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

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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.

1. 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]

2. Absorption

Terminally ill patients frequently suffer from gastro intestinal (GI) problems, such as constipation, nausea, vomiting, and diarrhea. 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 (T_{max}), whereas changes in bioavailability will affect the initial peak concentration (C_{max}) and total exposure, expressed as area under the curve (AUC). If and to what extent a drug is

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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.

2.1. 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.

2.1.1. 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, diarrhea, 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.

Diarrhea 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
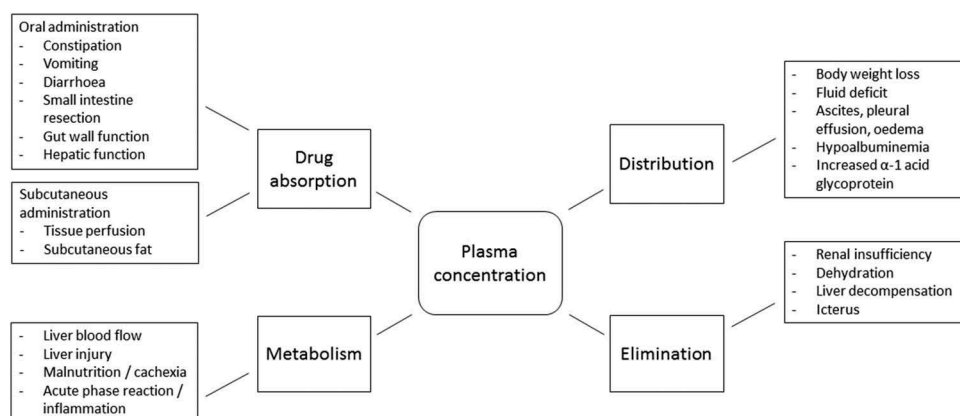

Figure 1. Physiological changes that can influence pharmacokinetics in the terminally ill adult patient.

Table 1. Physiological changes affecting drug absorption.

Physiological change in palliative care	Potential pharmacokinetic change	Consequence	Example drugs
Decreased GI motility	Increase in T_{max}	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 T_{max}	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
Diarrhea	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 T_{max} and possibly F of subcutaneously or transdermal administered drugs	Decrease in drug concentration and the effect may be delayed	Fentanyl patches, subcutaneous midazolam
Decreased subcutaneous fat	Increased T_{max} of subcutaneously or transdermal administered drugs	Drug concentration is unaffected yet the effect may be accelerated	Fentanyl patches, subcutaneous midazolam

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 diarrhea 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]

2.1.2. 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]

2.2. 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]

2.3. 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, edema, 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.

3. Distribution

The volume of distribution (V_d) 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 V_d 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 V_d 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 V_d is given in Table 2.

3.1. 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 favorable non-Hodgkin lymphoma, breast cancer, acute non-lymphocytic leukemia, 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 V_d for lipophilic drugs which will result in higher peak concentrations (C_{max}).

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 V_d for lipophilic drugs	Increase in drug concentration and effect	Midazolam
Fluid deficit	Decrease in V_d for hydrophilic drugs	Increase in drug concentration and effect	Morphine
Ascites, pleural effusion or generalized edema	Increase in V_d 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

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 V_d 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 edema leading to a higher V_d and lower initial concentrations.[13,22–24]

3.2. Protein binding

Besides body composition, alterations in protein binding can also affect V_d. 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 tumors 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.

3.3. 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 edema may probably need a higher initial dose of morphine (a hydrophilic drug) than a dehydrated patient.

4. 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 (Cl_H), 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 Cl_H 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.

4.1. 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.

4.2. 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

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 metabolized 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

cancer patients can be due to primary liver tumors 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 co-factors, 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.

4.3. 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.

5. 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 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.

5.1. 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.

6. 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.

7. Morphine

Morphine is widely used to treat pain and dyspnea 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′-diphospho-glucuronosyl-transferase (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

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 renal-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

influenced by changes in total body water (by influencing V_d), 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 V_d 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.

8. 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 V_d), 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 V_d after the animals became cachectic. Increased plasma concentrations as a result of a decrease in V_d can be further enhanced as a result of hypoalbuminemia. Increased plasma concentrations as result of decreased V_d 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 V_d. 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.

9. 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 V_d), 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 V_d, 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 V_d) 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 tumors 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.

10. 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.

Declaration of interests

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•• of considerable interest

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