Clin Pharmacokinet (2016) 55:697–709
DOI 10.1007/s40262-015-0345-4

ORIGINAL RESEARCH ARTICLE

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

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Published online: 29 December 2015

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.

Key Points

This is the first study to accurately describe the pharmacokinetics of morphine and its two major metabolites in terminally ill patients.

Morphine clearance decreased exponentially as a patient was closer to the time of death, falling by more than 26 % in the last week before death.

In terminally ill patients, estimated glomerular filtration rate (eGFR) combined with albumin levels was a better predictor for metabolite clearance than eGFR alone.

1 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

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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.

2 Materials and Methods

2.1 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 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

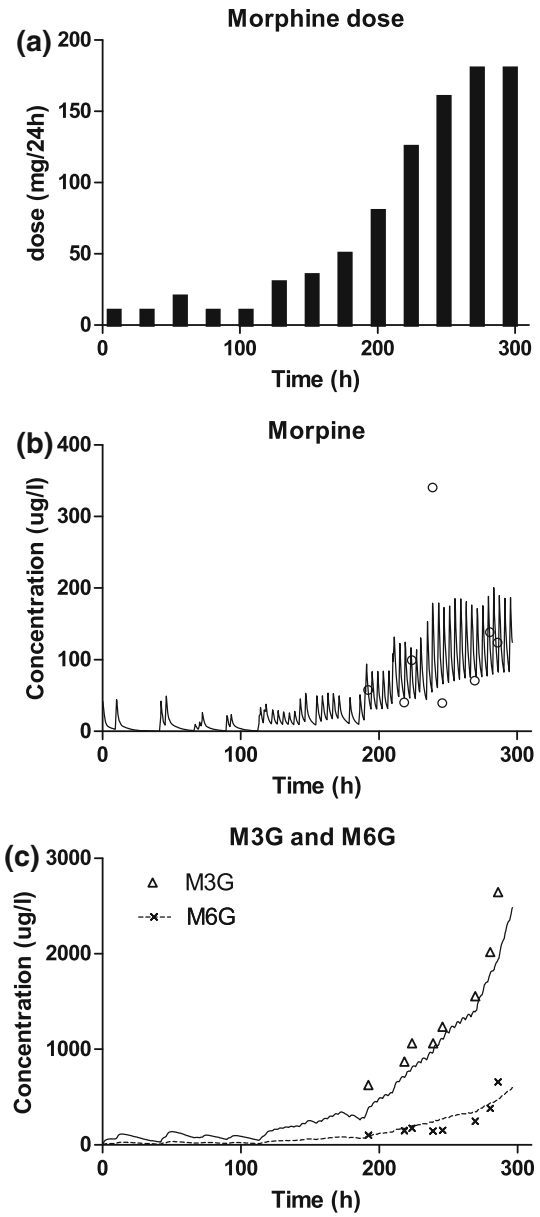

Fig. 1 Dose and concentration data of a patient representative for the study population over time. This individual had a decrease in renal function with a drop in eGFR from 41.4 to 16.3 at $T = 283$ h. **a** Daily doses of subcutaneous morphine over time until the time of death. **b** Morphine concentrations 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

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 venipuncture 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 in combination with sampling for clinical chemistry (standard of care) for which serum levels of albumin, creatinine, urea, bilirubin, γ-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.

2.2 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, M3G-d3 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 × 2.1 mm, 1.9 µm) 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.

2.3 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.

2.3.1 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.

2.3.2 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 ($p \leq 0.05$) 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.

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

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

with θi being the individual model-predicted pharmacokinetic parameter (e.g. clearance) for an individual with covariate value $\mathrm{cov_i}$, θpop being the population estimate for that parameter, $\mathrm{cov_m}$ representing the median covariate value and θcov representing the covariate effect. In the equation for categorical covariates, $\mathrm{cov_i}$ is either 1 or 0.

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),

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

in which θ_{Δ} is the change in parameter value from its initial value and θ_{rate} is a first-order rate constant determining the rate with which the parameter value changes over time.

2.3.3 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].

3 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].

3.1 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.

Including BSV on morphine clearance and bioavailability (F) of oral morphine both significantly improved the model fit with a change in OFV (ΔOFV) of −43.3 and −

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, μmol/L	8 (3–256)
γ-Glutamyl 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, μmol/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 consisted of four variables (age, sex, race and serum creatinine), as shown in Eq. 4

[b] The original MDRD formula consisted of six variables (age, sex, race, serum creatinine, serum albumin and serum urea), as shown in Eq. 5

[c] During any moment while receiving morphine treatment

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 (ΔOFV −75.97 vs −73.58 for creatinine levels and −66.77 for urea levels) and was therefore included in the structural model.

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

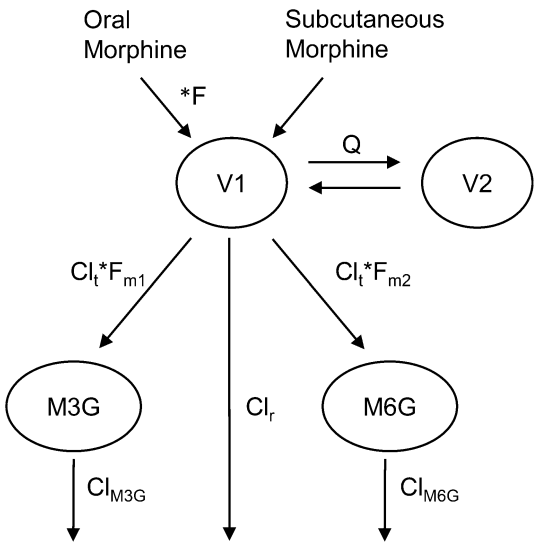

Fig. 2 Schematic representation of the two-compartment model for morphine and its two main metabolites. *F* bioavailability of oral morphine, *V1* central compartment for morphine, *V2* peripheral compartment for morphine, *Q* intercompartmental clearance of morphine, Cl_t total morphine clearance, F_{m1} fraction of morphine clearance responsible for M3G formation, F_{m2} fraction of morphine clearance responsible for M6G formation, Cl_r remaining morphine clearance ($Cl_t*1-(F_{m1} + F_{m2})$), Cl_{M3G} clearance of M3G, Cl_{M6G} clearance of M6G, *M3G* morphine-3-glucuronide, *M6G* morphine-6-glucuronide

3.2 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 volume 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

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
*V*1 (L)	185	190	28	–	190	116	369
Q (L/h)	75	76.1	35.7	–	65.1	9.95	146
*V*2 (L)	246	243	19	–	248	121	377
M3G							
F_{m1}	0.55[a]	0.55[a]	NA	–	0.55[a]	0.55[a]	0.55[a]
CL (L/h)	1.48	1.44	4.8	–	1.44	1.30	1.59
*V*1 (L)	7.65	8.02	33.2	–	7.75	3.62	14.9
M6G							
F_{m2}	0.1[a]	0.1[a]	NA	–	0.1[a]	0.1[a]	0.1[a]
CL (L/h)	1.87	1.78	6.8	–	1.79	1.56	2.05
*V*1 (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
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

RSE relative standard error, *CI* confidence interval, *OFV* objective function value, *F* bioavailability of oral morphine, *CL* clearance, *V1* central compartment for morphine, *V2* peripheral compartment for morphine, *Q* intercompartmental clearance of morphine, *M3G* morphine-3-glucuronide, *M6G* morphine-6-glucuronide, *NA* not applicable, F_{m1} fraction of morphine clearance responsible for M3G formation, F_{m2} fraction of morphine clearance responsible for M6G formation, *eGFR* estimated glomerular filtration rate, *TTD* time to death, *MDRD* Modification of Diet in Renal Disease, *GFR* glomerular filtration rate

[a] Transformation ratios for M3G and M6G were fixed to known literature values

[b] GFR was estimated using the standard four-variable MDRD equation

[c] TTD was incorporated as a first-order process, with TTD_{Δ} (overall change in clearance) as the change in parameter value from its initial value and TTD_{rate} (change in clearance per day as described by the first order process) as the first-order rate constant

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

Table 3 Covariate effects in univariate analysis compared with 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

OFV objective function value, *CL* clearance, *eGFR* estimated glomerular filtration rate, *CRP* C-reactive protein, *GGT* γ-glutamyl transpeptidase, *Vd* volume of distribution, *TTD* time to death, *GFR* glomerular filtration rate, *MDRD* Modification of Diet in Renal Disease

[a] Compared with subjects of Caucasian race

[b] 21.6 is the value for TTD_{Δ} (overall change in clearance) and 0.10 is the TTD rate (change in clearance per day as described by the first order process)

[c] GFR was estimated using the abbreviated MDRD equation

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).

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

3.3 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.

3.4 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).

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

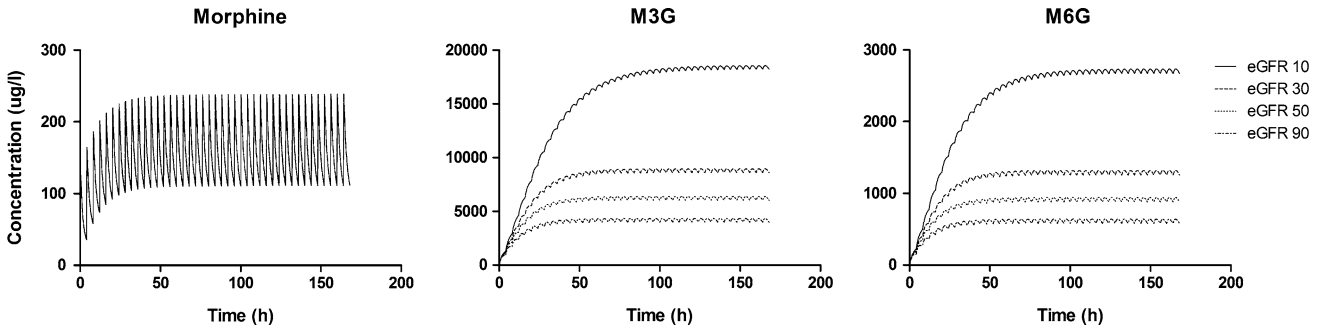

Fig. 3 Simulated plasma profiles of morphine, M3G and M6G for patients with an eGFR of 10 mL/min (*solid line*), 30 mL/min (*dashed line*), 50 mL/min (*dotted line*) and 90 mL/min (*dash-dotted line)* with a 30 mg six-daily subcutaneous bolus injection dosing regimen and stable plasma albumin levels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

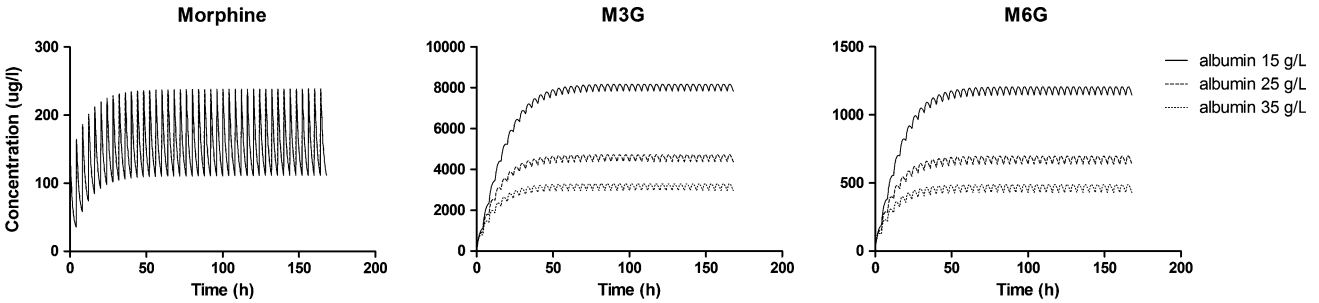

Fig. 4 Simulated plasma profiles of morphine, M3G and M6G for patients with plasma albumin levels of 15 g/L (*solid line*), 25 g/L (*dashed line*) and 35 g/L (*dotted line*) with a 30 mg six-daily subcutaneous bolus injection dosing regimen and stable plasma albumin levels of 78. *M3G* morphine-3-glucuronide, *M6G* morphine-6-glucuronide

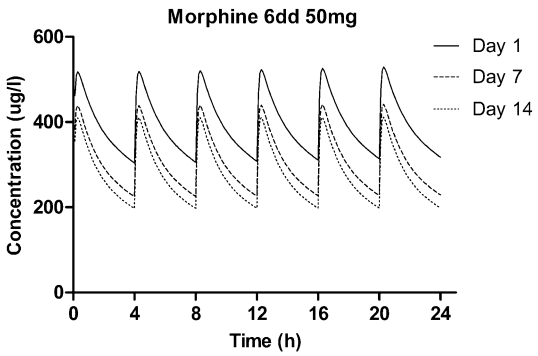

Fig. 5 Simulated plasma profiles of morphine in the case of 50 mg six times daily subcutaneous bolus infusion, 2 weeks (*dotted line*), 1 week (*dashed line*) and 1 day (*solid line*) before death

a 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).

4 Discussion

This is the first population pharmacokinetic study of morphine in end-of-life patients performed in a nonacademic 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].

In this same study, Säwe and co-workers found a morphine clearance ranging from 0.3 to 0.97 L/h/kg, which

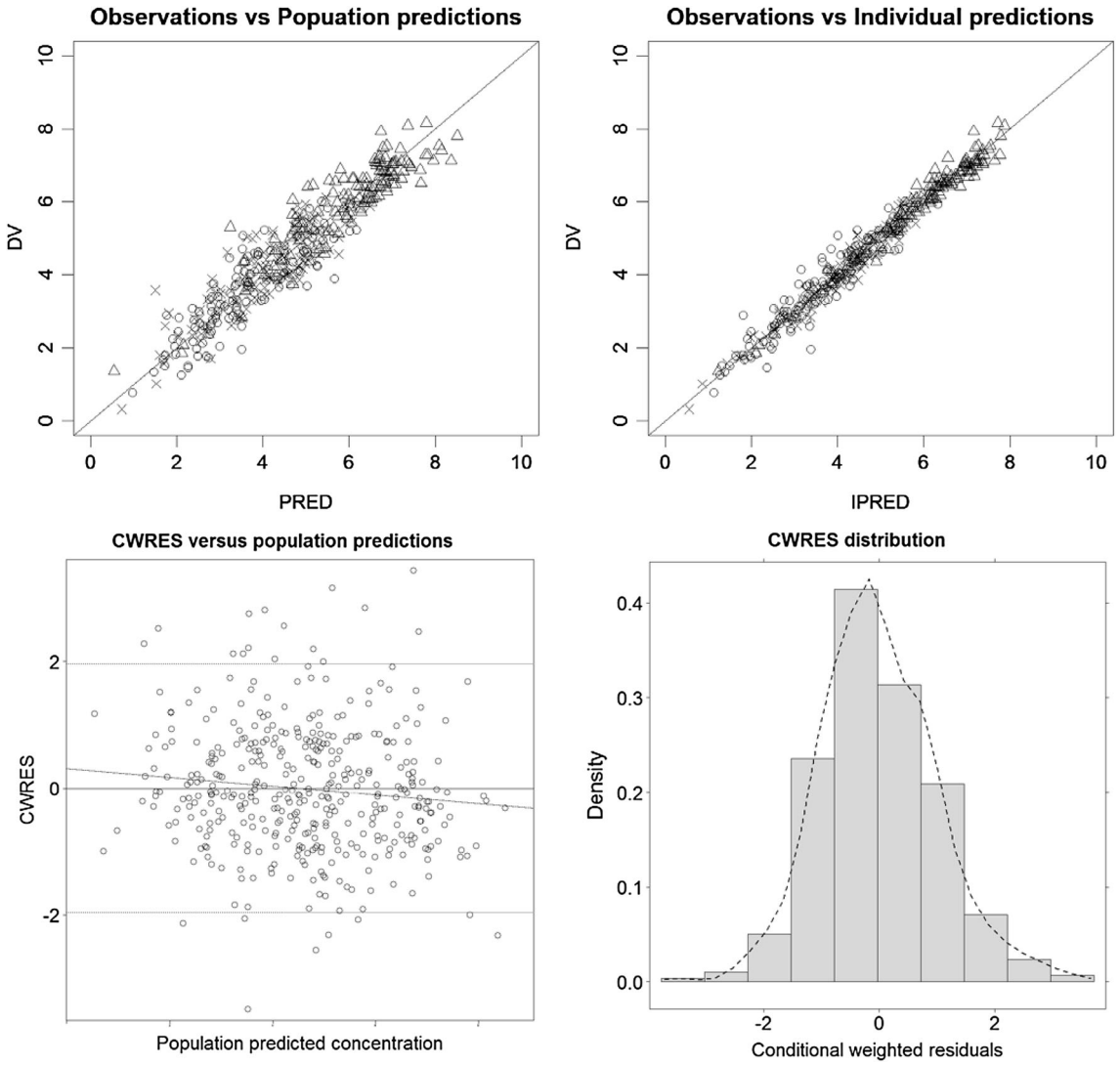

Fig. 6 Goodness-of-fit plots of the final model. The *top two panels* show the PRED and IPRED concentrations versus the DV for morphine (*open circles*), M3G (*open triangles*) and M6G (*crosses*), with the *solid line* displaying the line of unity. The *bottom two panels* show the correlation of CWRES 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

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 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, 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

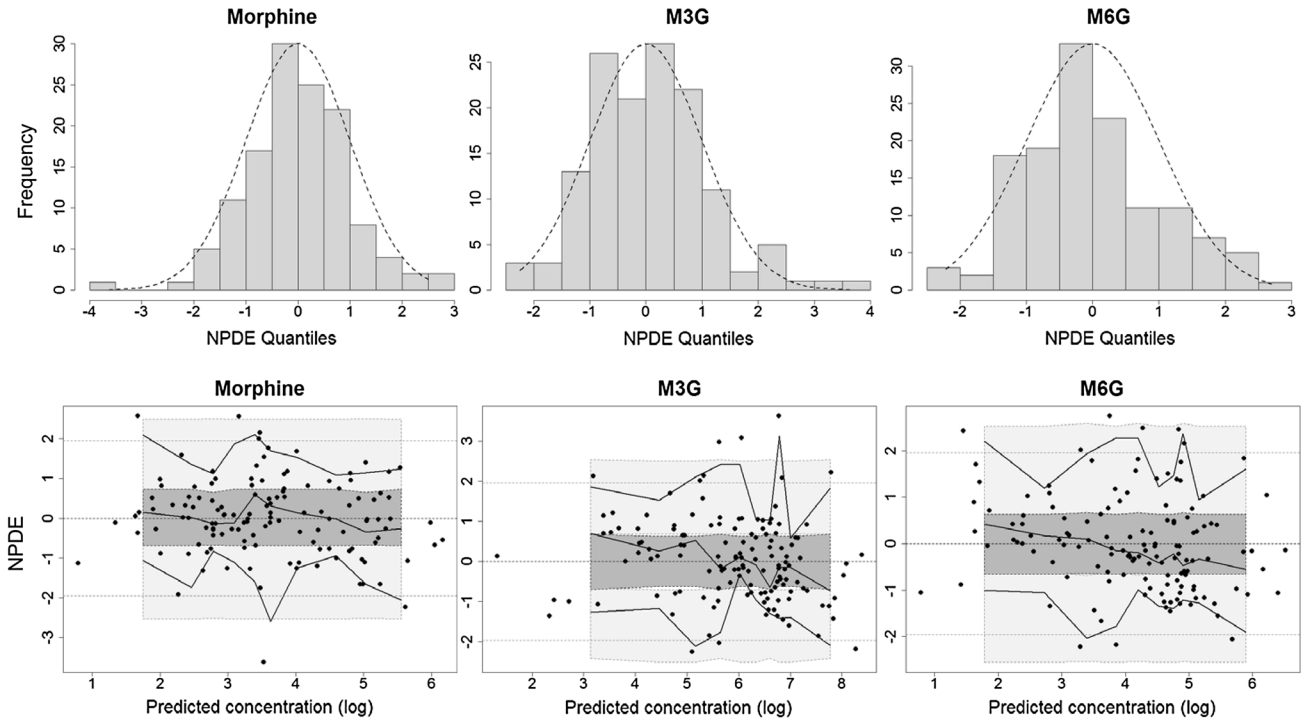

Fig. 7 NPDE analysis of the final model for morphine, M3G and M6G. The *top panels* show the distribution of the NPDE quantiles (*grey bars*), with the shape of a normal distribution also shown (*dashed line*). The *bottom panels* show the NPDEs versus the log of the predicted concentrations with individual 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

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 *V*d/*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.

5 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.

Funding No sources of funding were used in the preparation of this manuscript.

Conflict of interest Linda G. Franken, Anniek D. Masman, Brenda C.M. de Winter, Birgit C.P. Koch, Frans P.M. Baar, Dick Tibboel, Teun van Gelder, and Ron A.A. Mathôt have no conflicts of interest that are directly relevant to the content of this manuscript.

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