. Halliday et al. showed that hypoalbuminemia was associated with shorter time to induction suggesting that higher levels of free midazolam will give a more rapid response. [105] On the other hand, if midazolam is given continuously over a longer period of time the higher free plasma levels will also result in a higher elimination.

Midazolam metabolism can be reduced in terminally ill patients as a result of reduced liver blood flow. This has been shown in elderly patients who compared to younger adults had a decreased midazolam clearance. [102] As midazolam is primarily metabolized by CYP3A, a reduction of CYP3A activity can also lead to decreased midazolam metabolism. Reduced CYP3A activity as a result of cachexia has been suggested to occur in cachectic patients and decreased midazolam clearance has also been shown in an animal model of cancer cachexia.[41,106] Reduced CYP3A activity can also occur as a result of liver disease and a correlation between midazolam clearance and liver failure has been shown in intensive care unit (ICU) patients.[107] In palliative patients, no correlation was found between midazolam concentrations and liver disease, probably because liver diseases in this population are not as severe as in ICU patients.[108] Finally, CYP3A metabolism can also be affected by the use of other drugs. In the palliative setting, there might be a relevant interaction with dexamethasone. Dexamethasone is used for a variety of symptoms in the terminal phase, and there are suggestions that it may induce CYP3A. [109,110] However, the extent by which dexamethasone induces CYP3A has not been completely clarified.

Finally, the elimination of the glucuronidated metabolites by the liver is reduced in patients with renal insufficiency, resulting in accumulation. Although glucuronidated 1-hydroxymidazol has only 1/10th of the potency of midazolam itself, this can result in prolonged sedation. [111]

In clinical practice, the onset of sedation can be different between patients due to changes in Vd. Patients with higher body weight may, therefore, require a higher initial dose, whereas hypoalbumineamic patients may require a lower initial dose. Patients who have used a CYP3A inducer, such as carbamazepine, in the past week may need higher midazolam doses to achieve accurate sedation. Finally, in patients with renal insufficiency, the sedative effect may be prolonged. This will probably be of little clinical relevance in the case of palliative sedation as most patients will only require sedation for less than 48 h. Nevertheless, it is something to keep in mind if midazolam is given for anxiety or insomnia.

## HALOPERIDOL

Haloperidol is a typical antipsychotic drug that is used in palliative care to treat delirium and might also be prescribed to treat nausea and vomiting. [1,112] In terminally ill patients, it is administered either orally or as a subcutaneous injection. [113] If given orally, it has a bioavailability of 60–70% due to first-pass metabolism.[112,114,115] For the subcutaneous route, there is no information available but bioavailability is probably around 100% as it diffuses from the subcutaneous tissue directly to the systemic circulation. Haloperidol is a lipophilic drug, and it is bound to albumin for more than 90%. Therefore, haloperidol has a large volume of distribution. [116,117] The hepatic metabolism of haloperidol is extensive (<1% is excreted unchanged) and includes both irreversible and reversible metabolic biotransformation. The main metabolic pathway is glucuronidation by UGT, which accounts for 50–60% of the total metabolism. [118] An estimated 20–30% of haloperidol is metabolized via CYP3A4 and CYP2D6. [119] Both these pathways are irreversible. The reversible part of the haloperidol metabolism is its conversion into reduced haloperidol by carbonyl reductase, which accounts for approximately 23% of the total metabolism.[120–122] The reduction of haloperidol is reversible as reduced haloperidol can be converted back into haloperidol through oxidation by CYP3A4.[119,123,124] Haloperidol has an intermediate extraction ratio therefore its metabolism is dependent on both enzymatic activity and liver blood flow. [114] Haloperidol metabolites are eliminated both with the urine and via the bile.[125,126] Overall, this pharmacokinetic profile of haloperidol means that its concentrations and effect may be influenced by changes in body fat and albumin levels (by influencing Vd), liver blood flow and metabolic activity (by influencing metabolism and also via first-pass absorption).

In terminally ill patients, a reduction in body fat, and consequently Vd, can result in higher initial plasma concentrations. Furthermore, hypoalbuminemia can also result in higher free

haloperidol concentrations and thereby possibly shorter the time-to-peak plasma concentrations. These changes can be clinically relevant as a rapid onset of action is desired in treating delirium. A large interpatient variability in time-to-peak plasma concentrations, between 2 and 6 h, has been shown in patients taking oral haloperidol.[114,127] It is, however, not known if this is due to changes in plasma albumin if there are other explanations, for instance delayed gastric emptying.

Haloperidol metabolism might be reduced in terminally ill patients as a result of reduced liver blood flow. It has been shown that elderly patients had higher steady-state plasma concentrations than younger patients.[127] As steady-state concentrations are only influenced by changes in clearance (not in Vd) a decrease in liver blood flow, which is common in elderly, might explain this.

Finally, differences in metabolic capacity might also influence haloperidol metabolism and thereby plasma concentrations. Interpatient variability in metabolism is unlikely to be caused by changes in UGT activity, as its capacity is relatively large compared to the other metabolic pathways.[114] The conversion of haloperidol into reduced haloperidol is also unlikely to cause much interpatient variability as little variation in enzyme activity has been shown for carbonyl reductase. [114] Changes in CYP3A4 or CYP2D6 activity on the other hand may lead to altered plasma concentrations. In the case of CYP3A4, it has been shown that co-administration of haloperidol with carbamazepine, a CYP3A4 inducer, resulted in significantly lower haloperidol concentrations. [128–131] The combination of carbamazepine and haloperidol might be relevant in patients with brain tumours or metastases. Another drug that might induce CYP3A is dexamethasone, this is commonly used in palliative care but the relevance of this combination remains to be determined.[109,110] A decrease in haloperidol metabolism in terminally ill patients is also possible as result of reduced CYP3A activity due to cachexia.[41] Variability in CYP2D6 metabolic capacity may also influence haloperidol concentrations. This has been shown by Mihara et al. for patients with a genetic variation in CYP2D6 enzyme. [132] In terminally ill patients, this could be relevant in the case of co-administration of haloperidol with CYP2D6 inhibitors, like fluoxetine or paroxetine. Although these drugs are not commonly given in the terminal phase. There have been some studies on the effect of fluoxetine on haloperidol levels and this showed a 20–35% increase in plasma levels. However, this was not associated with clinical effects. [133–136] So far, the effect of alteration in haloperidol metabolism due to cachexia, dexamethasone use or fluoxetine, or paroxetine use are merely theoretical and more research on its clinical relevance is needed.

In clinical practice, it may be the case that patients with hypoalbuminemia or loss of body fat will have a more rapid onset of action, and a lower initial dose might be sufficient. In addition, patients with reduced liver blood flow, or co-administration of dexamethasone might also need a lower dose. While patients with cachexia or fluoxetine or paroxetine use might need higher doses, it is not yet possible to make any real recommendations as there

has been very little research on haloperidol pharmacokinetics in terminally ill patients, especially about the use of the subcutaneous injections.

## EXPERT OPINION

The pharmacokinetics of drugs in terminally ill patients can be complex due to the pathophysiological changes that occur near the end of life. Although there are several guidelines for symptom management in terminally ill patients, limited evidence exists on guided drug use in these patients. Even for the most commonly used medications in this population (i.e. morphine, midazolam, and haloperidol) much is still unknown. The medication dose is therefore usually guided by experience and clinical effect, resulting in adaptation of a universal starting dose rather than defining a personalized dose beforehand based on solid PK characteristics.

Besides comorbidities, co-medication can also influence the action of drugs (both on the level of pharmacokinetics as pharmacodynamics). If a new drug, which could potentially interfere with the current medication, is added to the regimen caution is essential and short acting formulations are preferred when treatment is initiated and polypharmacy should be avoided. This may be more relevant in the pre-terminal phase as medication is reassessed in the terminal phase and most medication (besides analgesic and anxiolytics) is usually discontinued.

Such personalized treatment may significantly improve the quality of life for these patients and their family members, especially in the final days of life. To achieve this not only more knowledge but also more studies on the pharmacokinetics in terminally ill patients are necessary. A growing number of pharmacokinetic studies are being performed in special patient populations (e.g. ICU patients), yet these studies in terminally ill patients are still lacking to a large extent. In addition, there is also a need for pharmacodynamic (Pd) studies in this population as pharmacokinetics will give information on the achieved drug concentrations but not on the preferred clinical effect. Pd studies that measure the effect on for instance pain, sedation, or delirium would be of great clinical importance. The fact that so little studies are being performed in terminally ill patients might be because terminally ill patients are considered a vulnerable population, and it has been argued that including them in clinical research is inappropriate or even unethical. These ethical concerns are, however, often unjustified and studies in this population, if carefully designed and executed, can be very valuable.[137] A crucial aspect is to minimize the burden for patients and their families. Population Pk/Pd studies using limited sampling strategies may therefore provide a solution and may eventually lead to individualized dosing guidelines.

While Pk/Pd studies are lacking, there are several studies on factors predicting death in terminally ill patients. [19, 25, 26,138] These studies give valuable insight in the changes in

body functions that occur in the final days of life. Together with the knowledge of pharmacokinetics mentioned in this review this should provide a base on which pharmacological interventions can be made which will improve the quality of life of terminally ill patients. The difficulty in this is, however, that although a common final pathway is hypothesized, the terminally ill population can be very heterogeneous, they require different types of medication and will have different comorbidities. As the net result of drug concentrations is dependent on both physiological changes as well as chemical drug properties, these are probably best assessed by a multi-disciplinary team with a specialist pharmacist or clinical pharmacologist with specific knowledge of the last phase of life.



**Acknowledgments**

The authors would like to thank W Bramer (Medical Library, Erasmus Medical Centre) for assistance with the literature search.

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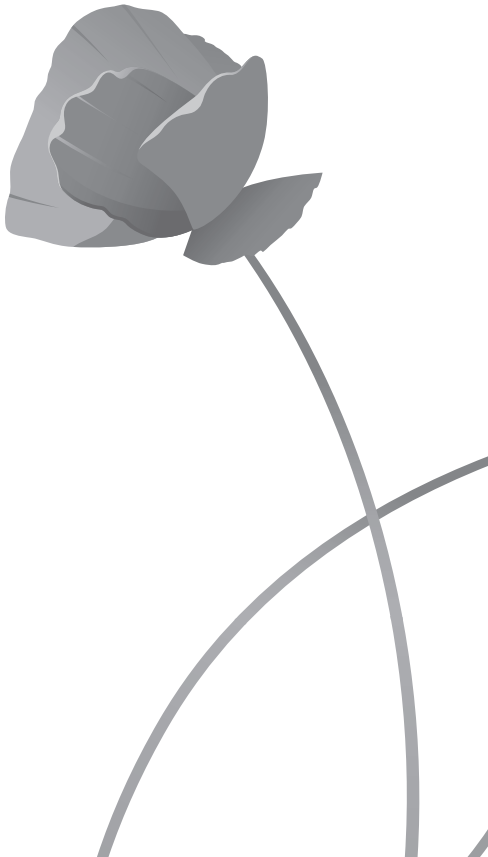

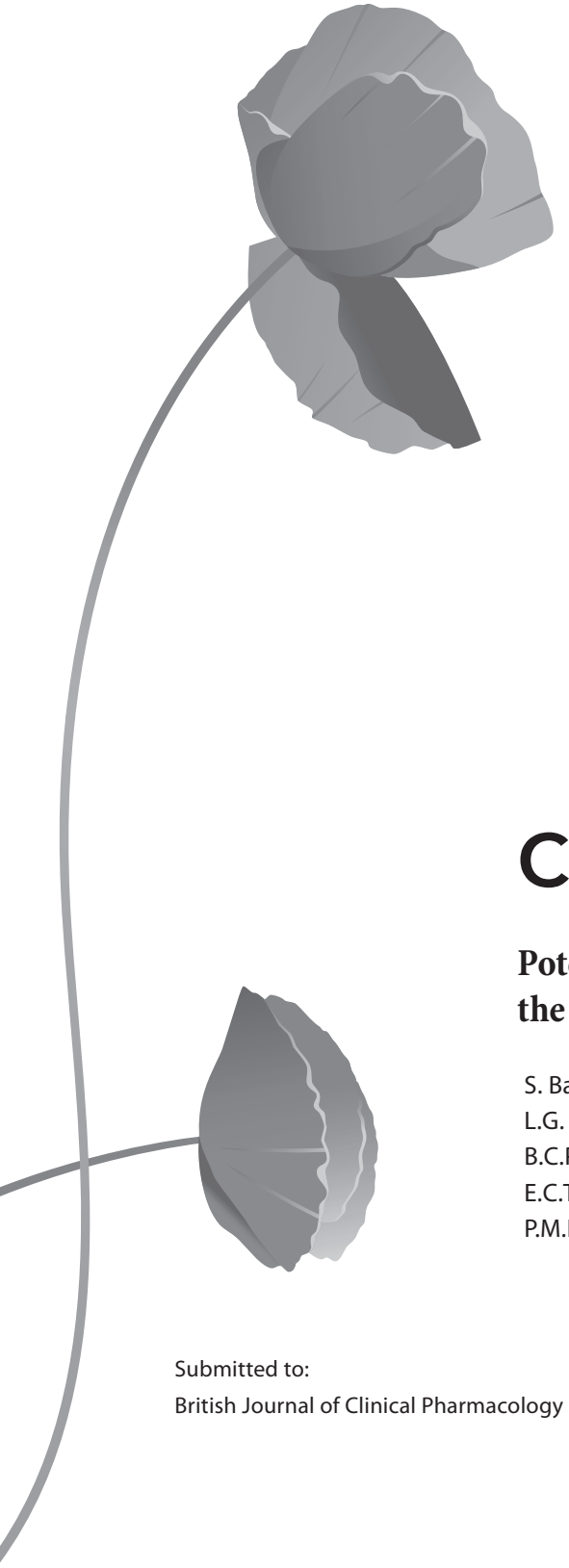

# CHAPTER 3

## Potential drug-drug interactions in the terminal phase of life

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Submitted to:
British Journal of Clinical Pharmacology

## ABSTRACT

### Purpose

To assess the frequency of potential drug-drug interactions in a palliative care centre. The secondary objectives are to study the most commonly involved drugs, drug-drug interaction characteristics (severity, clinical relevance, mechanism, scientific evidence) and to identify which risk factors are associated with the potential drug-drug interactions.

### Methods

A retrospective systematic analysis of potential drug-drug interactions was performed using the electronic prescription and drug monitoring system FarMedRx, which is linked to the "G-Standaard", the Dutch drug database for clinical decision support. Potential interactions were then independently scored by two experts to determine the clinical relevance within a palliative setting. Descriptive statistics and multivariate logistic regression analysis were used for assessment of the primary and secondary outcomes.

### Results

Among 127 included patients, 90 drug-drug interactions were identified in 42 patients (33.1%, 95% CI = 25.2 – 42.5%). The most commonly involved drugs were NSAIDs, glucocorticoids, SSRIs, dopamine (ant)agonists and antipsychotics. Most of the interactions (45.6% in 19.7% of patients) would lead to long-term discomfort without sequelae, and 51.1% were scored as clinically relevant by our expert team, affecting 29 patients (22.8%, 95% CI = 15.0 – 29.9%). The number of drugs used by patients was a potential risk factor of drug-drug interactions (adjusted OR = 1.50, 95% CI = 1.24 – 1.82).

### Conclusion

Although not all interactions are clinically relevant in end of life care, certain drug-drug interactions may still have serious consequences. As the number of drugs is a potential risk factor of interactions, unnecessary drugs should be stopped in the palliative setting. The use of some drugs, like NSAIDs and SSRIs should be carefully considered because of their side effects and the fact that the treatment may also be carried out by other drug classes.

## INTRODUCTION

Medication use in the terminal phase is focused on symptom control. In 2007, in response to a request of the World Health Organization (WHO), the International Association for Hospice and Palliative Care (IAHPC) prepared the list 'Essential Medicines in Palliative Care' based on the recommendations of palliative care experts from around the world. [1, 2] Terminally ill patients often suffer from a variety of complications. The management of these complications require the use of different drugs, which can lead to an increased risk of adverse effects, high pill burden and increased healthcare costs. In a randomized trial, discontinuation of statins in patients with a life expectancy of less than one year improved the quality of life and led to cost savings. The combined use of drugs could also lead to a higher risk of drug-drug interactions, which may have serious consequences even at the end of life. [3, 4, 5] However, insufficient attention is being paid to drug-drug interactions in palliative care. Literature that describes the prevalence of drug-drug interactions in palliative care is limited. Riechelmann et al. evaluated the epidemiology of drug-drug interactions in cancer patients. These patients were exclusively receiving supportive care in hospital. This study showed that one-third of these patients were exposed to at least one drug-drug interaction. Nearly 70% of the drug-drug interactions were of major or moderate severity and almost 42% were supported by levels 1-3 of scientific evidence. [6] Gaertner et al. identified the combination of drugs with the potential to interact in patients in a palliative care unit. This study showed that drug-drug interactions are mainly based on interactions via histamine, acetylcholine or dopamine receptors. In addition, non-steroidal anti-inflammatory drugs (NSAIDs) are frequently involved. [7] Frechen et al. identified which combinations of drugs and risk factors had the potential for drug-drug interactions in patients of two hospices. They also assessed the clinical relevance of these drug-drug interactions. According to this study, drug-drug interactions, were seen in 60% of patients. Of the 796 reported DDIs 419 (53%) were therapeutically relevant occur in 46% of patients. [8] Furthermore, Morgan et al. found that 72% of patients, who were referred to specialist palliative care, were at risk of one or more potential drug-drug interaction. [9] Due to the potential importance of drug-drug interactions in palliative care, this study is aimed at giving more insight into the frequency of drug-drug interactions in patients in an inpatient palliative care centre. The secondary objectives are to study (i) the most commonly involved drugs with the potential to interact, (ii) the degree of severity, clinical relevance, mechanism and level of scientific evidence of the potential drug-drug interactions, and (iii) which risk factors are associated with the potential drug-drug interactions

## MATERIALS AND METHODS

### Study design and setting

A retrospective observational study was designed to determine the drug-drug interactions in terminally ill patients admitted to the Regional Palliative Centre Laurens Cadenza in Rotterdam. This palliative care centre is a 20 beds high-care hospice. Around 200-250 patients are admitted to and die in Laurens Cadenza each year. The average length of admission for terminal care is approximately three weeks. The Medical Ethics Review Committee (METC) of Erasmus University Medical Centre approved the study.

### Study population

Patients were eligible to participate in this study if they were treated with one or more drugs. Exclusion criteria were (i) age < 18 years, (ii) life expectancy of less than two days, (iii) patients not deceased in the palliative care centre. Patients who did not decease in the palliative care centre were excluded due to incomplete medication use data.

### Outcome measures

The primary outcome measure was the frequency of potential drug-drug interactions in a palliative care centre. The secondary outcome measures were (i) the most commonly involved drugs with the potential to interact, (ii) the degree of severity, clinical relevance, mechanism and the level of scientific evidence of the potential drug-drug interactions and (iii) the potential risk factors that were associated with the drug-drug interactions.

### Data collection

Demographic patient characteristics like age, gender, primary diagnosis, number of comorbidities, number of drugs used and duration of admission were derived from the electronic medical records (mijnCaress, pinkroccade healthcare). The primary diagnosis of the patients was assigned by using the ICD-10, International Classification of Diseases and Related Health Problems, of WHO. [10]

To identify potential drug-drug interactions, as needed prescriptions, as well as regular prescriptions, were included for analysis. For fixed-dose combinations (e.g. triamterene/hydrochlorothiazide) each active pharmaceutical ingredient was evaluated separately. However, when a drug was used in different formulations (e.g. short- and long-acting morphine), the interaction was counted only once.

Potential interactions were identified using FarMedRx (FarMedvisie, Woerden, The Netherlands), an electronic prescription and drug monitoring system for healthcare facilities [11]. This system is linked to the so-called 'G-Standaard', the Dutch drug database for clinical decision support which is monthly updated by the Royal Dutch Pharmacist Association (KNMP). [12] The level of severity according to this system, the mechanism and the level

of scientific evidence of the potential interactions were derived from the G-Standaard. The level of severity of a drug-drug interaction was reported using a six-category scale (A-F), which were in order of increasing severity. Drug-drug interactions were categorized as pharmacokinetic (PK) and pharmacodynamic (PD) interactions, based on the underlying mechanism of the interaction. The level of scientific evidence for a drug-drug interaction was reported using a five-category scale (0-4). [12, 13] Potential interactions were scored independently by two experts to determine the relevance. One of the experts was a hospital pharmacist and clinical pharmacologist and the other one was a resident and a researcher in the area of palliative care. The scores of the experts were then compared and in case of disagreement on the scores, the two experts met to reach consensus.



### Statistical analysis

IBM SPSS Statistics 21 (IBM Corp., Armonk, New York, USA) was used for data collection and analysis.

Descriptive statistics were used to evaluate demographic patient characteristics, primary diagnosis, number of comorbidities, number of drugs used, duration of admission. Normally distributed variables were presented as mean with standard deviation (SD), while non-normally distributed variables were presented as median with interquartile range (IQR).

Descriptive statistics were also used to evaluate the frequency of drug-drug interactions. Normally distributed variables were presented as mean with standard deviation (SD), while non-normally distributed variables were presented as median with minimum-maximum range (range) and 95% confidence intervals (CIs) were calculated for proportions. The most commonly involved drugs with the potential to interact and drug-drug interaction characteristics (severity, clinical relevance, mechanism and scientific evidence) were also evaluated by using descriptive statistics and 95% CIs were calculated for proportions.

Potential risk factors of drug-drug interactions were determined by using univariate and multivariate binary logistic regression analyses. The dependent variable was defined as one or more drug-drug interactions per patient. Age, sex, number of drugs used, and number of comorbidities were included as predictor variables. A multivariate logistic regression analysis was performed using all predictor variables with $p < 0.05$ in the univariate analyses and leaving them in the model if the regression coefficient changed by >10%. For all analyses, p-values of less than 0.05 were regarded as statistically significant and 95% CIs were calculated for odds ratios (ORs).

## RESULTS

### Demography

A total of 146 patients were screened for eligibility, of which 127 patients were included for analysis (Figure 1). Mean age of included patients was 73.3 years (SD 12.4), of which 48.8% were male. The median duration of admission of these patients was 16 (IQR 7-35) days. The most frequent primary diagnosis was neoplasm, mainly of the digestive or respiratory and intrathoracic organs (85.8% of patients). Patients had a median of four comorbidities (IQR 2-5) and the median number of drugs used per patient was 4.7 (IQR 3.3-6.7). Demographic patient characteristics are presented in Table 1.

### Drug interactions

A total of 90 potential drug-drug interactions (Supplementary table 1) were identified in 42 patients (33.1%, 95% CI = 25.2 – 42.5%), with a median of 2 (range 1-7) potential drug-drug interactions per patient. Drugs most often involved in drug-drug interactions were NSAIDs, glucocorticoids, selective serotonin reuptake inhibitors (SSRIs), dopamine (ant)agonists and

**Table 1.** Patient characteristics (n=127)

| Characteristics | |
|---|---|
| Gender, n (%) | |
| Male | 62 (48.8) |
| Age, in years | |
| Mean ± SD | 73 ± 12 |
| Duration of admission, in days | |
| Median (IQR) | 16 (7-35) |
| Primary diagnosis, n (%) | |
| Neoplasm | 109 (85.8) |
| Lip, oral cavity and pharynx | 3 (2.7) |
| Digestive organs | 37 (33.9) |
| Respiratory and intrathoracic organs | 27 (24.8) |
| Melanoma and other malignant neoplasms of skin | 4 (3.7) |
| Breast | 4 (3.7) |
| Female genital organs | 5 (4.6) |
| Urinary tract | 4 (3.7) |
| Eye, brain and other parts of central nervous system | 6 (5.5) |
| Ill-defined, secondary and unspecified sites | 5 (4.6) |
| Lymphoid, hematopoietic and related tissue | 6 (5.5) |
| Other | 8 (7.3) |
| Diseases of the circulatory system | 11 (8.7) |
| Other | 7 (5.5) |
| No. of comorbidities per patient | |
| Median (IQR) | 4 (2-5) |
| No. of drugs used per patient | |
| Median (IQR) | 4.7 (3.3-6.7) |

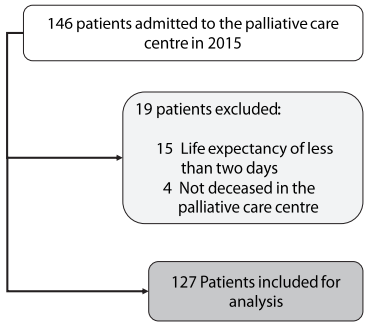


**Figure 1.** Study design



antipsychotics. When looking at the types of drug-drug interactions, the severity could be determined by using a pre-determined scoring system [1, 2]. According to this systematic approach 21.1% of the interactions could lead to long term (>7 days) clinical effects with possible sequelae, 2.2% could result long term severe clinical effects and 7.8% to very severe effect and death. These interactions affected 9.4%, 1.6% and 5.5% of patients respectively (figure 2). Most of the interactions (45.6% in 19.7% of patients) would lead to long-term (2-7 days) discomfort without sequelae. Of all drug-drug interactions, 51.1% were pharmacodynamic interactions and 62.2% were supported by controlled, published interaction studies in patients/volunteers with relevant surrogate endpoints.

As these pre-determined severity scores may not be applicable in the terminally ill population our team of experts also scored each interaction for clinical relevance. The independent scoring was consistent between the experts for 54 (60.0%) potential drug-drug interactions. The experts met to reach consensus about the other 36 (40.0%) potential drug-drug interactions and determined finally that 46 (51.1%) of these 90 potential drug-drug interactions qualified as relevant and affected 29 patients (22.8%, 95% CI = 15.0 – 29.9%). The mechanism of drug-drug interactions, level of severity, level of scientific evidence and the relevance are presented in the supplementary material and figure 2.

## Potential risk factors

The results of the logistic regression analysis are presented in Table 2. In the univariate analysis, age and number of drugs were risk factors with a high potential for drug-drug interactions. In the multivariate analysis, only the number of drugs remained statistically significantly associated with drug-drug interactions (adjusted OR = 1.50, 95% CI = 1.24 – 1.82).

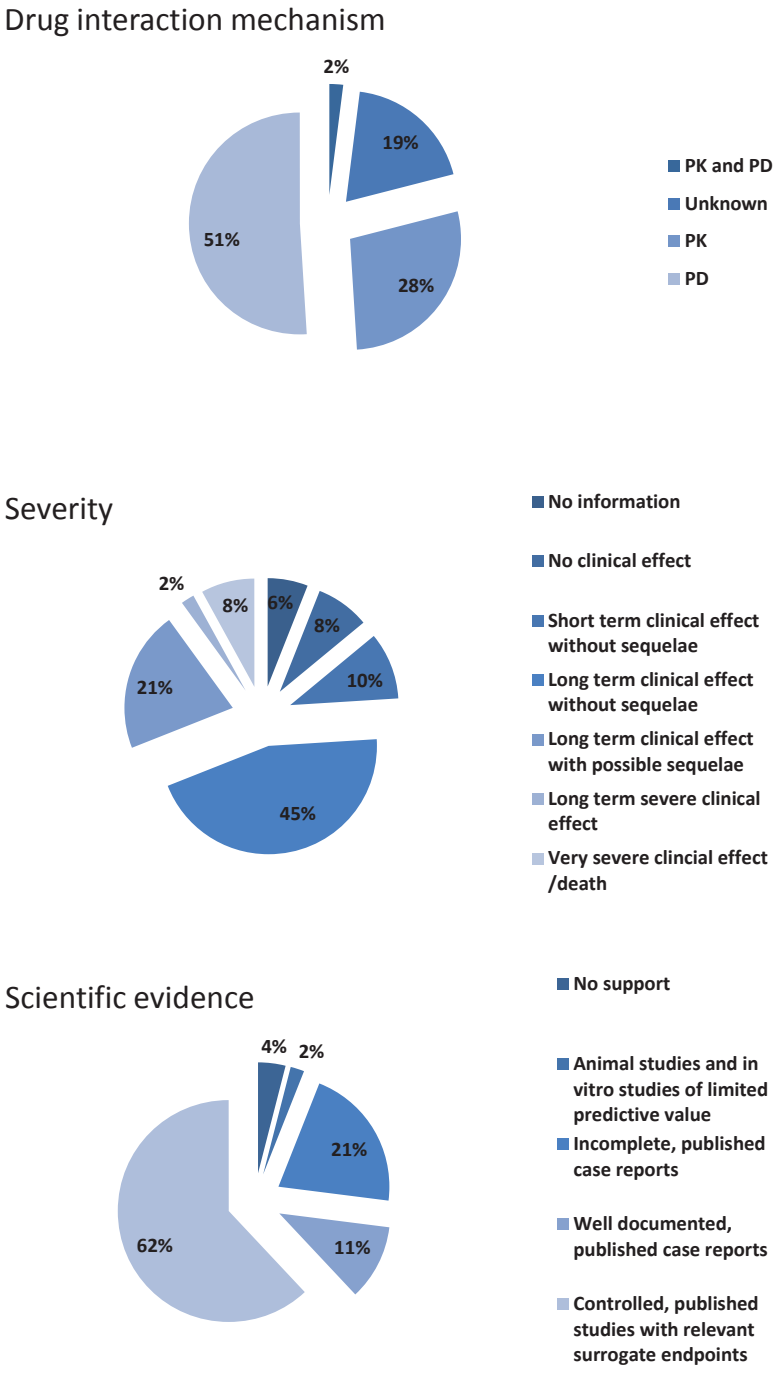


Figure 2. Mechanism of drug-drug interactions, level of severity, level of scientific evidence and relevance as scored by the expert team.

Table 2. Univariate and multivariate binary logistic regression analysis

| Variable | Crude OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|
| Age | 0.96 (0.93-0.99) | 0.97 (0.94-1.01)[a] |
| Gender | 0.93 (0.45-1.95) | – |
| No. of drugs | 1.52 (1.26-1.85) | 1.50 (1.24-1.82)[b] |
| No. of comorbidities | 1.05 (0.87-1.27) | – |

Abbreviations: CI = confidence interval, OR = odds ratio.
[a]Adjusted for no. of drugs.
[b]Adjusted for age.



## DISCUSSION

In the present study, drug-drug interactions were identified in 33.1% of patients. The most commonly involved drugs were NSAIDs, glucocorticoids, SSRIs, dopamine (ant)agonists and antipsychotics. Of these interactions, 7.8% can lead to serious clinical effects in 5.5% of patients, 2.2% to failure of live-saving therapy or severe clinical effects in 1.6% of patients and 21.1% to long-term/permanent sequelae or disability in 9.4% of patients. More than half of the drug-drug interactions were pharmacodynamic interactions and 62.2% were supported by controlled, published interaction studies in patients/volunteers with relevant surrogate endpoints. According to the experts, 51.1% of these drug-drug interactions were relevant and affected 22.8% of patients.

Similar to the study of Riechelmann et al., one third of terminally ill patients receiving palliative care were exposed to at least one drug combination with the potential to interact [6]. In other studies, this proportion was more than 60% [7-9]. Drugs most commonly involved in the interactions were NSAIDs, glucocorticoids, SSRIs, dopamine (ant)agonists and antipsychotics. These results correspond well with other studies. [6-8]

Drugs that belong to the interaction category 'severe' are combinations of drugs that might prolong the QT interval. In the present study, these concerned combinations of haloperidol with other QT prolonging drugs. Prolongation of the QTc interval is associated with serious and fatal risks, like torsade de pointes. [14] Other studies also identified these combinations as drug-drug interactions for which monitoring or adjustment is needed [7, 8]. In the palliative care setting EEG monitoring is not performed, therefore the possible benefit of haloperidol and the required dose should be carefully considered. Another interesting finding is that NSAIDs are a class of drugs that is often involved in drug-drug interactions. Considering the limited life expectancy of the patients, these drugs should perhaps be switched to opioids when drug-drug interactions occur. This could possibly prevent shortness of breath in the case of congestive heart failure or the risk of GI bleeding in elderly patients with corticosteroid use.

One of the possible events that is in general classified as serious are electrolyte disturbances. In our study we found two drug-drug interactions that increases the risk of electrolyte disturbances, i.e. SSRIs with thiazide diuretics and cotrimoxazole with captopril. Drug combinations of SSRIs and thiazide diuretics may potentiate the risk of hyponatremia. [15-17] The combination of cotrimoxazole and captopril could also lead to severe clinical effects by increasing the risk of hyperkalaemia [17, 18]. In a clinical setting sodium and potassium levels should be monitored closely, in the palliative setting however this is not standard practice. The use of drugs causing these interactions should therefore be carefully considered especially with regard to the risk of hyponatraemia for which some dehydrated patient may already be at risk. These combinations were not identified as drug-drug interactions in other studies [6-8]. This may be due to the fact that these drugs were not among the most frequently prescribed drugs in palliative care and their use depends on the comorbidities of patients. In the present and other studies, the most frequent underlying disease was cancer. [6-8, 19]

Combinations of central acting dopaminergic agents with antiemetic (antidopaminergic) drugs could result in serious effects or disability by antagonizing the pharmacological effects of dopamine agonists [20, 21]. The use of other antiemetic drugs, like domperidon, should be considered in case of nausea/vomiting and levodopa use. Domperidon leads to a reduced risk of extrapyramidal adverse effects by not crossing the blood-brain barrier. [21] Frechen et al. also identified these combinations as drug-drug interactions and classified them as 'contraindicated as a precaution'. [8] Combinations with antipsychotics also belong to this category. However, this combination is not detected in other studies [6-8]. As mentioned before, this may be due to the fact that these drugs were not among the most frequently prescribed drugs in palliative care, thus reducing the chance that this interaction will also be found in other studies. Another drug-drug interaction of this category is the combination of NSAIDs with diuretics or RAAS-inhibitors. These combinations are associated with worsening of existing heart failure. Therefore, NSAIDs should be used with caution in patients with a history of cardiac disease. [22] Other studies also identified these combinations as drug-drug interactions for which monitoring or adjustment is needed in certain cases. [7, 8] Combination of coumarins with certain drugs could enhance (antibiotics, SSRIs, (es)omeprazole) or antagonize (vitamin K) the effect of coumarins [12, 23-26]. So, the use of coumarins in combination with one of these drugs should be monitored closely and the dose of coumarins should be adjusted based on the anticoagulant effects. These combinations with coumarins were not found in other studies. [6-8] Riechelmann et al. only found combinations of warfarin with corticosteroids and paracetamol, which are not identified in the present study. [6] Therefore, the likelihood of these drug-drug interactions in palliative care depends on comorbidities of patients for which the use of different number of drugs are needed. Combination of corticosteroids and liver enzyme inducers are categorized in the same level of severity. Corticosteroids are used in the treatment of pain,

dyspnoea, nausea, fatigue and anorexia in palliative care [27, 28]. These combinations could antagonize the effect of corticosteroids and are also found in other studies [6, 7, and 29]. The use of these drug combinations should be monitored closely.

Our expert team determined that 51.1% of the drug-drug interactions were relevant. Other studies, in which the relevance was determined by an automated scoring system, have reported similar or higher proportions (53-72%) [7, 8]. The higher proportion may be explained by the fact that these automated systems are not specifically designed for the palliative care setting. This can cause overestimation of clinical relevance, especially in the case of interactions with consequences in the more distant future. Furthermore these systems score the relevance of drug-drug interactions by substances irrespective of dose-, sequence- and time of medication administration-dependent effects, which can also lead to overestimation of the relevance.



In the present study the number of drugs used by patients has been identified as a potential risk factor of drug-drug interactions. This result is consistent with other studies [6, 8]. The fact that an increase in the number of drugs used by patients is associated with an increase in risk for the occurrence of drug-drug interactions is not surprising. The use of drugs for the management of chronic diseases should be reconsidered in the final phase of life. The benefits of these drugs should be weighed against the potential drug-drug interactions, which could affect the quality of life. Beta blocking agents for instance are beneficial in preventing cardiac disease in the future, however their use may cause shortness of breath by antagonize the effects of beta-2 adrenergic bronchodilators. Discontinuation of these drugs in terminally ill patients may even improve their quality of life. Furthermore, the time until clinical benefit of these drugs may, in any case, exceed the life expectancy of terminally ill patients. [3, 4, 30]

**Strengths and limitations**

A strength of this study is the objective identification of drug-drug interactions based on the G-Standaard and the scoring of the relevance of interactions by two experts. Drug-drug interactions are identified using the G-standaard, which identifies interactions by substances irrespective of dose-, sequence- and time of medication administration-dependent effects. This can lead to overestimation of the incidence and risk of potential drug-drug interactions. But by having all interactions assessed with respect to relevance, this overestimation was reduced.

A major limitation of this study is that it has a retrospective design. Because the clinical relevance of an interaction will not only depend on the drug interaction itself but also on other risk factors, and more specifically for this population on the life expectancy. Patients are generally referred to a palliative care centre if their life expectancy is 3 months or less. This estimation can however be difficult and the actual time a patient spends in a palliative care centre can differ from 2 days to over a year. The lack of this information has impact

on the assessment of clinical consequences of the drug-drug interactions. It is therefore important to confirm these results by prospective studies to more accurately investigate the clinical consequences of drug-drug interactions in palliative care. Another limitations of this study is that it was a single-centre study, which means that the results cannot be simply extrapolated. In drugs used in palliative care may also differ between countries therefore the amount and relevance of interactions may also differ worldwide. Furthermore, considering that more than half of the drug-drug interactions were assessed as relevant by the experts, it is essential that palliative care specialists cooperate well with specialized palliative care pharmacists to prevent drug-drug interactions which may have serious consequences even at the end of life.

## CONCLUSION

Pharmacotherapy in palliative care should be strictly monitored. Although not all interactions are relevant in end of life care, certain drug-drug interactions may still have potentially serious consequences in these patients. As the number of drugs is a potential risk factor of interactions, unnecessary drugs should be stopped in the palliative setting.

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**Supplementary Table 1a.** Identified potential relevant drug-drug interactions

| Interaction | Interacting drugs | N | Description | Severity | Scientific evidence | PK/PD | Relevance according to experts |
|---|---|---|---|---|---|---|---|
| NSAIDs + corticosteroids | Acetylsalicylic acid; Etoricoxib; Diclofenac; Naproxen; Ibuprofen + Dexamethasone; Prednisolone | 14 | Increased risk of GI bleeding | C | 3 | ? | 6 Relevant<br>8 Not relevant |
| Diuretics + NSAIDs | Bumetanide; Furosemide; Spironolactone + Diclofenac; Naproxen; Ibuprofen | 5 | Drug combinations may adversely affect renal function. At the same time, hypotensive effect of the diuretics may be reduced | D | 3 | PD | Relevant |
| Beta blockers non-selective + betamimetics | Propranolol; Sotalol + Formoterol; Salbutamol; Salmeterol | 4 | Beta blockers may antagonize the effects of beta-2 adrenergic bronchodilators | C | 3 | PD | Relevant |
| Midazolam/alprazolam + CYP3A4 inhibitors | Midazolam + Verapamil; Fluconazole | 4 | CYP3A4 inhibitors may increase the plasma concentration of midazolam or alprazolam | B | 3 | PK | Relevant |
| QT prolonging drugs (with TDP) + QT prolonging drugs (with TDP) | Haloperidol + Ciprofloxacin; Levomepromazine; Citalopram; Domperidone; Methadone; Azithromycin | 7 | Drug combinations can prolong QT interval | F | 1 | PD | 2 Relevant<br>5 Not relevant |
| Dopaminergic agents + antiemetics (antidopamin.) | Levodopa; Pramipexole; Ropinirole + Domperidone; Metoclopramide | 5 | Drug combinations may antagonize the pharmacologic effects of dopamine agonists. | D | 2 | PD | 2 Relevant<br>3 Not relevant |
| NSAIDs + serotonin-acting drugs | Acetylsalicylic acid; Etoricoxib + Duloxetine; Sertraline; Trazodone | 3 | Increased risk of GI bleeding | C | 2 | PD | 2 Relevant<br>1 Not relevant |
| Midazolam/alprazolam + inductors | Midazolam + Phenytoin; Phenobarbital | 2 | Inductors like phenytoin and phenobarbital may induce the CYP3A4 hepatic metabolism of midazolam or alprazolam and increase their clearance. | C | 3 | PK | Relevant |
| Coumarins + (es)omeprazole | Acenocoumarol + Omeprazole | 2 | (Es)omeprazole may inhibit the hepatic metabolism of acenocoumarol | D | 1 | PK | Relevant |
| Tetracyclines + antacids/calcium | Doxycycline + Calcium carbonate; Magnesium hydroxide | 2 | Drug combinations may inhibit the absorption of tetracyclines | C | 3 | PK | Relevant |

**Supplementary Table 1a.** Identified potential relevant drug-drug interactions (*continued*)

| Interaction | Interacting drugs | N | Description | Severity | Scientific evidence | PK/PD | Relevance according to experts |
|---|---|---|---|---|---|---|---|
| Thyroid drugs + antacids/calcium | Levothyroxine + Aluminum hydroxide; Magnesium hydroxide | 2 | Drug combinations may inhibit the absorption of thyroid drugs | C | 3 | PK | Relevant |
| Beta blockers + NSAID's | Metoprolol + Diclofenac | 1 | NSAIDs may attenuate the antihypertensive effect of beta blockers | C | 3 | PD | Relevant |
| Bisphosphonates + antacids/iron/calcium | Alendronic acid + Calcium carbonate | 1 | Products containing aluminum, calcium, magnesium and other polyvalent cations such as antacids or vitamin with mineral supplements are likely to interfere with the gastrointestinal absorption of oral bisphosphonates. | – | – | PK | Relevant |
| Corticosteroids + inductors | Dexamethasone + Phenytoin | 1 | Phenytoin and other hydantoins may induce the CYP3A4 hepatic metabolism of corticosteroids and increase their clearance. | D | 3 | PK | Relevant |
| Coumarins + metformin | Phenprocoumon + Metformin | 1 | Metformin may inhibit the effect of coumarins | B | 2 | ? | Relevant |
| Coumarins + rosuvastatin | Acenocoumarol + Rosuvastatin | 1 | Rosuvastatin may enhance the hypoprothrombinemic effect of coumarins | – | 0 | ? | Relevant |
| Coumarins + salicylates antithrombotic (up to and including 100 mg) | Acenocoumarol + Acetylsalicylic acid | 1 | Acetylsalicylic acid and derivates of salicylic acid may enhance the anticoagulant effect of coumarins | – | 0 | PD | Relevant |
| Coumarins + SSRIs/Venlafaxine/Duloxetine/Trazodone | Acenocoumarol + Paroxetine | 1 | SSRIs, venlafaxine, duloxetine or trazodone may enhance the effect of coumarins | D | 1 | ? | Relevant |
| Dopaminergic agents + antipsychotics | Ropinirole + Olanzapine | 1 | Drug combinations may antagonize the pharmacologic effects of dopamine agonists | D | 3 | PD | Relevant |
| Phenytoin + coumarins | Phenytoin + Acenocoumarol | 1 | Coumarins may increase the plasma concentration of phenytoin. In addition, phenytoin may affect the metabolism of coumarins. The effect of the coumarins may increase or decrease | C | 3 | PK | Relevant |
| Iron + antacids/carbonate | Ferrous fumarate + Magnesium hydroxide | 1 | Drug combinations may inhibit the absorption of iron | C | 3 | PK | Relevant |

**Supplementary Table 1a.** Identified potential relevant drug-drug interactions (*continued*)

| Interaction | Interacting drugs | N | Description | Severity | Scientific evidence | PK/PD | Relevance according to experts |
|---|---|---|---|---|---|---|---|
| Tyrosine-kinase inhibitors + gastric acid secretion inhibitors | Pazopanib + Omeprazole | 1 | Gastric acid secretion inhibitors may decrease the oral bioavailability of tyrosine-kinase inhibitors and reduce their concentrations in plasma | A | 3 | PK | Relevant |
| Trimethoprim + RAAS inhibitors/ Spironolactone | Cotrimoxazole + Captopril | 1 | Drug combinations may increase the risk of hyperkalaemia | E | 3 | PD | Relevant |
| RAAS inhibitors + NSAIDs | Captopril + Diclofenac | 1 | NSAIDs may attenuate the antihypertensive effects of ACE inhibitors | D | 3 | PD | Relevant |

Severity score: A = no clinical effect, B = Short term clincial effect (< 48h) without sequelae, C = Long term clinical effect (48-168h) without sequelae, D = Long term clinical effect > 168 h with possible sequelae, E = Long term severe clinical effects, F = Very severe clinical effects / death
Level of scientific evidence: 0 = no support, 1 = animal studies or in vitro studies of limited predictive value, 2 = incomplete, published case reports, 3 = well documented, published case reports. Retrospective analysis of case series of interactions/side effects, 4 = Controlled, published interacion studies in patients/volunteers with relevant surrogate endpoints
Abbreviations: PK= pharmacokinetic, PD= pharmacodynamic, GI = gastrointestinal; ? = unknown.

**Supplementary Table 1b.** Identified non clinical relevant drug-drug interactions

| Interaction | Interacting drugs | N | Description | Severity | Scientific evidence | PK/PD | Relevance according to experts |
|---|---|---|---|---|---|---|---|
| SSRIs/Venlafaxine/Duloxetine/Vortrioxetine + Oxycodone | Citalopram; Duloxetine; Paroxetine; Sertraline; Venlafaxine + Oxycodone | 7 | Drug combinations may cause serotonin syndrome | C | 1 | PD | Not relevant |
| Calcium carbonate + gastric acid secretion inhibitors | Calcium carbonate + Pantoprazole | 4 | Gastric acid secretion inhibitors may inhibit the absorption of calcium carbonate | A | 3 | PK | Not relevant |
| Beta blockers selective + insulin | Bisoprolol + Insulin Aspart; Insulin Glargine | 2 | Beta blockers may inhibit some of the normal physiologic response to hypoglycemia | B | 3 | PD | Not relevant |
| Coumarins + antibiotics (ex. cotrim/metron/cefam) | Phenprocoumon + Azithromycin; Tobramycin | 2 | Drug combinations may enhance the hypoprothrombinemic effect of coumarins | D | 3 | PD | Not relevant |
| Alpha blockers non-selective + beta blockers/ca-ant. | Doxazosin + Carvedilol | 1 | Drug combinations can cause additive hypotensive effects | B | 3 | PD | Not relevant |
| Coumarins + antithyroid agents | Acenocoumarol + Thiamazole | 1 | Antithyroid drugs, by reducing the hyperthyroid state, may increase the hypoprothrombinemic response to oral anticoagulants | – | – | PD | Not relevant |
| Coumarins + Vitamin K | Phenprocoumon + Phytomenadione | 1 | Phytomenadione may antagonize the hypoprothrombinemic effect of coumarins | D | 1 | PD | Not relevant |
| Dextromethorphan/midazolam + pazopanib | Midazolam + Pazopanib | 1 | Pazopanib may increase the plasma concentration of dextromethorphan or midazolam | A | 3 | PK | Not relevant |
| Metoclopramide + SSRIs | Metoclopramide + Paroxetine | 2 | Drug combinations may cause serotonin syndrome and severe extrapyramidal reactions. In addition, SSRIs may increase the plasma concentration of metoclopramide. | C | 3 | PK/PD | Not relevant |
| Metoprolol + CYP2D6 inhibitors | Metoprolol + Paroxetine | 1 | CYP2D6 inhibitors may increase the plasma concentration of metoprolol | B | 3 | PK | Not relevant |
| Midazolam/alprazolam + INH/pill/(fos)aprepitant | Midazolam + Ethinyl estradiol/Levonorgestrel | 1 | INH, the pill or (fos)aprepitant may increase the plasma concentration of midazolam by inhibiting its CYP3A4 hepatic metabolism. | A | 3 | PK | Not relevant |
| Opioid agonist + partial agonist/antagonist | Morphine + Buprenorphine | 1 | Partial agonists/antagonists may reduce the analgesic effect of opioid agonists. | C | 3 | PD | Not relevant |

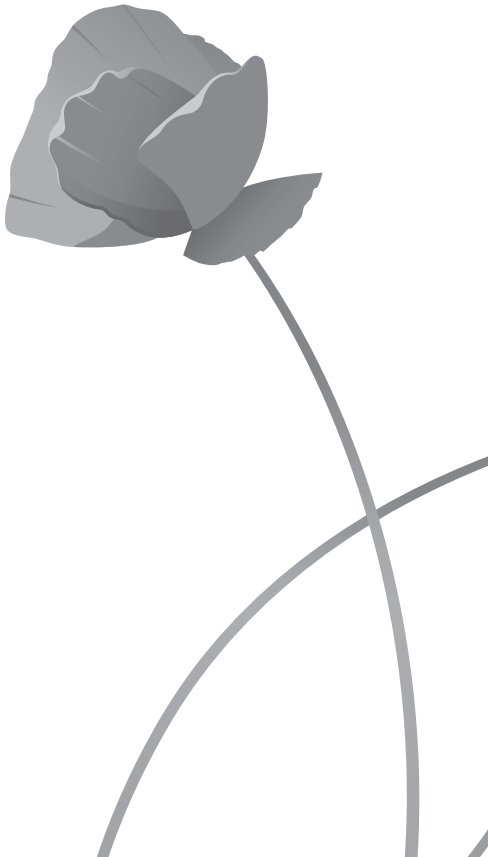
**Supplementary Table 1b.** Identified non clinical relevant drug-drug interactions (*continued*)

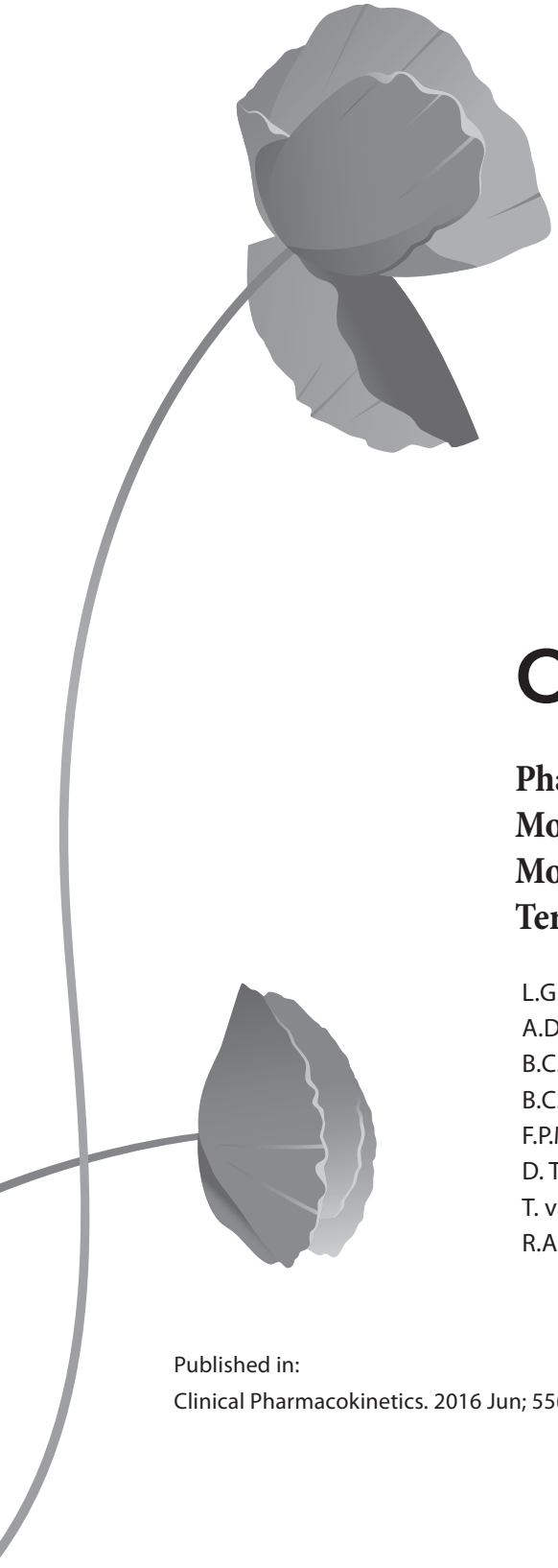
| Interaction | Interacting drugs | N | Description | Severity | Scientific evidence | PK/ PD | Relevance according to experts |
|---|---|---|---|---|---|---|---|
| SSRIs/Venlafaxine/Duloxetine + Thiazides | Paroxetine + Hydrochlorothiazide | 1 | Drug combinations may potentiate the risk of hyponatremia | E | 2 | PD | Not relevant |
| SSRIs/Venlafaxine/Duloxetine/ Vortrioxetine + Fentanyl | Duloxetine + Fentanyl | 1 | Drug combinations may cause serotonin syndrome | C | 1 | PD | Not relevant |

Severity score: A = no clinical effect, B = Short term clincial effect (< 48h) without sequelae, C = Long term clinical effect (48-168h) without sequelae, D = Long term clinical effect > 168 h with possible sequelae, E = Long term severe clinical effects, F = Very severe clinical effects / death

Level of scientific evidence: 0 = no support, 1 = animal studies or in vitro studies of limited predictive value, 2 = incomplete, published case reports, 3 = well documented, published case reports. Retrospective analysis of case series of interactions/side effects, 4 = Controlled, published interacion studies in patients/volunteers with relevant surrogate endpoints

Abbreviations: PK= pharmacokinetic, PD= pharmacodynamic, INH = isoniazid; pill = ethinyl estradiol/levonorgestrel





# CHAPTER 4

## Pharmacokinetics of Morphine, Morphine-3-Glucuronide and Morphine-6-Glucuronide in Terminally Ill Adult Patients

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Published in:
Clinical Pharmacokinetics. 2016 Jun; 55(6): 697-709

## ABSTRACT

### Background and Objective

Morphine dosing can be challenging in terminally ill adult patients due to the heterogeneous nature of the population and the difficulty of accurately assessing pain during sedation. To determine the pharmacokinetics of morphine, morphine-3-glucuronide (M3G) and morphine- 6-glucuronide (M6G) in this population, and to find clinically relevant parameters for dose individualisation, we performed a population pharmacokinetic analysis.

### Methods

Blood samples were randomly collected from 47 terminally ill patients in both the pre-terminal and terminal phases. Nonlinear mixed-effects modelling (NONMEM) was used to develop a population pharmacokinetic model and perform covariate analysis.

### Results

The data were accurately described by a two compartment model for morphine with two one-compartment models for both its metabolites. Typical morphine clearance was 48 L/h and fell exponentially by more than 10 L/h in the last week before death. Decreased albumin levels and a decreased estimated glomerular filtration rate (eGFR) resulted in lower metabolite clearance. Between subject variability in clearance was 52 % (morphine), 75 % (M3G) and 79 % (M6G), and changed to 53, 29 and 34 %, respectively, after inclusion of the covariates.

### Conclusions

Our results show that morphine clearance decreased up to the time of death, falling by more than 10 L/h (26 %) in the last week before death, and that M3G and M6G accumulated due to decreased renal function. Further studies are warranted to determine whether dose adjustment of morphine is required in terminally ill patients.

## INTRODUCTION

Morphine is widely used to treat pain and dyspnoea in terminally ill patients [1]. A recent study showed that at the time of death, 87 % of the patients in palliative care were treated with morphine [2]. Morphine is metabolised mainly into morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G is pharmacologically active and contributes to the analgesic effect [3–5]. M3G does not have any analgesic properties yet it has been suggested that it may be responsible for the side effects of morphine [6, 7]. As the morphine dose is determined clinically according to the patients' need, accurate pain assessment is crucial. However, in terminally ill patients this can be difficult as pain assessment can be complicated by delirium or palliative sedation [8–11]. Another difficulty with morphine dosing in this population is that its pharmacokinetics are likely to be highly variable. To date, no studies have been conducted on the pharmacokinetics of morphine in this specific population, although variability between patients is to be expected due to the heterogeneous nature of this population, e.g. differences in age, diagnosis and comorbidities. This variability is further increased by changes within patients over time, which can be caused by the physiological changes that occur as death approaches, such as cachexia and a decrease in renal function [12–15].



Together with the difficulty of assessing pain in these patients, this significant interpatient and intrapatient variability indicates the need for a dosing algorithm. The first step in developing an individualised dosing regimen is to gain more insight into the pharmacokinetics of this specific patient population. Very few studies have been performed in hospice patients, and to our knowledge no population pharmacokinetics of morphine have been performed in terminally ill patients. To determine the pharmacokinetics in this population and to find clinically relevant parameters for individualised dosing, we therefore performed a population pharmacokinetic analysis of morphine, M3G and M6G in terminally ill patients.

## MATERIALS AND METHODS

### Study Design

This prospective, observational study in terminally ill patients was approved by the Medical Ethics Committee of the Erasmus University Medical Centre, Rotterdam, and was performed in accordance with the principles of the Declaration of Helsinki and its later amendments. The study was conducted in the palliative care centre, Laurens Cadenza, Rotterdam, The Netherlands, over a 2-year period. Patients were included in the study upon admittance to the palliative care centre and were followed until the time of death. Inclusion criteria were terminal illness, prognosis survival of more than 2 days and less than 3 months, administration of morphine, and patients had given informed consent. Morphine was administered for pain and dyspnoea and was administered according to national palliative guidelines, with

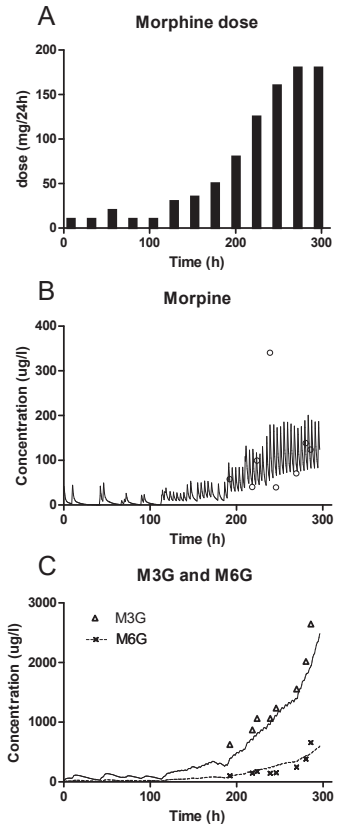


Figure 1. Dose and concentration data of a patient representative for the study population over time. This individual had a decrease in renal function with a drop in eGFR from 41.4 to 16.3 at T = 283 h. a Daily doses of subcutaneous morphine over time until the time of death. b Morphine concentrations over time. Post hoc predictions (solid line) and measured morphine concentrations (open circles). c Metabolite concentrations over time. Post hoc predictions of M3G (solid line) and M6G (dashed line), as well as measured M3G (triangles) and M6G (crosses) concentrations. eGFR estimated glomerular filtration rate, M3G morphine-3-glucuronide, M6G morphine-6-glucuronide.

daily doses ranging from 15 to 540 mg [16, 17]. Figure 1a shows a representative patient receiving increasing daily morphine doses over time. Morphine was administered orally as controlled release tablets or immediate-release liquid, or administered subcutaneously as a bolus injection or infusion. The exact times of administration were recorded in the patient record. Any concomitant use of codeine was also registered in the patient's record. Demographic characteristics (age, sex, weight, race, primary diagnosis and time of death) were extracted from the electronic medical records. Primary diagnosis of the patient's terminal illness was classified using the International Statistical Classification of Diseases and Related Health Problems–10th Revision (ICD-10).

Blood samples were collected randomly at various time points in both the pre-terminal and terminal phases. The terminal phase was defined as the last hours to days before death in which a patient becomes bed-bound, semi-comatose, is not able to take more than sips of fluid and is no longer able to take oral medication [18]. After collecting blood via either venapuncture or indwelling, venous catheter samples were centrifuged, after which the plasma was collected and stored at -80 C until analysis. Blood sampling was prefer-

ably performed in combination with sampling for clinical chemistry (standard of care) for which serum levels of albumin, creatinine, urea, bilirubin, c-glutamyl-transpeptidase (GGT), alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), and C-reactive protein (CRP) were determined. With regard to these clinical chemical values, blood was collected in heparin tubes, centrifuged and analysed by the clinical chemistry laboratory as standard care for these patients.

### Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Analysis

Morphine, M3G and M6G were analysed in the plasma samples using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with electrospray ionization in the positive ionization mode on a Shimadzu LC-30 (Nishinokyo-Kuwabaracho, Japan) system coupled to an ABSciex (Framingham, MA, USA) 5500 Qtrap MS. To 10 µL of patients' plasma, 75 µL acetonitrile/methanol 84:16 (v/v %) containing the internal standards morphine-d3, M3Gd3 and M6G-d3 was added to precipitate proteins. Samples were vortexed, stored at -20 °C for 30 min to optimise protein precipitation, vortexed again and centrifuged. A total of 3 µL was injected into a Thermo Scientific Hypersil Gold HILIC (50 9 2.1 mm, 1.9 lm) column. A stepwise chromatographic gradient was applied using 1 % ammonium formate/2 % formic acid in water as mobile phase A and acetonitrile as mobile phase B. The flow rate was 0.6 mL/min and the column was kept at 40 °C. Using multiple reaction monitoring (MRM), morphine, M3G and M6G were measured as [M + H] + using the mass transitions 286.1/165.1, 462.2/286.2 and 462.2/286.2, respectively. Retention times for morphine, M3G and M6G were 0.44, 2.77 and 2.58, respectively. For the internal standards, morphine-d3, M3G-d3 and M6G-d3 were used with the same retention times and mass transitions of 289.1/165.1, 465.2/289.2 and 465.2/289.2, respectively.

The method was validated over a range of 2–500 µg/L for all compounds with six calibration curves each containing seven concentrations. The accuracies ranged from 93.5 to 105.5 %. Intraday and interday precision were calculated with six replicates of four concentrations (2, 6, 60 and 500 µg/L) for all compounds, and resulted in intraday and interday precisions below 9.6 and 12.9 %, respectively. Three quality controls (low level 2 µg/L, medium level 60 µg/L and high level 500 µg/L) were validated and used for this method.

### Population Pharmacokinetic Modelling

Pharmacokinetic analysis was conducted by nonlinear mixed-effects modelling using NONMEM® version 7.2 (ICON Development Solutions, Ellicott City, MD, USA) and PsN® version 3.7.6.

#### *Base Model Development*

The data were log-transformed and concentrations of M3G and M6G were adjusted to their morphine equivalents using the molecular weight. Bioavailability of subcutaneous morphine was assumed to be 100 % [19, 20]. One two-and three-compartment models were

tested for morphine and its metabolites using the first-order conditional estimation method with interaction (FOCE+I) and the ADVAN5 subroutine. First, a structural model for morphine was developed. These parameters were then fixed to test the different structural models for M3G and M6G. In the final model, all parameters were estimated, with the exception of the transformation ratios for M3G and M6G. Since there was no information on the mass balance, the fractions of morphine transformed into metabolites and fractions excreted could not be determined independently. These ratios were therefore set to previously described values, i.e. 0.55 for M3G and 0.10 for M6G [21–23].

Between-subject variability (BSV) was assessed on each parameter using an exponential and additive model, and residual variability was incorporated as an additive error on the log scale. Model selection was based on minimum objective function values (OFVs), parameter precision, error estimates, shrinkage values and visual inspection of the goodness-of-fit plots.

*Covariate Model Development*

Demographic and disease characteristics, including age, sex, race, primary diagnosis, renal function (estimated glomerular filtration rate [eGFR], plasma creatinine and plasma urea), hepatic function (plasma levels of bilirubin, GGT, ALP, ALT, and AST), CRP, albumin, and the concomitant use of codeine, were evaluated as potential model covariates. Time to death (TTD) was also evaluated as a covariate. This parameter cannot be used as a covariate parameter for a priori prediction of individual pharmacokinetic changes but it may give insight into quantitative changes at the end of life that are not predicted by standard blood chemistry tests. As heart and respiratory rates are not measured in a palliative care centre, standard disease severity scoring systems used in internal medicine (e.g. the simple clinical score or rapid emergency medicine score) cannot be used in this situation. The relationship between covariates and individual estimates was first investigated graphically and was further tested in a univariate analysis. Covariates that significantly improved the model (p B 0.05) were added to the full model. A backward elimination process was then performed with statistical significance indicated by p B 0.001.

Continuous covariates were normalised to the population median values and incorporated as power model functions (Eq. 1). Categorical covariates were transformed to binary covariates and incorporated as shown in Eq. 2. with $\theta_i$ being the individual model-predicted pharmacokinetic parameter (e.g. clearance) for an individual with covariate value $cov_i$, $\theta_{pop}$ being the population estimate for that parameter, $cov_m$ representing the median covariate value and $\theta_{cov}$ representing the covariate effect. In the equation for categorical covariates, $cov_i$ is either 1 or 0.

$$\theta_{\mathrm{i}} = \theta_{\mathrm{pop}} * \left(\frac{\mathrm{cov_i}}{\mathrm{cov_m}}\right)^{\theta\mathrm{cov}} \quad (1)$$

$$\theta_{\mathrm{i}} = \theta_{\mathrm{pop}} * \theta_{\mathrm{cov}}^{\mathrm{cov_i}} \quad (2)$$

To evaluate the TTD as a covariate, time dependency of the parameters was modelled as a first-order process given to following equation (Eq. 3) in which $\theta_{\Delta}$ is the change in parameter value from its initial value and $\theta_{rate}$ is a first-order rate constant determining the rate with which the parameter value changes over time.

$$\theta_i = \theta_{\mathrm{pop}} - \theta_{\Delta} * \exp(-\theta_{\mathrm{rate}} * \mathrm{TTD}) \quad (3)$$

*Model Evaluation*

A bootstrap with 500 runs was performed on the final model to evaluate the validity of the parameter estimates and their corresponding 95 % confidence intervals (CIs). Due to the study design, i.e. sparse sampling, different dosing regimens and both oral and subcutaneous administrations, a visual predictive check could not be performed to evaluate the model. We therefore evaluated the predictive performance of the final model using a normalised prediction distribution errors (NPDE) analysis. NPDE is a simulation-based diagnostics which can be used to evaluate models developed on datasets with variable dosing regimens. The analytical value of this method has been previously described by Comets et al. [24].



## RESULTS

A total of 47 terminally ill patients were included in the study. Their median age was 71 years (range 43–93), 55.3 % were female and the median duration of admittance (from moment of admittance until the time of death) was 33 days (range 7–457). Almost all patients (95.7 %) had advanced malignancy as the primary diagnosis. Patient characteristics are given in Table 1. From these patients, a total of 152 blood samples were collected and analysed for morphine, M3G and M6G concentrations. Figure 1b and c show the concentrations of morphine, M3G and M6G over time for a representative patient. As shown in these graphs, the morphine concentration increases as the dose increases, and near the end of life M3G and M6G concentrations increase significantly. Circa 12 % of the plasma concentrations were below the quantification limit (BLQ), largely due to two patients who had had blood samples taken more than 10 days after the last morphine dose. BLQ data were therefore discarded using the M1 method previously discussed by Ahn et al. [25].

Table 1. Patient characteristics

| Characteristics | N = 47 |
|---|---|
| Age, years (median, range) | 71 (43 - 93) |
| Male, *n* (%) | 21 (44.7) |
| Female, *n* (%) | 26 (55.3) |
| Ethnic origin, *n* (%) | |
| Caucasian | 45 (95.7) |
| Afro-Caribbean | 2 (4.3) |
| Primary diagnosis, *n* (%) | |
| Neoplasm | 45 (95.7) |
| Disease of the circulatory system | 1 (2.1) |
| Disease of the respiratory system | 1 (2.1) |
| Blood chemistry, serum levels at admission (median, range) | |
| Albumin, g/l | 26 (14-39) |
| Urea, mmol/l | 7.2 (1.5-43.4) |
| Bilirubin, umol/l | 8 (3-256) |
| Gamma-glytamyl transpeptidase, U/l | 64 (7-3859) |
| Alkaline phosphatase, U/l | 112 (20-2117) |
| Alanine transaminase, U/l | 12 (7-406) |
| Aspartate transaminase, U/l | 32 (14-255) |
| C-reactive protein, U/l | 67 (1-188) |
| Creatinine, umol/l | 72 (22-229) |
| eGFR by standard MDRD[a], ml/min/1.73 $m^2$ | 96 (27-239) |
| eGFR by original MDRD[b], ml/min/1.73 $m^2$ | 83 (22-202) |
| Patients using codeine[c], *n* (%) | 2 (4.2) |
| Duration of stay, days (median, range) | 33 (7 - 457) |
| Blood samples collected, *n* (median, range) | 2 (1 – 10) |

eGFR: estimated glomerular filtration rate, MDRD: modification of diet in renal disease. [a] The abbreviated MDRD equation consists of 4 variables (age, gender, race and serum creatinine) as shown in Eq. 4. [b] the original MDRD formula consist of 6 variables (age, gender, race, serum creatinine, serum albumin and serum urea) as shown in Eq. 5 [c] during any moment while receiving morphine treatment

## Structural Model

The data were best described by a two-compartment model for morphine and two one-compartment models for both its glucuronidated metabolites (Fig. 2). Since limited data were available in the absorption phase, the absorption constants (Ka) could not be estimated, and were therefore fixed to known literature values (10 h-1 for subcutaneous injection, 6 h-1 for immediate-release liquid and 0.8 h-1 for controlled-release tablets) [26, 27]. The population mean estimates for volume of distribution were 185 L (relative standard error [RSE] 28 %) for the central morphine compartment (V1); 243 L (RSE 33 %) for the peripheral morphine compartment (V2); 7.65 L (RSE 33 %) for the M3G compartment; and 7.1

L (RSE 30 %) for the M6G compartment. The population mean estimates for clearance were 37.2 L/h (RSE 9 %) for morphine; 1.48 L/h (RSE 8 %) for M3G; and 1.87 L/h (RSE 8 %) for M6G. An overview of all parameter estimates is given in Table 2.

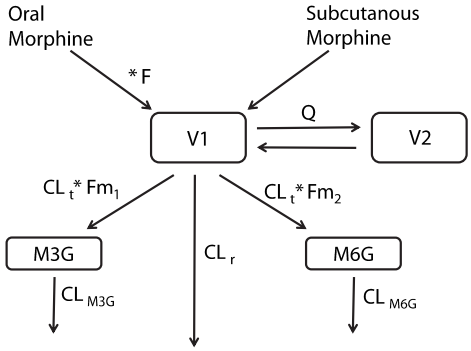


**Figure 2.** Schematic representation of the two-compartment model for morphine and its two main metabolites. F bioavailability of oral morphine, V1 central compartment for morphine, V2 peripheral compartment for morphine, Q intercompartmental clearance of morphine, Clt total morphine clearance, Fm1 fraction of morphine clearance responsible for M3G formation, Fm2 fraction of morphine clearance responsible for M6G formation, Clr remaining morphine clearance (Clt*1-(Fm1 + Fm2)), ClM3G clearance of M3G, ClM6G clearance of M6G, M3G morphine-3-glucuronide, M6G morphine-6-glucuronide.

**Table 2.** Parameter estimates of the base model, final model and bootstrap analysis.

| Parameter | Structural model | Final model | RSE % | Shrinkage % | Bootstrap of the final model | | |
|---|---|---|---|---|---|---|---|
| | | | | | Estimate | 95% CI (lower) | 95% CI (upper) |
| OFV | -323.7 | -351.6 | | | | | |
| Morphine | | | | | | | |
| F | 0.28 | 0.30 | 13.6 | - | 0.31 | 0.18 | 0.53 |
| Cl (L/h) | 37.2 | 47.5 | 11 | - | 49.9 | 39.1 | 75.6 |
| V1 (L) | 185 | 190 | 28 | - | 190 | 116 | 369 |
| Q (L/h) | 75 | 76.1 | 35.7 | - | 65.1 | 9.95 | 146 |
| V2 (L) | 246 | 243 | 19 | - | 248 | 121 | 377 |
| M3G | | | | | | | |
| Fm1 | 0.55[a] | 0.55 [a] | N/A | - | 0.55 [a] | 0.55 [a] | 0.55 [a] |
| Cl (L/h) | 1.48 | 1.44 | 4.8 | - | 1.44 | 1.30 | 1.59 |
| V1 (L) | 7.65 | 8.02 | 33.2 | - | 7.75 | 3.62 | 14.9 |
| M6G | | | | | | | |
| Fm2 | 0.1 [a] | 0.1 [a] | N/A | - | 0.1 [a] | 0.1 [a] | 0.1 [a] |
| Cl (L/h) | 1.87 | 1.78 | 6.8 | - | 1.79 | 1.56 | 2.05 |
| V1 (L) | 7.1 | 8.24 | 30.7 | - | 7.97 | 3.77 | 14.0 |
| Covariate effect on M3G and M6G clearance | | | | | | | |
| eGFR[b] | 0.83 | 0.673 | 16.8 | - | 0.67 | 0.50 | 1.03 |
| Albumin | - | 1.1 | 23.3 | - | 1.06 | 0.332 | 1.56 |
| Covariate effect on M3G and M6G clearance | | | | | | | |
| TTD[c] (Δ), days | - | 17.6 | 24.7 | - | 19.2 | 9.48 | 46.6 |
| TTD[c] (rate), days | - | 0.13 | 32 | - | 0.12 | 0.05 | 0.31 |

Table 2. Parameter estimates of the base model, final model and bootstrap analysis. (*continued*)

| Parameter | Structural model | Final model | RSE % | Shrinkage % | Bootstrap of the final model | | |
|---|---|---|---|---|---|---|---|
| | | | | | Estimate | 95% CI (lower) | 95% CI (upper) |
| Between subject variability (%) | | | | | | | |
| F | 48.2 | 37.8 | 38.3 | 9.5 | 38.7 | 1.7 | 58.0 |
| morphine Cl | 54.0 | 53.4 | 30.1 | 13.3 | 50.0 | 31.7 | 71.8 |
| M3G Cl | 39.7 | 29.3 | 29.2 | 5.5 | 29.3 | 20.4 | 41.7 |
| M6G Cl | 43.5 | 34.3 | 29.2 | 5.5 | 34.1 | 23.8 | 48.4 |
| M3G V1 | 135.5 | 151.7 | 31.4 | 6.1 | 147.9 | 80.3 | 203.1 |
| M6G V1 | 130.4 | 143.0 | 31.4 | 6.1 | 141.5 | 76.8 | 194.4 |
| Residual variability | | | | | | | |
| Morphine | 0.448 | 0.432 | 10.4 | 10 | 0.425 | 0.335 | 0.510 |
| M3G | 0.250 | 0.246 | 9.3 | 10 | 0.239 | 0.194 | 0.282 |
| M6G | 0.261 | 0.265 | 6.6 | 10 | 0.254 | 0.218 | 0.294 |

[a] transformation ratios for M3G and M6G were fixed to known literature values. [b] GFR was estimated using the standard 4-variable MDRD equation. [c] Time to death (TTD) was incorporated as a first order process With $TTD_{\Delta}$ as the change in parameter value from its initial value and $TTD_{rate\ as}$ the first order rate constant

Including BSV on morphine clearance and bioavailability (F) of oral morphine both significantly improved the model fit with a change in OFV (DOFV) of -43.3 and -7.05, respectively. The correlation between BSV of M3G and M6G clearance was high and fixed to unity. A similar approach was used for BSV on the volumes of distribution of M3G and M6G. Adding BSV on metabolite clearance and metabolite volume significantly improved the model fit with a change in objective function of 157.0 and 47.1, respectively. In all cases, an exponential model for BSV proved superior to an additive model.

Since M3G and M6G are renally cleared, and because there were patients who developed renal failure over time, a measure for renal failure was added to the structural model. This was done by evaluating the covariate effect of creatinine levels, urea levels, and eGFR on metabolite clearance. Glomerular filtration rate was estimated using the generally accepted, four-variable, Modification of Diet in Renal Disease (MDRD) equation consisting of age, sex, ethnicity, and serum creatinine levels (Eq. 4) [28]. Estimated GFR gave the best results (DOFV -75.97 vs -73.58 for creatinine levels and -66.77 for urea levels) and was therefore included in the structural model.

$$\begin{aligned}\text{eGFR} = {} & 186 \times \text{serum creatinine (mg/dl)}^{-1.154} \times \text{age}^{-0.203} \\ & \times (1.210 \text{ if black}) \times (0.742 \text{ if female})\end{aligned} \tag{4}$$

## Covariate Analysis

The structural model including eGFR on metabolite clearance was used as a reference for the covariate analysis. The univariate analysis resulted in a further eight significant covariates, three of which were correlated with morphine clearance (i.e. TTD, bilirubin, and urea), two were correlated with metabolite clearance (i.e. albumin and CRP), two were correlated with the vol-

Table 3. Covariate effects in univariate analysis compared to the structural model

| Covariate | ΔOFV | Covariate effect | Included after backward elimination |
|---|---|---|---|
| Structural model | - | | |
| Covariates on Bioavailability | | | |
| Afro-Caribbean Race[a] | 6.36 | 0.52 | No |
| Covariates on morphine Cl | | | |
| Time to Death | 9.65 | 20.2 and 0.11[b] | Yes |
| Plasma Urea | 7.04 | -0.28 | No |
| eGFR[c] | 4.38 | 0.18 | No |
| Plasma Bilirubin | 4.06 | -0.16 | No |
| Covariates on metabolite Cl | | | |
| CRP | 16.4 | -0.21 | No |
| Plasma Albumin | 15.4 | 1.10 | Yes |
| Plasma GGT | 6.10 | -0.11 | No |
| Covariates on metabolite Vd | | | |
| eGFR[c] | 9.42 | 0.33 | No |
| Plasma Creatinine | 8.16 | -0.40 | No |
| Time to Death | 7.92 | -14.7 and 0.08[b] | No |
| Plasma Urea | 6.65 | -0.26 | No |

[a] Compared with subjects of Caucasian race [b] 21.6 is the value for TTDΔ and 0.10 is TTD rate [c] GFR was estimated using the abbreviated MDRD equation.



ume of distribution of the metabolites (i.e. creatinine and urea), and one was correlated with bioavailability (i.e. race). The results of the univariate analysis, in terms of decrease in OFV and covariate effect, are shown in Table 3. After backwards elimination of p\0.001, only albumin levels on metabolite clearance and TTD on morphine clearance remained in the final model.

Because the final model had both eGFR and albumin levels as covariates on metabolite clearance, we also tested if these two covariates could be replaced by the eGFR estimated using the original six-variable MDRD formula (Eq. 5) [28]. This formula calculates GFR using not only sex, weight, race and creatinine levels but also takes into account albumin and urea levels. However, this more elaborate version of the MDRD equation did not improve the model fit (OFV -342.9 vs. -351.6 for the standard four-variable MDRD equation). Together, estimated GFR and serum albumin decreased the unexplained variability on M3G and M6G clearance from 75.4 and 79.1 to 29.3 and 34.3 %, respectively. They hereby explained 61.1 % of the BSV in M3G clearance and 56.6 % of the BSV on M6G clearance. The covariate TTD did not decrease the unexplained variability on morphine clearance; however, it did decrease the RSE on the volumes of both metabolites (from 65.7 to 33.2 % for M3G, and from 63.8 to 30.7 % for M6G).

$$\begin{aligned}\text{eGFR} = 170 \times \text{serum creatinine}\left(\frac{\text{mg}}{\text{dl}}\right)^{-0.999} \\ \times \text{age}^{-0.176} \times (1.180\text{if black}) \times (0.762\text{if female}) \\ \times \text{serum urea nitrogen (mg/dl)}^{-0.170} \\ \times \text{albumin (g/dl)}^{0.318}\end{aligned} \tag{5}$$

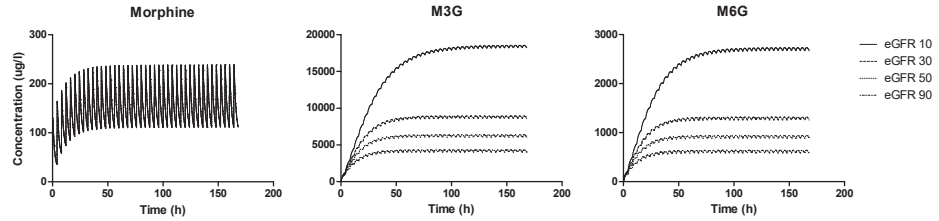


Figure 3. Simulated plasma profiles of morphine, M3G and M6G for patients with an eGFR of 10 mL/min (solid line), 30 mL/min (dashed line), 50 mL/min (dotted line) and 90 mL/min (dash-dotted line) with a 30 mg six-daily subcutaneous bolus injection dosing regimen and stable plasma albumin levels of 25 g/L. M3G morphine-3-glucuronide, M6Gmorphine-6-glucuronide, eGFR estimated glomerular filtration rate.

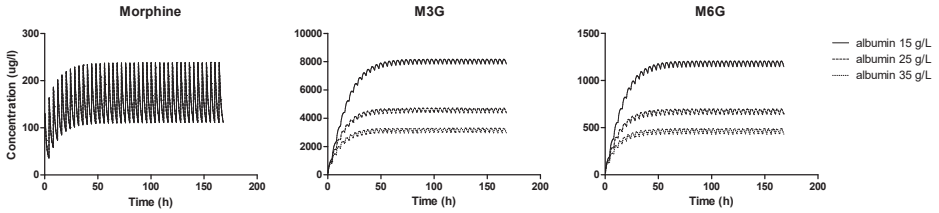


Figure 4. Simulated plasma profiles of morphine, M3G and M6G for patients with plasma albumin levels of 15 g/L (solid line), 25 g/L (dashed line) and 35 g/L (dotted line) with a 30 mg six-daily.

## Simulations

Based on the final model, M3G clearance is reduced by approximately 30 % (from 1.6 to 1.1 L/h), while eGFR decreases from 90 to 50 mL/min and albumin concentrations remain stable at 25 g/L. A further reduction of eGFR to 30 mL/min decreases M3G clearance to a value of 0.8 L/h (Fig. 3). The effect of a reduction of eGFR on metabolite clearance is shown in Fig. 1c, where the concentrations of M3G and M6G increase in the last few hours. Indeed, this individual had a decrease in renal function, with a drop in eGFR from 41.4 to 16.3 at T = 283 h. The final model also implies that with a stable eGFR of 78 mL/min, a decrease in albumin from 35 to 25 g/L produces a 31 % decrease in M3G clearance (from 2.1 L/h to 1.4 L/h) (Fig. 4). Respective changes in M6G clearance are also shown in Figs. 3 and 4, and are similar to changes in M3G clearances.

Based on the covariate model, morphine clearance will decrease by 13 %, from 46.4 L/h 3 weeks before death to 40.6 L/h 1 week before death. In the final week before death, morphine clearance would decrease by another 26–29.9 L/h on the day of death. As a result, the area under the curve of morphine will be significantly increased in the final days of life, as can be seen in the simulations of morphine concentrations in Fig. 5.

## Evaluation of the Final Model

Goodness-of-fit plots of the final model showed the population predictions and individual predictions were evenly distributed around the line of unity. The conditional weighted

residuals (CWRES) were normally distributed and did not show any correlation with the population predictions (Fig. 6).

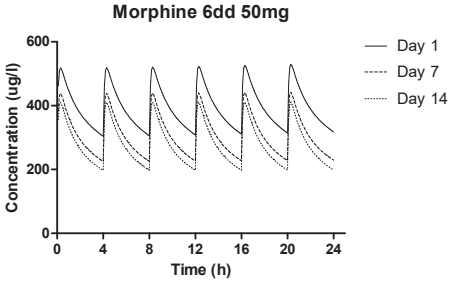


**Figure 5.** Simulated plasma profiles of morphine in the case of 50 mg six times daily subcutaneous bolus infusion, 2 weeks (dotted line), 1 week (dashed line) and 1 day (solid line) before death.

A bootstrap analysis was performed to obtain 95 % Cis for all parameters. Results of the bootstrap are shown in Table 2. Evaluation of the predictive performance by NPDE analysis showed accurate predictive ability, with distribution of the NPDEs not significantly deviating from a normal distribution (global adjusted p value, morphine 0.84, M3G 0.19, and M6G 0.09), and the majority of the NPDEs lay between the values -2 and 2 (Fig. 7).



## DISCUSSION

This is the first population pharmacokinetic study of morphine in end-of-life patients performed in a non-academic palliative care setting. We even included data of patients shortly before death, and were able to accurately describe the pharmacokinetics of morphine, M3G and M6G with a two-compartment model for morphine and two one-compartment models for both its metabolites. As we followed patients until the time of death, we were able to show a decrease in morphine clearance as patients were nearer to the time of death. We also showed that eGFR, together with albumin levels, were the best predictors for metabolite clearance, explaining approximately 60 % of the unexplained variability between patients.

To the best of our knowledge, there have not been any population pharmacokinetic studies on morphine, M3G, and M6G in terminally ill patients. In the 1980s, Säwe et al. demonstrated that the bioavailability of oral morphine in cancer patients ranged between 15 and 64 % [29], which is comparable with our results in which we found a variability in morphine bioavailability of 38 %, with individual values for morphine bioavailability of between 16 and 52 %. Because the bioavailability of morphine is dependent on first-pass metabolism, this variability is probably due to changes in liver blood flow as morphine has a high extraction ratio and glucuronidation is well-preserved, even in the case of severe liver disease [30–32].

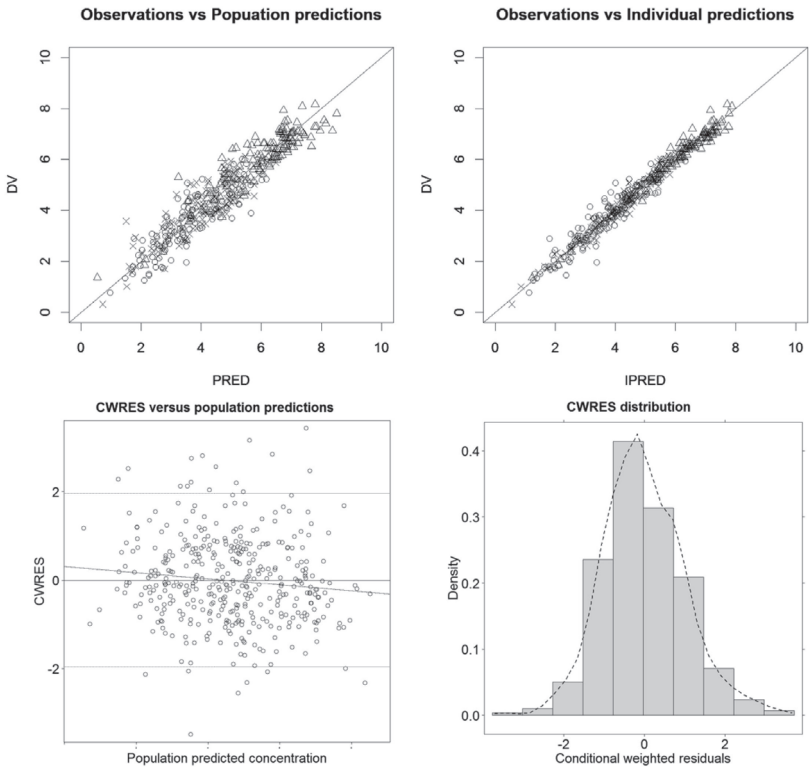


Figure 6. Goodness-of-fit plots of the final model. The top two panels show the PRED and IPRED concentrations versus the DV for morphine (open circles), M3G (open triangles) and M6G (crosses), with the solid line displaying the line of unity. The bottom two panels show the correlation of CWRES with the PRED concentrations, including the trend line and the distribution of the CWRES in grey bars and dashed line. PRED population predicted, IPRED individual prediction, DV observed concentrations, CWRES conditional weighted residuals, M3G morphine-3-glucuronide, M6G morphine-6-glucuronide.

In this same study, Säwe and co-workers found a morphine clearance ranging from 0.3 to 0.97 L/h/kg, which would mean 21–67 L/h for a 70-kg individual. The latter compares favourably with our finding of 47.5 L/h. Two other population pharmacokinetic studies on data from cancer patients and one study in intensive care patients reported similar values for morphine clearance of 63.8 and 35 L/h, respectively [27, 33, 34]. Interestingly, in studies of neurosurgical patients and healthy volunteers, higher clearances have been reported (110 L/h and 75.3 L/h, respectively) [21, 23]. This indicates that morphine clearance is reduced in critically ill patients [23].

In the referred study in healthy volunteers, Lötsch et al. showed a delay between the rise of morphine concentrations and the formation of M6G; this delay was modelled using a transit compartment [23]. In our study, the addition of transit compartments did not improve the fit of the metabolite concentration to the population model due to the sampling

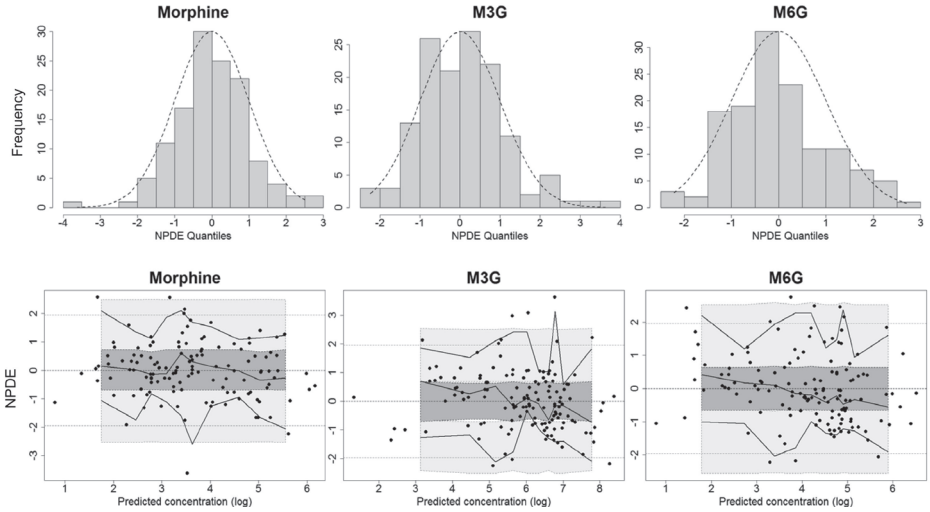


Figure 7. NPDE analysis of the final model for morphine, M3G and M6G. The top panels show the distribution of the NPDE quantiles (grey bars), with the shape of a normal distribution also shown (dashed line). The bottom panels show the NPDEs versus the log of the predicted concentrations with individual NPDE values (dots) and 5th, 50th and 95th percentile lines with their corresponding 90 % confidence intervals (grey-shaded areas). NPDE normalised prediction distribution error, M3G morphine-3-glucuronide, M6G morphine-6-glucuronide.



frequency in our study being too low in comparison with the reported transit time of 17 min for M6G [26].

In the previous studies in neurosurgical and cancer patients, a larger clearance for M3G and M6G was found than in our study (M3G clearance of 2.67 L/h in neurosurgical patients and 3.36 L/h in cancer patients; M6G clearance of 2.52 L/h in neurosurgical patients and 3.36 L/h in cancer patients [21, 27, and 34]. A possible explanation is that the patients in our study were closer to the time of death and therefore had reduced renal clearance. Similarly, in the study by Ahlers and colleagues it was demonstrated that M3G clearance was significantly reduced in intensive care patients compared with healthy individuals due to decreased creatinine clearance [33].

Our results show large interpatient variability, especially in the volume of distribution of M3G and M6G, with values of 152 and 143 %, respectively. A previous study in neurosurgical patients showed much less interpatient variability, which could be explained by this population being less heterogenic, and also that this study only included nine patients [21]. The high BSV in our study was mainly due to two patients had very high estimated volumes of distribution for M3G and M6G. A possible explanation for the large interpatient variability observed in our study might be a change in body weight, which we could not test as a covariate. Particularly during the last phases of life, patients can have decreased lean body weight or may have oedema, which could influence the volume of distribution of the metabolites [35].

The covariate analysis resulted in three significant covariates, with the first being TTD. Morphine clearance decreased exponentially as TTD decreased, falling by more than 10 L/h (26 %) in the last week before death. As none of the other covariates tested gave a similar significant effect on morphine clearance, this association may be caused by a combination of factors. It may be the result of a physiological change (e.g. a decrease in hepatic blood flow) that is not detected with standard blood chemistry tests. This observed decrease in clearance implicates that morphine dose may have to be decreased according to life expectancy. Life expectancy is difficult to predict, as is, for instance, shown by the range of admittance in this study being significantly longer than the 3 months stated as an admittance criterion for the hospice. However, the terminal phase (where a patient will die within hours or days) is usually well-recognised based on several clinical signs (i.e. the patient becoming bed-bound, semi-comatose, and that oral medication and fluid intake is no longer possible) [18, 36]. In this case, a clinical protocol, specific for the terminal phase, is started and specific domains will be registered in the patient record as standard of care [37]. Therefore, it might be possible to re-evaluate the morphine dose when this phase is started as our model showed the biggest decrease in morphine clearance in the last week of life.

The two other covariates, eGFR and plasma albumin levels, were correlated with M3G and M6G clearance. The fact that eGFR is correlated with M3G and M6G clearance was expected as both metabolites are eliminated through the kidneys. Previous studies have indeed shown that M3G and M6G can accumulate in patients with impaired renal function [38, 39].

The effect of albumin on metabolite clearance has not been previously shown in other studies. As M3G and M6G are not highly bound to plasma albumin, it is unlikely that this effect will be due to changes in unbound fractions of the metabolites. A possible explanation for this effect of albumin may lie in the fact that some terminally ill patients will become cachectic, which also leads to hypoalbuminemia [14]. The MDRD equation is not appropriate for calculating GFR in cachectic patients due to severe muscle loss and thereby overestimation of GFR based on creatinine levels. Therefore, low albumin levels may be an indicator for patients in which GFR is overestimated. Another explanation why the combination of albumin and eGFR are a better predictor than eGFR alone may be that albumin can be an indication that a patient is closer to the time of death. Several studies have shown that low albumin levels can predict prognosis in palliative cancer patients

[40–42]. If a patient is closer to the time of death, eGFR might be significantly decreased (for instance due to dehydration). As the MDRD formula also overestimates GFR when GFR is very low, in this case the addition of albumin levels in the model might partly compensate for this overestimation. Combining both eGFR and albumin levels will therefore result in better prediction of M3G and M6G clearance.

The main limitation of our study was that we lacked data to evaluate associations between weight and the pharmacokinetic parameters. As mentioned above, this might

affect the estimates of volume of distribution, and there is also a possible correlation with metabolite clearance since, as described before, renal function can be overestimated in patients with low body weight. Precise monitoring of weight is not common practice in palliative care because it does not contribute to the treatment and because patients might find it difficult to be confronted with their weight loss. However, as weight is possibly an important covariate, we recommend that it is monitored in future pharmacokinetic studies in terminally ill patients.

Another possible limitation of the study was that the absorption constant of all three dosing forms was fixed to known literature values. This was necessary as there were insufficient data points in the first 30 min after a dose administration due to the sparse sampling design. This could have biased the estimation of volume of distribution for the central compartment as absorption rate and volume of distribution both affect the initial concentration. In the terminally ill population, patients receive morphine for extended periods of time; therefore, clearance (and BSV on clearance) instead of volume of distribution is the predominant parameter effecting total morphine exposure.



In addition, it was not possible to determine the transformation ratios of M3G and M6G. These ratios were set to previously described values, i.e. 0.55 for M3G and 0.10 for M6G [21–23]. This could have biased the results for the parameters of metabolite clearance and volume of distribution as these are both proportional to the transformation ratio (CL/F and Vd/F). However, we consider the values of 0.55 and 0.10 to be valid as the liver's capacity for glucuronidation of drugs is reasonably stable, even in critically ill patients and patients with mild to moderate cirrhosis [30, 31, 33]. The fact that there is BSV on morphine bioavailability (which is a result of first-pass metabolism) is most likely to be caused by a variation in liver blood flow instead of metabolic capacity as morphine is a drug with a high extraction ratio [32]. In this case, the clearance of morphine will differ; however, the formation ratios should remain unchanged. Furthermore, setting the transformation ratios to 0.55 and 0.10 resulted in comparable estimates for clearance and volume of distribution for both metabolites (Table 2). This seems to be appropriate as both metabolites have an almost identical molecular structure and are therefore expected to have similar molecular properties. To establish whether the transformation ratios are not altered in these patients, information about the mass balance is required. This can be obtained by measuring the fractions of morphine, M3G, and M6G in urine samples.

## CONCLUSIONS

Our study again confirms that a reduction in eGFR resulted in a decreased clearance of M3G and M6G, which can have clinical consequences as M6G is a metabolite with analgesic activity, while M3G has been suggested to contribute to side effects. As a result, the morphine

dose may be reduced in patients with renal failure, or analgesic therapy may be switched to an opioid with less or no active metabolites (e.g. oxycodone or fentanyl). We also found that eGFR combined with albumin levels was a better predictor for M3G and M6G clearance than eGFR alone. Therefore, dose adjustments should also take into account albumin levels besides eGFR. In addition, a positive correlation was found between TTD and morphine clearance. This important insight into the pharmacokinetics of morphine in terminally ill patients is a first step in developing an individualised dosing regimen for terminally ill patients. It suggests that morphine doses might be adjusted to a patient's creatinine and albumin levels and life expectancy. However, accurate prediction of the time of death can be difficult and the need for morphine does not solely depend on pharmacokinetics. Therefore, further studies on the pharmacodynamics in this patient population are needed before any firm conclusions can be drawn on dose adjustments.

## COMPLIANCE WITH ETHICAL STANDARDS

This study was approved by the Medical Ethics Committee of the Erasmus University Medical Centre, Rotterdam, and was performed in accordance with the principles of the Declaration of Helsinki and its later amendments.

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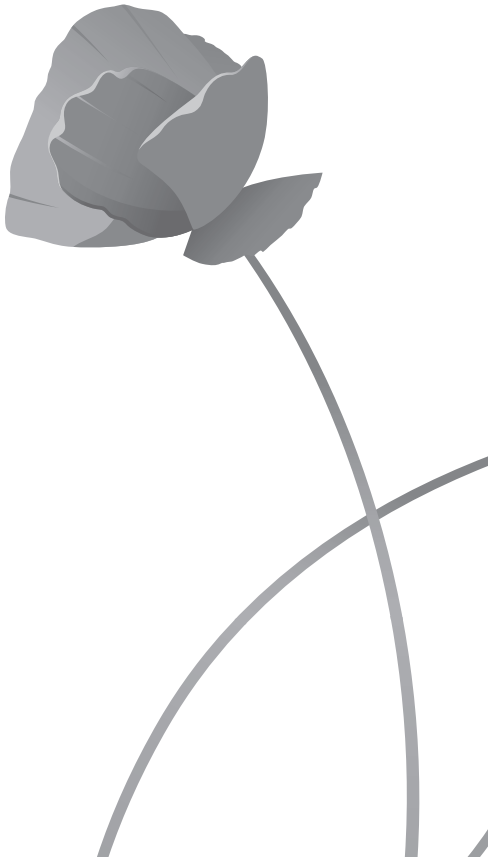

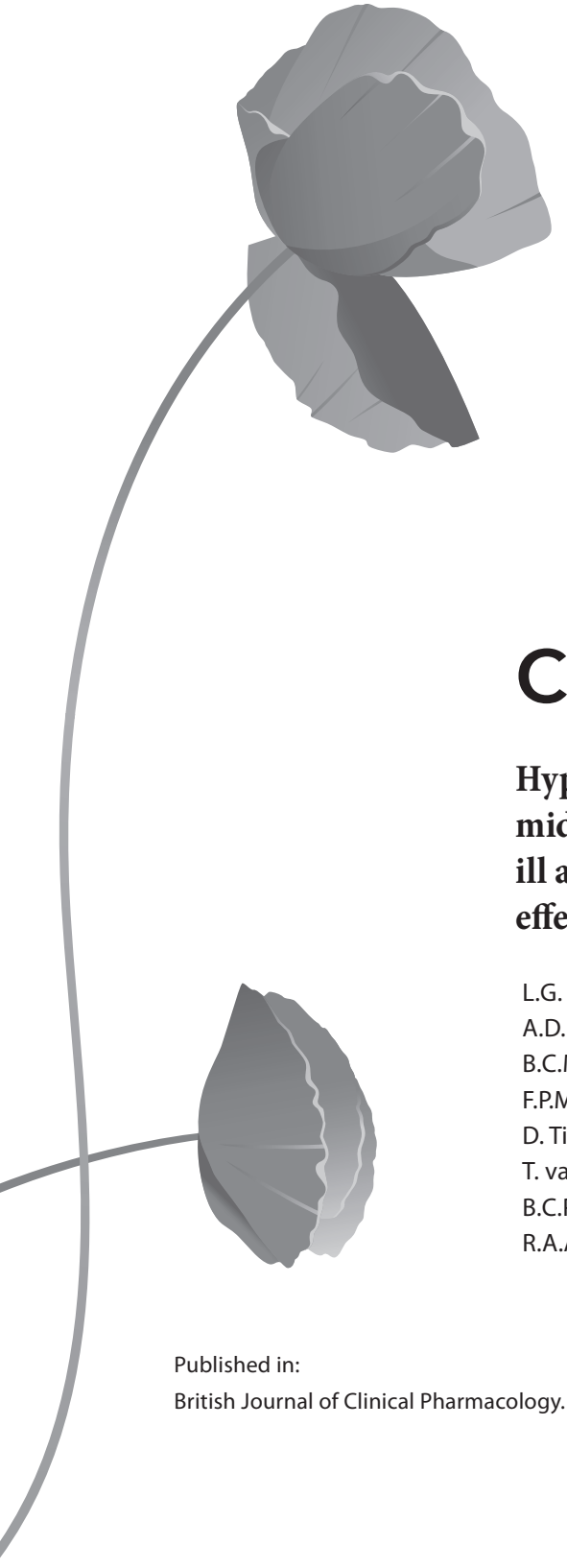

# CHAPTER 5

## Hypoalbuminaemia and decreased midazolam clearance in terminally ill adult patients, an inflammatory effect?

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British Journal of Clinical Pharmacology. 2017 Aug; 83(8): 1701-1712.

## ABSTRACT

### Background and objective

Midazolam is the drug of choice for palliative sedation and is titrated to achieve the desired level of sedation. Because of large inter-individual variability (IIV), however, the time it takes to achieve adequate sedation varies widely. It would therefore greatly improve clinical care if an individualised dose could be determined beforehand. To find clinically relevant parameters for dose individualisation we performed a pharmacokinetic study on midazolam, 1OH-midazolam (1-OH-M) and 1OH-midazolam-glucuronide (1-OH-MG) in terminally ill patients.

### Methods

Using non-linear mixed effects modelling (NONMEM 7.2), a population pharmacokinetic analysis was conducted with 192 samples from 45 terminally ill patients who received midazolam either orally or subcutaneously. The covariates analysed were patient characteristics, co-medication and blood chemistry levels.

### Results

The data were accurately described by a one-compartment model for midazolam, 1-OH-M and 1-OH-MG. The population mean estimates for midazolam, 1-OH-M and 1-OH-MG clearance were 8.4 L/h (RSE 9%, IIV 49%), 45.4 L/h (RSE 12%, IIV 60.5%) and 5.1L/h (RSE 11%, IIV 49.9%) respectively. 1-OH-MG clearance was correlated with the estimated glomular filtration rate (eGFR) explaining 28.4% of the IIV in 1-OH-MG clearance. In addition, low albumin levels were associated with decreased midazolam clearance, explaining 18.2% of the IIV.

### Conclusion

Our study indicates albumin levels and eGFR as relevant clinical parameters to optimise midazolam dosing in terminally ill patients. The correlation between low albumin levels and decreased midazolam clearance is probably a result of inflammatory response as high CRP levels were correlated in a similar way.

*What is known about this subject*

- While a lot of physiological changes occur at the end of life, very little is known about how these changes can affect the pharmacokinetics of drugs given in this phase.
- A recent study in critically ill children showed that inflammation and organ failure can result in decreased midazolam clearance.
- Animal studies and some preliminary studies in patients with cancer have shown that cancer and inflammation are associated with reduced hepatic metabolism of CYP-enzymes.

*What this study adds*

- Using a population approach with sparse sampling, we were able to accurately describe the pharmacokinetics of midazolam in terminally ill patients. As this method minimises the patient's burden it is a useful approach to use in future PK studies in this vulnerable population.
- Midazolam clearance was decreased in patients with low albumin levels. This is possibly due to inflammatory response or a catabolic state.

## INTRODUCTION

Midazolam is often used in terminally ill patients and is the drug of choice for palliative sedation (1-4). It is metabolised in a two phase process, the first step is hydroxylation via CYP3A mainly into α-hydroxy-midazolam (1-OH-M) and for a very small amount into 4-hydroxy-midazolam (4-OH-M). The 1-OH-M metabolite is active with an approximate potency of 80-100% of midazolam (5-7). After hydroxylation midazolam is further metabolised through UDP-glucuronosyltransferases (UGT) 1A4, 2B4 and 2B7 with α-hydroxy-midazolam glucuronide (1-OH-MG) as its major metabolite (8). 1-OH-MG is much less active (around 10% of the activity of midazolam) but in high concentrations, in the case of accumulation due to renal failure it can contribute substantially to the overall effect (5).

When midazolam is prescribed for palliative sedation its dose is titrated to achieve the desired level of sedation (1, 3). Unfortunately the time it takes to reach adequate sedation varies widely between patients and awaking from a sedative state occurs often (9). A possible explanation for this might be large inter-individual variability (IIV) in midazolam pharmacokinetics, which has already been shown in other populations (10-14). In terminally ill patient large variability is also expected due to the heterogeneity of the population including severe co-morbidities (e.g. renal failure) and physiological changes that occur over time (e.g. cachexia, inflammation and concomitant medication use) (15-18). Failure to respond (rapidly) to midazolam treatment is of clinical concern, especially when sedation is required to treat refractory symptoms. Patients could therefore potentially benefit if an individualised dose is determined beforehand. A first step in developing such an individualised dosing algorithm is to gain more insight in the pharmacokinetics in this population. To this end and to find clinically relevant parameters for dose individualisation, we performed a population pharmacokinetic study of midazolam and its two major metabolites (1-OH-M and 1-OH-MG) in terminally ill patients.

## METHODS

### Study design

The study (NL32520.078.10) was approved by the Medical Ethics Committee of the Erasmus University Medical Centre Rotterdam and was performed in accordance with the principles of the Declaration of Helsinki and its later amendments. The study was conducted in the palliative care centre, Laurens Cadenza Zuid in Rotterdam, the Netherlands, during two years. Patients were eligible if they had a terminal illness, survival prognosis of more than 2 days and less than 3 months and administration of midazolam. Informed consent was asked shortly after admittance to the palliative care centre and included patient were followed until the time of death. Midazolam was given to treat insomnia or as palliative sedation in accordance with the national guidelines (4). Midazolam was given orally or administered subcutaneously as bolus injection or

infusion. The exact times of administration were recorded in the patient record. Any concomitant medication was also registered in the patient's record. Demographic characteristics (age, gender, weight, race, primary diagnosis, and time of death) were extracted from the electronic medical records. Primary diagnosis of the patient's terminal illness was classified using the *International Statistical Classification of Diseases and Related Health Problems–10th Revision* (ICD-10).

### Blood sampling and assay

Sparse sampling was performed randomly and blood samples were collected during both the pre-terminal and terminal stages. Where the terminal stage for a patient was defined as the last hours to days before death in which a patient becomes bedbound, semi-comatose, is not able to take more than sips of fluid and is no longer able to take oral medication (19). Sample collection was done either via venapuncture or indwelling venous catheter, samples were centrifuged after which the plasma was collected and stored at -80°C until analysis. Blood sampling was preferably performed at the same time as sampling for clinical chemistry (standard of care) for which serum levels of albumin, creatinine, urea, bilirubin, gamma-glytamyl transpeptidase (GGT), alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), and C-reactive protein (CRP) were determined.

Midazolam, 1-OH-M, 4-OH-M and 1-OH-MG were analysed in the plasma samples using LC-MS/MS with electrospray ionization in the positive ionization mode on a Shimadzu LC-30 (Nishinokyo-Kuwabaracho, Japan) system coupled to an ABSciex (Framingham, MA, USA) API5500Q MS. To precipitate proteins 75 µl acetonitrile/methanol 84:16 (v/v%) containing the internal standards midazolam-d5, 1-OH-midazolam-d5, and 4-OH-midazolam-d5 was added to 10 µl of patients' plasma. Samples were vortexed, stored at -20°C for 30 minutes to optimise protein precipitation, vortexed again and centrifuged. Three µl was injected onto a Thermo Scientific Hypersil Gold (50 x 2.1 mm, 1.9 µm) column. A stepwise chromatographic gradient was applied using 0.05% ammonium formate / 0.10% formic acid in water as mobile phase A and acetonitrile as mobile phase B. The flow rate was 0.4 ml/min and the column was kept at 40°C. Using multiple reaction monitoring (MRM) with positive ionisation mode, midazolam, 1-OH-M, 4-OH-M and 1-OH-MG were measured as $[M+H]^+$ using the mass transitions 326.1/291.1, 342.1/168.1, 342.1/234.1 and 518.1/324.1 respectively. The lower limit of quantification was 4 µg/L for midazolam 2 µg/L for 1-OH-M and 4-OH-M and 8 µg/L for 1-OH-MG. The method was validated over a range of 4 – 1000 µg/L for midazolam and 2 – 500 µg/L for 1-OH-M and 4-OH-M and 8-2000 µg/L for 1-OH-MG. The accuracies ranged from 94.3% to 104.7%. Intra-day precision was below 8.2% and inter-day precisions below 12.9%.

### Population pharmacokinetic method

Pharmacokinetic analysis was conducted using non-linear mixed effects modelling using NONMEM® version 7.2 (ICON Development Solutions, Ellicott City, MD), PsN® (version 4.4.8) and Pirana (version 2.9.2).

*Base model development*

The data were log-transformed and concentrations of 1-OH-M and 1-OH-MG were adjusted to their midazolam equivalents using the molecular weight. Bioavailability of subcutaneous midazolam was assumed to be 100% (20). One-, two- and three-compartment models were tested for midazolam and its metabolites using the first-order conditional estimation method with interaction (FOCE+I) and the ADVAN7 subroutine. First a structural model for midazolam was developed. These parameters were then fixed to test the different structural models for 1-OH-M and 1-OH-MG. The volume of distribution (V) of 1-OH-M was assumed to be equal to the volume of distribution of midazolam. IIV was assessed on each parameter using an exponential model. Residual variability was tested as additive, proportional and combined error models. Since the parent and metabolite concentrations were measured in the same samples using 1 assay, a correlation between the residual errors was incorporated in the model. Model selection was based on minimum objective function value (OFV) parameter precision, error estimates, shrinkage values and visual inspection of the goodness of fit plots.

*Covariate model development*

Demographic and disease characteristics including age, gender, race, primary diagnosis, renal function (estimated glomerular filtration rate (eGFR), plasma creatinine, and plasma urea), hepatic function (plasma levels of bilirubin, GGT, ALP, ALT, and AST), C-reactive protein (CRP), albumin, and the concomitant use of CYP3A inductor and inhibitors were evaluated as potential model covariates. Time to death (TTD) was also evaluated as a covariate. This parameter cannot be used as a covariate parameter for a priori prediction of individual pharmacokinetic changes but it may give insight in quantitative changes at the end of life that are not predicted by standard blood chemistry tests. The relationship between covariates and individual estimates was first investigated graphically and was further tested in a univariate analysis. Covariates that significantly improved the model, $p \leq 0.05$ were added to the full model. A backward elimination process was then performed with statistical significance indicated by $p \leq 0.001$.

Continuous covariates were normalised to the population median values and incorporated as power model functions (Eq. 1). Categorical covariates were transformed to binary covariates and incorporated as shown in Eq. 2. With θi being the individual model predicted pharmacokinetic parameter (e.g. clearance) for an individual with covariate value $cov_i$, θpop being the population estimate for that parameter, $cov_m$ representing the median covariate value and θcov the covariate effect. In the equation for categorical covariates $cov_i$ is either 1 or 0.

$$\theta_i = \theta_{pop} * \left(\frac{cov_i}{cov_m}\right)^{\theta cov} \quad (1)$$

$$\theta_i = \theta_{pop} * {\theta_{cov}}^{cov_i} \quad (2)$$

To evaluate the time to death (TTD) as a covariate, time-dependency of the parameters was modelled as a first order process given to following equation (Eq. 3). In which $\theta_{\Delta}$ is the change in parameter value from its initial value and $\theta_{rate}$ is a first order rate constant determining the rate with which the parameter value changes over time. $\theta_{rate}$ was not constrained to be positive or negative so, although physiologically unlikely, an increase in time was also possible.

$$\theta_i = \theta_{pop} - \theta_{\Delta} * \exp(-\theta_{rate} * \mathrm{TTD}) \quad (3)$$

*Model evaluation*

A bootstrap with 200 runs was performed on the final model to evaluate the validity of the parameters estimates and their corresponding 95% confidence intervals. Due to the study design, i.e. sparse sampling, different dosing regimens and both oral and subcutaneous administrations, a visual predictive check could not be performed to evaluate the model. We therefore evaluated the predictive performance of the final model using a normalised prediction distribution errors (NPDE) analysis. This simulation-based analysis can be used to evaluate models developed on datasets with variable dosing regimens. The analytical value of this method has been previously described by Comets et al (21).

*Simulations*

To give an illustration of the effect of the significant covariates found in the covariate analysis, deterministic simulations were performed. The plasma concentrations of midazolam, 1-OH-M and 1-OH-MG are simulated over a time course of 72 hours after the administration of a 10 mg midazolam loading dose followed by 5 mg midazolam 6 times daily via subcutaneous bolus injection. To simulate the plasma concentration in the typical patient, the IIV and residual error were set to zero.

## RESULTS

A total of 45 terminally ill patients were included in the study. Their median age was 71 years (range 43 – 93), 51.1% were female and the median duration of admittance (from moment of admittance until time of death) was 29 days (range 7 – 457). All but one patient (97.8%) had advanced malignancy as primary diagnosis. Patient characteristics are given in table 1. Oral midazolam was administered as a 7.5 mg dose up to four times daily. The subcutaneous doses used were between 2.5 and 180 mg a day. A total of 139 blood samples were collected which were analysed for midazolam, 1-OH-M, 4-OH-M and 1-OH-MG, concentrations. Figure 1 gives the plasma concentration versus time profiles of a representative patient in the last week before death.

**Table 1.** Patient characteristics over the time course of the study

| Characteristics | N=45 |
|---|---|
| Age, years (median, range) | 71 (43 - 93) |
| Male, *n* (%) | 22 (48.9) |
| Female, *n* (%) | 23 (51.1) |
| Ethnic origin, *n* (%) | |
| Caucasian | 41 (91.1) |
| Afro-Caribbean | 3 (6.7) |
| Unknown | 1 (2.2) |
| Primary diagnosis, *n* (%) | |
| Neoplasm | 44 (97.8) |
| Disease of the respiratory system | 1 (2.1) |
| Blood chemistry, serum levels at admission (median, range) | |
| Albumin, g/l | 25 (13-39) |
| Urea, mmol/l | 7.6 (1.5-66.9) |
| Bilirubin, umol/l | 9 (2-256) |
| Gamma-glytamyl transpeptidase, U/l | 62 (7-3859) |
| Alkaline phosphatase, U/l | 118 (20-2371) |
| Alanine transaminase, U/l | 14 (7-632) |
| Aspartate transaminase, U/l | 30 (13-2710) |
| C-reactive protein, U/l | 92 (1-625) |
| Creatinine, umol/l | 67 (20-806) |
| eGFR by standard MDRD[a], ml/min/1.73 $m^2$ | 104 (6-328) |
| eGFR by original MDRD[b], ml/min/1.73 $m^2$ | 85 (4-228) |
| Patients using dexamethasone[c], *n* (%) | 17 (37.8) |
| Patients using phenytoin[c], *n* (%) | 1 (2.2) |
| Duration of stay, days (median, range) | 29 (7 - 457) |
| Blood samples collected, *n* (median, range) | 2 (1 – 10) |

eGFR: estimated glomerular filtration rate, MDRD: modification of diet in renal disease. [a] The abbreviated MDRD equation consists of 4 variables (age, gender, race and serum creatinine) as shown in Eq. 4. [b] the original MDRD formula consist of 6 variables (age, gender, race, serum creatinine, serum albumin and serum urea) as shown in Eq. 5 [c] during any moment while receiving midazolam treatment

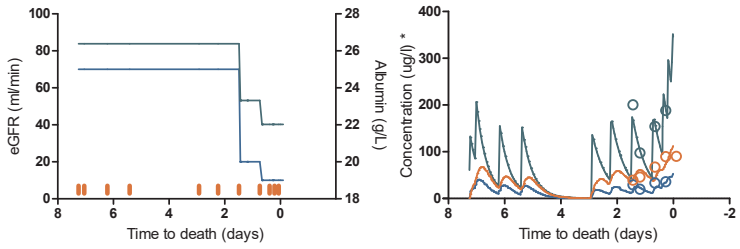


**Figure 1.** Dose and concentration data of a patient representative for the study population in the last week before death. Top: Time profile of the estimated glomerular filtration rate (eGFR) (green) and albumin levels (blue) and the 5 mg subcutaneous midazolam doses (orange) over time in the last week before death. Bottom: Post-hoc predictions of concentration of midazolam (green), 1-OH-M (blue) and 1-OH-MG (orange) and their corresponding measured midazolam concentrations (open circles) in the last week before death. The concentrations of both metabolites are shown as the therapeutic equivalents of midazolam, so 1-OH-M concentrations are multiplied by 0.8 and 1-OH-MG by 0.1.

## Structural model

The percentage of concentrations below the quantification limit (BQL) were 14%, 16% and 10% for midazolam, 1-OH-M and 1-OH-MG respectively. More than half of these BQL concentrations where measured in samples taken more than 3 days after the last midazolam dose and 92% of these BQL concentrations were measured in samples taken more than 12h after the last dose. As a result midazolam, 1-OH-M and in most cases also 1-OH-MG were no longer detectable. The BQL data were therefore discarded using the M1 method discussed before by Ahn et al (22). The amount of BQL data of 4-OH-M was 75% and as data on 4-hydroxy-midazolam-glucuronide were lacking, this metabolite was not incorporated in the pharmacokinetic model.

The data were best described by a one-compartment model for midazolam and two one-compartment models for both its metabolites (1-OH-M and 1-OH-MG) (Fig. 2) with an additive residual error on logarithmic transformed concentrations. Since there was limited data available in the absorption phase the absorption constants (Ka) could not be estimated. They were therefore derived from literature (5.5 $h^{-1}$ for oral administration, 10 $h^{-1}$ for subcutaneous injection) (14, 20, 23). IIV was included on midazolam clearance, F of oral midazolam, V of midazolam, 1-OH-M clearance and 1-OH-MG clearance as all of these significantly improved the model. The correlation between IIV of midazolam clearance and F of oral midazolam was high (0.93) and therefore fixed to unity. In all cases an exponential model for IIV proved superior to an additive model.

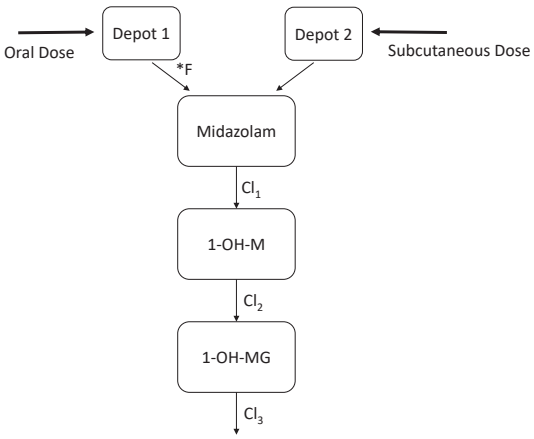


**Figure 2.** Schematic representation of the structural model for midazolam and its two main metabolites. F: bioavailability of oral midazolam; Cl1: midazolam clearance and formation of 1-OH-M; Cl2: 1-OH-M clearance and formation of 1-OH-MG; Cl3: 1-OH-MG clearance.

## Covariate analysis

In the covariate analysis all possible covariates, as mentioned in the methods section, were tested on all parameters including IIV (F, V of midazolam and clearance of midazolam, 1-OH-M and 1-OH-MG). This univariate analysis with a p-threshold of 0.05 resulted in 16 significant

covariates. After backward elimination with a lower threshold of 0.001 only two covariates remained in the final model. The first covariate was estimated glomular filtration rate (eGFR) on 1-OH-MG clearance (Eq. 4), and the second covariate was the correlation of albumin on midazolam clearance (Eq. 5). CRP levels were also correlated with midazolam clearance, and depending on the order of the backwards elimination, either albumin or CRP remained in the final model. As the difference in these OFV between albumin and CRP was minimal the choice to include albumin instead of CRP was based on the fact that albumin is a more specific marker for overall condition than CRP. The results of the univariate analysis, in terms of decrease in OFV and covariate effect are shown in table 3. The addition of albumin on midazolam clearance reduced the IIV from 59.9 % to 49.0% thus explaining 18.2% of the IIV on midazolam clearance. Incorporation of eGFR as a covariate on 1-OH-MG clearance reduced the IIV from 69.7% to 49.9% thereby explaining 28.4% of the IIV on 1-OH-MG clearance.

$$\mathrm{Cl}_{1-\mathrm{OH}-\mathrm{MG}} = 5.1 * \left(\mathrm{eGFR}_{\mathrm{ml/min}} / 104.1\right)^{0.53} \quad (4)$$

$$\mathrm{Cl}_{\mathrm{midazolam}} = 8.42 * \left(\mathrm{serum\ albumin}_{\mathrm{g/L}} 25\right)^{1.08} \quad (5)$$

In the final model the population mean estimates for clearance were, 8.42 L/h (RSE 9%) for midazolam; 45.4 L/h (RSE 12%) for 1-OH-M and 5.1 L/h (RSE 11%) for 1-OH-MG. The population mean estimates for volume of distribution were 113 L (RSE 13%) for midazolam and 1-OH-M compartments (which were assumed to be equal) and 2.98 L (RSE 71%) for the 1-OH-MG compartment. The bioavailability (F) of oral midazolam was 27.9%. An overview of all parameter estimates is given in table 2.

**Table 2.** Parameter estimates of the base model, final model and bootstrap analysis.

| Parameter | Structural model | Final model | RSE % | Shrinkage % | Bootstrap of the final model | | |
|---|---|---|---|---|---|---|---|
| | | | | | Average | 95% CI (lower) | 95% CI (upper) |
| OFV | -109.113 | -146.519 | | | | | |
| *Midazolam* | | | | | | | |
| F | 0.204 | 0.279 | 12.6 | - | 0.288 | 0.227 | 0.857 |
| Cl (L/h) | 7.76 | 8.42 | 9.0 | - | 8.52 | 7.18 | 10.4 |
| V (L) | 117 | 113 | 13.1 | - | 111 | 84.0 | 137 |
| *1-OH-Midazolam (1-OH-M)*[a] | | | | | | | |
| Cl (L/h) | 43.8 | 45.4 | 11.5 | - | 46.0 | 36.8 | 60.4 |
| *1-OH-Midazolam glucuronide (1-OH-MG)* | | | | | | | |
| Cl (L/h) | 3.82 | 5.10 | 11.0 | - | 5.18 | 4.08 | 6.50 |
| V (L) | 3.47 | 2.98 | 71.5 | - | 2.97 | 0.85 | 13.7 |
| *Covariate effect midazolam clearance* | | | | | | | |
| Albumin | - | 1.08 | 21.2 | - | 1.02 | 0.38 | 1.47 |
| *Covariate effect on 1OH-midazolam glucuronide clearance* | | | | | | | |
| eGFR [b] | - | 0.53 | 20.7 | - | 0.52 | 0.31 | 0.82 |

Table 2. Parameter estimates of the base model, final model and bootstrap analysis. (*continued*)

| Parameter | Structural model | Final model | RSE % | Shrinkage % | Bootstrap of the final model | | |
|---|---|---|---|---|---|---|---|
| | | | | | Average | 95% CI (lower) | 95% CI (upper) |
| *IIV (%)* | | | | | | | |
| F | 48.7% | 50.6% | 17.4 | 12.8 | 48.4% | 32.0% | 61.3% |
| Midazolam Cl | 59.9% | 49.0% | 14.0 | 12.8 | 47.5% | 31.4% | 60.2% |
| Midazolam V | 72.6% | 70.9% | 15.1 | 16.6 | 70.2% | 46.9% | 93.2% |
| 1-OH-M Cl | 55.4% | 60.5% | 18.0 | 12.2 | 58.0% | 32.8% | 79.6% |
| 1-OH-MG Cl | 69.4% | 49.9% | 23.1 | 23.0 | 49.0% | 26.7% | 73.4% |
| *Residual variability* | | | | | | | |
| Midazolam | 26.7% | 26.8% | 13.3 | 20.4 | 26.8% | 21.3% | 34.2% |
| 1-OH-M | 42.7% | 42.3% | 21.6 | 18.5 | 41.3% | 21.7% | 56.7% |
| 1-OH-MG | 48.4% | 46.4% | 13.1 | 18.6 | 44.4% | 30.1% | 55.2% |

OFV: objective function value, F: bioavailability, CL: clearance, V: volume of distribution, eGFR: estimated glomerular filtration rate, MDRD: modification of diet in renal disease, 1-OH-M: 1OH-midazolam, 1-OH-MG: 1OH-midazolam-glucuronide. [a] The volume of distribution of 1-OH-M was set equal to that of midazolam itself. [b] GFR was estimated using the standard 4-variable MDRD equation.

Table 3. Covariate effects in univariate analysis compared to the structural model

| Covariate | ΔOFV | Covariate effect | Included after backward elimination |
|---|---|---|---|
| On midazolam clearance | | | |
| Serum albumin | -7.54 | 0.84 | Yes |
| CRP | -7.51 | -0.12 | No |
| AST | -4.73 | -0.16 | No |
| Time to Death[a] | -4.69 | 2.29 and 0.05 | No |
| On midazolam volume of distribution | | | |
| ALT | -6.29 | 0.22 | |
| AST | -9.06 | 0.22 | No |
| Weight | -4.73 | 1.52 | No |
| Dexamethasone use[b] | -4.56 | 1.67 | No |
| Time to Death[a] | -6.50 | -71.6 and 0.05 | No |
| On 1-OH-M clearance | | | |
| eGFR-b[c] | -3.86 | -0.21 | No |
| CRP | -10.18 | 0.19 | No |
| On 1-OH-MG clearance | | | |
| Serum Creatinine | -17.20 | -0.50 | No |
| eGFR-a[c] | -20.92 | 0.47 | Yes |
| eGFR-b[c] | -22.49 | 0.49 | No |
| Serum urea | -19.74 | -0.53 | No |
| Time to Death[a] | -15.25 | 4.21 and 0.11 | No |

CRP: C-reactive protein, AST: aspartate transaminase, ALT: alanine transaminase, eGFR: estimated glomerular filtration rate [a] Time to death was incorporated as a covariate as a first order process, therefore the first mentioned value describes the total change in the parameter value (ΔTTD) and the second value the rate in days (see equation 3). [b] Dexamethasone use was defined as the use of dexamethasone for at least 2, no longer than 7 days ago [c] The glomular filtration rate was calculated using both the standard 4-variable MDRD equation (eGFR-a) and the original 6-variable MDRD (eGFR-b)

## Model evaluation

Figure 3 (a-f) shows that both the population predictions and individual predictions were evenly distributed around the line of unity when plotted against the observations. A bootstrap analysis of the final model was performed to obtain 95% confidence intervals for all parameters. Results of the bootstrap are shown in table 2. Evaluation of the predictive performance by NPDE analysis showed accurate predictive ability, with the distribution of the NPDEs not significantly deviating from a normal distribution (with global adjusted P values of 0.75, 0.20 and 0.41 for midazolam, 1-OH-M and 1OH-MG respectively), and the majority of the NPDEs laying between the values -2 and 2 (Figure 3: g-i).

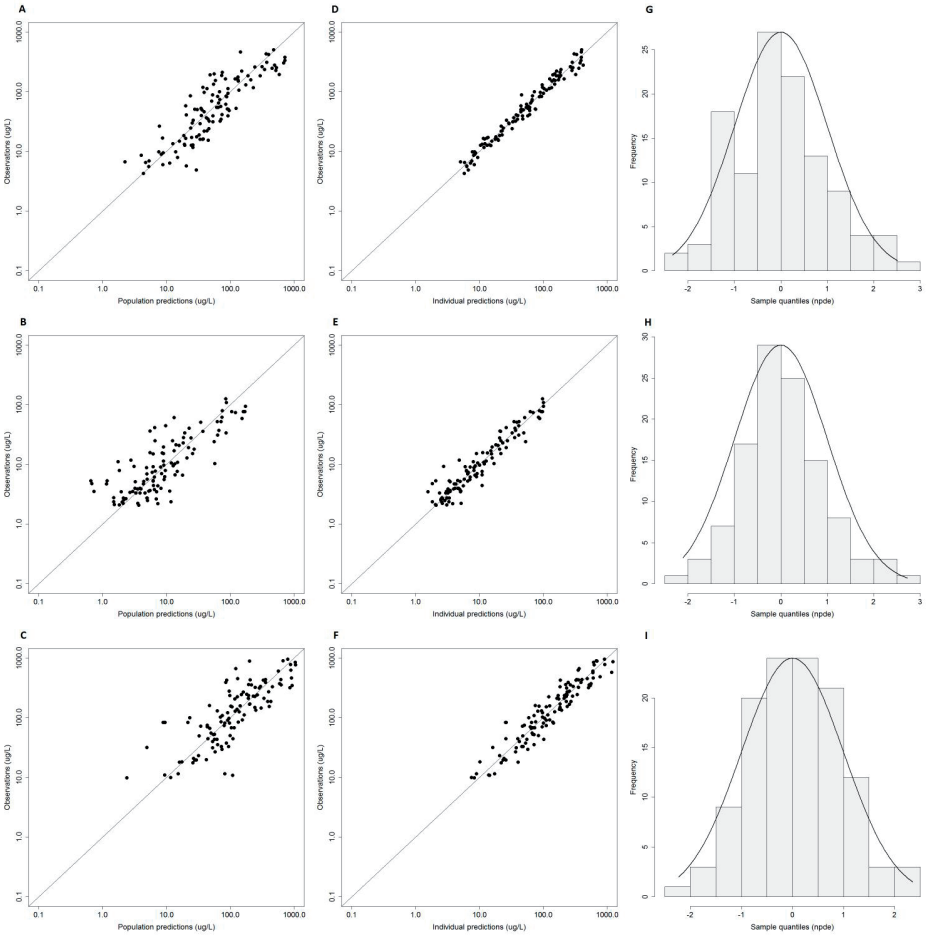


Figure 3. Goodness of fit plots of the final model. Population predictions vs. observations of midazolam (A), 1-OH-M (B) and 1-OH-MG (C) and individual predictions vs. observations of midazolam (D), 1-OH-M (E) and 1-OH-MG (F) with the solid line displaying the line of unity. Normalized prediction distribution error (NPDE) plots for midazolam (G), 1-OH-M (H) and 1-OH-MG (I) showing NPDE quantiles (grey bars) vs. a normal distribution (solid line).

## Simulations

Based on the final model the midazolam clearance is reduced by 30% (from 12.1 L/h to 8.4 L/h) when albumin decreases from 35 g/L to 25 g/L. A further decrease in albumin to 15 g/L decreases midazolam clearance by another 42% to a value of 4.8 L/h. The effect of this drop in midazolam clearance on midazolam and metabolite concentrations is shown in figure 4. The effect of eGFR on 1-OH-MG clearance in our final model results in a reduction of clearance of 27% (from 4.7 L/h to 3.5 L/h) when eGFR decreases from 90 to 50 ml/min. A further decline of eGFR to 30ml/min reduces the 1-OH-MG clearance by another 24 % to 2.7 L/h. The effect of this decrease in clearance on the plasma concentrations is shown in figure 5.

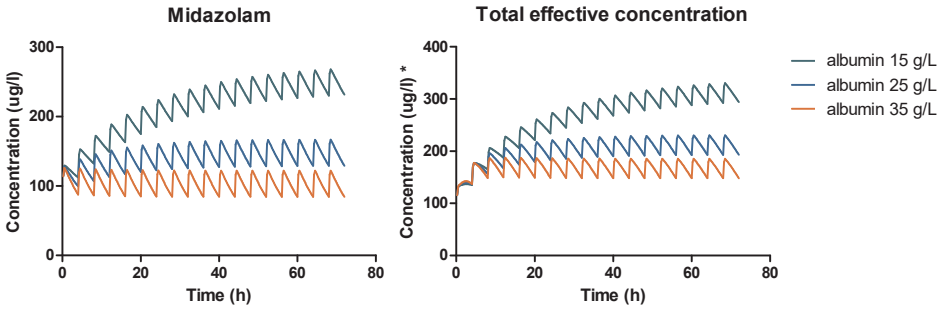


Figure 4. Simulated plasma profiles of midazolam and the total effective concentration (calculated as the sum of parent and both metabolites with 1-OH-M accounting for 80% and 1-OH-MG for 10% of the midazolam potency) for patients with plasma albumin levels of 15 g/l (green), 25 g/l (blue), and 35 g/l (orange) and stable eGFR of 90ml/min. After a 10mgmidazolam loading dose followed by 5 mg six times daily all via subcutaneous bolus injection.

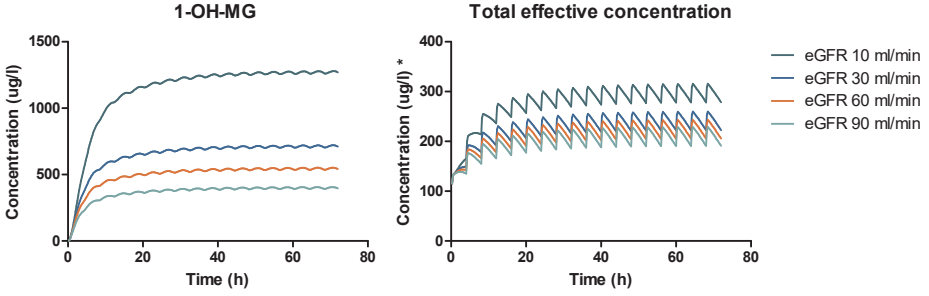


Figure 5. Simulated plasma profiles of midazolam and the total effective concentration (calculated as the sum of parent and both metabolites with 1-OH-M accounting for 80% and 1-OH-MG for 10% of the midazolam potency) for patients with an estimated glomerular filtration rate (eGFR) of 10 ml/min (green), 30 ml/min (blue), 60 ml/min (orange) and 90 ml/min (light green) and stable plasma albumin levels of 25 g/l. After a 10 mg midazolam loading dose followed by 5 mg six times daily all via subcutaneous bolus injection.

## DISCUSSION

To our knowledge, this is the first population pharmacokinetic study of midazolam and its metabolites in terminally ill adult patients. With sparse sampling we were able to accurately describe the pharmacokinetics of midazolam, 1-OH-M and 1-OH-MG. The large IIV in pharmacokinetics may contribute to the large inter-patient difference in sedation in clinical practice. About one-third of the IIV in 1-OH-MG clearance could be explained by incorporating eGFR as a covariate in the model, confirming that 1-OH-MG clearance declined as a result of renal insufficiency. We also observed a positive correlation between albumin levels and midazolam clearance, explaining 18.2% of the IIV on midazolam clearance. These are important findings as these patient characteristics may be used to develop an individualised dosing regimen.

A positive correlation between albumin levels and midazolam clearance (with low albumin levels relating to a decrease in clearance) has been described before in the 80's by Vree et al. (24). It was suggested that this reduced clearance was a result of decreased protein binding. Although midazolam is indeed highly protein bound (95-98%) primarily to albumin (25, 26). It seems unlikely that protein binding is the cause of the decreased clearance shown in our study when we take into account the following equation (eq. 6) for clearance. Based on this equation a decrease in albumin, which would increase the unbound drug concentration ($F_u$), would result in either an unchanged or increased clearance, depending on the extraction ratio of the drug (27, 28). With an increase in $F_u$ an increase of volume of distribution would also be expected. This was however not the case as albumin was not found to be a significant covariate on volume of distribution in our study (ΔOFV 0.014) furthermore contradicting an effect via protein binding.

$$\frac{Q(F_u{*}Cl_{int})}{Q + (F_u{*}Cl_{int})} \quad (6)$$

We therefore propose that the mechanism behind the reduced clearance may be due to an underlying inflammatory response or catabolic state. In cancer patients, hypoalbuminemia can be an expression of inflammation and it has already been shown that inflammation can result in reduced CYP3A activity (17, 18, 29-31). Furthermore albumin levels showed some correlation (r =-0.69) with CRP levels (fig 1 supplementary material) and in the univariate covariate analysis CRP also showed a correlation with midazolam clearance, supporting our theory of an underlying common process. Albumin and not CRP was incorporated in the model, because in terminally ill patients albumin is a more pronounced marker of overall condition and more commonly used in clinical practice (32, 33). In addition albumin does not fluctuate as much as CRP, which makes it a better candidate for a future dosing regimen. If albumin is also a better marker for CYP3A clearance in other populations remains unclear. It might be that albumin has a better correlation with CYP3A activity in this population as

it is sign of a prolonged inflammatory/catabolic state whereas CRP is more an expression of an acute process. To determine whether albumin, CRP or possibly another inflammatory marker, is the best indicator for CYP3A activity more research is needed. The correlation between midazolam clearance and inflammation is clinically important as inflammation plays a crucial role in cancer and the CYP3A enzyme metabolises not only midazolam but more than 50% of all therapeutic drugs (34, 35)."

Our study also showed that eGFR was correlated with 1-OH-MG clearance. This correlation is a result of the fact that 1-OH-MG is renally excreted. It is relevant in the terminally ill population as renal insufficiency is common and, although 1-OH-MG is only 10% as potent as midazolam itself, high concentrations can lead to increased sedation (5). As shown in figure 5 an eGFR of 50 mL/min can already contribute significantly to the sedative effect of midazolam. Midazolam is believed to be sedative from concentrations of 100 µg/L and up and since 1-OH-MG has a potency of around 10%, 1-OH-MG concentrations of 500 µg/L, which were also seen in our study, already contribute to half of the sedative effect. It is however important to note that the method to estimate the globular filtration rate probably overestimates the renal function in terminally ill patients as it is dependent on the creatinine production from muscle tissue. In our study tested eGFR calculated by the 4-variable modification of diet in renal disease (MDRD) equation (eq. 7) as well as eGFR calculated by the original 6 variable equation (eq. 8) as a covariate (36). As the difference between the two was minimal we incorporated the simpler 4-variable equation in our final model as this is the most commonly used equation.



$$\text{eGFR} = 186 \times \text{serum creatinine}\left(\text{mg/dl}^{-1}\right)^{-1.154} \times \text{age}^{-0.203} \times (1.210 \text{ if black}) \times (0.742 \text{ if female}) \quad (7)$$

$$\text{eGFR} = 170 \times \text{serum creatinine}\left(\frac{\text{mg}}{\text{dl}}\right)^{-0.999} \times \text{age}^{-0.176} \times (1.180 \text{ if black}) \times (0.762 \text{ if female}) \times \text{serum urea nitrogen}\left(\text{mg/dl}^{-1}\right)^{-0.170} \times \text{albumin}\left(\text{g/dl}^{-1}\right)^{0.318} \quad (8)$$

Our finding for midazolam clearance (population mean: 8.42 L/h) is in agreement with previous studies in critically ill patients (37, 38). It is also comparable to the estimated clearance found in a recent study in critically ill children where they also found an effect of inflammation (to compare these values the results of Vet et al. were adapted to values for a 70 kg individual) (30). In our model a patient with a healthy albumin level of 45 g/L would have a midazolam clearance of 15.3 L/h which is also in line with the results of other studies in healthy volunteers and obese patients (14, 23, 39). Although some studies in obese patients

and patients who undergone bariatric surgery have even higher clearance values (23, 40). The estimated value for volume of distribution is also similar to that of the studies in critically ill patients and that of the most recent study in obese patients (30, 37, 40). However we were not able to accurately quantify a peripheral compartment for midazolam where some of the other studies were. This is due to the sparse sampling in this study which has presumably resulted in insufficient data to quantify a two-compartment model. Another contrast with previous studies is the lower estimate for the volume of distribution of 1-OH-MG, of 2.98 L. As 1-OH-MG is a hydrophilic metabolite a low volume of distribution was expected. In terminally ill patients this could be even more reduced as these patients are older (median age of 71), have a diminished intake of oral fluids and become dehydrated. The high RSE of 71% for this parameter however indicates that it was difficult to estimate the V of 1-OH-MG accurately. This is probably due to the fact that in patients without renal insufficiency 1-OH-MG is rapidly eliminated.

Finally a notable difference with previous studies is the large inter-individual variability in volume of distribution of midazolam in the final model. Other studies also found large IIV in their base models but were able to correct for this using weight as a covariate (14, 40). Unfortunately in our study data on weight was available for only 53 % of the patients, and the weights that were available were only collected at time of admission. As a result the plots showing the available data on weight vs volume of distribution or the IIV on volume of distribution did seem to show a correlation (supplementary material). However this effect was not significant in the covariate analysis. This lack of data on weight is a limitation in our study. We therefore highly recommend that in future pharmacokinetic studies in the terminally ill population, weight is monitored regularly.

A possible limitation of our study is that it did not include intravenously administered midazolam, as this route of administration is seldom used in palliative care. As a result the bioavailability of subcutaneous midazolam could not be estimated and was assumed to be 100%. This seems reasonable and is in line with the study of Pecking et al. However in that study F was reported as 0.96 +/- 0.14 so there is some uncertainty in this number, which could have affected the estimates for clearance and volume of midazolam to a small extend.

Another possible limitation of our study was that we did not include the 4-OH-M metabolite in our model. We did measure 4-OH-M in our samples, however as only a low percentage of midazolam is converted into 4-OH-M, 75% of these concentrations were below the lower limit of detection. This lack of data meant that we were only able to estimate the fraction of midazolam that is metabolised into 4-OH-M (which was around 10%) but we were unable to accurately estimate a volume of distribution or clearance for 4-OH-M. As only a low percentage is converted into 4-OH-M and this metabolite has a lower affinity to the receptor compared to the 1-OH-M metabolite, this is probably of low clinical interest (41). As the 4-OH-M metabolite was not included in the model and true fraction metabolised is unknown, the clearance and distribution volumes of the other metabolites are apparent values.

Overall this study shows that it is possible to accurately describe a drug's pharmacokinetics and find clinical relevant parameters for dose individualisation using population pharmacokinetics in terminally ill patients. This is very important as large interpatient variability in these patients is of clinical concern and therefore more research is needed in this population. As a population approach can be used with sparse sampling it minimises the patient's burden which is crucial in this vulnerable population. Concerning midazolam we have showed that low albumin levels may indicate a decreased capacity to metabolise midazolam, possibly as a result of inflammatory response. This is of clinical importance as hypoalbuminemia is common in both cancer patients and cachectic patients. Therefore the dose of midazolam (and possibly also other drugs that are metabolised via CYP3A) may have to be decreased in these patients. Another possible reason to adjust the midazolam dose might be a decrease in renal function, as in these patients the 1-OH-MG metabolite can accumulate. These important insights into the pharmacokinetics of midazolam and its metabolites in terminally ill patients may be a first step explaining the different response to midazolam treatment. However it is also known that there is a large variability in response to plasma levels (10, 11). Therefore, further studies on the pharmacodynamics in this population are needed before any firm conclusions can be drawn on dose adjustments.

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## SUPPORTING INFORMATION

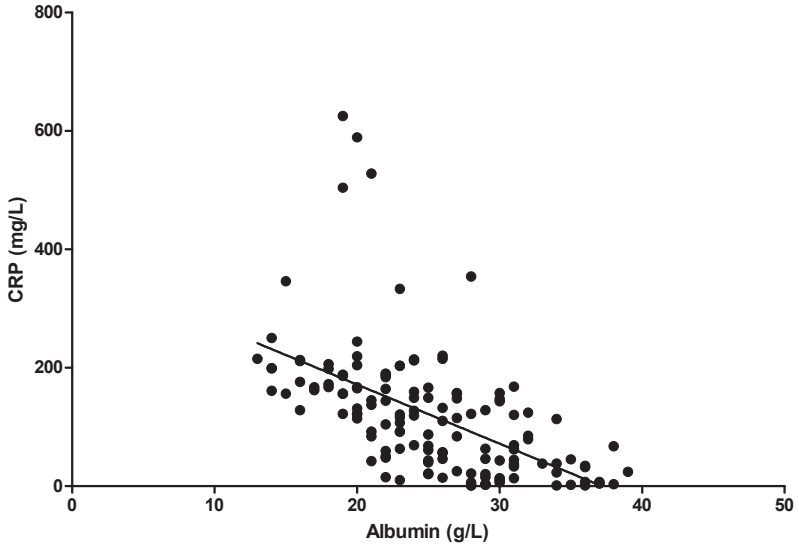



Figure S1. Correlation of albumin (g/l) and CRP (mg/l) with the corresponding linear regression line.



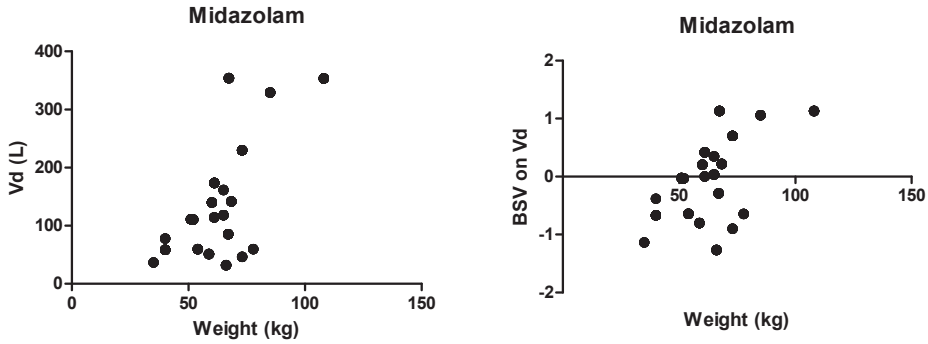



Figure S2. Correlation of weight (the known weights at time of admission) vs. volume of distribution (V) of midazolam and the inter-individual variability (IIV) on volume of distribution (V) of midazolam with the corresponding linear regression lines.

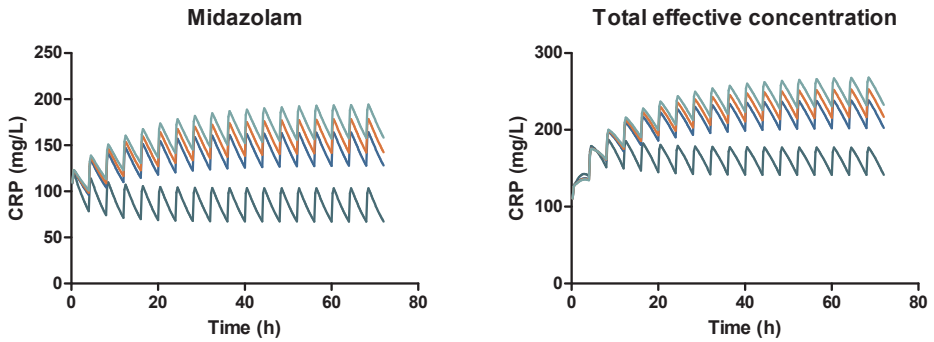
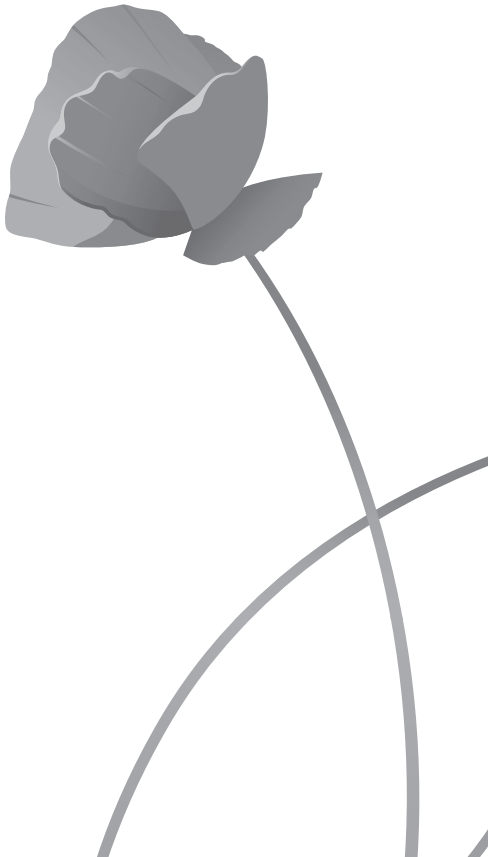
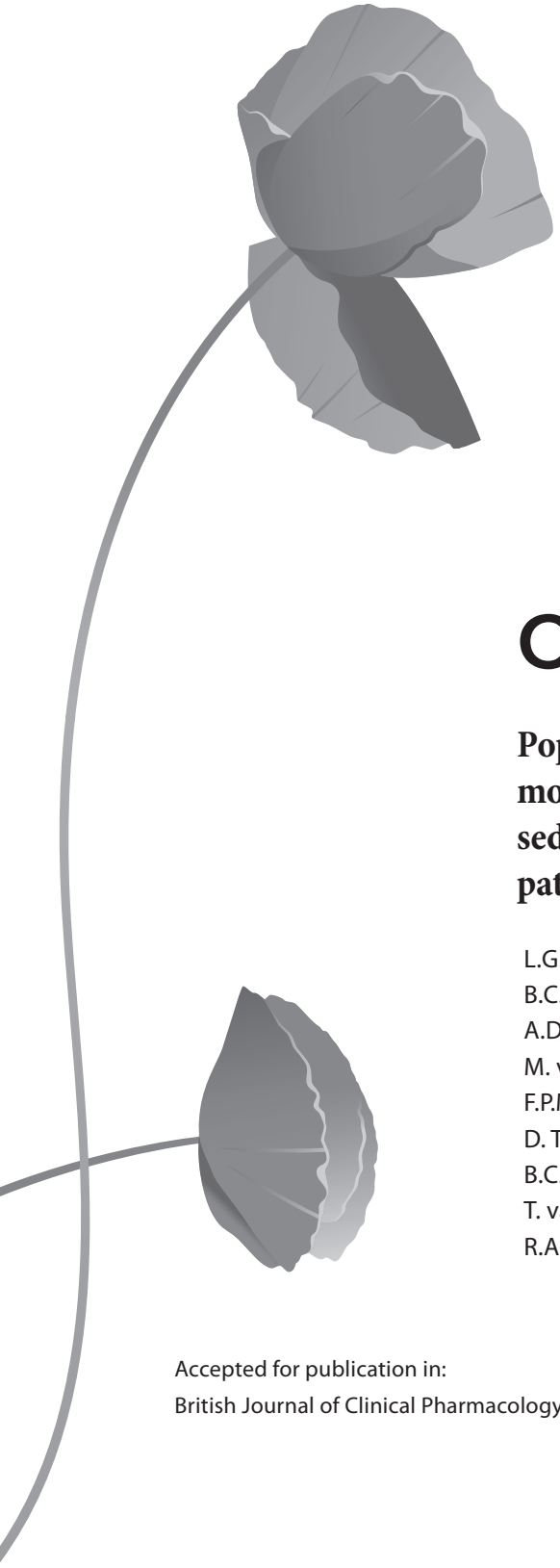



Figure S3. Simulated plasma profiles of midazolam and the total effective concentration (calculated as the sum of parent and both metabolites with 1-OH-M accounting for 80% and 1-OH-MG for 10% of the midazolam potency) for patients with an C-reactive protein (CRP) concentration of 1 mg/l (green), 50 mg/l (blue), 100 mg/l (orange) and 200 mg/l (light green) and stable eGFR of 90 ml/min, after a 10 mg midazolam loading dose followed by 5 mg six times daily all via subcutaneous bolus injection





# CHAPTER 6

## Population pharmacodynamic modelling of midazolam induced sedation in terminally ill adult patients

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Accepted for publication in:
British Journal of Clinical Pharmacology. 13 sep 2017

## ABSTRACT

### Introduction

Midazolam is the drug of choice for palliative sedation and is titrated to achieve the desired level of sedation. A previous pharmacokinetic (PK) study showed that variability between patients could be partly explained by renal function and inflammatory status. The goal of this study was to combine this PK information with pharmacodynamic (PD) data, to evaluate the variability in response to midazolam and to find clinically relevant covariates that may predict PD response.

### Method

A population pharmacodynamic analysis using nonlinear mixed effect models was performed with data from 43 terminally ill patients. PK profiles were predicted by a previously described PK model and depth of sedation was measured using the Ramsay sedation score. Patient and disease characteristics were evaluated as possible covariates. The final model was evaluated using a visual predictive check (VPC).

### Results

The effect of midazolam on the sedation level was best described by a differential odds model including a baseline probability, Emax model and inter individual variability (IIV) on the overall effect. The EC50 value was 68.7 µg/L for a Ramsay score of 3-5 and 117.1 µg/L for a Ramsay score of 6. Co-medication with haloperidol was the only significant covariate. The VPC of the final model showed good model predictability. **Conclusion** We were able to accurately describe the clinical response to midazolam. As expected there was large variability in response to midazolam. The use of haloperidol was associated with a lower probability of sedation. This may be a result of confounding by indication as haloperidol was used to treat delirium, and deliria has been linked to a more difficult sedation procedure.

*What is known about this subject*

- In terminally ill patients pharmacokinetic variability can be reduced by taking in to account a patients' albumin levels and estimated glomular filtration rate.
- There is large inter individual variability in clinical response to midazolam.
- Delirious patients are regarded as more difficult to sedate in general, as well as in the case of palliative sedation.

*What this study adds*

- Using a population approach with categorical sedation scores we were able to accurately describe the pharmacodynamics of midazolam in terminally ill patients.
- Haloperidol as co-medication was associated with lower Ramsay scores, and therefore a less sedative state.
- With this population pharmacodynamic model target levels of midazolam can be attained that can be used in the development of an individualised dosing algorithm.

## INTRODUCTION

In terminally ill end-of-life patients the most important goal is to provide adequate symptom relief (1-3). When symptoms are so severe that none of the conventional modes of treatment is effective within a reasonable time frame and/or these treatments are accompanied by unacceptable side effects, i.e. in case of refractory symptoms, palliative sedation may be initiated. In a hospice setting palliative sedation is commonly used. Several studies looked at how often palliative sedation was initiated and showed that on average 46% (range 22 – 67%) of the terminally ill patients in a hospice were being sedated for refractory symptoms at the end of life (4-8). The drug of choice to achieve palliative sedation is midazolam (4, 9). Although midazolam has been shown to be effective in achieving adequate sedation, the response between patients varies widely. In clinical practice the midazolam dose is titrated according to clinical response which results in a wide range of both effective dose and time to adequate sedation (10, 11). Furthermore, the study by Morita et al showed that almost half of the patients awoke at least once from the sedated state (11).

A more individualised dose could therefore potentially lead to more adequate sedation in these patients. To investigate this, a population pharmacokinetic model was developed which demonstrated large inter individual variability (IIV) on clearance of both midazolam and its metabolites with values ranging from 49 to 61% (12). It also showed that IIV could be significantly reduced if patients' serum albumin levels and estimated glomerular filtration rate (eGFR) were to be taken into account. This suggests that a dosing regimen based on albumin levels and eGFR may result in better clinical outcome. However, such a pharmacokinetic model only predicts midazolam concentrations and does not include the pharmacodynamic variability, which is likely to be considerable and may vary with age, gender or disease severity (13-15). This information is crucial when generating an individualized dosing advice.

To investigate the clinical response to midazolam plasma concentration on sedation level, to assess the amount of variability, and to find clinically significant covariates, we performed a population pharmacodynamic study in terminally ill adult patients using the Ramsay sedation score.

## METHODS

### Study design

The study (NL32520.078.10) was approved by the Medical Ethics Committee of the Erasmus University Medical Centre Rotterdam and was performed in accordance with the principles of the Declaration of Helsinki and its later amendments. The design of the study and study population are presented in detail in chapter 5, the article of Franken et al in which the

population pharmacokinetic model of midazolam is described (12). Parts of the methods are briefly mentioned in this article when relevant. The study design with sparse regimen of random PK and PD sampling is shown in figure 1.

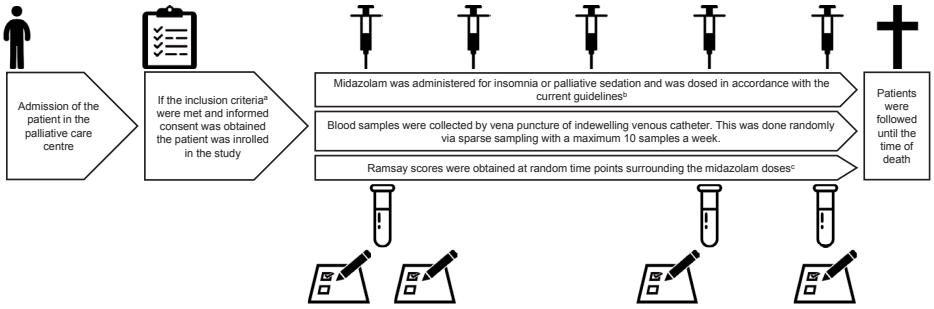


Figure 1. Regimen of pharmacokinetic and pharmacodynamic sampling. (A) The inclusion criteria for this study were terminal illness, a survival prognosis of more than 2 days and less than 3 months, administration of midazolam.(B) The current Dutch guidelines states that midazolam can be administered either as subcutaneous bolus injection (with a starting dose of 10 mg followed 5 mg every 2 h if necessary) or as a continuous subcutaneous infusion (with a starting dose of 1,5–2.5 mg/h and the possibility to up the dose if sedation was insufficient with 50% every 4 h in combination with a 5-mg bolus injection). (C) In general, the Ramsay score was obtained at the start of the midazolam treatment with consecutive assessments at 2-h intervals.

## Data collection

Demographic characteristics (age, gender, ethnicity, primary diagnosis, and time of death) were extracted from the electronic medical records. Midazolam administration times were recorded in the patient record as well as any concomitant medication. Sparse blood samples were collected at random time points during both the pre-terminal and terminal stage of the disease. Using these samples midazolam and its two major metabolites, 1-hydroxymidazolam (1-OH-M) and 1-hydroxymidazolam glucuronide (1-OH-MG) were determined by an LC-MS/MS method described before (12). Blood samples for clinical chemistry were taken at the same time and serum levels of albumin, creatinine, urea, bilirubin, gamma-glytamyl transpeptidase (GGT), alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), and C-reactive protein (CRP) were determined. Sedation was assessed using the Ramsay sedation score and was typically scored at the start of the midazolam treatment with consecutive assessments at 2 hour intervals (16). This scale consists of 6 sedation levels: 1, patient is anxious and agitated or restless; 2, patient is co-operative, orientated and tranquil; 3, patient is drowsy or asleep and responds to commands only; 4, patient is asleep and has a brisk to a light glabellar tap or loud auditory stimulus 5, patient is asleep and has a sluggish response to a light glabellar tap or loud auditory stimulus; 6, patient is asleep and has no response to a glabellar tap or loud auditory stimulus. The Ramsay sedation score has been used before in a palliative care setting and enables doctors and nursing staff to assess

the level of sedation as self-reporting is usually not possible (17, 18). The Ramsay score was measured by a trained and experienced nurse, using a standard operating procedure.

## Pharmacokinetic data integration

A previously described population pharmacokinetic model was used to predict PK profiles for all individual patients (12). This model was based on the same study population and contained data from 45 patients and 139 collected blood samples. This model was systematically developed based on minimum objective function value (OFV), parameter precision, error estimates, shrinkage values and visual inspection of the goodness of fit plots, bootstrapping and normalised prediction distribution errors (NPDE) analyses. In summary the model was a one-compartment model for both midazolam, 1-OH-M and 1-OH-MG and contained two covariates albumin levels on midazolam clearance and eGFR on 1-OH-MG clearance. Since all 43 patients for whom Ramsay scores were available, were also included in the PK dataset, the individual PK parameters together with the midazolam doses were used as input for the sequential PD model. From the remaining 2 patients, no Ramsay scores were available and they were excluded from the PD model.

## Population pharmacodynamic method

A population pharmacodynamic analysis using nonlinear mixed effect models was performed with NONMEM® 7.2, in combination with Pirana (version 2.9.2) for the model building process and R (version 3.3.0) and PsN (version 4.6.0) to generate diagnostic plots.

### *Population PD model development*

Both a proportional odds model and a differential odds model were tested for the possibilities of observing a certain Ramsay sedation score. These methods have been described before by Kjellsson et al and the difference between these models was tested by dichotomising the data and performing logistic regression (19). In short these methods estimate the logit and corresponding probability of the Ramsay score being equal or greater than a particular value. At any given concentration, there is a finite probability of having a Ramsay score of 1, 2, 3, 4, 5 and 6 with the sum of these probabilities being 1. The probability (P) of a particular sedation score (n) follows from calculating the difference of two consecutive scores, as is shown in equation 1.

$$P\ (Ramsay = n) = P(Ramsay\ \geq\ n) - P(Ramsay\ \geq n + 1) \quad (1)$$

To describe the clinical response to midazolam concentrations on the probability of a certain Ramsay score linear models, log linear models, Emax models and a sigmoidal Emax models were tested both direct and indirect (20). Model evaluation was based on objective function value (OFV), parameter precision, shrinkage values and visual predictive checks (VPC). Pharmacodynamic parameter estimates were obtained using the Laplacian estima-

tion method. To evaluate the effect of the midazolam metabolites, 1-hydroxy midazolam (1-OH-M) and 1-hydroxy midazolam glucuronide (1-OH-MG) an additive interaction model (eq 2) was used with equal maximal effect (Emax) for midazolam and the metabolite of interest. In this equation $EC_{50,1}$ $EC_{50,2}$ represent the half maximal effective concentrations of midazolam and the metabolite respectively and $C_1$ and $C_2$ represent the concentrations of midazolam and the particular metabolite.

$$Effect = Emax_{1,2} * \frac{\left(\frac{C_1}{EC_{50,1}} + \frac{C_2}{EC_{50,2}}\right)}{1 + \left(\frac{C_1}{EC_{50,1}} + \frac{C_2}{EC_{50,2}}\right)} \quad (2)$$

*Covariate model development*

Patient characteristics (age and gender), disease characteristics (albumin levels, C-reactive protein levels, estimated glomular filtration rate, and time to death (TTD)), all concomitant medication with sedative effects and the time of day were evaluated as possible covariates in the PD model. Significance of a covariate was evaluated using a forward inclusion, backward elimination method with P-values of 0.05 and 0.001 respectively. Continuous covariates were incorporated using equation 3 and categorical covariates using equation 4. All concomitant medication, with the exception of morphine, was tested as a categorical covariate with the value being 1 if the patients used that type of co-medication on the day of the Ramsay observations. Morphine concentrations as well as the concentrations of the morphine metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) were tested as a continuous covariate. This was possible since the patients in this study were also included in a population pharmacokinetic study on morphine and its metabolites (21). This PK model was used to predict the morphine, M3G and M6G concentrations at the time of the Ramsay observation.

$$Covariate\ effect = 1 - \left(\frac{cov_i}{cov_m}\right)^{\theta_{cov}} \quad (3)$$

$$Covariate\ \ effect = 1 - \theta_{cov}{}^{cov_i} \quad (4)$$

With $cov_i$ being the individual covariate value, $cov_m$ represents the median covariate value and $\theta_{cov}$ the covariate coefficient. In the equation for categorical covariates $cov_i$ is either 1 or 0. The covariate effect that was obtained with this equation was added to the sum of the logits. Because of the transformation used, a negative covariate coefficient described a positive correlation and vice versa. The difference in time between the observation and the recorded time of death was tested as a covariate using equation 3 as well as using a first order equation. In this second equation (eq 5) one theta represents the maximum effect ($\theta_{\Delta}$ and a second theta the rate ($\theta_{rate}$) at which the change takes place, with TTD representing the time to death.

$$Covariate\ \ effect = \theta_{\Delta} * \exp(\theta_{rate} * TTD) \quad (5)$$

*Model evaluation*

The intermediate and final models were evaluated using the objective function value, parameter precision and shrinkage values. As the pharmacodynamic model predicts probabilities rather than actual sedation scores, residual errors could not be calculated and the standard observed versus predicted plots could not be generated. We therefore used visual predictive checks to visually evaluate the goodness of fit.

## RESULTS

A total of 941 Ramsay sedation scores from 43 patients were available, with a median of 14 (IQR 7-30) observations per patient. The number of observations for the Ramsay categories of 1 to 6 were 68 (7.2%), 161 (17.1%), 31 (3.3%), 30 (3.2%), 146 (15.5%) and 505 (53.7%), respectively. Since there were very few data in category three and four these were taken together with category 5. This decision was made as for clinical outcome a score of 3 or more will be sufficient in most cases. For a complete overview of the patient characteristics see table 1.

**Table 1.** Patient characteristics of terminally ill patients receiving midazolam

| Characteristics | N=43 |
|---|---|
| Age, years (median, range) | 71 (43 - 93) |
| Male, *n* (%) | 22 (51.2) |
| Female, *n* (%) | 21 (48.8) |
| Ethnic origin, *n* (%) | |
| Caucasian | 39 (90.7) |
| Afro-Caribbean | 3 (7.0) |
| Unknown | 1 (2.3) |
| Primary diagnosis, *n* (%) | |
| Neoplasm | 42 (97.7) |
| Disease of the respiratory system | 1 (2.3) |
| Daily dose midazolam, mg/day (range) | 2.5 - 180 |
| Blood chemistry, serum levels at admission (median, range) | |
| Albumin, g/l | 24 (13 - 38) |
| eGFR[a], ml/min/1.73 $m^2$ | 69.4 (6 - 328) |
| C-reactive protein, U/l | 128 (1 - 625) |
| Comedication used[b] | |
| Other benzodiazepines[c], *n* (%) | 8 (18.6) |
| Haloperidol, *n* (%) | 18 (41.9) |

| | |
|---|---|
| Levomepromazine, *n* (%) | 2 (4.7) |
| Dexamethasone *n* (%) | 13 (30.2) |
| Anti-epileptic drugs[d], *n* (%) | 3 (7.0) |
| Anti-depressant drugs[e], *n* (%) | 2 (4.7) |
| Morphine, ug/L (median, range) | 41.9 (0 - 609.2) |
| M3G, ug/L (median, range) | 825.9 (0 - 5433.5) |
| M6G, ug/L (median, range) | 119.9 (0 - 826.5) |
| Blood samples collected, *n* (median, range) | 2 (1 – 10) |

eGFR: estimated glomerular filtration rate M3G: morphine-3-glucuronide M6G: morphine-6-glucuronide [a] calculated using the abbreviated MDRD equation [b] during the same day when Ramsay observations were collected [c] Benzodiazepines used included lorazepam, oxazepam and temazepam [d] Antiepileptic drugs used included levetiracetam and pregabaline [e] Antidepressant drugs included only amitriptyline

## Structural model

Sedation in the terminally ill patients, using the Ramsay sedation scores was best described by a differential odds model including a baseline probability, midazolam effect and inter individual variability (IIV). The effect of midazolam on the sedation was best described by a direct Emax response model. IIV was tested on baseline, EC50 and overall effect, where the latter gave the best results. Incorporating more than one IIV in the model resulted in large eigenvalues, indicating over-parameterisation. This resulted in the structural model as shown by equation 6. In this model *n* represents a particular Ramsay score. Per Ramsay score there are different baseline values and EC50 values, but the Emax is the same for all scores.

Implementing the concentrations of the metabolites 1-OH-M and 1-OH-MG did not improve the model. The final structural model resulted in baseline probabilities of 0.23, 0.49, 0.16 and 0.13 for Ramsay scores of 1, 2, 3-5 and 6 respectively and the following EC50 values 30.1 µg/L, 62.8 µg/L and 111.6 µg/L for Ramsay scores of 2, 3-5 and 6. In the structural model the value for IIV on overall effect was 0.81 on the logit scale. Calculating the probability from that it means that 1SD is equal to a probability of 69% (eq 6a and b).

$$logit\ (Ramsay\ \geq n) = Base_n + \frac{Emax - Base_n * CP}{CP + EC50_n} + IIV \qquad (6)$$

$$P\ (Ramsay\ \geq n) = e^{logit} / 1 + e^{logit}$$

## Covariate analysis

The forward inclusion step of the covariate analysis resulted in three significant (P<0.05) covariates. These were age, time of day (night-time vs daytime) and concomitant use of haloperidol. After the backward elimination step only co-medication with haloperidol remained significant (P<0.001). The coefficient for this effect was 1.76. Due to the transformation used (Eq 4) patients who were also treated with haloperidol had a lower probability for the sedation scores 2 or higher compared to patients without haloperidol co-administration. The

Table 2. Covariate effects in univariate analysis compared to the structural model

| Covariate[a] | Parameter value[b] | ΔOFV[c] | ΔIIV[d] | Included after backward elimination |
|---|---|---|---|---|
| Age | -1.67 | -5.776 | - 8.0 % | No |
| Use of haloperidol | 1.76 | -11.975 | + 6.3 % | Yes |
| Day vs Night-time[e] | 0.675 | -4.919 | + 4.1 % | No |

a: Covariates included in the full model after forward inclusion. b:Parameter value, note that due to the transformation used, positive values are negative correlations and vice versa. c: Decrease in objective function value (OFV) after the univariate analysis. d: Decrease in inter individual variability (IIV) after the univariate analysis. e: with daytime being the reference value

coefficients, decrease in OFV and effect on IIV in the univariate analysis of all three covariates are shown in table 2. The final model including the use of haloperidol as a covariate resulted in baseline probabilities of 0.18, 0.48, 0.18 and 0.15 for Ramsay scores 1, 2 3-5 and 6 in patients without haloperidol use and baseline probabilities of 0.33, 0.57, 0.06 and 0.04 for Ramsay scores 1, 2 3-5 and 6 in patients with concomitant use of haloperidol (figure 2). The EC50 values of the final model were the following for all patients with and without haloperidol: 39.5 µg/L, 68.7 µg/L, and 117.1 µg/L for Ramsay scores of 2, 3-5 and 6. Figure 3 shows the probabilities of the different Ramsay scores as a function of the midazolam concentration. From the upper two graphs it can be seen that without the use of haloperidol (fig 3A) the probability of a Ramsay score of 3 or more is 80% at a midazolam concentration of about 50 µg/L, whereas with the concomitant use of haloperidol this concentration is around 80 µg/L. From the bottom left graphs it is clear that at a concentration of 30 µg /L (and no haloperidol co-medication) the probabilities for a Ramsay score of 2, 3-5 and 6 are almost equal. To also show the effect of the high IIV in the model simulations were performed. Figure 4 shows the probabilities of a Ramsay score of 3 or more and the probability of a Ramsay score of 6 with their corresponding 95% confidence intervals. As mentioned before these confidence intervals are large and as a result, the confidence intervals of both scores overlap.

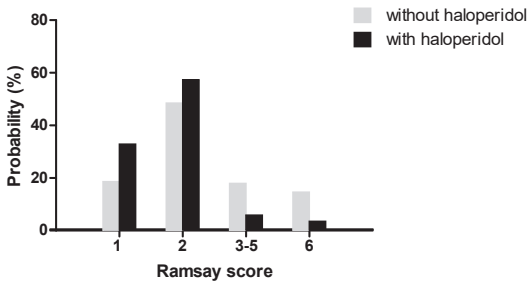


Figure 2. Baseline probabilities for Ramsay scores of 1, 2, 3–5 and 6 without the use haloperidol (black bars) and with concomitant haloperidol use (grey bars).

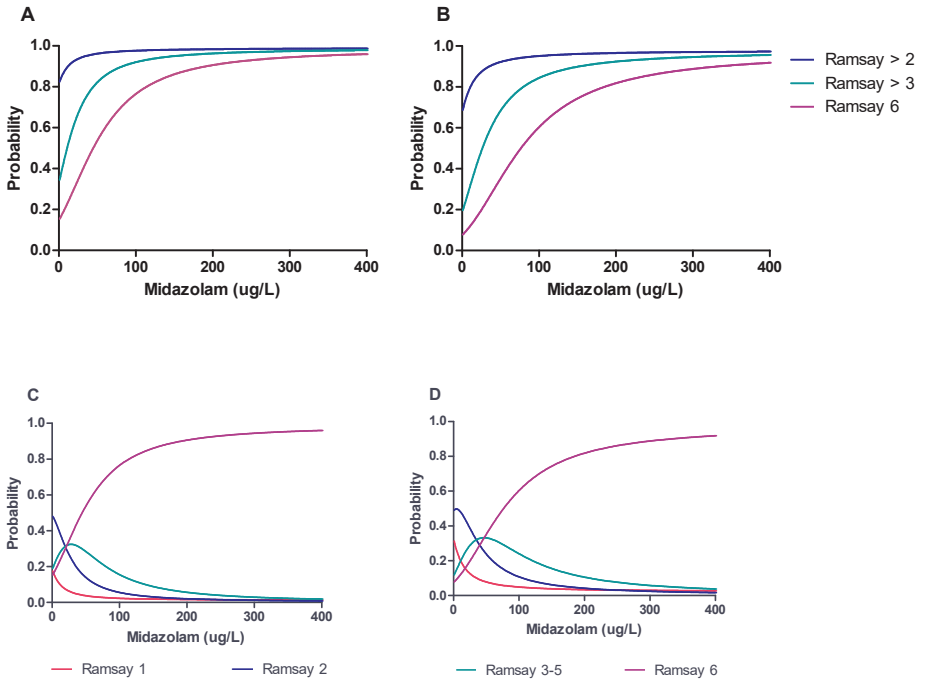


Figure 3. (A) Probabilities of a Ramsay score≥2 (blue) ≥3 (green) and ≥6 (purple) without the use of haloperidol. (B) Probabilities of a Ramsay score≥2 (blue) ≥3 (green) and ≥6 (purple) with concomitant haloperidol use. (C) Probabilities of a Ramsay score of 1 (red), 2 (blue), 3–5(green) and 6 (purple) without the use of haloperidol. (D) Probabilities of a Ramsay score of 1 (red), 2 (blue), 3–5 (green) and 6 (purple) with concomitant haloperidol use.



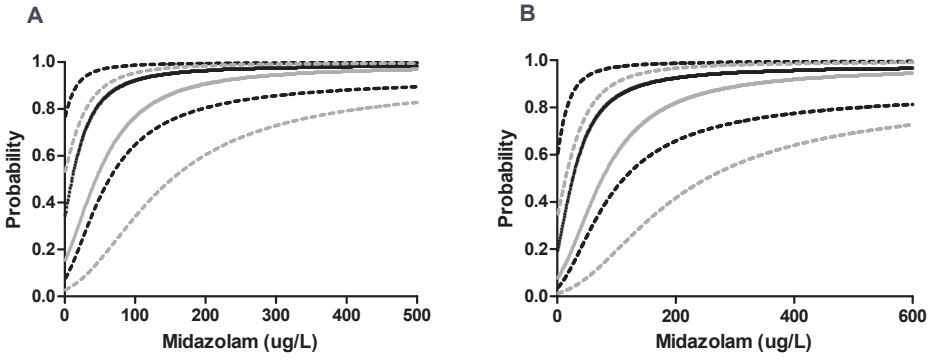


Figure 4. Simulations of the average probabilities and corresponding 95% confidence intervals (dashed lines) of Ramsay score 3 or more (black) and Ramsay score 6 (grey) without the use of haloperidol on the left (A) and with concomitant haloperidol use on the right (B).

## Model evaluation

Of the initial bootstrap of 500 runs just over 70% of the runs resulted in a successful covariance step and were used to calculate the 95 confidence intervals. The median values and 95% confidence intervals of the bootstrap are shown in table 3. The VPC of the final model showed good model predictability with the observations (line) laying within 95% confidence interval of the model predictions (shaded area) for most of the Ramsay scores (figure 5). In the VPC plot it can however also be seen that at midazolam concentrations of around 150 to 350 µg/L, Ramsay scores of 3-5 are somewhat over predicted while Ramsay scores of 6 are somewhat under predicted.

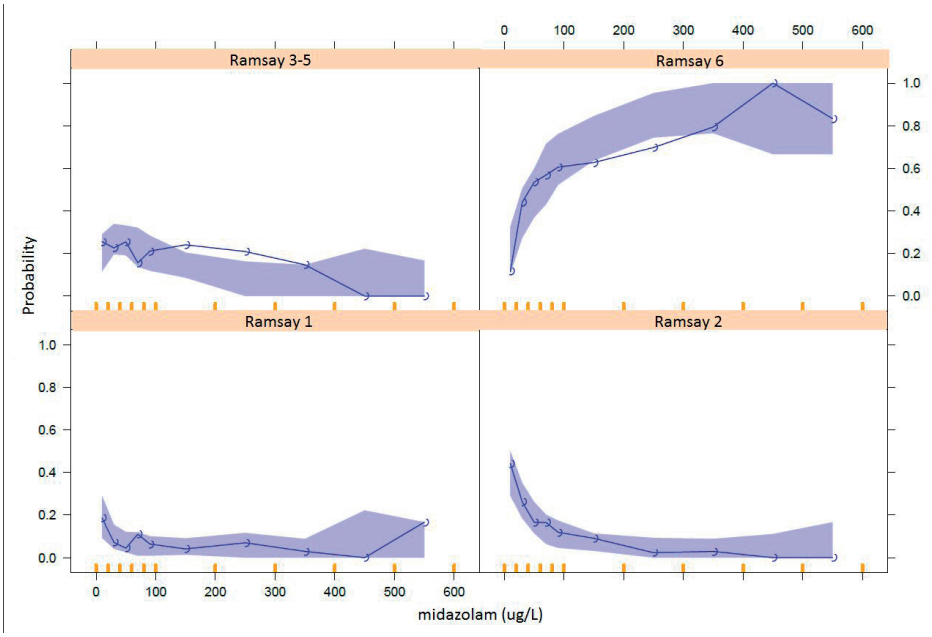


**Figure 5.** Visual predictive check of thefinalmodelforRamsayscoresof1, 2, 3–5 and 6. With the line depicting the observed probabilities and the shaded area the 95% prediction interval of the model. Yellow lines are the concentration intervals.

Table 3. Population pharmacodynamic parameter estimates of the structural and final models

| Parameter | Structural model | Final model | RSE % | Shrinkage % | Bootstrap of the final model | | |
|---|---|---|---|---|---|---|---|
| | | | | | Average | 95% CI (lower) | 95% CI (upper) |
| *Baseline* | | | | | | | |
| B2 | 1.22 | 1.47 | 32 | - | 1.33 | 0.46 | 2.15 |
| B3-5 | -0.91 | -0.72 | 19 | - | -0.81 | -2.53 | 0.98 |
| B6 | -1.93 | -1.76 | 38 | - | -1.83 | -4.58 | 0.59 |
| *Emax model* | | | | | | | |
| Emax | 4.08 | 4.62 | 24 | - | 4.54 | 3.57 | 6.30 |
| $EC50_2$ (ug/L) | 30.1 | 39.5 | 69 | - | 33.4 | 7.1 | 109.3 |
| $EC50_{3\text{-}5}$ (ug/L) | 62.8 | 68.7 | 51 | - | 62.8 | 10.9 | 165.0 |
| $EC50_6$ (ug/L) | 111.6 | 117.1 | 50 | - | 109.4 | 23.6 | 280.0 |
| *Covariate effect* | | | | | | | |
| haloperidol | | 1.76 | 18 | - | 1.74 | 0.88 | 2.41 |
| Inter Individual Variability (IIV) | | | | | | | |
| Overall effect | 0.81 | 0.92 | 29 | 18 | 0.94 | 0.45 | 1.63 |

B*n*: baseline logit for a Ramsay score of *n*. Emax: maximum effect. EC50*n* : concentration at half of the maximum effect for a ramsay score of *n* .

## DISCUSSION

To our knowledge this is the first study to describe the clinical response to midazolam in terminally ill patients with a population pharmacodynamic model. Our study population consisted primarily of patients with cancer, admitted to a hospice, for terminal care in the last phase of life. Others have done pharmacodynamic studies with midazolam in populations of critically ill patients admitted to intensive care units (22, 23). For the lower Ramsay scores the EC50 values found in our study are in accordance with the results of Somma et al who studied the effect of midazolam in patients after heart surgery (22). However, the EC50 value for the highest Ramsay score in our study was less than half of that found in the study of Somma et al (118 µg/L vs 352 µg/L). A possible explanation for this difference may be the different study populations. In our terminally ill patients high doses of morphine were used, which may have increased the sedative effect of midazolam. However as both other studies also had opiates as co-medication a more likely explanation may lay the advanced illness itself. As a consequence of their advanced illness terminally ill patients may be unable to respond thereby causing the overall Ramsay scores to be higher. Furthermore, environmental factors may play a role. A hospice setting offers more tranquillity than a hospital's intensive care unit (with more medical equipment and noises), as described in the study of Somma. A more stressful situation is also one of the arguments Swart and colleague used to explain why their study in IC patients found even higher EC50 values than Somma et al (23).

In contrast to the two previously mentioned studies, we did not only investigate the response to midazolam but also analysed its two major metabolites 1-OH-M and 1-OH-MG. Interestingly neither of these metabolites showed an additive effect, while it is known from the literature that 1-OH-M is about 80% as effective as midazolam and 1-OH-MG has a potency of about 10% (24, 25). The lack of an additive effect can be explained by the fact that 1-OH-M is a formation rate limited metabolite, and therefore closely follows the midazolam concentrations. As a result, it is impossible to separate the effect of these two substances. 1-OH-MG on the other hand is elimination rate limited and it has been shown before that this metabolite can accumulate in patients with renal failure, causing prolonged sedation (26). We did not see an effect of the 1-OH-MG concentrations or renal function on sedation in our study. The lack of an effect may be because the treatment period is relatively short (palliative sedation is usually given for around 48 hours) and the dose low, compared to an ICU setting where the starting dose may be 10 times higher (27). As result, the treatment period may have been too short for any significant accumulation to occur. Furthermore in palliative sedation midazolam is not discontinued, therefore high 1-OH-MG concentrations never occurred in the absence of midazolam concentrations and as the sedation scale has an upper limit an additive effect of 1-OH-MG may not be seen. Furthermore, renal function did not seem to be that severely affected in the population, with only 6% of the patients having an estimated GFR below 30ml/min. Although it should be noted, that estimating GFR in this population is difficult due to the possible low lean body weight and muscle atrophy.

The only covariate that showed a significant effect was the concomitant use of haloperidol. Patients who also used haloperidol had a higher probability of lower Ramsay scores, meaning that they were less likely to be sedated. A possible explanation is that this effect is a result of confounding by indication, as patients receive haloperidol to treat agitation or delirium and deliria has been mentioned to be a risk factor for a difficult sedation process (28, 29). The IIV did not decrease when haloperidol use was incorporated as a covariate. This can be caused by the fact that the use of haloperidol could change within an individual patient over time, and it is therefore not a reflection of the IIV but rather a result of inter occasion variability. Two other covariates, i.e. age and time of day, showed a significant effect in the forward inclusion that did not hold up or stay after the backward elimination. Age was positively correlated with sedation, meaning that elderly patients were more likely to be deeply sedated compared to younger patients. These data are in accordance with a study by Sun, who showed sedation scores after midazolam treatment differed significantly with age (15). However, as the age range of patients in this study is not that large, our patient numbers may have been too small to show a significant effect of age in the backward elimination step. Time of day was also not significant in the backward elimination step. This may be due to the fact that its influence was tested using a fairly basic dichotomous equation, with night-time vs daytime. A previous study by Peeters and colleagues used a more elabo-

rate sinus equation to describe the circadian rhythm (30). As our study had more sparsely collected data this was not feasible in our model. No correlation was found between the sedation level and the time to death, or albumin levels. While we would have expected that if a patients is closer to the time of death (for which low albumin levels are also a marker) they would be more deeply sedated. Incorporating TTD and albumin as a covariate did show a trend (ΔOFV 3.27 for TTD and 3.32 for albumin). However this did not meet the criteria of statistical significance. . To further investigate this more continuous measurements of level of sedation may be helpful as the dying phase is a gradual process. Furthermore, we initially would have expected an effect of morphine (and possibly its metabolites) on sedation levels, however this was not the case (31). This could have been caused by the fact that in 88% of the Ramsay observations the patient also used morphine making the group of data without morphine too small for an adequate comparison. In addition, it is also possible that the sedative effect of morphine may be less prominent in patients who have used it for a prolonged period of time.

This study also a few limitations, firstly the Ramsay sedation score is not validated for terminally ill patients. In addition, the scores are measured only at certain time points thereby making it difficult to evaluate a possible delay in response onset. Due to the limited number of observations shortly after a midazolam dose, we were unable to include an effect compartment and to estimate a first-order effect compartment rate constant ($K_{e0}$). Although midazolam has a rapid onset and we therefore would not expect a great variability in this $K_{e0}$ value, it would be interesting to see if there is any variability on $K_{e0}$ as this would impact the onset of sedation and is therefore of considerable clinical interest. To evaluate this a more continuous PD observation method, like EEG measurements would be needed.

Another limitation in our model is that the Ramsay scores of 3, 4 and 5 were taken together as one category due to the limited data in the 3 and 4 category. This is most likely also a consequences of the lack of observations shortly after a midazolam dose. We also tested a model with all categories separately, which resulted in similar parameter estimates and almost equal EC50 values and baseline probabilities for the scores 3, 4 and 5, as expected due to the low number of observations. This will not affect our results and conclusions. a. The main goal of palliative sedation is to make sure the patient is comfortable and although this is not exactly reflected by the Ramsay score, a score of 2 to 3 or more will be sufficient. The distinction between scores 3-5 and 6 may be relevant from the point of view of the relatives and for side effects.

A third limitation of our study is that individual PK parameters were used from a previously performed PK modelling study, instead of a simultaneous PK PD analysis. This may have led to some overestimation of the IIV in the PD model. Finally, previously performed PD studies on midazolam included a naive pooled analysis to assess the model accuracy (22, 32). We instead used a visual predictive check (VPC) for the model evaluation, which is a newer evaluation method and has the additional benefit that it also shows the amount of

variability in the model. In conclusion, we described the response to midazolam on sedation levels in terminally ill patients using a population pharmacodynamic model with the Ramsay sedation score as outcome variable.

## THERAPEUTIC IMPLICATIONS

As expected, the variability in response was large. We found that the use of haloperidol was correlated with a lower response. This effect is best visualised by figure 4, where the graph in 4a shows that without haloperidol use a typical individual (solid line) will have an 80% chance of a Ramsay score of 3 or mora at midazolam concentration of around 50 µg/L. The graph also shows that due to the large interindividual variability, a concentration of around 200 µg/L would be needed to assure this same chance for 95% of the population (dashed line). The adjacent figure 4b shows that with concomitant haloperidol, the midazolam concentration needed to give a typical patient (solid line) an 80% change of a Ramsay score of 3 or more would be around 80 µg/L. Again to ensure this chance for 95% of the population a much higher concentration would be needed (of approximately 600 µg/L) due to the large IIV (fig dashed line). Of course aiming for the higher midazolam concentrations will also increase the probability of Ramsay score of 6 (grey lines), which may not always be desirable.

Combining these results with our previous knowledge of the pharmacokinetics of midazolam we performed some simulation of dosing regimens for patients with and without the haloperidol as concomitant medication and different albumin levels. The results are shown in table 4 and it can be seen that the loading dose depends on the use of haloperidol and the additional doses on the albumin concentrations. For instance a loading dose of 7,5 mg followed by 2 mg every 4 hours to a patient without haloperidol use and an albumin levels of 25 g/L will on average give an 85% of a Ramsay score of 3 or more (with its 95 CI between 48 and 97 %). This dose is slightly lower than the current guidelines. However aiming for an 80% change of a Ramsay of 3 or more for 95% of the population would result in higher doses than the current guidelines, especially in patients with haloperidol as co-medication. These values may be used as a reference in developing an individualised dosing regimen, which may improve clinical care for these terminally ill patients. However, it should be noted that with increasing the target concentration to ensure an adequate level of sedation for a larger proportion of the population, overdosing in part of the population would occur. It may therefore be advantageous to initially dose with the aim to achieve an 80% chance of an adequate sedation (Ramsay ≥3) for the typical patient and to titrate up according to the clinical response. To achieve an adequate response as soon as possible the dose could be increased if adequate sedation is not yet reached at the time of the additional dose (after 4 hours). For patients without haloperidol increasing the additional dose with 50% with a bolus of 6 mg would ensure that the concentrations at which 95% of the population will

have an 80% chance of adequate sedation will be reached within 12 hours. For patients with haloperidol use, doubling the additional dose (with a maximum increase of 10mg) in combination with an 8mg bolus would ensure these higher concentration within around 16 hours. Figure 6 shows the concentrations time profiles and corresponding probabilities that would be achieved with these dosing regimens. However as the interindividual variability remains high more research remains necessary to further explore possible the underlying causes. Other interests for future study arising from our results, would be a PD study with a continuous observation to investigate variability in onset of sedation and the effect of haloperidol on sedation. A continuous measurement using a Bispectral Index Monitor (BIS) has been tested before in terminally ill patients. However large variability in BIS values for patients with Ramsay scores of 6 were found (18). Although it may give insight in the onset of sedation, BIS values may be more difficult to use for clinical recommendations. The same goes for other continuous PD measurements like saccadic eye movement analysis (33). With haloperidol it would be interesting to investigate if the correlating is due to the effect of deliria or because of a paradoxal response on haloperidol (34, 35). Future research is complicated due to the complexity of the clinical setting in palliative care, such as the process of disease, comorbidities and the lack of validated rating scales. However, more insight is needed and more PK/PD research is needed to improve the care of these patients. Validated PD endpoints are necessary and a focus on relevant questions such as onset of sedation of relief of symptoms is needed.



**Table 4.** Simulated dosing regimens and corresponding probabilities

| | - haloperidol | | | | + haloperidol | | | |
|---|---|---|---|---|---|---|---|---|
| | albumin 15 g/l | | albumin 25 g/L | | albumin 15 g/l | | albumin 25 g/L | |
| Dosing regimen[a] (mg) | 7,5 / 1 | 25 / 4 | 7,5 / 2 | 25 / 7 | 10 / 1.5 | 75 / 12 | 10 / 3 | 75 / 21 |
| Midazolam concentration (ug/L) | 50 | 200 | 60 | 200 | 75 | 600 | 85 | 600 |
| Ramsay ≥ 3<br>Mean (95 CI) (%) | 82 (42-97) | 96<br>(80-99) | 85<br>(48-97) | 96<br>(80-99) | 78<br>(36-96) | 96<br>(81-99) | 81<br>(41-96) | 96<br>(81-99) |
| Ramsay = 6<br>Mean (95 CI) (%) | 54<br>(16-88) | 90<br>(60-98) | 60<br>(19-90) | 90<br>(60-98) | 49<br>(13-86) | 94<br>(73-99) | 54<br>(16-88) | 94<br>(73-99) |

A: dosing regimen in loading dose / additional doses every 4 hours

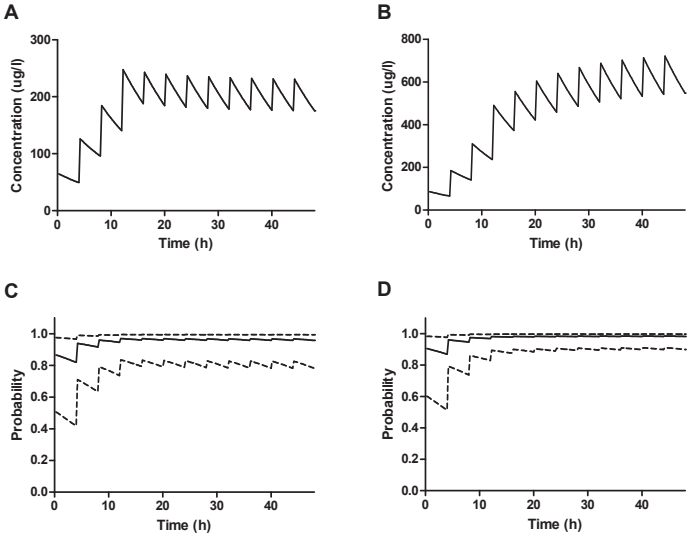


Figure 6. Concentration time profiles and corresponding probabilities (mean: solid line 95% confidence interval: dashed line) of a Ramsay score of 3 or more for a patient without haloperidol and albumin level of 25 g/l (A and C). For this patient a dosing regimen was simulated with an initial loading dose of 7.5 mg loading dose the additional dose of 2 mg every 4 h was increased 3 times with 50% together with a bolus dose of 6 mg to simulate a patient with inadequate response. B and D show the concentrations and probabilities (mean: solid line 95% confidence interval: dashed line) for a patient with haloperidol and albumin levels of 25 g/l. For this patient a dosing regimen was simulated with an initial loading dose of 10 mg loading dose the additional dose of 3 mg every 4 h was doubled 3 times together with a bolus dose of 8 mg to simulate a patient with inadequate response.

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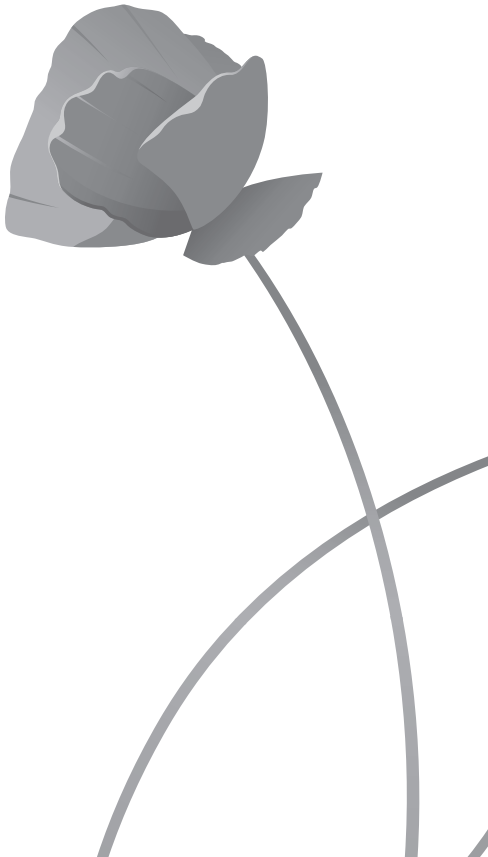

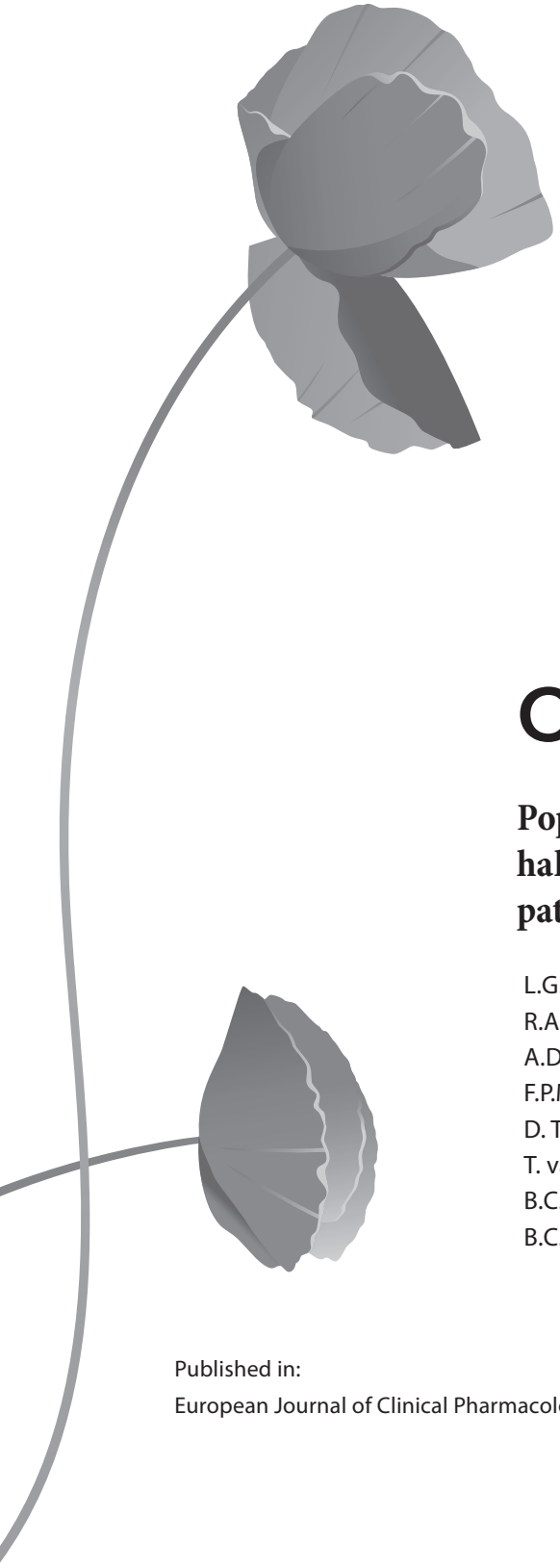

# CHAPTER 7

## Population pharmacokinetics of haloperidol in terminally ill adult patients

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Published in:
European Journal of Clinical Pharmacology 2017; 73: 1271–1277

## ABSTRACT

### Purpose

Over 80% of the terminally ill patients experience delirium in their final days. In the treatment of delirium, haloperidol is the drug of choice. Very little is known about the pharmacokinetics of haloperidol in this patient population. We therefore designed a population pharmacokinetic study to gain more insight into the pharmacokinetics of haloperidol in terminally ill patients and to find clinically relevant covariates that may be used in developing an individualised dosing regimen.

### Methods

Using non-linear mixed effects modelling (NONMEM 7.2), a population pharmacokinetic analysis was conducted with 87 samples from 28 terminally ill patients who received haloperidol either orally or subcutaneously. The covariates analysed were patient and disease characteristics as well as co-medication.

### Results

The data were accurately described by a one compartment model. The population mean estimates for oral bioavailability, clearance and volume of distribution for an average patient were 0.86 (IIV 55%), 29.3 L/h (IIV 43%) and 1260 L (IIV 70%), respectively. This resulted in an average terminal half-life of haloperidol of around 30 h.

### Conclusion

Our study showed that the pharmacokinetics of haloperidol could be adequately described by a one compartment model. The pharmacokinetics in terminally ill patients was comparable to other patients. We were not able to explain the wide variability using covariates.

## INTRODUCTION

In palliative care, (terminal) delirium is a frequently seen symptom with over 80% of the advanced cancer patients experiencing delirium in their final days [1]. Although randomised clinical trials are scarce, most guidelines and specialist consider haloperidol, a typical/classic antipsychotic, to be the first-line treatment of delirium [2–4]. Haloperidol is metabolised by several different pathways, involving cytochrome P450 (CYP), carbonyl-reductase and uridine diphosphoglucose glucuronosyltransferases (UGT) enzymes. Glucuronidation appears to be the major metabolic route followed by the reversible reduction of haloperidol to reduced haloperidol and CYP-mediated oxidation by CYP3A and CYP2D6.

The dose of haloperidol is determined based on the clinical effect. As haloperidol can cause motor (or extrapyramidal) and cardiovascular adverse/side effects, it is normally started at a low dose (0.5–2.0 mg) and increased slowly until the desired effect is reached. This can be disadvantageous in the case of refractory symptoms when rapid symptom relief is required. In addition, haloperidol has a relative long terminal half-life (t1/2) of approximately 20 h causing steady state to be reached after 4 to 5 days. Patients could therefore potentially benefit if an individualised dose is determined beforehand. In palliative patients, this is even more important, as rapid symptom relief is essential in the last phase of life.

Several studies on the pharmacokinetics of haloperidol in healthy volunteers or psychiatric patients showed large interindividual variability (IIV) [5–11]. As haloperidol has a moderate hepatic extraction ratio of 0.3–0.7, its metabolism may be influenced by hepatic blood flow as well as intrinsic enzyme activity and protein binding [7, 12, and 13]. Therefore, the IIV in palliative care patients may be even more pronounced as these patients may suffer from decreased blood flow, altered plasma protein levels and possibly hepatic dysfunction [14]. We performed a population pharmacokinetic study in terminally ill patients to gain more insight into the pharmacokinetics in this population and to find clinically relevant parameters for dose individualisation.



## METHODS

The study was performed in accordance with the principles of the Declaration of Helsinki and its later amendments. Ethical approval was obtained from the Medical Ethics Committee of the Erasmus University Medical Centre, Rotterdam, and all patients provided written informed consent.

### Data

Data was collected in the palliative care centre, Laurens Cadenza Zuid in Rotterdam, The Netherlands, during 2 years. Patients were eligible if they had a terminal illness, survival

prognosis of more than 2 days and less than 3 months and administration of haloperidol. Informed consent was asked shortly after admittance to the palliative care centre, and included patient were followed until the time of death, unless informed consent was withdrawn at any point. Only patients who can give their consent themselves were asked for consent. The patients gave consent after contacting their family about the study. The partner/legal representative co-signed the informed consent form as witness of the consent. The investigator kept close contact with the patients and their family during the study. In the terminal phase, when the patient cannot be asked anymore, all aspects of the study were communicated with the family.

Haloperidol was given to treat deliria and was dosed in accordance with the current guidelines [4]. Haloperidol was administered orally (either as tablets or as a liquid formulation) or via subcutaneous bolus injection. The exact times of administration were recorded in the patient record. Any concomitant medication was also registered in the patient's record. Demographic characteristics (age, gender, weight, race, primary diagnosis and time of death) were extracted from the electronic medical records.

**Blood sampling and assay**

Blood samples were collected randomly via sparse sampling in both the pre-terminal and terminal phases on average at one to two occasions during the day, with a maximum of ten a week, 0.5 to 1 mL of blood. The moment of sampling is not strictly defined, but follows the clinical condition of the patient. For example, before and after the change to another administration route or in case of inadequate effect of a drug, blood will be sampled. Blood for clinical chemistry is routinely sampled by venous puncture. For this study, sampling is as much as possible combined with those venous punctures. Otherwise, sampling from an indwelling venous catheters is preferred. With the terminal phase being the last hours or days before death, a patient becomes bedbound, semi-comatose, and is not able to take more than sips of fluid [15]. During the terminal phase, blood is sampled only from an indwelling venous catheter. This method prevents repeated puncturing and causes minimal or no discomfort to the patient. The samples were centrifuged after which the plasma was collected and stored at −80 °C until analysis. The blood samples were preferably collected at the same time as sampling for clinical chemistry (standard of care). In the clinical chemistry samples, serum levels of albumin, creatinine, urea, bilirubin, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST) and C-reactive protein (CRP) were determined.

Haloperidol concentrations were analysed in the plasma samples using LC-MS/MS with electrospray ionisation in the positive ionisation mode on a Shimadzu LC-30 (Nishinokyo-Kuwabaracho, Japan) system coupled to an AB Sciex (Framingham, MA, USA) API5500Q MS. Seventy-five microliters of acetonitrile/methanol 84:16 (v/v%) containing the internal standard haloperidol-d4 was added to 10 µL of patient's plasma to precipitate proteins.

Afterwards, samples were vortexed and stored at −20 °C for 30 min to optimise protein precipitation, vortexed again and centrifuged. A three microliter sample was injected onto a Thermo Scientific Hypersil Gold (50 × 2.1 mm, 1.9 µm) column. A stepwise chromatographic gradient was applied using 0.05% ammonium formate/0.10%formic acid in water as mobile phase A and acetonitrile as mobile phase B. The flow rate was 0.4 mL/min and the column was kept at 40 °C. Using multiple reaction monitoring (MRM) with positive ionisation mode, haloperidol was measured as [M + H]+ using the mass transition 376.1/ 165.1. The lower limit of quantification was 0.5 µg/L and the method was validated over a range of 0.5–125 µg/L. The accuracies ranged from 93.5 to 107.4%.

## Software

Pharmacokinetic analysis was conducted by the NONMEM® Version 7.2 (ICON Development Solutions, Ellicott City, MD), PsN® (version 4.4.8), R (version 3.3.0) and Pirana (version 2.9.2).

## Population pharmacokinetic method

*Model development*

Log-transformed plasma haloperidol concentrations were used and the bioavailability of subcutaneous haloperidol was assumed to be 100% [16]. One-compartment and two compartment models were tested for haloperidol using the first-order conditional estimation method with interaction (FOCE + I). To account for the two different administration routes (oral and subcutaneously), the ADVAN5 subroutine was used. Interindividual variability (IIV) was assessed on each parameter using an exponential model. Residual variability was included as a combined error model.

As weight has been shown to be a covariate in other haloperidol pharmacokinetic models, and as the relationship between body weight and clearance is well documented, this effect was tested using algometric scaling [11, 17]. In the covariate analysis, demographic and disease characteristics including weight, age, gender, primary diagnosis, renal function (plasma creatinine and plasma urea), hepatic function (plasma levels of bilirubin, GGT, ALP, ALT and AST), Creative protein (CRP), albumin and the concomitant use of

CYP2D6 and CYP3A inductors and inhibitors were evaluated for their influence on clearance (CL), volume of distribution (Vd) and bioavailability (F). Time to death (TTD) was also evaluated as a covariate. This parameter cannot be used as a covariate parameter for a priori prediction of individual pharmacokinetic changes but it may give insight into quantitative changes at the end of life that are not predicted by standard blood chemistry tests. The relationship between covariates and individual estimates was first investigated graphically and was further tested with a forward inclusion, backward elimination approach with P values of 0.05 and 0.001, respectively.

Continuous covariates were normalised to the population median values and incorporated as power model functions (Eq. 1). Categorical covariates were transformed to binary covariates and incorporated as shown in Eq. 2. with θi being the individual model predicted pharmacokinetic parameter (e.g. clearance) for an individual with covariate value covi, θpop being the population estimate for that parameter, covm representing the median covariate value and $\theta_{cov}$ the covariate effect. In the equation, for categorical covariates, covi is either 1 or 0.

$$\theta_i = \theta_{pop} * \left(\frac{cov_i}{cov_m}\right)^{\theta cov} \quad (1)$$

$$\theta_i = \theta_{pop} * \theta_{cov}{}^{cov_i} \quad (2)$$

To evaluate the time to death (TTD) as a covariate, time dependency of the parameters was modelled as a first-order process given to following equation (Eq. 3). In which θΔ is the change in parameter value from its initial value and θrate is a first-order rate constant determining the rate with which the parameter value changes over time.

$$\theta_i = \theta_{pop} - \theta_{\Delta} * \exp(-\theta_{rate} * TTD) \quad (3)$$

*Model evaluation*

Intermediate models were evaluated based on minimum OFV parameter precision, error estimates, shrinkage values and visual inspection of the goodness of fit plots. A bootstrap with 500 runs was performed on the final model to evaluate the validity of the parameters estimates and their corresponding 95% percentile ranges. The final model was evaluated with a normalised prediction distribution error (NPDE) analysis. NPDE is a simulation-based diagnostics which can be used to evaluate models developed on datasets with variable dosing regimens. The analytical value of this method has been previously described by Comets et al. [18].

*Simulations*

To give an illustration of the effect of dose on the plasma concentrations of haloperidol and the variability, deterministic simulations were performed. The haloperidol plasma concentrations were simulated over a time course of 72 h in which six subcutaneous doses were administered every 12 h. To show the interpatient variability, the mean and 90% confidence interval are shown graphically.

## RESULTS

A total of 28 terminally ill patients were included in the study. Their median age was 69.5 years (range 43–93), 54% were male and all patients had advanced malignancy as primary diagnosis with the majority (87%) having epithelial tissue as the primary malignant site. On average at one to two occasions during the day, with a maximum of ten a week, 0.5 to 1 mL of blood was collected from the patient by vena puncture or indwelling venous catheter to determine drug concentrations.

An overview of all patient characteristics is given in Table 1. Oral doses of haloperidol ranged from 0.5 to 2 mg a day and subcutaneous doses ranged from 0.5 to 5 mg a day. A total of 86 blood samples were collected. 26.7% of the concentrations were below the quantification limit (BQL). On closer inspection, half of these plasma concentrations were measured in samples taken over 200 h after the last haloperidol dose. Discarding these resulted in 14.6% BQL data left within 200 h after the last dose. As this is still more than 10%, the M3 method of handling BQL data was used to estimate if BQL data were indeed below the lower limit of quantification of 0.5 mg/L [19, 20]. As this resulted in similar parameter estimates but stability issues, the M1 method (of discarding the BQL data) was used for the final model.

### Structural model

The data were best described by a one-compartment model with an additive residual error on logarithmic transformed concentrations. Since there was limited data available in the absorption phase, the absorption constants (Ka) could not be estimated. We therefore derived this value from literature, and as there was no literature available for the absorption time of subcutaneous injection of the iv formulation, intramuscular administration was used as a reference [21]. Changing this assumption to half of the absorption rate did not affect the other parameters, which indicates that the model is stable and not influenced by this assumption. IIV was included on the parameters CL, F and Vd. As the IIV on CL and F showed a high degree of correlations (99%), these were fixed to unity with the addition of an extra theta.

### Covariate analysis

Allometric scaling was tested both with an estimated scaling factor for CL and Vd as well as fixed scaling factors of 0.75 and 1, respectively (Eq. (4)). As the values of 0.75 and 1 lay within the 95 confidence intervals of the estimated scaling factors, and because estimating the scaling factors did not significantly improve the model fit, fixed values of 0.75 and 1 were used. Including allometric scaling significantly improved the model fit (ΔOFV 7.47, $P < 0.05$) and decreased the IIV on Vd with 13%. If the weight of an individual was unknown,

the median weight of the population (67 kg) was imputed. This was the case for 35% of the study population.

$$\theta_i = \theta_{pop} * \left(\frac{WGT_i}{WGT_{median}}\right)^{scaling\ factor} \quad (4)$$

Besides bodyweight, plasma bilirubin concentration was significant on the volume of distribution in the forward inclusion. This resulted in statistically significant improvement of the model fit, with a drop in objective function value (OFV) of 7.22 points and a decrease in IIV on Vd from 61 to 43.2%, thereby explaining 31% of the IIV on Vd. Both parameters were not significant in the backward elimination. After inspecting the individual influence on the decrease in OFV using sharkplots, it was shown that for both covariates, there were two very influencing individuals, with just one individual being responsible for reaching the statistical significance. Bodyweight and plasma bilirubin were therefore not included in the final model. An overview of all parameter estimates is given in Table 2.

## Model evaluation

Figure 1a, b shows that both the population predictions and individual predictions were evenly distributed around the line of unity when plotted against the observations. A bootstrap analysis of the final model was performed to obtain 95% percentile ranges for all parameters. Results of the bootstrap are shown in Table 2. Evaluation of the predictive performance by NPDE analysis showed accurate predictive ability, with the distribution of the NPDEs not significantly deviating from a normal distribution (with a global adjusted P values of 0.4), and the majority of the NPDEs laying between the values −2 and 2 (Fig. 1c).

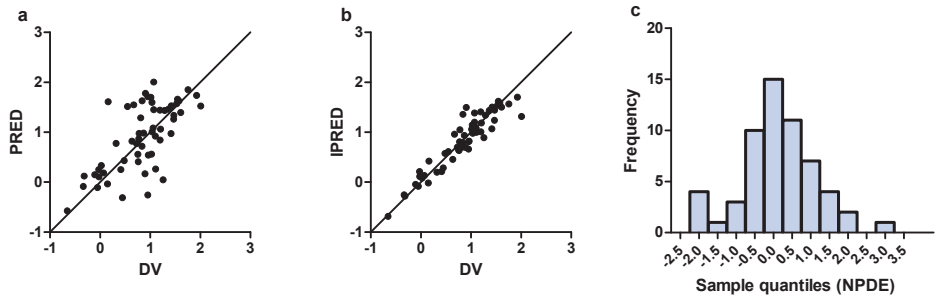


Figure 1. Goodness of fit plots of the final model. Population predictions (PRED) versus observations of haloperidol (a), individual predictions (IPRED) versus observations of haloperidol (b) and the normalised prediction distribution error (NPDE) distribution plot (c) for of the final model showing NPDE quantiles.

### Simulations

The effect of 0.5 mg of subcutaneously administered haloperidol every 12 h is shown in Fig. 2. The plasma concentration is very variable between patients.

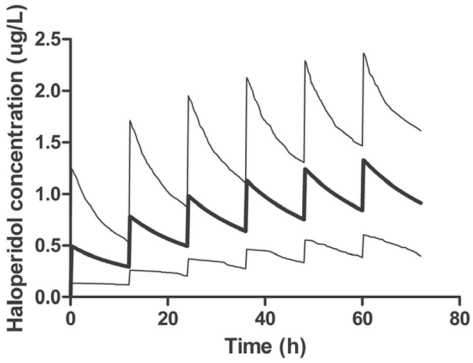


**Figure 2.** Simulated plasma profiles of haloperidol 0.5 mg every 12 h. The mean concentration and 90% confidence interval are presented from a simulation of 1000 patients.

## DISCUSSION

To our knowledge, this is the first population pharmacokinetic study of haloperidol in terminally ill adult patients. We were able to describe the pharmacokinetics of haloperidol with adequate accuracy using a sparse sampling method. The simulations show the high interpatient variability in the pharmacokinetics and the effect of the long terminal half-life of haloperidol. The t1/2 of around 30 h from our study means it would take a long time to reach steady-state levels and it would take about 6 days to completely eliminate a single haloperidol dose from the body.

The covariate analysis did not result in any significant covariates. Initially, body weight and plasma bilirubin levels seemed to be correlated; however, as this was mainly due to influence of one or two individuals, these were not included as a covariate in the final model. Body weight was shown to be correlated in other studies [11, 17]. In our study, body weight was not registered for all patients and can vary a lot in the terminal phase, which might explain the lack of this correlation in this group of patients. It does not seem likely that hepatic dysfunction is correlated with the volume of distribution. A correlation with clearance seems more logical as haloperidol has a moderate hepatic extraction ratio of 0.3–0.7. The fact that none of the hepatic markers showed a correlation with clearance may be because of the limited data in our study or because of the fact that the liver has a high over capacity for metabolising drugs. Furthermore, the fact that none of the co-medication showed a correlation with clearance may also be due to the low number of patients using concomitant medication at the time of haloperidol use. This is common in the palliative population as the majority of medication is discontinued in the palliative phase. In addition, a lack of effect of

co-medication may have been expected as there are several different metabolic pathways involved in the metabolism of haloperidol; therefore, co-medication that affects only one of these routes will most likely have no effect on the overall clearance of haloperidol.

There have been previous studies in patients with schizophrenia which showed estimates for clearance which were 1.5 to more than 2 times higher than the 29.3 L/h found in our study, when corrected for bioavailability of 86% [10, 11]. However, as both studies also reported higher estimates for the total volume of distribution, these together result in t1/2 values of 25 and 39.5 h which is comparable to the t1/2 of 30 h found in our study. It seems reasonable that terminally ill patients have a lower clearance and a lower volume of distribution compared to schizophrenia patients, who on average are younger and are less physically ill. Another difference with the study by Pilla Redy et al. is that they found haloperidol to be best described by a two-compartment model. This can possibly be explained by the fact that in our study, we had more sparse data and were therefore unable to accurately describe a peripheral compartment and inter-compartmental clearance. This is supported by the fact that their study had over 500 samples which still resulted in a broad 95% CI for the peripheral volume of distribution.

Both studies had weight incorporated in their final model. Unfortunately, one of the limitations of this study is that for about one third of the patients, the weight was unknown, and in fact, if the weight was known, this was a single value reflecting the weight at admission rather than several measurements over the study period. One of the reasons for the lack of data on weight is that almost none of the drugs given in the hospice setting were based on the patient's weight, and therefore, it was unnecessary for clinical practice to collect data on weight. Another reason is that doctors and nurses were reluctant to weigh patients as it could be disturbing for the patient to be faced with their weight loss. There are several ways to handle missing covariate data in population pharmacokinetic analysis [22]. We tried to incorporate these methods in our model. However, as we did not find a correlation between weight and any of the other known covariates, a method to handle missing data was not feasible. We also tested a model with different population values or IIV values for known and unknown weights. This did not result in significant improvements and resulted in large shrinkage values and model instability due to the already sparse sample numbers, and it was therefore not feasible to use in the final model.

Probably, the most important limitation, in general, is the fact that an effective plasma concentration of haloperidol is still unknown. The study of Pilla Redy et al. showed that the overall EC50 value was 2.7 mg/L on an overall scale of schizophrenia, with considerably lower effective concentrations for the positive symptoms (0.5 mg/L) than the negative symptoms (31 mg/L). When we look at deliria, this may show more similarities with the positive symptoms of schizophrenia than the negative. However, the underlying cause in the case of (terminal) deliria is completely different, making it difficult to give any target concentrations for haloperidol in terminally ill population. Reference values of haloperidol

are only based on schizophrenia dosing and more studies on delirium and PK/PD of haloperidol are needed.

Overall, this study showed that it is possible to describe the pharmacokinetics of haloperidol with adequate accuracy in terminally ill patients. We were not able to explain the variability in the pharmacokinetics using covariates. Before any recommendations can be made, more research is necessary, especially to the pharmacodynamic effects of haloperidol in this population as well as the possible effect of liver failure. The current Dutch guidelines recommends a dose of 0.5–2mg subcutaneously every half an hour until an adequate effect is reached. Looking at the simulated plasma profiles in our study and keeping in mind the lack of any known effective dose, this seems a very reasonable recommendation, as the absorption constant of haloperidol is fast. The effect can probably be adequately assessed after half an hour and titrating up. Too fast dosing may result in adverse events that would take a long time to wear off due to the long terminal half-life.

In conclusion, this study describes the pharmacokinetics of haloperidol with adequate accuracy in terminally ill patients. More information on pharmacodynamics are needed to optimise dosing regimens of haloperidol in this patient group

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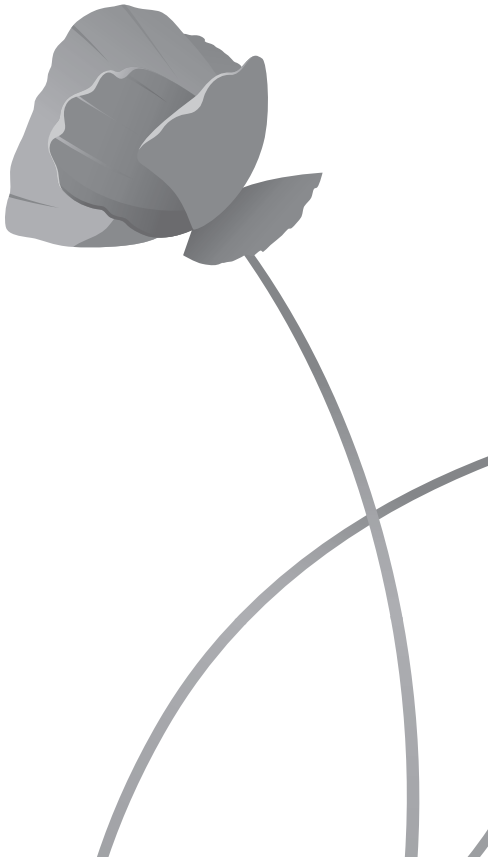

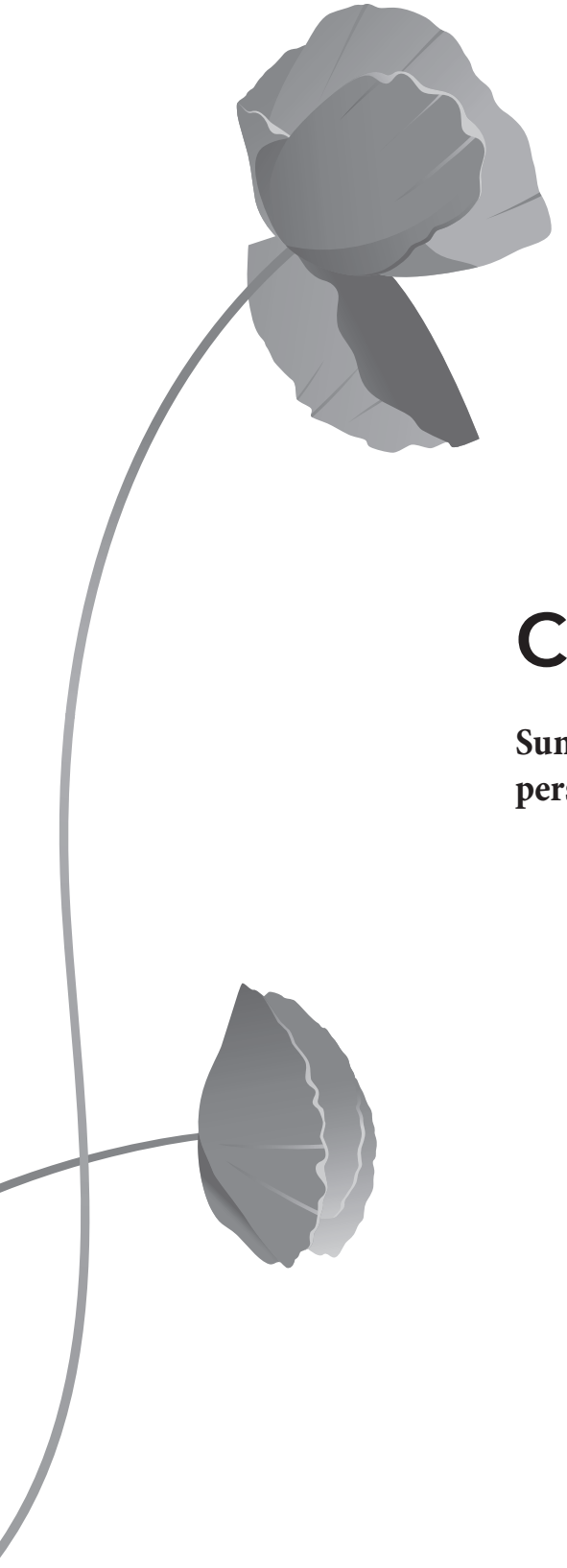

# CHAPTER 8

## Summary, discussion and future perspectives

## SUMMARY AND DISCUSSION

In the Netherlands, every year around 108.500 terminally ill patients will receive some form of palliative care [1]. With palliative care (gradually) replacing curative therapy the focus will shift form curation to symptom management in order to improve the quality of life for these patients. Adequate symptom control is crucial as the symptoms that occur in the final year of life (like fatigue, pain and dyspnoea) can cause severe distress [2]. Relieving distress form these symptoms be achieved by treating the underlying cause or trigger, by symptomatic treatment (both with and without medication) and with supportive care. However, in some cases symptoms remain uncontrolled, in that case palliative sedation can be initiated to relieve distress by reducing consciousness. Previous research on the efficacy and safety of palliative sedation however showed that it can take up to 48 hours until adequate sedation is reached and in 17% of the cases symptoms remain uncontrolled [3]. As these patients are in severe distress it is of the greatest importance to improve these numbers. This high variability in response may be caused by the fact that the terminally ill population is very heterogeneous, with differences in co-morbidities, concomitant medication and disease severity. These differences can influence both pharmacokinetic (PK) and pharmacodynamic (PD) process. Which can result in variability in response between patients as well as within a single patient over time. The current guidelines on symptom management in palliative care however lack individualised dosing recommendations. Instead doses are often titrated according to their clinical effect. Such dose adjustments however take time and this is unwanted in the case of severe distress and a limited life expectancy. In order to improve clinical care for these patients, individualised dosing regimens should be developed. A first step in this process is to expand our knowledge on pharmacokinetics and pharmacodynamics in terminally ill patients which we have done with the research presented in this thesis.

In the first chapter, we explored the different factors that could affect drug efficiency and safety in palliative care patients. In this review, we focused mainly on how the pathophysiological changes at the end of life, could affect drug concentrations. Looking at the four main processes in pharmacokinetics (i.e. absorption, distribution, metabolism and elimination) we found that terminal illnesses may influence each of these processes substantially. The whole process however is complex and the eventual impact on drug concentrations can differ both between patients (depending on their symptoms) and between drugs (depending on their chemical properties). It is therefore impossible to give a "one size fits all" recommendation and dosing strategies will have to be evaluated on a case by case basis. To provide the prescribers with more guidance we made recommendations on the three most prescribed drugs in palliative care, i.e. morphine, midazolam and haloperidol. However as pharmacokinetic studies in terminally ill patients are very limited these recommendations remained partly theoretical.

Another factor, besides pathophysiological changes, that may alter the efficacy and safety of drugs are drug-drug interactions. As terminally ill patients often suffer from several co-morbidities and may use multiple drugs for symptom management polypharmacy is common. As know from other studies that this increases the risk of (serious) drug-drug interactions, we evaluated this risk in the palliative population in chapter two [4]. In the study presented here we did not solely evaluated the amount of drug-drug interactions but also focused on the clinical relevance of the interactions. As clinical relevance may be different in a palliative care setting compared to a general hospital (with less focus on the interactions that can cause damage in the long term), the relevance was assessed by an expert team instead of an automated scoring system. Our study showed that drug-drug interactions occurred in a third of the population and half of these interactions were regarded as clinically relevant. We also found that the number of drugs used by a patient was a potential risk factor of drug-drug interactions (adjusted OR = 1.50, 95% CI = 1.24 – 1.82). Although not all interaction are clinically relevant in a palliative care setting, certain drug-drug interactions may still have serious consequences. As the number of drugs is a potential risk factor of interactions, unnecessary drugs should be stopped in the palliative setting.

As both pathophysiological changes and co-medication can cause alteration in drug concentration, we performed three population pharmacokinetic studies on morphine, midazolam and haloperidol. The use of population pharmacokinetics has three important advantages. Firstly, this method makes it possible to study pharmacokinetic parameters with only sparse sampling. This minimizes the burden for patients which is important in this fragile population. Secondly it allows us to not only estimate the average values for the pharmacokinetic parameters like clearance volume of distribution etc. but it also makes it possible to quantify the variability. Several covariates can be tested (e.g. disease characteristics and co-medication) to examine their influence on the pharmacokinetic parameters. Based on these results, the amount of variability can be decreased by taking these covariates into account. Finally, population pharmacokinetic modelling enables us to evaluate new dosing regimens by simulating concentration time curves for different circumstances, using the covariate effects found.

In chapter 3 the population pharmacokinetic study on morphine in terminally ill patients is described. Morphine is used by over 80% of the terminally ill patients in the last days of life and is dosed according to the clinical response. Assessing pain may however be challenging in the final days of life when patients are unresponsive due to advanced illness or palliative sedation. In our study, we did not only look at the concentrations of morphine but also included the two major metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in our analysis, as literature data support that they are active metabolites. The M6G metabolite has been shown to have analgesic properties [5-7]. While M3G on the other hand is being linked to the side effects seen with morphine use [8, 9]. Our study confirms the results of previous studies by showing that clearance of M3G and M6G is

reduced in patients with decreased renal function [10, 11]. Our study also showed that low albumin levels were also associated with decreased clearance of the glucuronide metabolites. This may be due to the fact that hypoalbuminemia can be caused by a catabolic state or cachexia, and that in these severely ill patients eGFR is overestimated. Finally, this study revealed that morphine clearance decreases as a patient is closer to the time of death. This is an interesting finding that indicates that there may be another factor that is influencing the pharmacokinetics that is not detected with standard blood chemistry analysis. This may for instance be due to reduced liver blood flow.

The current guideline on pain management mentions the fact that in the case of renal dysfunction (stated as an eGFR < 50 ml/min) morphine metabolites can accumulate. Based on the results from our study we hypothesize that it would be better to not only take eGFR as a measurement for renal function but to also include albumin levels as a risk factor for metabolite accumulation. It is however important to note that creatinine and albumin are not routinely measured in terminally ill patients, as this is seen as an unnecessary burden for the patient. These values may therefore be unknown and since morphine clearance reduces when a patient is closer to its time of death (which may also be difficult to predict) the eventual balance between morphine and metabolite concentrations may be difficult to predict. The current guideline does discriminate between the different opioids and morphine remains the most commonly used opioid probably due to physician preferences. However, given the outcome of our study, drugs without active metabolites, like fentanyl or oxycodone, should perhaps have a more prominent role in the treatment of pain in terminally ill patients.

The fourth chapter of this theses describes the pharmacokinetics of midazolam. As mentioned before there is a high degree of variability in response to midazolam [12, 13]. Currently it is dosed according to clinical response, this is however disadvantageous in the case of refractory symptoms as it may take a long time to achieve adequate relief [3]. As in the study of morphine, with this study we also incorporated the active metabolites of midazolam i.e. 1-OH-midazolam (1-OH-M) and 1-OH-midazolam glucuronide (1-OH-MG) in our model. Similar to M3G and M6G the clearance of the glucuronide metabolite of midazolam was shown to be decreased in patients with renal dysfunction, which is in accordance with previous research [10]. In this study, we also found an effect of albumin on the pharmacokinetics, however not on the clearance of the glucuronidated metabolite but on midazolam itself. This is an interesting finding as low albumin levels were associated with decreased midazolam clearance. A possible explanation for this effect may be that hypoalbuminemia is related to an inflammatory response or catabolic state, which may result in a decreased activity of CYP3A, as seen in other studies [14, 15]. In the current guideline for palliative sedation hypoalbuminemia and renal dysfunction are already mentioned as risk factors for overdosing, as well as body weight of less than 60kg and hepatic impairment. In the case of any of these risk factors the guideline recommends a lower starting dose (0.5 to 1.5 mg/

hour instead of 1.5-2.5 mg/hour) and a longer interval before the dose should be increased in the case of no effect (6-8 hours instead of at least 4 hours). Using our pharmacokinetic model, we simulated the plasma concentration that would be achieved with these dosing recommendations.

In figure 1 the top row shows the total effective concentration (calculated as the midazolam concentrations plus 0.8 times the 1-OH-M concentration and 0.1 times the 1-OH-MG concentration) achieved by following the current guidelines for a patient with normal eGFR and albumin levels (albumin of 35 g/l and eGFR of 90 ml/min) in black as well as for a patient with decreased albumin levels (25g/L in dark blue and 15g/L in light blue) and for a patient with decreased renal function (eGFR of 50ml/min in dark green, 30 ml/min in medium green and 10 ml/min in light green). As the current guideline advises a 10mg starting dose followed by either 1.5 or 2.5 mg per hour via continuous infusion (with the ability to increase the dose with 50% after 4 hours combined with a 5mg bolus injection), we simulated concentrations for both the lower and upper range of this recommendation. The graph on the left depicts the lower range of the recommendations and the graph on the right the upper range. It can be seen that in a patient without low albumin or decreased renal function the concentration increases much faster (shown by the steep increase of the black curve) than for patients with low albumin or decreased renal function. To improve this, we suggest to only reduce the dose but not increase the dosing interval. Simulation of this recommendation are shown in the lower to graphs and it can be seen that this results in

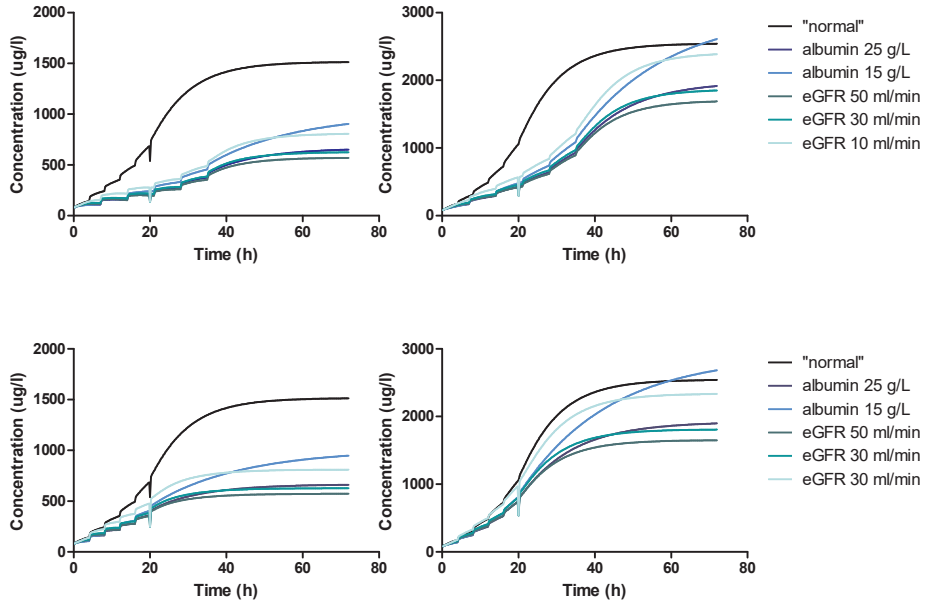


Figure 1. Simulated concentration time profiles of the current guideline (top row), and suggested individualised dosing regimens for patients with different albumin levels and renal function.

a similarly steep increase in concentrations for patients with low albumin or reduced renal function compared to a "normal" patient.

Since dosing recommendations cannot be made solely on pharmacokinetic data we also performed a study on the pharmacodynamics of midazolam, shown in chapter 4. In this study, the inter-individual variability of response to midazolam was high, with a wide range of sedation scores occurring at the same midazolam concentrations. Therefore, dose titration according to response seems logical. However, dose titration takes time and symptom relief is required as soon as possible in the case refractory symptoms. It would therefore be very useful if there was a way to identify patients who are at risk for under-dosing. Our results showed that co-medication with haloperidol was associated with a less sedative states. This is probably an effect of the delirium for which haloperidol is used. The current guideline on palliative sedation only gives risk factors for overdosing (e.g. age > 60, and the use of co-medication with sedative effects). It therefore does not mention delirium as an indication to increase midazolam dose. In fact, according to this guideline patients with haloperidol may even be given a lower dose than normal since haloperidol can be considered a drug with sedative effects. We therefore propose that patients with haloperidol, or agitated delirium should receive a higher dose of midazolam.

The population pharmacodynamic model showed that a midazolam concentration of 50 µg/L would give the typical patient without haloperidol use an 80% chance of adequate sedation, however as there is large inter-individual variability a target concentration of 200 µg/L would be required to give 95% of the patients without haloperidol co-medication an 80% chance of adequate sedation. With haloperidol as co-medication the target levels for the typical patient and 95% of the population would be even higher (80 µg/L and 600 µg/L respectively).

Combining this with the knowledge of our PK model we performed some simulations of different dosing regimens. First we simulated a dosing regimen with the aim of achieving an 80% chance of adequate sedation (given by a Ramsay score of 3 or more) for 95% of the population. The results of this can be seen in figure 2. The far-right graph shows that a loading dose of 25 mg followed by a 10mg dose every 4 hours should result in an average plasma concentration of 200 µg/L for a patient with a plasma albumin level of 35 g/L. The middle and right graphs show that average plasma concentrations of 200 µg/L are reached by administering the same loading dose followed by 7 mg and 4 mg every 4 hours in the case of respective albumin levels of 25g/L and 15 g/L. To achieve a target concentrations of 600 µg/L the dose would have to be tripled. Meaning a loading dose of 75 mg followed by 30 mg every 4 hours for an albumin level of 35 g/L and 21mg and 12mg every 4 hours in the case of an albumin level of 25 or 15g/L respectively.

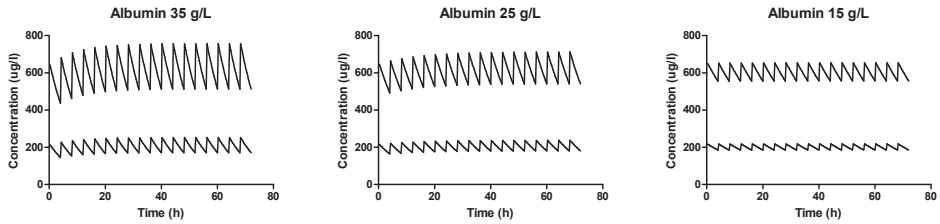


Figure 2. Simulated concentration time profiles of dosing regimens adjusted to plasma albumin levels.

Compared to the current guidelines, these dosing regimens are much higher, especially in the case of haloperidol co-medication. It should also be noted that by setting the target level for 95% of the population, a large part of the population will be overdosed. It may therefore be more desirable to develop a dosing regimen that is initially based on the typical patient, but with the option to escalate the dose quickly in case of inadequate response. We have therefore also developed a dosing regimens that aims for an initial concentration of 50 µg/L (and 80 µg/L for patients with haloperidol use) and can reach the higher concentrations of 200 µg/L (and 600 µg/L for patients with haloperidol use) within 16 hours. For a patient with an albumin level of 25 g/L and no concomitant haloperidol use this would mean a loading dose of 7.5 mg followed by 2 mg every 4 hours. Which is slightly lower than the current guideline. In the case of inadequate response increasing each additional dose with 50% combined with a bolus of 6 mg would ensure that the concentrations at which 95% of the population will have an 80% chance of adequate sedation will be reached within 12 hours. For patients with haloperidol use, a slightly higher initial dose of 10mg with 3mg every 4 hours should result in an initial concentration of 80 µg/L. For these patients, doubling the additional dose (up to a maximum dose of 10mg) combined with an 8mg bolus in the case of inadequate response should ensure that a concentration of 600 µg/L is reached within 16 hours.

From our pharmacokinetic and pharmacodynamic studies on midazolam we can conclude that patients who are treated with haloperidol should receive doses that are 25-33% higher than patients without haloperidol co-medication, and that the additional dose of a patient with an albumin level of 15g/L should be half of that of a patient with an albumin level of 25g/L (which in turn should be half of that of a patient with an albumin level of 35g/L). As these suggestions are only based on simulations, a prospective study with these new dosing regimens is still needed.

The fact that haloperidol was associated with a less sedative state in our pharmacodynamic study on midazolam may indicate that haloperidol is not effective enough in reducing delirium and agitation. We therefore also looked at the pharmacokinetics of haloperidol in the terminally ill population. As described in chapter 5, this study showed that the terminal half-life of haloperidol is long (around 30 hours). The current guideline for delirium gives a dosing recommendation of 0.5-2 mg every half hour until an effect is reached. This recom-

mendation seems adequate, since overdosing should be avoided especially because of its long terminal half-life. However, like with palliative sedation this dose titration takes time which is unwanted in a population with limited life expectancy. Unfortunately our study did not find any relevant covariates on which to adjust the initial dose. Therefore more research into the pharmacokinetics of haloperidol is necessary. However, making any recommendation based on pharmacokinetic information remains difficult as there is no target concentration available and the evidence for haloperidol in the treatment of (terminal) delirium in general is very sparse.

## GENERAL CONCLUSIONS AND FUTURE PERSPECTIVES

With the studies described above we have gained more insight in the pharmacokinetics and pharmacodynamics in terminally ill patients. This is first step in the process to developing more evidenced based and individualised dosing guidelines. The research on midazolam for instance show that to achieve adequate sedation in a large proportion of the population the doses recommended should probably be higher, especially in agitated patients. However, before these recommendations can be incorporated in new guidelines the developed models will have to be externally validated in a new set of patients and a prospective study evaluating a new dosing algorithm should be performed.

Nevertheless, our work has a first step in this process and has shown it is feasible to perform clinical studies in the palliative care population with minimal burden for the patients. We therefore hope that our work will generate more studies in terminally ill patients, as there are still many aspects that require investigation. First of all, the covariates tested in our studies e.g. blood chemistry levels provide insight in the underlying processes that can affect pharmacokinetics. However, measuring these parameters is not part of the regular clinical care, and recommendations based on these covariates may be of limited value in clinical practise. Furthermore, the study in morphine showed us that there are also factors influencing PK that may not be even detected by these blood chemistry tests. It would therefore be very interesting to see if other factors that are part of the regular care, and do not require blood sampling, may also be associated with pharmacokinetics. Fluid intake or urinary output may for instance serve as a proxy for clearance of drugs eliminated by the kidney. And although time of death remains difficult to predict there is a clinical pathway that is followed in clinical care when a patient has a life expectancy of days or hours, and the staff of a palliative care centre is well trained in estimating this life expectancy. It would therefore be very interesting to see if this moment can be used as a cut of point to possibly adjust medication. Investigating these kinds of covariates will also make it more easily to eventually incorporate them in dosing recommendations. There will probably always be unexplained variability in this heterogeneous population however by combining pharma-

cokinetic aspects with the clinical knowledge of the palliative care staff we should be able to improve clinical care.

Other interesting aspects of future research may result from some of the limitations of our current studies. In the current research presented in this thesis we for instance lacked enough data to test pharmacogenetic factors as covariates. Since we know that pharmacogenetic polymorphisms can influence the metabolic capacity of CYP3A (by which midazolam is metabolised) and CYP2D6 (which also plays a role in the metabolism of haloperidol) more research including these polymorphisms is needed. Especially since pharmacogenetics do not change over time this could be of interest as patients would only need to be tested once, which can even be done before treatment is started. We also lacked data on weight for a substantial proportion of the patients, and if weight was recorded this was only done at the time of admission. In future research, it would be recommended to weigh patients more than once as in this population weight loss is very common and this may affect pharmacokinetics. One of the reasons weight was not recorded was that it may be emotionally difficult for patients to see their weight loss. A recommendation for future research may therefore be not to physically weigh each patient but to have their weight estimated by the nursing staff. To do this a pilot study will have to be performed first to see how accurate these estimations would be. The lack of data sometimes came from the sparse sampling method, which made it sometimes necessary to make assumptions based on literature. For all three pharmacokinetic studies, we lacked blood samples shortly after dose administration. As a result, it was not possible to estimate an absorption constant. A study that focuses on this absorption phase would be of clinical interest as it gives information about the onset of the effect which is highly relevant in the case of symptomatic treatment, and may differ between patients according to their gastro intestinal motility, or fat tissue in the case of subcutaneous administration. Also in the pharmacodynamics of midazolam it would be beneficial to perform a study with a more continuous measurement for sedation. This would also provide information on the onset of sedation. Furthermore, it might possibly also show an effect of disease severity on depth of sedation, as this effect (represented in the form of hypoalbuminemia or measured retrospectively from the time of death) did not meet our criteria of statistical significance in the study but did show a trend.

Another important recommendation for future research would be a pharmacodynamic study on haloperidol for the treatment of delirium. As mentioned before evidence on the efficacy of haloperidol in delirium is lacking. It would therefore be interesting to combine our pharmacokinetic results with a pharmacodynamic measurement. Also, a study on the efficacy of haloperidol and possibly other psychotic drugs that are used for this indication (e.g. clozapine, olanzapine risperidone and quetiapine) in delirium would be of great clinical interest. This would not only be of value for palliative care but also for other populations, like elderly and critically ill patients in hospital. Finally, our study in midazolam showed that inflammation may have an effect on the metabolic capacity of CYP3A. This is an interest-

ing finding more than half of the drugs are metabolised by CYP3A and inflammation is also common in other diseases. Therefore, more research on the effect of inflammation on pharmacokinetics in general and CYP3A in particular is needed.

All further research needs financial support and in the beginning of our studies we observed that this was difficult to obtain for studies in palliative care. This may be due to a number of causes. For instance, pharmaceutical industries may be unwilling to support studies as the population is fragile and the drugs that are generally used have been on the market for a long time. Funding from the private sector proved difficult to obtain as questions were raised about the feasibility and ethical aspects. Our studies have showed that it is feasible to preform research in this population. And by using population based approaches the burden for patients is minimal. Furthermore, we found that although it is indeed a fragile population, the willingness to participate in research was high and patients were capable of making a well-informed decision on whether or not to participate. Of course, there is an important task for medical ethical committees to assure that fragile patients are not subject to unnecessary invasive research. However, it is important to keep in mind that participating in academic research may also give a sense of purpose to patients and to respect their autonomy in making this decision. We therefore hope that our studies not only provide more insight the changes in pharmacokinetics and pharmacodynamics in the final months of life, but also help to gain more awareness for palliative care as a research field.

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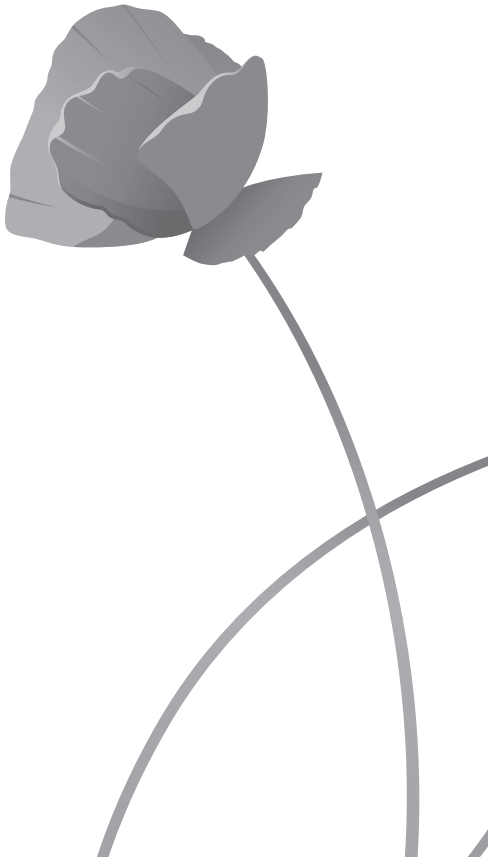


# CHAPTER 9

**Samenvatting, discussie en aanbevelingen**

## SAMENVATTING EN DISCUSSIE

In Nederland, ontvangen jaarlijks 108.500 terminaal zieke patiënten palliatieve zorg [1]. Wanneer een curatieve behandeling (geleidelijk) overgaat in palliatieve zorg zal de focus verschuiven van genezing naar symptoombestrijding, om op deze manier te zorgen voor de best mogelijke de kwaliteit van leven in de laatste dagen. Adequate symptoombestrijding is hierbij cruciaal omdat de symptomen waaraan men in het laatste levensjaar lijdt, zoals vermoeidheid, pijn en dyspneu, het leven aanzienlijk kunnen verzwaren [2]. Om dit lijden te verlichten kan men proberen de oorzaak weg te nemen, de bestaande symptomen behandelen (al of niet met behulp van medicatie) of ondersteunende zorg bieden. Helaas zijn er gevallen waarbij ondanks deze interventies het lijden ondragelijk blijft. In dergelijke situaties kan palliatieve sedatie worden ingezet. Hiermee wordt het lijden van de patiënt verlicht door het bewustzijn te verminderen. Eerder onderzoek naar de effectiviteit en veiligheid van palliatieve sedatie liet ziet dat het tot 48 uur kan duren voordat adequate sedatie wordt bereikt, en dat in 17% van de gevallen de symptomen onvoldoende onder controle blijven [3]. Gezien de ondragelijke toestand voor de patiënten is het essentieel om deze therapie te verbeteren. De grote variabiliteit die bij palliatieve sedatie gezien wordt, wordt mogelijk veroorzaakt door het feit dat de palliatieve populatie zeer heterogeen is. Zo verschillen hebben de patiënten verschillende co-morbiditeiten, gebruiken zij verschillende typen medicatie en zal er ook een verschil zitten in hun mate van ziekte op het moment dat palliatieve sedatie wordt gestart. Deze verschillen kunnen ervoor zorgen dat patiënten bij eenzelfde dosis andere concentraties van het geneesmiddel in het lichaam zullen hebben (een verschil in farmacokinetiek). Ook kan het zijn dat er bij dezelfde concentraties van een geneesmiddel bij patiënten verschillende effecten op treden (een verschil in farmacodynamiek). Deze verschillen in farmacokinetiek en farmacodynamiek kunnen resulteren in een variabele respons tussen patiënten alsmede een variatie in respons binnen één patiënt over de tijd. Ondanks deze verschillen zijn in de huidige richtlijnen voor symptoombestrijding geen geïndividualiseerde doseerregimes terug te vinden. In plaats daarvan wordt de dosis veelal gestuurd op geleide van het klinisch effect. Een groot nadeel van dergelijke dosis titratie is dat het tijd kost en dit is nadelig voor patiënten met ondragelijk lijden en een zeer beperkte levensverwachting. Meer geïndividualiseerde doseerrichtlijnen zijn dan ook nodig om de klinische zorg voor deze patiënten te verbeteren. Om dit te bereiken is een belangrijke eerste stap, het in kaart brengen van de farmacokinetische en farmacodynamische processen in deze populatie. Dit is dan ook waar de onderzoeken in dit proefschrift op gericht zijn.

In het eerste hoofdstuk hebben we onderzocht welke factoren van invloed kunnen zijn op de effectiviteit en veiligheid van geneesmiddelen bij palliatieve patiënten. In dit review focussen we ons voornamelijk op de pathofysiologische veranderingen die optreden aan het eind van het leven en hoe deze de concentratie van geneesmiddelen in het lichaam

kunnen beïnvloeden. Kijkend naar de vier algemene farmacokinetische principes (te weten: absorptie, distributie, metabolisme en eliminatie) zagen we dat elk van deze processen substantieel beïnvloed kan worden door het ziekteproces. De uiteindelijke invloed van de ziekte op de geneesmiddelconcentraties is echter lastig te voorspellen en kan sterk verschillen, zowel tussen patiënten (afhankelijk van hun co-morbiditeiten) als tussen geneesmiddelen (afhankelijk van hun chemische eigenschappen). Dit maakt het geheel complex en het is dan ook onmogelijk een eenduidig advies te geven wat geldt voor alle geneesmiddelen in deze populatie. In plaats daarvan zal de dosering per individueel geval bekeken moeten worden. Om behandelaars meer handvaten te bieden bij het voorschrijven van geneesmiddelen aan palliatieve patiënten, hebben we in dit review een aantal aanbevelingen gedaan voor de meest gebruikte geneesmiddelen in de palliatieve zorg, d.w.z. morfine, midazolam en haloperidol. Omdat farmacokinetische studies in palliatieve patiënten erg schaars zijn, is het belangrijk op te merken dat de genoemde aanbevelingen vooral gebaseerd zijn op theoretische gronden.

Naast pathofysiologische veranderingen kunnen ook interacties tussen geneesmiddelen de effectiviteit en veiligheid ervan beïnvloeden. Doordat palliatieve patiënten vaak meerdere co-morbiditeiten hebben en verschillende geneesmiddelen gebruiken voor symptoombestrijding, is polyfarmacie niet ongebruikelijk. We weten van studies in andere populaties dat polyfarmacie het risico op geneesmiddelinteracties verhoogt [4]. Daarom hebben we in hoofdstuk 2 het risico op geneesmiddelinteracties en de gevolgen hiervan bij palliatieve patiënten geëvalueerd. In deze studie is niet alleen gekeken naar het aantal geneesmiddel interacties dat voor kwam maar is tevens de klinische relevantie beoordeeld. De klinische relevantie in een palliatieve setting kan verschillen van de klinische setting, waarbij in de palliatieve setting interactie de focus minder op de lange termijn gevolgen ligt. In onze studie is de relevantie daarom gescoord door een team van experts in plaats van door een automatisch scoring systeem. Uit deze studie bleek dat bij een derde van de patiënten een geneesmiddel interactie optrad en de helft hiervan werd als klinisch relevant beschouwd. Daarnaast bleek dat het aantal geneesmiddelen dat een patiënt gebruikt een risico factor was voor het voorkomen van geneesmiddel interacties (aangepaste OR = 1.50, 95% CI = 1.24-1.82). Doordat de palliatieve setting verschilt van die in het ziekenhuis zijn niet alle geneesmiddel-interacties relevant. Desalniettemin zijn er nog steeds interacties die wel serieuze gevolgen kunnen hebben voor de patiënt, omdat het risico op een interactie toeneemt met het geneesmiddelengebruik is het belangrijk de medicatie kritisch te evalueren, en waar nodig te switchen of middelen te saneren.

Omdat zowel pathofysiologische veranderingen als interacties tussen geneesmiddelen de uiteindelijke concentraties van een geneesmiddel in het bloed kunnen veranderen, hebben we van de drie meest gebruikte middelen (morfine, midazolam en haloperidol) een populatie farmacokinetiek studie uitgevoerd. Het gebruik van populatie farmacokinetiek heeft een aantal belangrijke voordelen. Ten eerste maakt deze methode het mogelijk om

de kinetiek van een middel te bestuderen met slechts enkele bloedmonsters per patiënt. Hierdoor is de belasting voor patiënten minimaal, wat een belangrijke voorwaarde is voor het doen van onderzoek bij een dergelijk kwetsbare populatie. Een tweede voordeel is dat met behulp van deze methode niet alleen gemiddelde waardes voor parameters zoals klaring en verdelingsvolume kunnen worden geschat, maar dat ook de mate van variabiliteit gekwantificeerd kan worden. Hiermee kan door middel van een covariaat analyse vervolgens gekeken worden welke factoren (zoals patiënteigenschappen of comedicatie) van invloed zijn op de kinetiek. En vervolgens kan bekeken worden of door rekening te houden met deze factoren de variabiliteit verminderd kan worden. Tot slot maakt modeleren met populatie farmacokinetiek het mogelijk om nieuwe doseerregimes te simuleren. Zo kan er gesimuleerd worden wat voor concentraties men bereikt met een nieuw geïndividualiseerd doseer regime, op basis van de gevonden covariaten.

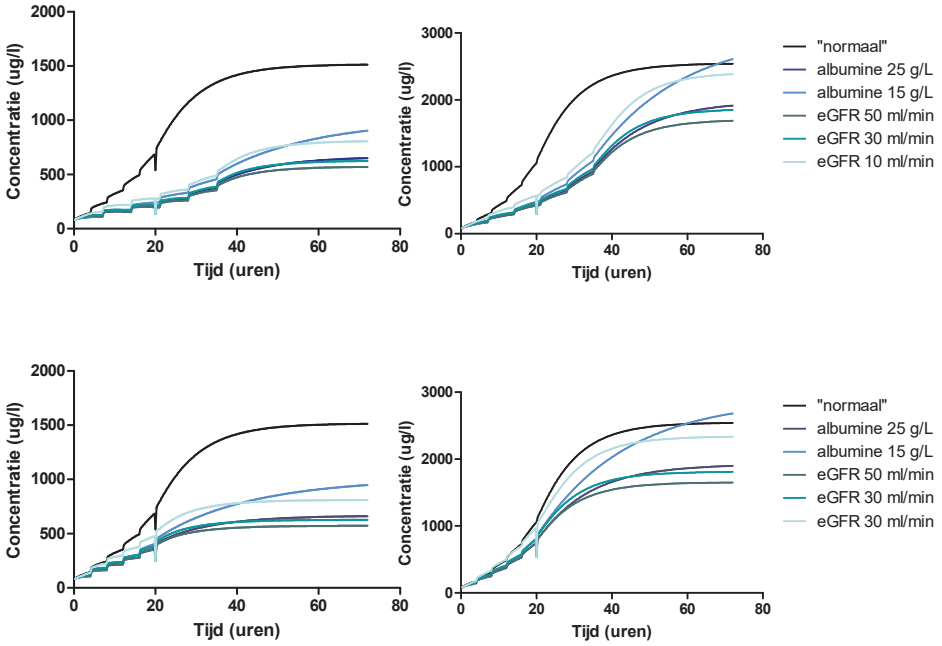
In hoofdstuk 3 wordt de populatie farmacokinetische studie naar morfine bij palliatieve patiënten beschreven. 80% van de palliatieve patiënten gebruikt morfine de laatste dagen van hun leven. Het doseren gebeurt veelal op geleide van het klinisch beeld. Echter kan het inschatten van pijn in de laatste levensdagen lastig zijn. Zo kan het vermogen van patiënten om zich te uiten sterk verminderd zijn door hun vanwege hun vergevorderd ziekte, of door de inzet van palliatieve sedatie. In onze studie is niet alleen gekeken naar de concentraties van morfine zelf maar zijn ook de twee belangrijkste metabolieten, morfine-3-glucuronide (M3G) en morfine-6-glucuronide (M6G) meegenomen in de analyse. Deze twee afbraakproducten van morfine zijn mee geanalyseerd omdat er uit de literatuur bekend is dat het actieve metabolieten zijn. Van M6G is het bekend dat het net als morfine een analgetische werking heeft [5-7]. De M3G metaboliet daarentegen wordt juist geassocieerd met de bijwerkingen van morfine worden [8, 9]. Onze studie bevestigde de resultaten van eerder studies door aan te tonen dat de klaring van M3G en M6G verminderd is in patiënten met een verminderd nierfunctie [9, 10]. Daarnaast liet onze studie een associatie zien tussen lage albumine waardes en een verminderde klaring van de metabolieten. Dit zou kunnen komen doordat hypoalbuminemie vaak samenhangt met cachexie of een katabole toestand, en in dergelijk zieke patiënten kan de nierfunctie (zoals berekend met de MDRD formule) een overschatting zijn. Tot slot liet onze studie zien dat de klaring van morfine afnam naarmate patiënten dichter bij het tijdstip van overlijden kwamen. Dit is een interessante bevinden en dit laat zien dat er waarschijnlijk nog een factor is die niet te beschrijven is met de standaard klinisch chemische test maar die wel de farmacokinetiek kan beïnvloeden. Een vermindering van de leverdoorbloeding is een factor die hier aan ten grondslag zou kunnen liggen.

In de huidige richtlijnen voor pijnbestrijding in de palliatieve fase, wordt reeds vermeld dat bij een verminderd nierfunctie (gedefinieerd als een eGFR < 50ml/min) morfine metabolieten kunnen accumuleren. Op basis van onze resultaten kunnen we stellen dat het beter is om niet enkel de eGFR als maat voor nierfunctie te nemen maar om ook de albumine waarden als risico factor mee te nemen. Het is echter wel belangrijk om op te mer-

ken dat creatinine (die nodig zijn voor de berekening van de eGFR) en albumine waardes niet standaard worden bepaald bij palliatieve patiënten, en dat de bloedafname hiervoor als een onnodige belasting kan worden gezien. Deze waardes zijn daarom in de klinische praktijk mogelijk niet bekend. Aangezien ook de morfine klaring afneemt wanneer patiënten dichter bij het moment van overlijden zijn (wat weer voor lagere metaboliet spiegels zorgt), is de uiteindelijke balans tussen morfine en de metabolieten moeilijk te voorspellen. Bovendien is het uiteraard lastig te voorspellen wanneer een patiënt exact zal komen te overlijden. De huidige richtlijnen maken nu geen onderscheid tussen de verschillende opioïden die ingezet kunnen worden voor pijnbestrijding. En morfine blijft vanwege de uitgebreide ervaring ermee, het meest gebruikte middel. Uit bovenstaande resultaten kan echter geconcludeerd worden dat een opioïd zonder actieve metabolieten, zoals fentanyl of oxycodon, wellicht een meer prominente rol zou moeten krijgen in de behandeling van pijn bij terminale patiënten.

Het vierde hoofdstuk van deze thesis beschrijft de farmacokinetiek van midazolam. De reactie van patiënten op midazolam is, zoals reeds gezegd, in grote mate variabel [11, 12]. Ook midazolam wordt gedoseerd op geleide van effect, wat als nadeel heeft dat het tijd kost. Dit is ongewenst bij de refractaire symptomen waarvoor het wordt ingezet omdat het hierdoor lang kan duren voordat er symptoomverlichting wordt bereikt [3]. Ook bij deze studie zijn de concentraties van de metabolieten, d.w.z. 1-OH-midazolam (1-OH-M) en 1-OH-midazolam glucuronide (1-OH-MG), meegenomen. Uit onze resultaten bleek dat net als bij de morfine metabolieten ook de klaring van 1-OH-MG afnam bij patiënten met een verminderde nierfunctie, wat overeenkomt met eerder onderzoek [13]. Daarnaast zagen we ook in deze farmacokinetiek studie een correlatie met albumine, echter dit maal niet met betrekking op de klaring van de metaboliet maar op de klaring van midazolam zelf. Het feit dat lage albuminewaardes geassocieerd waren met een verminderde midazolam klaring is een interessante bevinden. Een mogelijke verklaring hiervoor is dat hypoalbuminemie het gevolg kan zijn van een inflammatoire reactie of katabole toestand, wat mogelijk leidt tot een verminderde activiteit van het CYP3A enzym wat betrokken is bij het metabolisme van midazolam [14, 15]. In de huidige richtlijn voor palliatieve sedatie worden zowel hypoalbuminemie als renale dysfunctie genoemd als mogelijke risicofactoren voor overdosering (samen met een gewicht van minder dan 60kg en hepatische dysfunctie). In het geval van dergelijke risicofactoren wordt een lagere startdosering (0,5 tot 1,5 mg/uur i.p.v. 1,5 tot 2,5 mg/uur) geadviseerd alsmede een langer interval (6 tot 8 uur i.p.v. 4 uur) tot dosis ophoging in het geval van onvoldoende klinisch effect. Met het farmacokinetisch model uit onze studie hebben we de concentraties men bereikt worden op basis van deze richtlijnen gesimuleerd.

In figuur 1 geven de bovenste twee grafieken de totale effectieve concentratie weer (berekend als de midazolam concentratie plus 0,8 maal de 1-OH-M concentratie en 0,1 maal de 1-OH-MG concentratie) wanneer er gedoseerd wordt volgens de geldende richtlijnen.




**Figuur 1.** Gesimuleerde concentratie tijd curves van de huidige richtlijn (bovenste rij), en voorgestelde geïndividualiseerde doseer regimes voor patiënten met verschillende albumine waardes en nierfunctie.

In deze grafiek zijn in het zwart de gesimuleerde concentraties te zien voor een patiënt met een normale nierfunctie en albumine waardes (eGFR 90 ml/min en albumine 35 g/l)/ Daarnaast zijn ook de concentraties voor een patiënt met verminderde albumine waardes ( 25g/l in donkerblauw en 15g/l in lichtblauw) en een patiënt met verminderde nierfunctie ( eGFR van 50ml/min in donkergroen, 30ml/min in groen en 10ml/min in lichtgroen) te zien. De huidige richtlijn adviseert een startdosering van 10mg en geeft vervolgens een range van 1,5 tot 2,5 mg per uur via continue infusie (met de mogelijkheid om de dosering elke 4 uur met 50% te verhogen in combinatie met een 5mg bolus injectie). Omdat er een range wordt gegeven hebben we simulaties gemaakt voor zowel de hoogste als laagste doseringen hierin (met in figuur 1 links de lage en rechts de hoge dosering). In deze simulaties valt te zien dat bij een patiënt met normale nierfunctie en albumine waardes, de concentratie veel sneller stijgt dan bij de andere patiënten. Om dit te verbeteren hebben we een alternatief doseerregime opgesteld waarin enkel de keerdosis wordt verlaagd maar het interval niet wordt verlengt. Deze simulaties zijn weergegeven in de onderste twee grafieken. Hier valt te zien dat met deze aanpassing de curves van de patiënten met verminder nierfunctie of albumine waardes even hard stijgen als die van een "normale" patiënt.

Aangezien een doseeradvies niet enkel gebaseerd kan worden op farmacokinetische studies hebben we tevens een studie uitgevoerd naar de farmacodynamiek van midazolam,

te lezen in hoofdstuk 4. Deze studie liet een hoge interindividuele variabiliteit in effect zien, met een grote variatie in sedatie scores bij dezelfde midazolam concentraties. Doseren op geleide van effect lijkt dan ook logisch. Zoals reeds gezegd kost een dergelijke dosistitratie echter tijd en aangezien symptoomverlichting zo snel mogelijk dient te worden bereikt is dit niet gewenst. Het zou daarom nuttig zijn als er een manier was om patiënten met een verminderde respons op midazolam van te voren te identificeren. Een van de belangrijkste resultaten van onze studie was dan ook dat

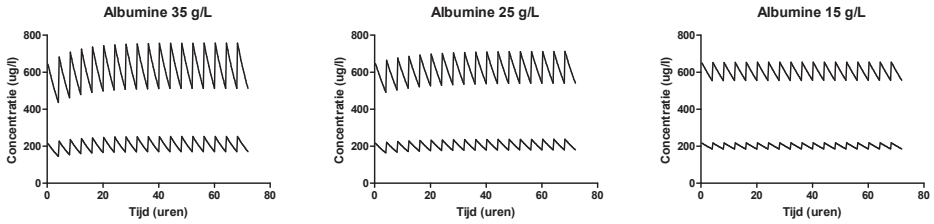
comedicatie met haloperidol geassocieerd was met een lagere kans op diepe sedatie. Dit is waarschijnlijk niet een effect van de haloperidol zelf maar van het delier of de onrust waarvoor haloperidol wordt gebruikt. In de huidige richtlijn worden geen risicofactoren gegeven voor onderdosering maar worden enkel enkel risicofactoren voor overdosering gegeven (namelijk leeftijd > 60 en het gebruik van comedicatie met een sederend effect).

Delier wordt dan ook niet als reden genoemd om de midazolam dosering te verhogen. In tegendeel, doordat haloperidol gezien kan worden als geneesmiddel met een sederende werking zou volgens de geldende richtlijn zelfs met een lagere dosering midazolam kunnen worden gestart. Op basis van onze resultaten zouden we dan ook willen adviseren patiënten met haloperidol, of een geagiteerd delier, een hogere startdosis midazolam voor te schrijven.

Het farmacodynamisch model liet zijn dat bij een midazolam concentratie van 50 µg/l de gemiddelde patiënt zonder haloperidol gebruik een 80% kans heeft op adequate sedatie (gedefinieerd als een Ramsay-score van 3 of meer). Door de grote variabiliteit is echter een streefspiegel van 200 µg/l nodig om deze zelfde kans te garanderen voor 95% van deze populatie. Voor patiënten met haloperidol gebruik liggen deze streefconcentraties hoger. Voor de gemiddelde patiënt is hier een midazolam concentratie van 80 µg/l nodig om een 80% kans op adequate sedatie te bereiken en om dit te bereiken bij 95% van de populatie is zelfs een concentratie van 600 µg/l nodig.

De resultaten van onze farmacokinetiek en farmacodynamiek studies combinerend, hebben we een aantal doseerregimes gesimuleerd. Allereerst hebben we een simulatie gemaakt waarbij het streven een 80% kans op adequate sedatie voor 95% van de populatie was. Deze resultaten zijn te zien in figuur 2. In de meest linker figuur laat de onderste lijn zien dat een regime met een oplaaddosis van 25 mg gevolgd door 10mg elke 4 uur bij een patiënt met een albumine waarde van 35 g/l leidt tot de gewenste plasmaconcentraties van 200 µg/l. De onderste lijn in de middelste en rechter grafiek laten zien dat deze plasmaconcentratie van 200 µg/l bij patiënten met een albumine waarde van 25 en 15 g/l worden bereikt door de dezelfde startdosering gevolgd door een onderhoudsdosis van respectievelijk 7 en 4 mg elke 4 uur. Om de hogere concentraties van 600 µg/l te bereiken (wat nodig is om 95% van de haloperidol gebruikers een 80% kans op adequate sedatie te geven) is het noodzakelijk de dosering te verdrievoudigen. Dit komt neer op een oplaaddosis van 75 mg gevolgd door

30 mg elke 4 uur bij een albumine waarde van 35 g/l en 21 en 12 mg elke 4 uur bij albumine waardes van respectievelijk 25 en 15g/l.




Figuur 2. Gesimuleerde concentratie tijd curves van doseerregimes aangepast aan de albumine waardes.

Deze doseringen liggen hoger dan de huidige richtlijn, met name in het geval van haloperidol gebruik. Het is daarom belangrijk om op te merken dat het streven naar een adequate sedatie voor 95% van de populatie, een overdosering in een groot gedeelte van de patiënten tot gevolg zal hebben. Het zou dan ook beter zijn een doseerrichtlijn op te stellen waarbij initieel wordt uitgegaan van de gemiddelde patiënt, maar met de mogelijkheid om snel op te hogen in geval van onvoldoende respons. Hiervoor hebben we doseerregimes gesimuleerd met als initiële streefwaarde 50 µg/l (en 80 µg/l voor patiënten met haloperidol als comedicatie) die vervolgens binnen 16 uur op kan lopen tot de hogere concentratie van 200 µg/l (en 600 µg/l voor patiënten met haloperidol als comedicatie). Voor een patiënt met een albumine waarde van 25g/l zonder haloperidol gebruik komt dit neer op een oplaaddosis van 7,5 mg gevolgd door 2mg elke 4 uur. Dit is iets lager dan de huidige richtlijn, maar door de mogelijkheid te bieden de onderhoudsdosering met 50% te verhogen i.c.m. een bolus van 6mg zal binnen 12 uur de concentratie van 200 µg/l worden bereikt waarbij 95% van de populatie 80% kans op adequate sedatie heeft. Voor patiënten met haloperidol gebruik (en albumine waardes van 25 g/l) is een iets hogere dosering nodig van 10mg gevolgd door 3mg elke 4uur om te resulteren in een initiële midazolam concentratie van 80 µg/ll. Bij deze patiënten zal het verdubbelen van de onderhoudsdosering (met een maximum dosis van 10mg) in combinatie met een 8mg bolus ervoor zorgen dat de concentratie van 600 µg/l binnen 16 uur wordt bereikt.

Uit onze farmacokinetiek en farmacodynamiek studies naar midazolam kunnen we concluderen dat patiënten die haloperidol als comedicatie gebruiken een 25-33% hogere dosis nodig hebben dan patiënten zonder haloperidol. Bovendien zal de onderhoudsdosering van een patiënt met een albumine spiegel van 15 g/l de helft moeten zijn van die van een patiënt met een albumine spiegel van 25 g/l (die op zijn beurt weer de helft dient te zijn van die van een patiënt met een albumine spiegel van 35 g/l). Aangezien deze aanbevelingen enkel gebaseerd zijn op simulaties is eerst nog een prospectieve studie naar deze doseerregimes nodig alvorens deze geïmplementeerd kunnen worden in de dagelijkse praktijk.

Het feit dat haloperidol geassocieerd was met een mindere mate van sedatie bij dezelfde concentraties midazolam, impliceert dat haloperidol wellicht niet effectief genoeg is in het behandelen van delier en agitatie in de palliatieve fase. Om meer inzicht te krijgen in de farmacokinetiek van haloperidol hebben we ook hiernaar een studie uitgevoerd. Zoals beschreven in hoofdstuk 5, laat deze studie zien dat haloperidol een lange halfwaardetijd heeft van ongeveer 30 uur. De huidige richtlijn voor delier beveelt een dosering van 0,5 tot 2 mg haloperidol aan elke 30 minuten totdat het gewenste effect wordt bereikt. Deze aanbeveling lijkt adequaat aangezien een te hoge startdosis zou kunnen lijden tot overdosering, wat vervolgens lang aan kan houden.

Echter geldt ook hier dat het titreren van de dosis op geleide van klinisch effect tijd kost en ongewenst is bij patiënten met een korte levensverwachting. Helaas heeft ons onderzoek geen relevante covariaten aan kunnen tonen op basis waarvan de haloperidol dosis geïndividualiseerd kan worden. Meer onderzoek is dan ook nodig naar de farmacokinetiek van haloperidol. Bovendien is het lastig aanbevelingen te geven op basis van elke farmacokinetische informatie aangezien er geen streefwaarde bekend zijn. Daarbij is het bewijs voor de effectiviteit van haloperidol voor de behandeling van (terminaal) delier überhaupt niet onomstreden.

## ALGEMENE CONCLUSIE EN AANBEVELINGEN

Met de hierboven genoemde studies hebben we meer inzicht gekregen in zowel de farmacokinetiek als de farmacodynamiek bij palliatieve patiënten. Dit is een belangrijke eerste stap op weg naar meer evidence-based en geïndividualiseerde richtlijnen. Zo liet het onderzoek naar midazolam bijvoorbeeld zien dat om adequate sedatie te bereiken een groot deel van de patiënten (met name de geagiteerde patiënten) een hogere dosis zou moeten krijgen. Echter voordat dit soort aanbevelingen in de richtlijnen kunnen worden opgenomen zullen de modellen eerst extern gevalideerd dienen te worden en is tevens een prospectieve studie naar het effect van het nieuwe doseeralgoritme nodig.

Desondanks, is dit werk een eerste stap in deze richting en bovendien heeft het laten zien dat het mogelijk is om klinische studies bij palliatieve patiënten uit te voeren met een minimale belasting voor de patiënten. Ik hoop dan ook dat dit werk ervoor zal zorgen dat er meer onderzoek in terminale patiënten zal worden uitgevoerd, aangezien er nog veel onderzoeksvragen liggen. Zo zou het bijvoorbeeld interessant zijn om te kijken naar andere voorspellende covariaten dan nu in deze onderzoeken zijn meegenomen. De klinisch chemische paramaters die wij in ons onderzoek gebruikt hebben, geven namelijk wel inzicht in de onderliggende processen maar worden in de klinische praktijk niet standaard gemeten, en zijn daardoor lastiger te implementeren in nieuwe richtlijnen. Bovendien liet ons onderzoek naar morfine zien dat er naast deze klinisch chemische waardes wellicht nog andere

factoren zijn die de farmacokinetiek beïnvloeden. Het zou dan ook erg interessant zijn om te kijken of factoren die wel routine matig worden beoordeeld, en niet afhankelijk zijn van bloedafnames, ook een relatie hebben met de farmacokinetiek. Vochtinname en urineproductie zouden bijvoorbeeld een maat kunnen zijn voor de eliminatie van geneesmiddelen met een renale klaring. En ondanks dat de exacte levensverwachting lastig te voorspellen is, is er wel een redelijk goed gedefinieerd moment in het palliatieve traject waar de stervensfase start. Op dit moment wordt in de praktijk het zorgpad stervensfase gestart. Het zou dan ook interessant zijn om te onderzoeken of dit moment gebruikt kan worden als punt om de medicatie aan te passen (en bijvoorbeeld de morfine dosis te verlagen). Dergelijk onderzoek naar andere typen covariaten maken het ook haalbaarder om uiteindelijk doseeralgoritmes te implementeren in de klinische praktijk. Er zal altijd onverklaarbare variabiliteit blijven bestaan in de heterogene palliatieve populatie, maar door het integreren van farmacokinetische kennis met de praktijk ervaring van de behandelaars moet het mogelijk zijn om de zorg voor deze patiënten te verbeteren.

Andere interessante mogelijkheden voor verder onderzoek komen voort uit de tekortkomingen van de huidige studies. In de genoemde studies ontbrak het bijvoorbeeld aan voldoende farmacogentische data om de invloed hiervan te testen. Omdat we weten dat genetische polymorfismen van invloed kunnen zijn op de metabole capaciteit van CYP3A (wat verantwoordelijk is voor de omzetting van midazolam) en CYP2D6 (wat een rol speelt bij het metabolisme van haloperidol) zou meer onderzoek naar effect hiervan nuttig zijn. Vooral omdat, in tegenstelling tot alle pathofysiologische veranderingen, de farmacogenetica niet veranderen over de tijd. Hiervoor zou dus een eenmalige test volstaan en dit zou ook al voorafgaand aan het starten van een therapie kunnen gebeuren. Een andere tekortkoming in onze studies was dat voor veel patiënten gegevens over hun gewicht ontbraken, en als het al was vastgelegd was dit slechts enkel genoteerd bij opname. Voor toekomstig onderzoek is het sterk aan te bevelen de gewichten van patiënten regelmatiger te noteren, aangezien gewicht vaak van invloed is op de kinetiek van geneesmiddelen en het bekend is dat patiënten veel gewicht kunnen verliezen in de laatste levensfase. Een van de redenen dat gegevens over het gewicht vaak ontbraken was dat men het te belastend vond voor de patiënten om hen regelmatig te wegen. Een mogelijke oplossing voor toekomstig onderzoek zou dan ook zijn om patiënten niet te wegen maar de verpleging een inschatting van het gewicht te laten maken. Om na te gaan hoe accuraat dit te schatten is zou eerst een pilot studie uitgevoerd kunnen worden.

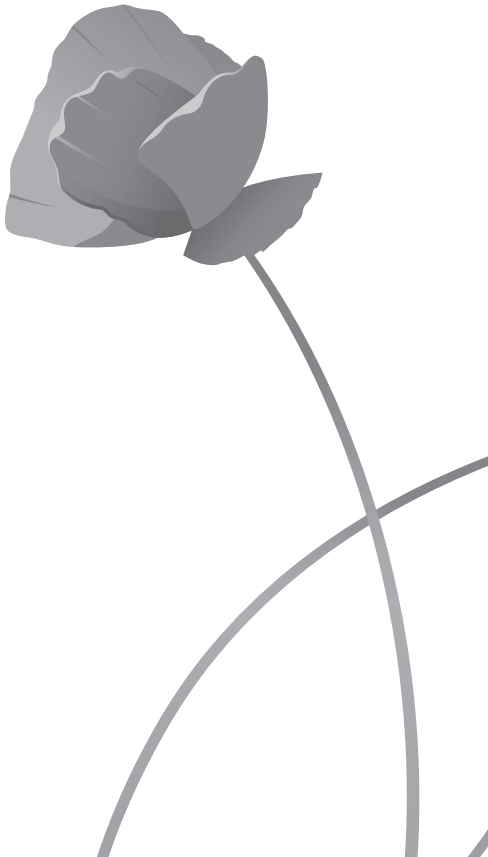
Bij de uitgevoerde studies was het door het spaarzaam verzamelen van bloed monsters, soms nodig aannames te doen op basis van bekende literatuur. Zo ontbrak het in alle drie de farmacokinetische studies aan bloedafnames kort na toediening van het geneesmiddel. Hierdoor was niet mogelijk een absorptie constante te bepalen. Een studie die focust op de opnamesnelheid interessant zijn omdat het inzicht kan geven in de snelheid waarmee de maximale concentratie wordt bereikt. Voor de palliatieve populatie zal dit klinisch relevant

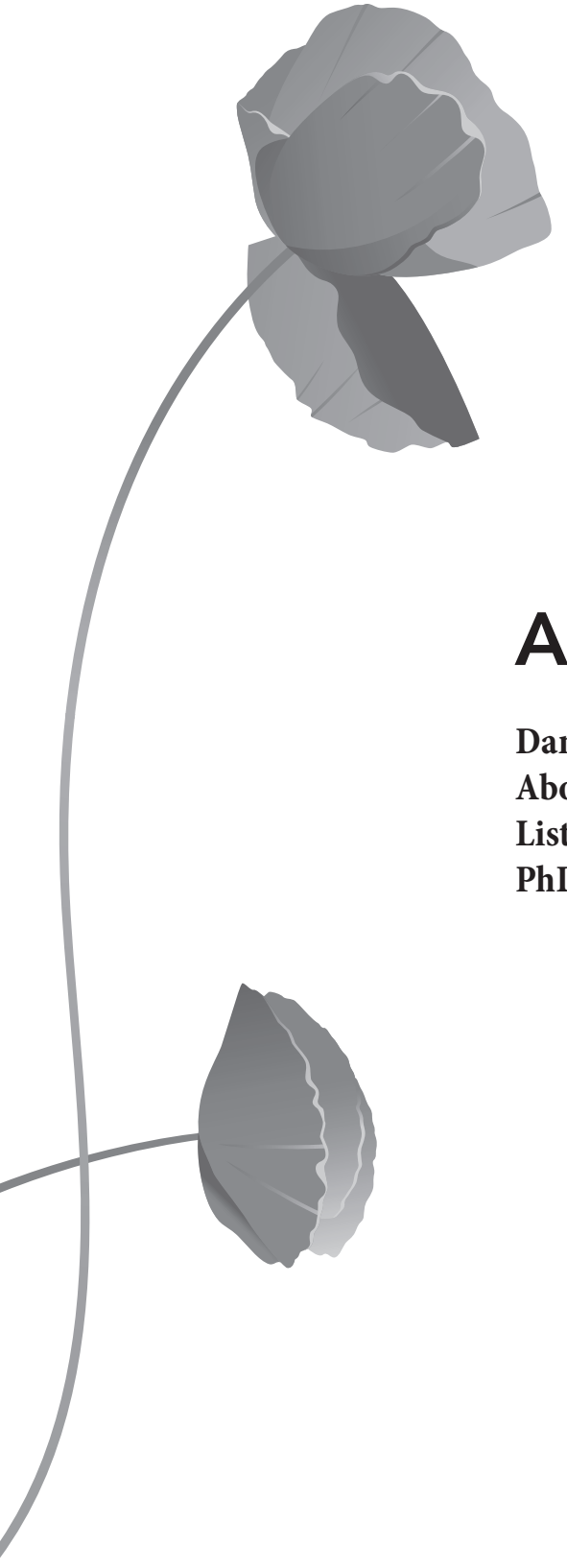
zijn omdat het in veel gevallen belangrijk is zo snel mogelijk effect te bereiken en omdat er redenen zijn om aan te nemen dat de absorptie bij deze patiënten anders is dan bij andere populaties, bijvoorbeeld door een verminderd maaglediging bij orale toedieningen en minder onderhuids vetweefsel bij subcutane toepassingen. Ook in het farmacodynamiek onderzoek naar het effect van midazolam zou het interessant zijn om meer te focussen op de snelheid in het optreden van het effect. Om dit optimaal te kunnen beschrijven zal een studie met een continue sedatie meting nodig zijn. Daarnaast is het met een dergelijk onderzoek wellicht mogelijk om tevens een effect van het ziekteproces op de mate van sedatie te beschrijven. Een dergelijk effect (weergegeven door hypoalbuminemie of retrospectief berekend aan de hand van het tijdstip van overlijden) liet in onze farmacodynamiek studie namelijk wel een trend zien maar er was te weinig data om dit statistisch significant aan te tonen.

Een andere belangrijke aanbeveling is het uitvoeren van een farmacodynamische studie naar haloperidol bij de behandeling van terminaal delier. Zoals eerder gezegd is er nog onvoldoende bewijs naar de effectiviteit van haloperidol bij deze toepassing. Het verdient dan ook de aanbeveling om de resultaten uit onze farmacokinetiek studie te combineren met een farmacodynamische parameter om hier meer inzicht in te krijgen. Ook een klinische trial naar de effectiviteit van haloperidol en andere antipsychotica (zoals clozapine, olanzapine, risperidon of quetiapine) bij (terminaal) delier zou zeker van klinische waarde zijn. Dit kan namelijk niet alleen van waarde zijn voor de palliatieve populatie maar ook voor ouderen en kritische zieke patiënten in het ziekenhuis. Tot slot liet onze studie naar midazolam zien dat inflammatie mogelijk resulteert in een verminderde metabole capaciteit van het CYP3A enzym. Dit is een belangrijke bevinding aangezien de helft van alle geneesmiddelen door dit enzym wordt omgezet. Meer onderzoek naar het effect van inflammatie op de farmacokinetiek in zijn algemeenheid, en op het CYP3A metabolisme specifiek, is dan ook nodig.

Voor alle toekomstige onderzoeken kunnen is financiële ondersteuning essentieel, en in het begin van dit project is gebleken dat het financieren van onderzoek in de palliatieve setting lastig is. Dit kan een aantal redenen hebben. Zo is er weinig incentive vanuit de farmaceutische industrie om onderzoek in deze kwetsbare populatie uit te voeren, ook omdat de middelen die gebruikt worden al lange tijd op de markt zijn. Daarnaast bleek ook financiering met private gelden lastig omdat men bedenkingen had bij de haalbaarheid en ethische aspecten. Onze onderzoeken hebben laten zien dat het wel degelijk haalbaar is om met populatie farmacologie onderzoek uit te voeren met een minimale belasting voor de patiënten. Bovendien hebben we gemerkt dat, ondanks dat het een kwetsbare populatie is, er wel degelijk bereidheid is deel te nemen aan wetenschappelijk onderzoek en dat een groot deel van de populatie goed in staat is om hier een weloverwogen beslissing in te nemen. De medisch ethische toetsingscommissies hebben uiteraard een belangrijke taak in het beschermen van (kwetsbare) patiëntengroepen tegen onnodig invasief onderzoek. Echter is het tevens net zo belangrijk om de autonomie van de patiënten hierin te respec-

teren indien zij in staat zijn zelf een weloverwogen keuze te maken. Sommige patiënten zien bijvoorbeeld deelname aan een wetenschappelijk onderzoek als een betekenisvolle bijdrage in hun laatste levensdagen. Ik hoop dan ook dat onze studies niet alleen meer kennis hebben opgeleverd, maar dat ze ook kunnen bijdragen aan het vergroten van de interesse in wetenschappelijk onderzoek in de palliatieve zorg.





# APPENDICES

**Dankwoord**
**About the author**
**List of publications**
**PhD portfolio**

## DANKWOORD

En toen was het daar toch opeens, het eind van mijn boekje. Dit proefschrift en de hierin gepresenteerde onderzoeken zijn zeker niet alleen mijn verdienste. Ik wil dan ook bij dezen een aantal personen bijzonder bedanken voor hun bijdrage.

Allereerst wil ik graag alle patiënten en hun naasten bedanken voor hun deelname aan de onderzoeken. Zonder hen zou dit alles nooit mogelijk zijn geweest.

Mijn promotoren, Prof. dr. Teun van Gelder en Prof. dr. Ron Mathôt.
Beste Teun, veel dank voor al je begeleiding en meedenken. Jij hebt mij laten zien hoeveel meer we kunnen bereiken voor onze patiënten als we als apothekers en artsen samenwerken (zowel in het onderzoek als in de reguliere patiëntenzorg).
Beste Ron, dank voor de begeleiding bij het modeleren. Toen je mij na ons eerste overleg de NONMEM handleiding gaf als leesvoer, zonk mij de moed toch wel een beetje in de schoenen. Even was ik bang dat ik dit nooit zou gaan begrijpen, maar gelukkig is dat mede door jouw hulp toch nog helemaal goed gekomen.

Mijn copromotor, dr. Birgit Koch.
Beste Birgit, dank dat je niet alleen mijn onderzoek hebt begeleid maar ook, samen met Teun, mijn opleiding tot klinisch farmacoloog. En dat je me naast dit alles ook nog de mogelijkheid hebt gegeven om af en toe klinisch werk te doen op het apotheek lab. Jouw enthousiasme voor het lab (en de incidentele exotische tox-en) waren aanstekelijk en ik ben blij dat ik me hier de komende jaren nog verder in mag gaan verdiepen.

Prof. dr. van der Rijt, Prof. dr. Huitema en Prof. dr. Vissers, hartelijk dank voor het beoordelen van mijn manuscript.

Prof. dr. Tibboel, Prof. dr. Knibbe, Prof. dr. van Dijk en Prof. dr. van der Heide dank voor het plaats nemen in de commissie. Beste Dick en Monique zonder jullie inzet was dit project, en dus ook mijn proefschrift, nooit van de grond gekomen. Het opstarten van een onderzoek in een nieuwe setting, buiten het ziekenhuis, is niet eenvoudig gebleken maar dit heeft jullie gelukkig niet tegen gehouden.

Alle medeauteurs wil ik bedanken voor hun input en de fijne samenwerking.
Brenda dank voor al je hulp bij het modeleren. Ondanks dat je niet officieel mijn begeleider was, was jij natuurlijk wel onze enige echte "in-house NONMEM-expert". Heel veel dank voor alle keren dat jij mijn runs aan de praat hebt gekregen (al was het natuurlijk wel een tikkie frustrerend dat jij soms in twee tellen de fout zag, waar ik blijkbaar al dagen overheen keek).

Anniek dank voor al het werk wat hebt verricht in Laurens Cadenza. De bananendozen vol met formulieren die je meebracht bij onze eerste ontmoeting laten wel zien hoeveel werk je hebt verzet.

Dank ook aan alle medewerkers van Laurens Cadenza, met in het bijzonder Frans Baar, Jet van Esch, Ellen van Bebber, Sarie Schneider en alle researchverpleegkundigen. Jullie hebben me een hele nieuwe wereld van patiëntenzorg laten zien. Het was inspirerend om te zien hoe jullie je inzetten om de patiënten de best mogelijke zorg te bieden in hun laatste levensdagen.

Naast de collega's in Laurens Cadenza wil ik ook graag al mijn collega's van de ziekenhuisapotheek bedanken.
Peter bedankt dat je mij de mogelijkheid hebt gegeven om hier te komen werken, eerst als projectapotheker toen als onderzoeker en inmiddels als AIOS ziekenhuisfarmacie. Patricia en Liesbeth dank dat jullie me, ondanks dat mijn onderzoek nog niet af was, de kans hebben gegeven om te starten met de specialisatie tot ziekenhuisapotheker. Ik ga hiervoor graag nog even door met forenzen en kijk ernaar uit om nog drie jaar samen te werken en van jullie te mogen leren.

Een promotie afronden en tegelijkertijd starten met je specialisatie, dat is een uitdagende combinatie. Hierbij zijn fijne collega's dan ook geen overbodige luxe. Ik wil hen allemaal dan ook heel erg bedanken voor alles, van het overnemen van dagdiensten zodat ik de laatste stukken de deur uit kon werken tot het organiseren van tennistoernooien en wintersportvakanties. Lidwien en Birgit nogmaals bedankt voor het in het leven roepen van dit laatste. En Floor en Jan-Dietert alvast bedankt voor de voorzetting hiervan (misschien een beetje voorbarig, maar met de fondue-meister aan het roer kan niet anders dan een succes worden).

Ook alle collega's van het lab wil ik nog speciaal bedanken voor de fijne samenwerking en het altijd gevuld houden van de snoeppot. Willemijn heel veel dank voor het opzetten van de analysemethodes. Ruud dank voor al je technische hulp bij zowel computers als fietswielen.

Mijn mede-NONMEM'ers uit het Erasmus wil ik bedanken voor al hun input en het meedenken bij onze wekelijkse overleggen. Femke, met jouw nauwkeurigheid was je de ideale vraagbaak. Rixt, wat is jouw enthousiasme aanstekelijk, houd dat vast en dan zullen vast meer mensen met liefde voor je in een maatbeker plassen.

Tijdens mijn onderzoek heb ik de afgelopen jaren ook heel wat uren achter de computer/ laptop doorgebracht. En hoewel het wellicht niet altijd de productiviteit verhoogde, had ik dit toch nooit kunnen doen zonder de gezelligheid van mijn mede-onderzoekers, AIOS en Na-206-roomies.
Florine, mijn reis-maatje uit Amsterdam en onze briljante skilerares, wat ben ik blij dat jij vandaag naast me staat.
Sanne, dank voor jouw altijd fantastische verhalen, die van de eerste keer DBS-monsters verzamelen had ik voor geen goud willen missen.
Louise, wat was ik blij dat ik een medestander had in zoetigheid halen bij de AH to go, ongelooflijk dat jij na al die jaren chocola, koekjes en de mug-cake nooit uitgedijd bent.
Annette, onze stille kracht achterin en de bezemwagen bij het mountainbiken.
Sophie, degene die altijd de juiste krachttermen wist te vinden, alleen is er van onze stilte-uurtjes nooit veel terecht gekomen.
Zina, dank dat jij er altijd was als luisterend oor, Edmé wat was het fijn om niet de enige met lichtelijk onhandige acties te zijn en Alan dank voor al je tips voor de opleiding ik ben blij dat je nog een tijdje blijft. Naast deze vaste crew wil ik ook graag onze tijdelijke kamergenoten, van de klinische farmacologie bedanken voor de leuke tijd.

Alle jonge apothekers uit de OOR bedankt voor de mooie, sportieve weekendjes weg en de verkleedpartijen, dat er nog veel mogen volgen.

Lotte, Andrew, Niels, Midas en Tim wat ben ik blij met zo'n leuk en relaxt AIOS clubje, ik kijk uit naar de komende jaren, en alle meerdaagse cursussen.

Sinem bedankt voor je harde werk in Laurens Cadenza, het heeft een mooi artikel opgeleverd.

Ook al lijkt het al weer heel lang geleden, toch wil ik ook graag mijn oud-AMC collega's bedanken voor deze tijd. Die 9 maanden waren namelijk niet alleen mijn kennismaking met de ziekenhuisfarmacie, maar ook met het fenomeen Apo-ski en hiervoor ben ik jullie oneindig dankbaar. Ook mijn nieuwere AMC collega's van het NONMEM klasje (wat inmiddels zelfs is geüpgraded naar een NONMEM+ klasje) wil ik heel erg bedanken voor al het meedenken en de vele modelling-tips.

Merel, Stef en Simoontje ik ben blij dat we al zo lang vriendinnen zijn. Nu dit boekje af is ga ik ook zeker weer wat vaker naar Brabant komen.

Marlou wat fijn dat je mijn paranimf wilt zijn, met dit straks achter de rug wordt weer eens hoog tijd voor een nieuwe wijncursus en misschien ook wat nieuwe tennislessen.

Lieve mam, bedankt dat jij en pap alles voor mij mogelijk hebben gemaakt ook al liet je me met tegenzin naar de andere kant van de wereld vertrekken.

Lieve Joost, bedankt dat je er altijd voor me bent en dat jij het als geen ander begrijpt dat het werk niet altijd ophoud na zessen. En wat is het fijn om tussen alle drukte door af en toe samen ver weg te gaan. Nu het boekje af is, zullen we de Lonely Planets maar weer eens uit de kast trekken.

## ABOUT THE AUTHOR

Linda Franken was born in Etten-Leur on the 20th of November 1985. After graduating secondary school at the Catholic college of Etten-Leur (KSE) in the year 2004 she first went to Nijmegen to study dietetics. After obtaining her propaedeutic diploma she moved to Utrecht to study pharmacy. During her study she developed an interest for academic research and went to Sydney, Australia for an internship at the Children's Hospital Burns Research Institute (CHBRI). At this institute, which is part of the Children's Hospital at Westmead, she studied the release of the flightless I (FLii), an enzyme involved in wound healing. The results of these studies were published in the Journal of Cell Science and Communicative & Integrative Biology.

During her internship at the VU medical centre in Amsterdam she developed a growing interest in clinical pharmacy and pharmacology and after finishing her pharmaceutical training she started work at the Academic Medical Centre in Amsterdam. After 9 months she transferred to the Erasmus Medical centre where in 2013 she got the opportunity to start her PhD project under supervision of Prof. dr. T van Gelder, Prof. dr.R.A.A. Mathôt from the Academic Medical Centre in Amsterdam and dr. B.C.P. Koch. Also under the supervision of Prof. dr. T. van Gelder and dr. B.C.P. Koch she started a fellowship in Clinical Pharmacy, which she expects to finish beginning of 2018. In December of 2017 she has started her fellowship to become a hospital pharmacist, which she expects to finish in 2020.

## LIST OF PUBLICATIONS

### this tesis

Barutcu S, **Franken LG**, Koch BCP, Geijteman ECT, van den Bemt PMLA. Potential drug-drug interactions in the terminal phase of life, *Submitted* Br J Clin Pharmacol

**Franken LG**, de Winter BCM, Masman AD, van Dijk M, Baar FPM, Tibboel D, Koch BCP, van Gelder T, Mathot RAA. Population pharmacodynamic modelling of midazolam induced sedation in terminally ill adult patients. Br J Clin Pharmacol. 2017

**Franken LG**, Mathot RAA, Masman AD, Baar FPM, Tibboel D, van Gelder T, Koch BCP, de Winter BCM. Population pharmacokinetics of haloperidol in terminally ill adult patients. Eur J Clin Pharmacol. 2017 Oct; 73(10):1271-1277

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## PHD PORTFOLIO

Name PhD student: L.G.W. Franken
Erasmus MC Department: Hospital Pharmacy

PhD period: 1/11/2012 – 7-2-2018
Promotor(s): T. van Gelder; R.A.A. Mathot
Supervisor: B.C.M. Koch

### 1. PhD training

| | Year | Workload (ECTS) |
|---|---|---|
| **General courses** | | |
| - Biomedical English Writing and Communication | 2015 | 2 |
| - Research Integrity | 2015 | 0.3 |
| - Systematic literature Retrieval in PubMed and other data- | 2013 | 0.5 |
| bases | 2013 | 0.5 |
| - Endnote | 2014 | 1 |
| - BROK ('Basiscursus Regelgeving Klinisch Onderzoek' | | |
| **Specific courses (e.g. Research school, Medical Training)** | | |
| - PK and PK/PD modelling with NONMEM – at CHDR | 2013 | 1 |
| - Basic Course on R | 2015 | 1.4 |
| - NIH 'Principles of Clincal Pharmacology" | 2015 | 2 |
| - Pharmacometrics summerschool, Uppsala University | 2016 | 3 |
| **Seminars and workshops** | | |
| - PGx Workshop | 2014 | 0.2 |
| - NIH Principles of Clinical Pharmacology | 2014-2015 | 1.4 |
| - Anselmus Colloquium "de laatste fase" | 2014 | 0.2 |
| - Congress Research Integrity | 2015 | 0.3 |
| - DDMORE Workshop | 2016 | 0.3 |
| **Presentations** | | |
| - PAGE meeting, Chersonisos, Greece, poster presentation | 2015 | 1 |
| - FIGON dutch medicine days, Ede, poster presentation | 2014 | 1 |
| - IATDMCT meeting, Rotterdam, oral presentation | 2015 | 1 |
| - PAGE meeting, Lisbon, Portugal, poster presentation | 2016 | 1 |
| - Voorjaarsdag NVKFB | 2017 | 1 |
| - Ziekenhuisfarmaciedagen, Bunnik, oral presentation | 2017 | 1 |

(Inter)national conferences

| | | | |
|---|---|---|---|
| - | Lareb Bijwerkingen dag, Leiden | 2014 | 1 |
| - | Ziekenhuisfarmaciedagen, Rotterdam | 2014 | 1 |
| - | Symposium of alternative sampling strategies in toxicology and TDM, Gent, Belgium | 2014<br>2014 | 1<br>1 |
| - | Lage landen symposium intoxicaties, Gent, Belgium | 2015 | 1 |

Other

| | | | |
|---|---|---|---|
| - | NONMEM workgroup AMC | 2013-2017 | 0.5 |
| - | NVKFB scientific meeting | 2014-2015 | 0.4 |
| - | PhD day | 2014 | 0.5 |
| - | Journal club, monthly (oral presentations) | 2013-2017 | 1 |
| - | NONMEM research meetings, weekly (oral presentations) | 2014-2017 | 2 |
| - | Clinical pharmacology meetings weekly (oral presentations) | 2013-2017 | 2 |

2. Teaching

| | | Year | Workload (Hours/ ECTS) |
|---|---|---|---|
| Lecturing | | | |
| - | Lecture on basic pharmacokinetics, Winter course Master Infection and Immunity, Erasmus MC Rotterdam | 2013, 2015 | 0.5 |
| - | Lecture on medication interactions and pharmacokinetics in palliative care, Zorg academie Erasmus MC Rotterdam | 2013, 2015 | 0.5 |
| - | Lecture on TDM and toxicology (3rd year medical students) | 2013-2017 | 0.5 |
| - | Lecture on polypharmacy (3rd year medical students) | 2014-2017 | 0.5 |
| - | Lecture on pharmacokinetics and dynamic in the elderly | 2016 | 0.2 |
| - | Prescribing course for medical students | 2015-2016 | 0.5 |
| Supervising Master's theses | | | |
| - | S. Barutcu 6 month research theses | 2017 | 2 |
| Other | | | |
| - | Basis Kwalificatie Onderwijs (deel registratie) | 2016-2017 | 1 |