Morphine in Postoperative Patients: Pharmacokinetics and Pharmacodynamics of Metabolites

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BACKGROUND: There is great variability in the need for morphine in the postoperative period. We performed a pharmacokinetic–pharmacodynamic study considering the potential effect of the two main metabolites of morphine.
METHODS: Fifty patients with moderate to severe pain received morphine as an IV titration, followed by IM administration postoperatively. The plasma concentration of morphine, morphine-6-glucuronide (M-6-G), morphine-3-glucuronide (M-3-G), and pain intensity were measured at frequent intervals. Pharmacokinetic and pharmacodynamic fitting was performed with the software NONMEM.
RESULTS: The pharmacokinetics were largely predictable. M-6-G and M-3-G clearances were markedly decreased in patients with renal failure. The pharmacodynamics was less predictable, with an important interindividual variability. M-6-G was 7.8 times more potent than morphine, but the average time to peak concentration in the effect compartment after a bolus injection of morphine was 4.25 h for M-6-G, when compared to 0.33 h for morphine. M-3-G showed mild inhibition of the analgesic properties of morphine and of M-6-G. The time to M-3-G peak concentration in the effect compartment after a bolus injection of morphine was 10 h.
CONCLUSIONS: M-6-G is a potent opioid agonist and M-3-G a mild opioid antagonist. Both are poorly excreted in patients with renal failure. However, the metabolism of morphine was rapid when compared to the transfer of metabolites through the blood–brain barrier, which appears to be the limiting process. Because poor analgesia due to M-3-G's effect may occur in some patients after 1 or 2 days, a switch to other molecules should be considered.
(Anesth Analg 2007;105:70–8)

Morphine is the preferred drug for relieving pain in the immediate postoperative period. However, there is great interpatient variability in the efficient dosing of morphine and it is still difficult to precisely adapt dosing to the patient's needs (1). The variability in consumption of morphine has been described both in cancer patients and in postoperative patients (1,2). Pharmacogenomic factors already described only partly explain the variability, and simple efficient clinical or biological factors leading to individualized dosing remain to be found.

Pharmacokinetic factors such as the effect of morphine-6-glucuronide (M-6-G), an active metabolite of morphine poorly excreted in patients with renal failure (3,4), are known to modify the extent and duration of morphine's action. M-6-G does not easily cross the blood–brain barrier in normal patients. However, even after a single dose of morphine given orally in patients requiring hemodialysis, the concentration of M-6-G in plasma dramatically increases, and the cerebrospinal fluid (CSF) concentration measured 24 h after administration reaches 15 times the concentration measured in the CSF of patients with normal kidney function (5). Variations in the extent of metabolism of morphine have also been described (6,7), but this effect mainly due to genetic polymorphism in the UDP-glucuronosyltransferase (UGT)2B7 (8,9) appears to be of clinical relevance only after oral administration because of the hepatic first pass effect.

Pharmacodynamic factors are considered to be the major cause of variability in morphine effect. Individual pain intensity markedly varies among subjects depending on the extent of surgical wounds, and also on patient's traits and their previous experience of pain (10,11). The response to morphine administration is highly variable—a variability not explained by the polymorphism of the μ-opioid receptor (12,13). Demographic factors such as age (14) or gender (15) have been proposed as predictive factors of morphine requirements. However, none of these factors appears to clearly explain the interindividual variability of morphine needs, in as much their relevance is controversial (14,15).

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Accepted for publication March 19, 2007.

Supported by a grant from INSERM 91CN05.

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DOI: 10.1213/01.ane.0000265557.73688.32

Finally, the respective contribution of morphine and its 6-glucuronide metabolite in antinociception remains controversial (16,17).

We therefore designed a study to address the respective role of morphine and its glucuronide metabolites in analgesia, with a particular attention to the role of pharmacokinetics. We also addressed the role of simple demographic and biological markers in morphine requirements.

METHODS

Patients and Study Design

Fifty patients (25 males, 25 females) participated to the study. The protocol was approved by the ethical committee at the time of initiation of the study (INSERM 91CN05, 1990) and all patients gave their informed consent. Because of the extensive computing time required when the study was performed, it was not possible to complete the modeling part of the study. The clinical part has been published elsewhere (18). The study was designed to include 50 patients with significant (moderate to severe) pain in this pharmacokinetic–pharmacodynamic (PK–PD) segment. None of the patients had any opioid intake in the preceding months, and none seemed to be a drug user. When the patients arrived in the postanesthesia care unit (PACU), their pain intensity was assessed using a visual analog pain scale (VAS) (from 0 cm = no pain to 10 cm = the worse possible pain). If they had a VAS scale more than 4 cm, they were included in the PK–PD part of the study. They received morphine as a titration with boluses of 3 mg every 10 min. Titration was stopped when the patient's VAS pain scale was <3 cm. If they received 0 or 3 mg morphine as titration, patient were not included in the study. If they received at least 6 mg morphine IV as titration, they were randomly assigned to a low or high IM (IM) maintenance group (18). Patients in the high- and low-dose group received, respectively, 2/3 and 1/2 of the total titrated dose 3 h after the end of titration, followed by 1/2 and 1/3 of the titrated dose every 4 h.

Blood Sampling and Pain Measurements

Five milliliters of blood was sampled in heparinized tubes (Vacutainer®) 10 min after the end of the IV titration, before the first IM injection, 30 min after the first IM injection, and the next morning. Additional samples were drawn in some patients when samples for clinical purpose were required and in six patients (three males and three females) who were sampled more frequently. Pain intensity was recorded in the PACU before each injection (IV and IM) and at the time of blood sampling. When the patients were discharged to the ward, pain intensity was also recorded before the second IM injection and at all times of blood sampling.

Assay

Blood samples were rapidly centrifuged and the plasma was stored at −20°C until analysis. Morphine and glucuronides were measured in plasma using high-performance liquid chromatography with combined coulometric and fluorimetric detections (19,20). The limit of detection was 3.5, 10, and 22 nM for morphine, M-6-G, and M-3-G, respectively.

Modeling Procedure

Pharmacokinetics (morphine, M-6-G, and M-3-G plasma concentrations) and pharmacodynamics (pain intensity) were fitted separately using nonlinear mixed effect modeling with the software NONMEM version V level 1.1 (21). For both steps, the procedure ADVAN5 was used.

The logarithm of the concentration versus time data was fitted using the first order estimation method with an additive error model. Two different errors were used to account for the observed difference in the measurement errors between morphine and glucuronides (due to the difference between coulometric and fluorimetric detections). The *post hoc* Bayesian parameter estimates obtained during the pharmacokinetic step were used in the data set for fitting pharmacodynamic data. We used the conditional estimation method with interaction to fit the pain intensity versus time data with an additive error model. For both models, an exponential interindividual error was associated to each structural parameter.

The pharmacokinetic model used was derived from that of Lotsch et al. (22) (Fig. 1). For pharmacokinetics, the model is built in terms of clearances and volumes. Because we did not sample urine, and because the calculation of the ratio of metabolic formation of glucuronides assumed a common volume of distribution, we fixed the nonglucuronide clearance and assigned a common volume of distribution for M-6-G and M-3-G. The nonglucuronide clearance (direct unchanged urinary clearance and nonglucuronide metabolic clearance) was fixed to the value of 26.0 ± 12.0 L/h using the data of Hasselström and Säwe (23). This value is the result of the addition of a urinary clearance of 9.0 ± 2.0 L/h and a nonurinary, nonmetabolic (i.e., non-glucuronide) clearance of 17.2 ± 10.9 L/h considering an arbitrary correlation of 50% between the two values. The pharmacodynamic model was the E_{max} model (24). For both PK–PD, covariates were successively entered in the model and tested against the full model without covariates. The covariates tested for pharmacokinetics were body weight, lean body weight, body surface area, age, gender, and creatinine clearance (CRCL) calculated according to the Cockcroft–Gault formula (25). For pharmacodynamics, the candidate covariates were age and gender. In addition, the inhibitory effect of M-3-G was tested using the Gaddum formula:

$$E = E_0\left(1 - \frac{\sum(\mathrm{Ce}/\mathrm{Cpss50})^{\gamma}}{\mathrm{IC}_{50}^{\gamma} + \sum(\grave{\mathrm{C}}\mathrm{e}/\mathrm{Cpss50})^{\gamma}}\right)$$

where E_0 is the basal pain intensity (VAS0), $\Sigma(\mathrm{Ce}/\mathrm{Cpss50})^{\gamma}$ is the sum of the concentrations of

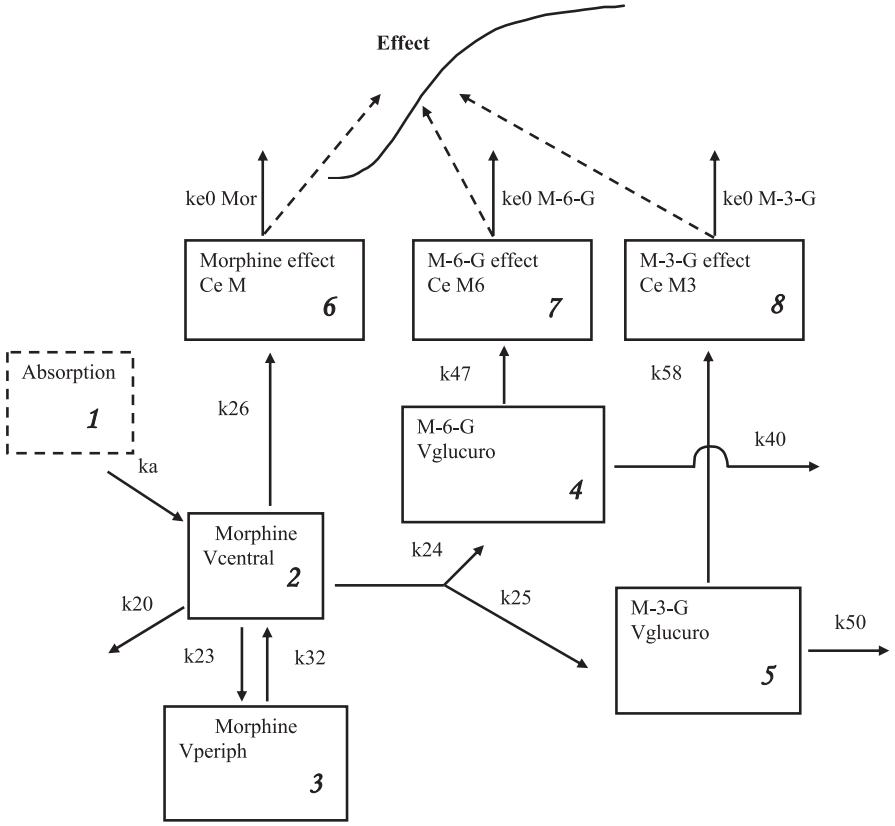

Figure 1. Pharmacokinetic-pharmacodynamic model. Pharmacokinetics is described by a first-order mammillary model with five compartments (compartments 1–5). The pharmacodynamic model is an extension of the pharmacokinetic model with three effect compartments linked to morphine, morphine-6-glucuronide (M-6-G), and morphine-3-glucuronide (M-3-G) concentrations (compartments 6, 7, 8, respectively). k_a is the absorption rate constant after IM administration. k_{24} and k_{25} are the morphine to glucuronide metabolic rate constants. Elimination from each effect compartment occurs via ke0, the rate constant describing the steady-state temporal distance between the central and the effect compartments. Because the concentration in the effect compartment is only known to a scaling factor, we used Cpss50, the steady-state concentration in the central compartment leading to half-maximum effect as the normalizing factor: Ce/Cpss50 (Methods and Ref. 24). The final effect results from the addition of the effect of each drug (morphine and M-6-G agonists, and M-3-G antagonist) (Methods and Appendix, available online at http://www.anesthesia-analgesia.org/).

morphine and M-6-G in their respective effect compartment (the concentrations are normalized by Cpss50, the concentration of the molecule in the central compartment leading to half-maximum effect at steady-state), γ is the Hill coefficient and $IC_{50} = 1 + (Ce_{M3G}/Cpss50_{M3G})^{\gamma}$, where $Ce_{M\text{-}3\text{-}G}$ is the concentration of M-3-G in its effect compartment and $Cpss50_{M\text{-}3\text{-}G}$ is the concentration of M-3-G in the central compartment leading to half-maximum effect at steady-state (Fig. 1 and Appendix[1], available online at http://www.anesthesia-analgesia.org/). In case of absence of inhibition, the formula reduces to:

$$E = E_0\left(1 - \frac{\sum(Ce/Cpss50)^{\gamma}}{1 + \sum(Ce/Cpss50)^{\gamma}}\right)$$

A time varying basal pain intensity was also tested (linear decrease in VAS0 with time). A nonparametric Bootstrap was used to calculate the interindividual variability of the structural parameters. However, because of the extensive computer time, only 400 replications were done for kinetics and 160 for dynamics.

The initial pain intensity upon arriving in the PACU and the titrated dose of morphine were compared between genders and types of surgery using the Mann–Whitney test or a Kruskall–Wallis test. The different models were tested using the log-likelihood ratio test for nested models considering the principle of parsimony. Because of the asymptotic nature of convergence and tests, a conservative value of 0.01 was chosen for statistical significance. Data are given with three significant digits.

RESULTS

A total of 225, 226, and 216 concentration-time data points were obtained for morphine, M-6-G, and M-3-G, respectively (Fig. 2). Similarly, 450 VAS-time data points were obtained in the 50 patients. The demographic data of the 50 patients are displayed in Table 1. We did not observe any significant difference in initial pain intensity (VAS0) or in titrated dose between genders or types of surgery. Similarly, we

[1]This appendix is available on request to jean-xavier.mazoit@u-psud.fr.

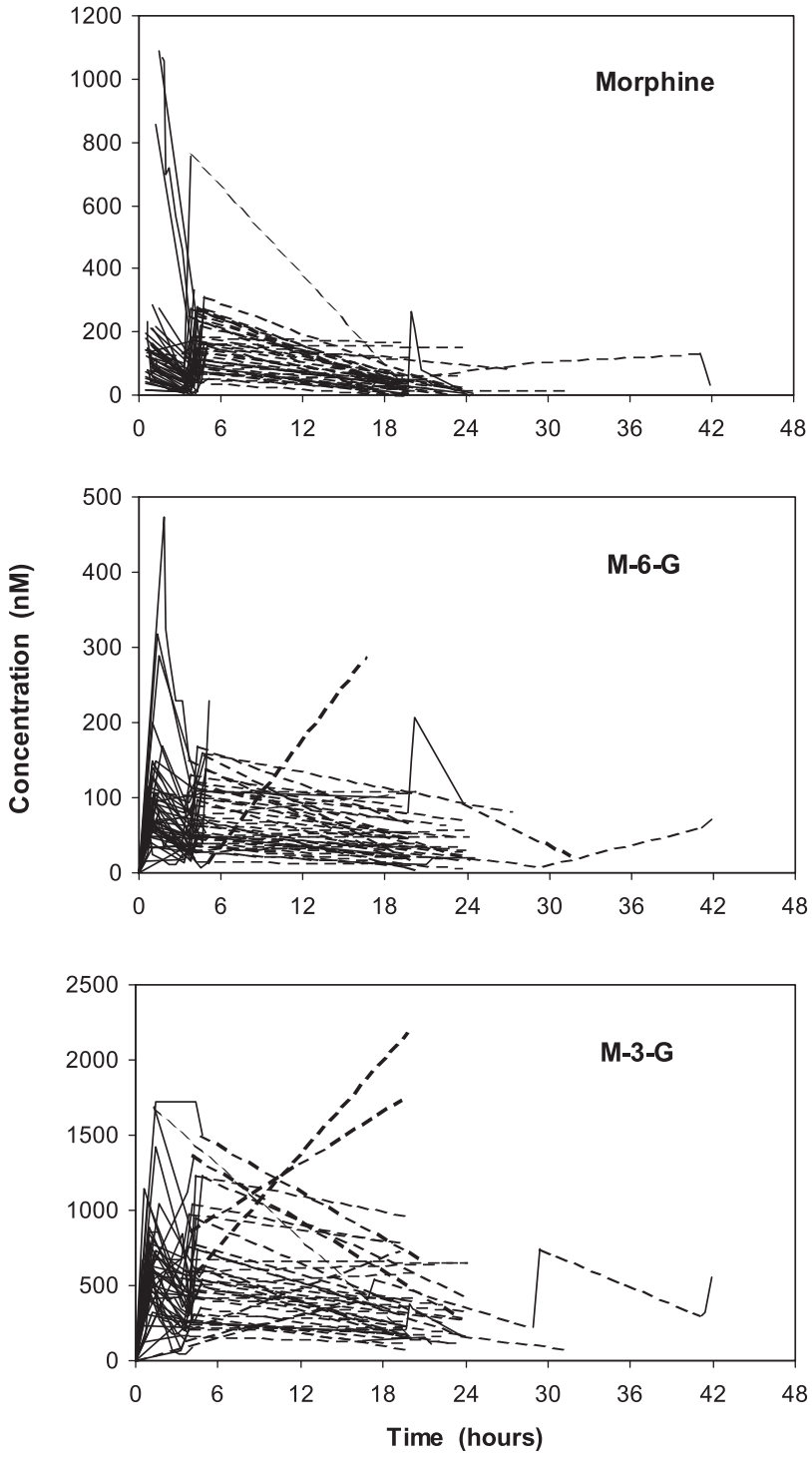

Figure 2. Measured concentrations of morphine, morphine-6-glucuronide (M-6-G), and morphine-3-glucuronide (M-3-G) in each patient.

failed to show any difference in the patients' age between types of surgery. Despite the limited number of data points (1.5 and 1.8 point per subject per structural parameter on average for the PK and PD models, respectively), the fitting was adequate (Fig. 3).

Pharmacokinetics

The incorporation of CRCL in the model markedly improved the fitting (the objective function decreased from 124.8 to 92.05). The typical metabolic clearances of M-6-G and of M-3-G from morphine were 13.7 and 62.3 L/h, respectively. The typical values of M-6-G clearance were then 12.7, 6.36, and 3.18 L/h in patients with a CRCL of 120, 60, and 30 mL/min, respectively. Similarly, the typical values of M-3-G clearance were 6.85, 3.43, and 1.71 L/h in patients with a CRCL of 120, 60, and 30 mL/min, respectively (Table 2). No other covariate successfully entered in the model: clearances and volumes were not influenced by body weight, lean body weight, body surface area, age, or gender.

Pharmacodynamics

The model with inhibition by M-3-G markedly improved the fitting (the objective function decreased

Table 1. Demography of the 50 Patients

Surgery	Gender (M/F)	Age (yr)	Weight (kg)	CRCL (mL/min)	VAS0 (cm)	Titrated dose (mg)
Abdomen	6/6	54 ± 19	75 ± 14	81 ± 27	10 (4.5–10)	15 (9–30)
Ankle	2/1	46 ± 8	70 ± 20	93 ± 12	9 (8–10)	18 (9–21)
Shoulder	5/4	57 ± 8	69 ± 20	84 ± 32	7.5 (6–10)	15 (9–27)
Knee	6/3	52 ± 22	69 ± 17	87 ± 32	10 (8–10)	21 (9–30)
Hip	3/7	52 ± 15	64 ± 14	81 ± 26	7.5 (7–10)	10.5 (6–30)
Spine (diskectomy)	3/5	41 ± 4	68 ± 13	91 ± 14	8 (7–10)	12 (9–18)
Total	*25/25*	*51 ± 15*	*69 ± 17*	*85 ± 26*	*8.5 (4.5–10)*	*12 (3–30)*

Data are counts, mean ± SD, or median (range).

VAS = visual analog pain scale; CRCL = creatinine clearance.

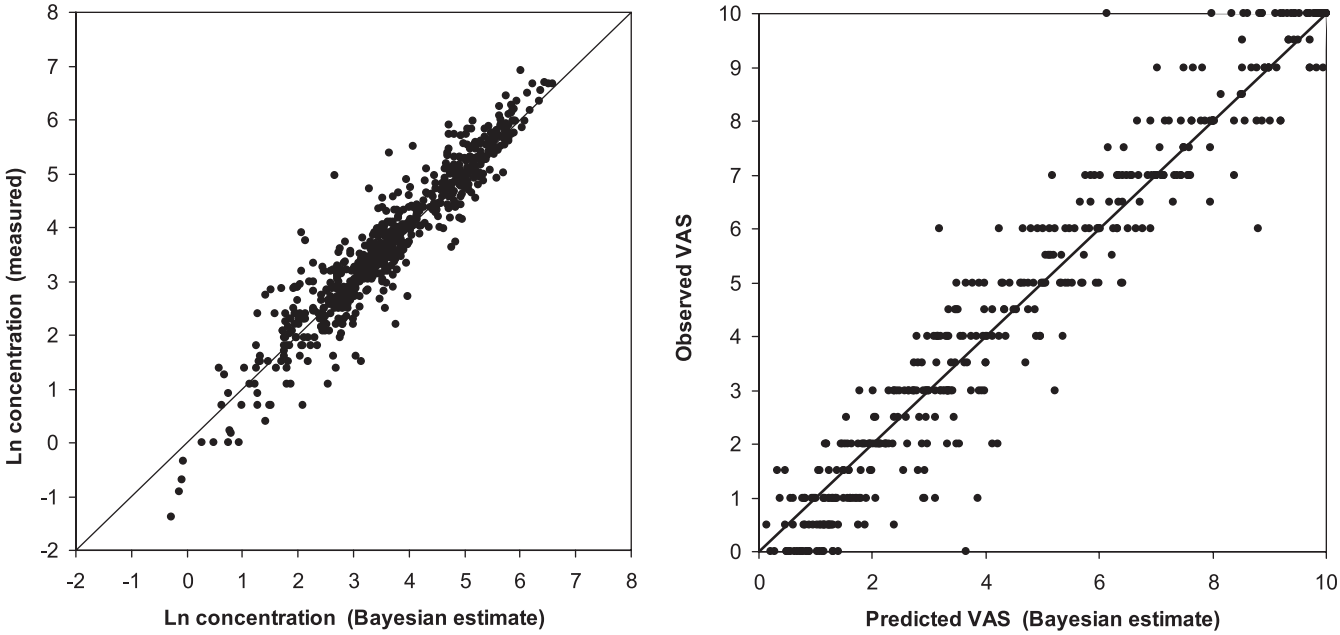

Figure 3. Adequacy of fitting (pharmacokinetic (PK) concentrations–time data [left] and pharmacodynamic (PD) visual analog pain scale (VAS) time data [right]). PK was modeled as the logarithm of the concentration with the first-order method and PD was modeled with the conditional method.

from 856.1 to 749.9 when the effect of M-6-G is added to that of morphine and to 698.1 when the effect of M-3-G is added to the effects of morphine and M-6-G). M-3-G Cpss50 (the concentration at steady-state in the central (sampling) compartment leading to half-inhibition of morphine and M-6-G effect) was 880 nM (Table 2). A M-3-G concentration in plasma higher than this value was observed at least once in 13 of the 50 patients (Fig. 2). None of the tested covariates (gender, age, CRCL) successfully entered in the model. Also, the incorporation of time-varying basal pain intensity (VAS0) did not improve the fitting. It was not possible to differentiate the two metabolites for the transfer rate constant from central to effect compartment (ke0). The corresponding half-life ($T_{1/2}$ ke0) was 2.89 h for M-6-G and M-3-G when compared to 1.66 h for morphine. M-6-G Cpss50 was 9.7 times lower than morphine Cpss50 (M-6-G was about 10 times more potent than morphine, but with a marked lag-time in the appearance of the effect). Also, the interindividual variability parameters for morphine and M-6-G Cpss50 were indistinguishable. The Hill coefficient (allosteric factor) was not significantly different from 2, and no significant interindividual variability parameter could be associated to this sigmoidicity factor. A significant negative correlation was observed between the VAS scores and the ratio M-6-G/M-3-G concentration observed after the fourth hour of administration (Fig. 4).

DISCUSSION

The main finding of this PK–PD study of morphine in postoperative patients is that morphine's antinociceptive action in the postoperative period is modulated by its own metabolites. In these patients with moderate to severe pain, neither age, weight, gender influenced the kinetics or the effect of morphine. Renal failure decreased the rate of elimination of the glucuronide metabolites, and therefore increased their effect relative to the effect of morphine itself, at least after several hours of administration. M-6-G acts as an opioid agonist, while M-3-G seems to act as an antagonist.

Table 2. Pharmacokinetic and Pharmacodynamic Parameters

	Structural parameter (population value)	95% Confidence interval (Bootstrap)
Pharmacokinetics		
k_a (h^{-1})	1.03 (23%)	0.832–2.3
CL (L/h)	102 (13%)	86.2–129
$CL_{NON\ GLUCURO}$ (L/h)	26.0 (FIXED)	(FIXED)
CL_{PERIPH} (L/h)	101 (21%)	67.8–170
V_c (L)	14.2 (26%)	8.83–40.3
V_{PERIPH} (L)	258 (18%)	231–769
$V_{GLUCURO}$ (L)	20.8 (17%)	10.4–23.9*
Q_R	4.54 (16%)	4.01–5.51
$CL_{M\text{-}6\text{-}G}$ (L/h)	slope 0.106 (18%)†	0.069–0.134
$CL_{M\text{-}3\text{-}G}$ (L/h)	slope 0.0571 (12%)†	0.0462–0.0683
Pharmacodynamics		
$ke0_{MOR}$ (h^{-1})	0.418 (32%) $T_{1/2}\ ke0_M$ = 1.66 h	0.321–0.623
$ke0_{M\text{-}6\text{-}G}$ (h^{-1})	0.240 (40%) $T_{1/2}\ ke0_{M\text{-}6\text{-}G}$ = 2.89 h	0.193–0.337
$ke0_{M\text{-}3\text{-}G}$ (h^{-1})	0.240 (40%) $T_{1/2}\ ke0_{M\text{-}3\text{-}G}$ = 2.89 h	0.193–0.337
Cpss50 MOR (nM)	124 (20%)	105–168
Cpss50 M-6-G (nM)	12.8 (29%)	10.6–17.8
Cpss50 M-3-G (nM)‡	880 (84%)	610–2800

Structural parameters are the average population value with the coefficient of variation of the estimate in parentheses.

Values inside parentheses indicate percentages.

MOR = morphine; M-6-G = morphine-6-glucuronide; M-3-G = morphine-3-glucuronide; k_a = absorption rate constant after intramuscular administration; CL = total body clearance (MOR); $CL_{NON\ GLUCURO}$ = nonglucuronide clearance (MOR); CL_{PERIPH} = intercompartmental clearance (central-peripheral compartment) (MOR); V_c = volume of central compartment (MOR); V_{PERIPH} = volume of peripheral compartment (MOR); $V_{GLUCURO}$ = volume of distribution (M-6-G and M-3-G); Q_R = ratio of metabolic formation (M-3-G/M-6-G); $CL_{M\text{-}6\text{-}G}$ and $CL_{M\text{-}3\text{-}G}$ = elimination clearance (M-6-G and M-3-G, respectively); ke0 = transfer rate constant from central to effect compartment; Cpss50 = concentration in the central compartment leading to half-maximum effect at steady-state; ke0 and Cpss50 are indexed with MOR, M-6-G, and M-3-G, respectively; NS = nonsignificant: the incorporation of the parameter had no effect (random parameter $<10^{-10}$).

* The interindividual variability parameter was only significant for M-3-G.

† The glucuronide clearance is expressed as slope × creatinine clearance (mL/min).

‡ Cpss50 M-3-G is the concentration leading to half-maximum inhibition.

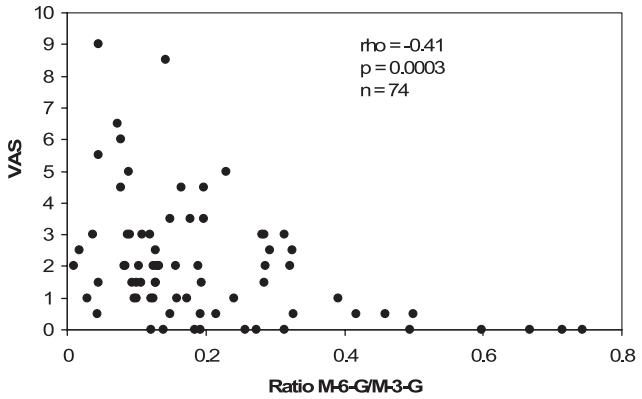

Figure 4. Correlation between the morphine-6-glucuronide (M-6-G)/and morphine-3-glucuronide (M-3-G) concentration ratio and the visual analog pain scale (VAS) (data are only from the fourth hour after the beginning of morphine administration to the end of observation). Despite the supposed important lag-time between metabolite concentration in plasma and effect, it is clear that after several hours, the ratio is correlated with pain suppression.

Morphine kinetics calculated by mixed-effect regression are similar to those already reported in the literature, either in volunteers (22,23) or in patients (4,6), with a clearance equivalent to the hepatic blood flow (or slightly higher). By fixing the nonglucuronide clearance of morphine, we were able to calculate the metabolic and the elimination clearances of M-6-G and M-3-G, which were similar to those already published in the literature, calculated either after biotransformation of morphine or after direct administration of the metabolite(s) in volunteers or in patients (4,22,23,26). The metabolic clearances of M-6-G and of M-3-G from morphine were close to the values already published (13.7 and 62.3 L/h, respectively) (23). As already described, the two metabolites had their elimination impaired in patients with decreased renal filtration rate. When compared with patients with an ideal renal function (CRCL = 120 mL/min), patients with a CRCL equal to 30 mL/min had their elimination clearance of M-6-G and of M-3-G divided by 4. Because M-6-G is 10 times more potent than morphine, patients with renal failure are at increased risk of respiratory depression. This risk is delayed because the glucuronide metabolites, which are more polar than morphine, cross the blood–brain barrier with some delay when compared to the parent drug. We calculated a similar blood-effect site equilibration half-life ($T_{1/2}$ ke0) of 2.89 h for both metabolites. This half-life is slightly less than twice the half-life for morphine itself (1.66 h), but the time elapsed between injection and effect must also consider the biotransformation process (Fig. 5).

Pharmacodynamic parameters showed an important interindividual variability, which reflects the usual variability in pain intensity between patients

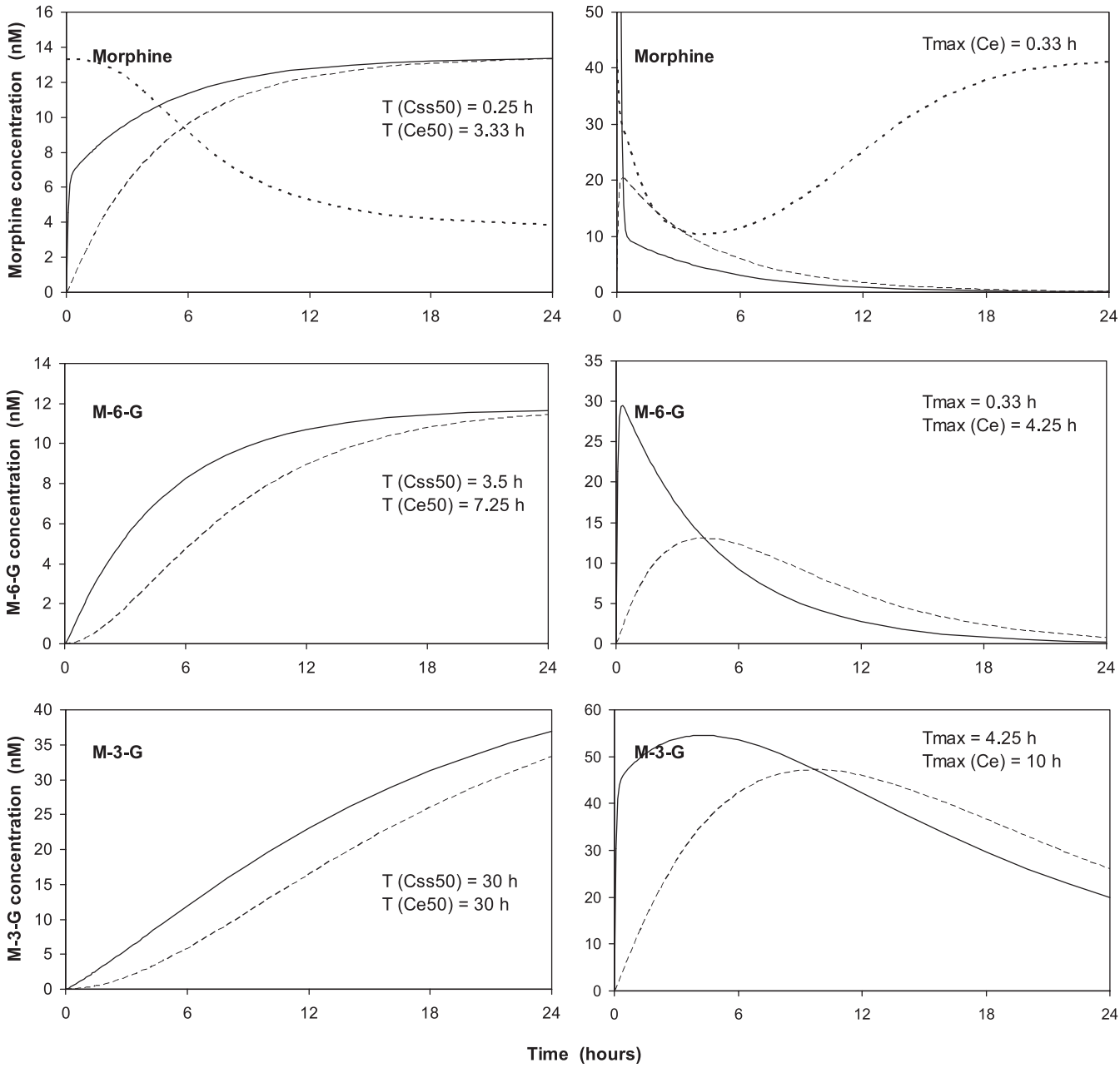

Figure 5. Simulated concentration of morphine (top), morphine-6-glucuronide (M-6-G) (middle), morphine-3-glucuronide (M-3-G) (bottom) after continuous infusion of a arbitrary dose of 10 mg of morphine over 1 day (0.42 mg/h) (left) or after a single bolus injection of 10 mg (right). The typical average values of the parameters have been used for the simulation. The solid line represents the concentration in the central compartment (blood) and the dashed line the concentration in the effect compartment. *T* (Css50) and *T* (Ce50) are the time to half steady-state concentration in the central and effect compartment respectively. T_{max} and T_{max} (Ce) are the time to peak concentration in the central and effect compartment, respectively. On the upper part (labeled Morphine) is superimposed the time-course of the visual analog pain scale (VAS) pain measurement (thick dashed line). After a single IV bolus injection, a rapid decline in pain intensity is observed (inflection at 20 min) followed by a slow decline (maximum at 4 h).

and in the dose of morphine needed to treat pain (Table 2).

Binding experiments have shown that morphine and M-6-G affinities for both μ receptors are within the same order of magnitude (27). Behavioral studies in rodents, as well as studies done in volunteers or in patients, show large discrepancies depending on the experimental conditions (16,17,27). In animals and in cancer patients receiving M-6-G over a prolonged period, M-6-G appears 2–100 times more potent than morphine, whereas in volunteers receiving M-6-G for a shorter period of time, the molecule exhibits only a weak analgesic effect. In patients receiving M-6-G for postoperative analgesia, the drug seems either ineffective when given at the end of surgery as a single dose of 0.1 mg/kg (17) or of similar efficacy as morphine when given postoperatively as patient-controlled analgesia on a 1:1 ratio (28). Interestingly, in the latter study, morphine was more potent than M-6-G only during the first 4 h of treatment. In our patients, when

VAS scores were plotted against the ratio M-6-G/M-3-G concentration observed after the fourth hour of administration, a significant negative correlation was observed (Fig. 3). This is, indeed, an additional reason to think that M-6-G is an important factor of analgesia. In our patients with severe postoperative pain, M-6-G was 10 times more potent than morphine on average (Table 2), but there was an important delay between injection and effect, explaining why M-6-G effect appears only after several hours of morphine administration (Fig. 5). This is in accordance with the delayed effect observed when morphine is administered orally in the postoperative period (29). In this case, the major first-pass effect leads to an important production of M-6-G, which is considered to be effective only 12 h after administration (29).

Actually, after parenteral (IV or IM) administration, metabolism is a comparatively rapid process when compared to the transfer of the metabolites through the blood–brain barrier. Although the slow appearance of morphine, M-6-G, and M-3-G in CSF has been previously reported in patients (4,5), little attention has been paid to this phenomenon. The transfer across the blood–brain barrier is, then, the limiting process and this may explain both the delayed respiratory depression observed in patients with renal failure and the fact that, despite numerous studies, the effect of M-6-G is still controversial.

Neither age, gender, or body weight significantly improved the pharmacodynamic model. However, because of the relatively few patients studied, a lack of power may be the reason. The effect of age on morphine requirements is controversial. For example, Macintyre and Jarvis (14) observed that older patients need less morphine than younger patients during the first postoperative day. Other authors did not find any correlation between the dose of morphine administered by titration in the PACU and age (15,30,31), but most of them observed that older patients had smaller morphine requirements once discharged to the ward. We were unable to demonstrate such a time-varying effect. Similarly, we did not find any effect of gender on basal pain intensity nor on morphine requirements and pain intensity during the study course. Sex-related differences in pain intensity and in the effect of opioids have been reported (15,32–34). Because, these two factors (basal pain intensity and sensitivity to opioids) may act in opposite directions, it is difficult to draw any definite conclusion from our negative results.

M-3-G is the main metabolite of morphine. It is usually considered as inactive, although animal studies and case reports in humans have suggested an antianalgesic, and possibly, an excitatory effect of the molecule (35,36). M-3-G has been injected in only two studies done in volunteers (37,38). The results are not conclusive, likely because the subjects were studied during a very short period (2 h). We show that M-3-G has an antinociceptive effect. This effect is moderate, and because of the very long transfer half-life from injection site to effect compartment, a significant antinociceptive effect of M-3-G is not thought to occur before the 9th–18th h after initiation of analgesia (Fig. 5). However, this may be important for some patients who may not have analgesia once discharged to the ward. In these patients, the increase in morphine administration may be of poor analgesic effect and the use of alternate drugs, such as fentanyl, may be beneficial.

In conclusion, morphine given to patients suffering from moderate to severe pain in the postoperative period is modulated by its own metabolites. M-6-G is a potent opioid agonist and M-3-G a mild opioid antagonist. Both are poorly excreted in patients with renal failure. Because of the long transfer half-life from blood to effect compartment, the effects of the metabolites appear only after an important delay. Therefore, the use of other opioids, such as fentanyl, should be considered in patients with renal failure to avoid delayed respiratory depression. In addition, because poor analgesia due to accumulation of M-3-G may occur in some patients after 1 or 2 days of treatment, a switch to other opioids should also be considered if this mechanism is suspected.

ACKNOWLEDGMENTS

The authors acknowledge the reviewers for their comments.

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