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Intravenous morphine titration in immediate postoperative pain management: Population kinetic–pharmacodynamic and logistic regression analysis

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ABSTRACT

Morphine is widely used to treat moderate to severe postoperative pain. The goal of this study was to characterize the pharmacodynamics of morphine-induced analgesia during intravenous morphine titration in the immediate postoperative period and to evaluate sedation occurrence according to morphine dose in this setting. Two hundred and twenty-eight patients undergoing major orthopedic surgery were included. They received intravenous (iv) morphine titration in the post-anesthesia care unit as boluses of 2 or 3 mg, every 5 min until analgesia was established. Pain was assessed using visual analogue scale (VAS) scores. Morphine analgesia-time data were analysed via a kinetic–pharmacodynamic population approach using non-linear mixed-effect modeling NONMEM. Sedation was assessed by the Ramsay score with scores >2 representing clinically significant sedation. The relationship between sedation occurrence and morphine dose was modeled using logistic regression. Morphine pharmacodynamic was best described by an indirect response model with an inhibitory function affecting pain onset, and it showed that decreasing delay between extubation and titration, decreasing initial VAS and intra-operative non-steroidal anti-inflammatory drug resulted in increased morphine potency. Logistic regression showed that a morphine dose of 20 mg was associated with a high likelihood of sedation occurrence. Our study supported the possibility of modeling the time course of a complex response in the absence of pharmacokinetic data. The current data should lead to a more rational management of the immediate postoperative pain.

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1. Introduction

Morphine is widely used to control moderate to severe postoperative pain. Its clinical use is characterized by a very large inter-individual variability in the analgesic effect, implying that individualization of morphine therapy is the key to optimize its practice [42]. Consequently, intravenous morphine titration has currently become the gold standard for pain management notably in the post-anesthesia care unit (PACU) [2,6,43]. Based on iterative morphine bolus titration, this method allows a rapid and an efficient analgesia [2,3,16]. In spite of the considerable progress provided by morphine titration in the PACU, concerns persist over accurate morphine titration adapted to the patient's need. Up to now, i.v. morphine titration in the PACU has been uniform for all patients due to the absence of identification of factors underlying the large inter-individual variability in its analgesic effect (titrated number of boluses ranges from 1 to 12) [2]. Moreover, i.v. morphine titration is subject to be discontinued before obtaining sufficient analgesia if adverse effects or sedation occur. Growing evidence points out the significance of sedation as an early warning of morphine overdose rather than an indicator of appropriate analgesia [5,10,30,37]. Taking into account that sedation may occur in up to 60% of patients in the PACU, both the safety and the efficacy of morphine titration remain questionable.

In order to optimize such titration procedure and to achieve better analgesia, a dose–response model should be available to allow individual adaptation of morphine titration in terms of dose, number of boluses and associated analgesic treatments. At present, no such pharmacodynamic model has been established for the immediate postoperative morphine titration setting. Furthermore, taking into account that sedation should be considered as a danger signal, it would be helpful to identify morphine doses above which the likelihood of sedation occurrence should be regarded as significant.

The purpose of this study was to develop a population pharmacodynamic (PD) model describing the morphine-induced analgesia

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in the immediate postoperative period of i.v. morphine titration, using routine titration data where no pharmacokinetic (PK) data are available (K–PD) and to identify the covariates that will significantly affect the pharmacodynamic parameters of the model, and then to evaluate the relationship between sedation occurrence and morphine dose in this clinical setting.

2. Methods

2.1. Patient population

Data were collected from 228 patients undergoing major orthopedic surgery (at Pitié-Salpêtrière University Hospital), who received titrated i.v. morphine for analgesia during the immediate postoperative period. Because data were recorded without any specific intervention and according to a protocol already used routinely in the PACU [2,3,6], authorization was given by the ethical committee (CPP Pitié-Salpêtrière) to waive informed consent.

The postoperative pain was classified as moderate or severe according to the study results of Aubrun et al. [4]. Severe pain was defined as a score of 70 or greater on the visual analogue scale (VAS) score unless pain was considered as moderate. Exclusion criteria were: age <18 year, American Society of Anesthesiology (ASA) status >III, intra-operative administration of morphine, allergy or contraindication to morphine, renal insufficiency (serum creatinine >120 μmol l^{-1}) or hepatic insufficiency (ALAT or ASAT or alkaline phosphatases level three times greater than the normal value, and/or prothrombin time <60% of control), and emergency surgery. Patients with delirium or dementia, who did not understand the pain scales, or who were not French speaking were also excluded.

2.2. Anesthesia and postoperative pain management

General anesthesia was standardized for all patients. Anesthesia was induced with propofol (2.5 mg kg^{-1}). Tracheal intubation was performed after muscle relaxation had been achieved with atracurium (0.5 mg kg^{-1}). Anesthesia was maintained with i.v. boluses of sufentanil and isoflurane or sevoflurane administered with oxygen and 50% nitrous oxide. Sufentanil was switched off at least 60 min before the expected end of surgery. Thirty minutes before the end of surgery, 1 g of paracetamol could be administered intravenously. The use of non-steroidal anti-inflammatory drugs (NSAIDs) (50 mg of ketoprofen) was authorized in the intra-operative period with the strict respect of the contraindications and the recommendations. A strict protocol of morphine titration was implemented in the PACU after a previous study determined the optimal regimen of morphine titration [2,3,6]. All nurses in the PACU had been trained to assess pain using uni-dimensional scales and to perform morphine titration. They used the VAS (0–100 mm, hand-held slide rule type) [24] and a special form for data collection. When patients had difficulties in manipulating the VAS, nurses were allowed to use a numerical rating scale (0–100) [24] as these two methods are equivalent [13].

After the patients' arrival in the PACU, immediately after they underwent tracheal extubation and after they were awake, they were questioned as to the presence of pain (at least every 15 min before the onset of morphine titration) and were asked to rate pain intensity on a VAS. When the VAS score was greater than 30 mm (VASi = initial VAS), intravenous morphine was titrated every 5 min in 3-mg increments (2-mg in patients weighing ⩽60 kg), and pain was assessed every 5 min until analgesia, defined as a VAS score of 30 mm or less. When the patient was asleep, no attempt was made to wake him up, and the patient was considered as having analgesia and a score of 0 mm was assigned to the patient. A score of 100 mm was assigned to the patient when pain was too severe. The delay of morphine titration was defined as time elapsed between the arrival in the PACU and the onset of i.v. morphine titration. Clinical monitoring included respiratory rate measurements; oxygen saturation measured by pulse oximetry (SpO_2), arterial blood pressure, and heart rate. Sedation was also assessed, every 5 min together with pain assessment during i.v. morphine titration, according to the Ramsay score [40], and then clinically significant sedation was defined by a Ramsay score >2, and, therefore coded as either 0 or 1. Morphine titration was stopped if the patient had a respiratory rate lower than 12 breaths/min and/or an SpO_2 lower than 95% and/or experienced a serious adverse event related to morphine administration (allergy with cutaneous rash and/or hypotension, vomiting, severe pruritus) and also if the patient was asleep.

2.1. Population pharmacodynamic modeling

The objective of the study was to investigate the dose–effect relationship of morphine-induced analgesia using the VAS score as an assessment of pain intensity during administration of successive boluses in the immediate postoperative period, for which only patients who were awake were taken into account; followed by the evaluation of sedation occurrence, coded as 0 or 1, in relation to morphine dose.

As morphine showed a dissociation between pharmacokinetics and effects [31,42], the physiologic indirect-effect models were investigated to describe morphine analgesia. These models for response produced by indirect mechanism, such as by inhibition or stimulation of the production or dissipation of factors controlling the measured effect, have been presented previously [12,41] and have been applied to several drugs [27]. Furthermore, since model development depended solely on the assessed PD data where no PK data are available, the proposed (kinetic of drug action) K–PD approach, with a virtual kinetic compartment, was employed [23].

The time course of the morphine-induced analgesia was best described by an indirect response model with an inhibition process affecting the onset of pain [12; model I]. The basic assumption of this model is that the pain variation which results in the observed analgesia can be expressed by the equilibrium of K_{in} (the apparent zero-order rate constant of the apparition of the pain) and K_{out} (the first-order rate constant for the dissipation of the pain) at all times, and the morphine dose has an inhibitory effect on the K_{in} and thus decreases the apparition of the pain as shown in Fig. 1 (Supplementary material appendix A). This inhibitory effect was parame-

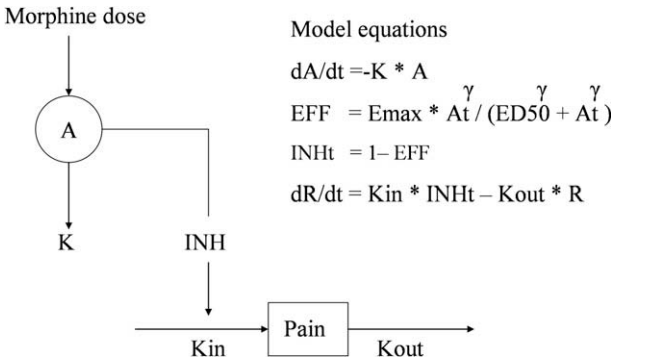

Fig. 1. The kinetic–pharmacodynamic (K–PD) model used to describe the time course of morphine-induced analgesia during titration process with the appropriate equations. dA/dt = rate of change of morphine amount in the virtual compartment; EFF = effect; INH_t = morphine inhibition effect; dR/dt = rate of change of pain; E_{max} = maximum morphine analgesia, ED_{50} = dose that produces 50% of the maximum analgesia; A_t = morphine amount in the virtual compartment; γ = sigmoidicity coefficient; K = elimination rate constant; K_{in} = zero-order apparition rate pain; K_{out} = first-order dissipation rate of pain.

terized as a sigmoidal relation with the following parameters: E_{max} is the maximum morphine analgesia, ED_{50} is the dose that produces 50% of the maximum analgesia, A_t is the amount of morphine in the virtual compartment at the same time and γ is the sigmoidicity parameter (see Supplementary material appendix for formulae).

Considering that morphine analgesia reflects changes from a baseline value, before the beginning of titration, the pain baseline (mm) at time 0 was defined as:

$$BASE = K_{in}/K_{out}.$$

As morphine titration resulted in either analgesia or sedation in all patients, morphine was assumed to be able to completely inhibit K_{in} and therefore E_{max} was set at 1 and its associated inter-subject variability was set at 0. Since no pharmacokinetic data were available in this study, the elimination half-life for morphine ($t_{1/2}$) was fixed at 180 min, within a range reported in the previous studies (for review, see [34]) and the associated inter-subject variability was set at 0.

The occurrence of sedation was evaluated by a logistic regression analysis; hence, the probability of its incidence was modeled in relation to A_t of morphine in the virtual kinetic compartment (see Supplementary material appendix for more details).

Data were analysed using the non-linear mixed-effect modeling software program NONMEM (version VI, level 1.1, double precision) with the Digital Fortran Compiler 6.5 [43] by the use of the subroutine ADVAN6. The first-order conditional method (FOCE) with INTERACTION was used for the estimation of the pharmacodynamic model parameters. For the logistic regression, the LAPLACE LIKELIHOOD options were used. Several error models were investigated (i.e., additive, proportional, exponential and mixed error models) to describe inter-individual and residual variabilities. First analysis was carried out to find the base model that best described the data. Once the base model was defined the influence of each covariate on the pharmacodynamic parameters was tested. The covariates were the following: age, sex, body weight, duration of surgery, intra-operative sufentanil dose, intra-operative non-steroidal anti-inflammatory drugs (NSAIDs), intra-operative analgesic, delay between extubation and titration (DEL), American Society of Anaesthesiologists status (ASA), the initial postoperative pain score (VASi), and titrated boluses (2 or 3 mg).

The covariates were selected in the final population model if (i) their effect was biologically plausible, (ii) they produced a minimum reduction of 4 (chi-squared distribution with one degree of freedom for $p < 0.05$) relative to the base model, and (iii) they produced a reduction in the variability of the pharmacodynamic parameter, assessed by the associated inter-individual variability.

Criteria to assess the goodness-of-fit included evaluation of the objective function value (OFV), parameter estimates, and diagnostic graphs. In graphical model diagnosis, the following graphs were compared: observed versus predicted (PRED-DV) effect, weighted residuals (WRES) versus time and weighted residuals versus PRED (WRES-PRED) as well as individual predicted versus observed (IPRED-DV) effect. Diagnostic plots and distribution statistics were obtained using the R program [22].

The stability and performance of the final population model were assessed by a bootstrap method [15], using the package Wings for NONMEM (N. Holford, Version 613, Auckland, New Zealand). This method involves repeated random sampling, with replacement, of the original data set to produce another data set of the same size as the original but with a different combination of subjects. The bootstrap re-sampling was repeated 400 times, and then the values of the parameters were compared with those obtained from the original data set.

Table 1
Characteristics of patients ($N = 228$).

Characteristic	Mean	SD	Median	Range
Age (yr)	60	14	62	20–90
Body weight (kg)	70	13	69	39–115
Sex (*n*/%)				
Male	113 (50%)			
Female	115 (50%)			
Type of surgery (*n*/%)				
Total hip replacement	204 (89%)			
Spine surgery	24 (11%)			
ASA (*n*/%)				
I	87 (38%)			
II	109 (48%)			
III	32 (14%)			
Duration of surgery (min)	129	52	120	30–450
Intra-operative sufentanil dose (μg)	62	25	60	15–225
Intra-operative NSAIDs	82 (36%)			
Intra-operative non-opioid analgesic	171 (75%)			
Delay between extubation and titration (min)	102	103	70	0–720
Initial VAS (mm)	71	19	70	33–100
Total morphine dose (mg)	11	7	9	2–45
Number of boluses	4	2	3	1–15

ASA, American Society of Anaesthesiology status; VAS, visual analogue pain score; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation.

Table 2
Population pharmacodynamic parameters of morphine following intravenous titration in patients in postoperative period.

Structural model	Mean	SE	Median	5–95th percentiles
BASE (mm)	67	1.4	66.2	61–70
ED_{50}				
$TVED_{50}$ (mg)	10.2	0.8	9.3	0.1–11.5
θED_{50}VASi	1.45	0.26	1.63	0.37–5.83
θED_{50}NSAIDs	0.76	0.08	0.75	0.36–1.04
θED_{50}DEL (h)	5.0	1.2	4.1	0.7–12.0
K_{out} (min^{-1})	0.26	0.02	0.20	0.03–0.28
GAM	1.9	0.3	2.0	0.2–6.1
Statistical model				
Residual variability (ε)	0.25	0.05	0.27	0.21–0.33
Inter-subject variability (η)				
$\eta BASE$	0.22	0.05	0.24	0.19–0.30
ηED_{50}	0.65	0.11	0.63	0.02–1.10

BASE, pain baseline; ED_{50}, morphine dose that produces 50% of the maximum analgesia.

$$ED_{50} = TVED_{50} \times [\text{VASi}/\text{median}(\text{VASi})]^{\theta ED50\text{VASi}} \times \theta ED^{50}\text{NSAIDs} \times e^{[-(\text{DEL}-\text{median DEL}/\theta ED50\text{DEL})]}$$

$TVED_{50}$: the typical value of ED_{50} for a patient with the median covariate value, θED_{50}VASi, estimated influential factor of initial VAS on ED_{50}; θED_{50}NSAIDs estimated influential factor of NSAIDs on ED_{50}; θED_{50}DEL, estimated influential factor of delay between extubation and titration on ED_{50}; K_{out}, first-order dissipation rate of pain; *GAM*, sigmoidicity coefficient; ε, residual error; η, inter-subject variability; SE, standard error.

A visual predictive check was performed [43]. Four hundred data sets were simulated from the final model using the original data set to describe population time courses of the analgesia-time profiles. The distribution of the observations was compared to the simulated distribution.

Since some patients required a prolonged time to achieve sufficient analgesia during morphine titration, simulations ($N = 400$) using the obtained pharmacodynamic parameters were performed with greater titrated boluses, of (3, 4.5 mg) and of (4, 6 mg) instead of the usually used (2 mg and 3 mg, respectively).

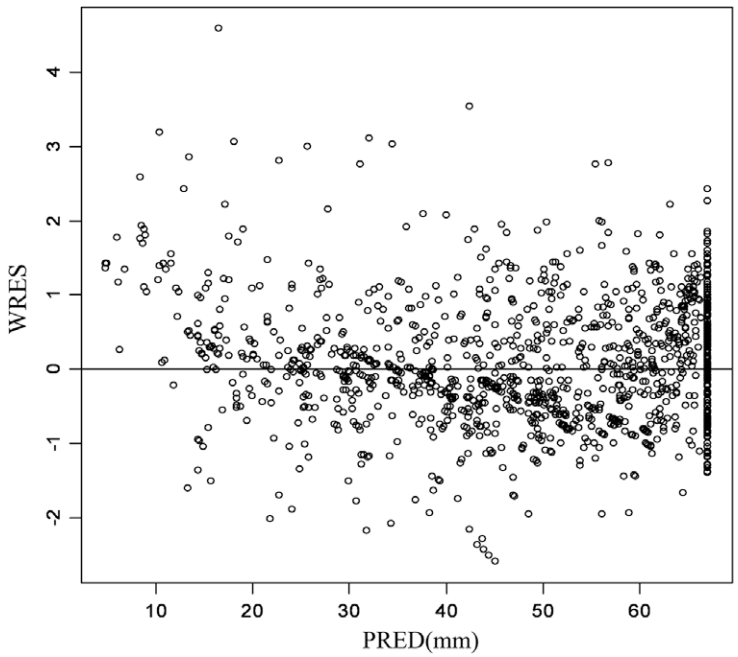

Fig. 2. Goodness of weighted residuals (WRES) versus predicted effect (PRED) plots for the final pharmacodynamic analysis of morphine-induced analgesia during i.v. morphine titration.

3. Results

3.1. Patient characteristics

A total of 1289 pain assessments from 228 patients receiving titrated i.v. morphine in the immediate postoperative period were available for population modeling (with a mean of 6 pain assessments per patient). The mean VASi was 71 ± 19. The mean morphine dose required to obtain analgesia was 11 ± 7 mg (varying between 2 and 45 mg). Analgesia was obtained after a mean of 4 boluses, with extremes ranging from 1 to 15 boluses. Among the 228 patients included in this study, morphine titration was interrupted in 103 patients who were sedated during the titration. As serious side effects (such as respiratory depression) did not occur, the adverse side effects experienced in 33 patients did not prevent titration process from continuing. All patients were included in the pharmacodynamic analysis as long as they were awake. Table 1 summarizes the data and the characteristics of patients used to develop the model of the time course of morphine-induced analgesia.

3.2. Population pharmacodynamics

The time course of morphine-induced analgesia was adequately described using an indirect response model with an inhibitory function affecting the onset of pain. Inter-individual and residual variabilities were best modeled as exponential error models. Inter-individual variabilities on *BASE* and ED_{50} were well estimated whereas those on *GAM* and on K_{out} could not be estimated.

The effects of (i) the delay between extubation and titration DEL, (ii) the intra-operative NSAIDs, and (iii) the initial postoperative pain VASi on ED_{50} (OFV decreases of 19.8, 6.3, and 62.2 units, respectively) remained significant during the backward deletion, and thus retained in the final model.

The final population parameters are summarized in Table 2. The final model was then subjected to a bootstrap analysis, the parameters obtained from the bootstrap process were similar to those estimated with the original dataset (Table 2). Figs. 2 and 3 depict the good fit of the final model. The plots of WRES versus time (Fig. 2) confirmed the performance of the model without any observed formal bias. The visual predictive checks (400 Monte Carlo simulations) showed that the observations were satisfactorily distributed relative to the model predictions (median and 5th and 95th percentiles curves). The expected 10% of observations outside the lower and upper limits were consistent with the observed values, 8% and 12% of data, for the titrated boluses of 2 and 3 mg, respectively (Fig. 3).

The analgesia profiles over time (median, first and third quartile) during the candidate titration regimens with titrated boluses of (3, 4.5 mg) and of (4, 6 mg) instead of the usually used (2 mg and 3 mg respectively), are shown in Fig. 4. For titrated boluses of 3 mg and 4.5 mg, the required times to obtain adequate analgesia (median, first and third quartile) for patients usually requiring titrated boluses of 2 and 3 mg were 25, 15, and 40 min, and 20, 15, and 30 min, respectively, whereas, for titrated boluses of 4 mg and 6 mg, the required times to obtain adequate analgesia (median, first and third quartile) for patients usually using titrated boluses of 2 and 3 mg were 20, 10, and 35 min, and 15, 10, and 25 min, respectively.

As the only pharmacokinetic parameter used in this study (i.e., morphine elimination half-life, $t_{1/2}$) was fixed, a ±25% change in this fixed value was investigated to examine its influence on the present model. As shown in Table 3, none of the model parameters were significantly dependent upon the fixed $t_{1/2}$, which emphasizes upon the stability of our model towards the fixed pharmacokinetic value.

For the sedative effect, the model with *b*0,1,2 coefficients was superior to the *b*0,1 model (drop in OFV of 42 U). None of the covariates tested were able to significantly improve the model. The estimates of model parameters are summarized in Table 4. Fig. 5 depicts the probability of sedation occurrence as a function of morphine dose and shows that at doses greater than 15 mg, a considerable increase in sedation occurrence may be observed (>50%), and that doses of 20 mg may result in a high probability of sedation occurrence (about 100%).

4. Discussion

We developed a kinetic–pharmacodynamic (K–PD) model to describe the time course of morphine-induced analgesia during

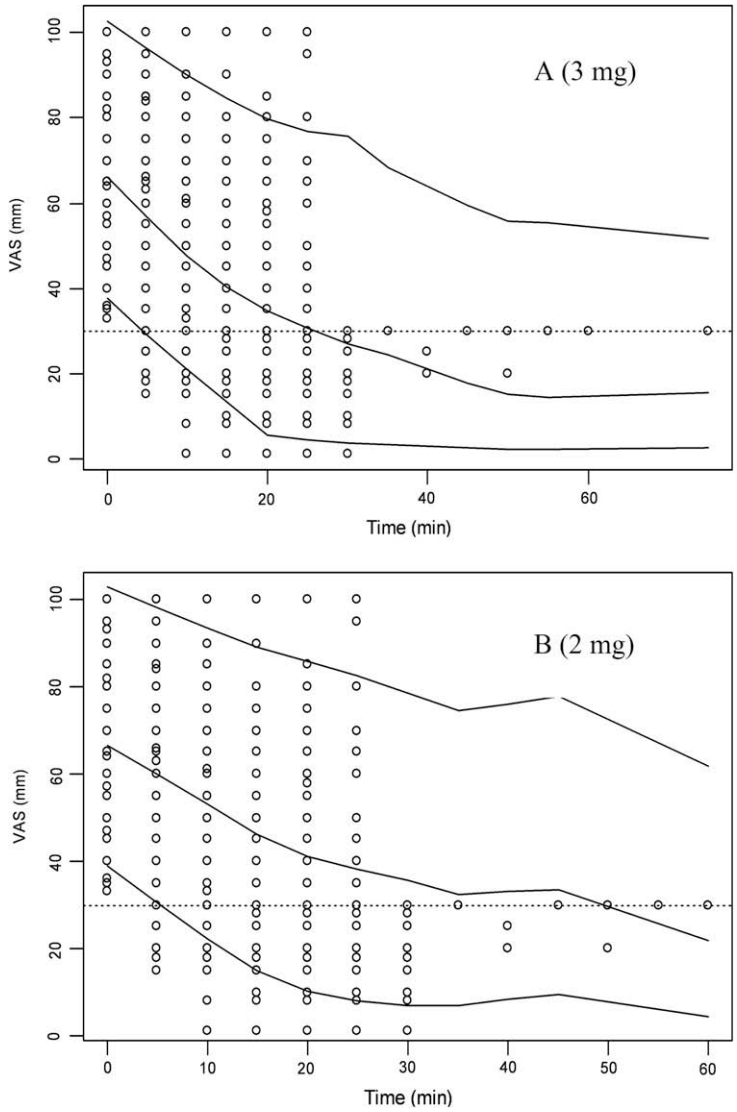

Fig. 3. Morphine observed and simulated pharmacodynamic profiles during i.v. morphine titration using boluses of (A) 3 mg or (B) 2 mg in the immediate postoperative period.

the titration process in the immediate postoperative period via an indirect response model with inhibition of pain onset. In this model, increasing morphine potency was associated with decreasing delay between extubation and titration, intra-operative NSAIDs, and decreasing initial postoperative pain.

Analgesics have been proposed as candidates for indirect response models [18]. After binding to its receptors, morphine induces analgesia by blocking neurotransmitter release, thereby inhibiting pain transmission [19]. Taking into account that i.v. morphine titration needs regular pain and sedation assessment, with a short-time interval between boluses (5 min), it is difficult to collect simultaneously the required PK data. Thus, the application of the recently used K–PD approach appeared appropriate [18,23,39].

The use of VAS score to assess pain intensity in the immediate postoperative period has been widely accepted because of its simplicity, sensitivity and good reproducibility [25]. Morphine potency, represented by ED_{50}, agrees well with the previously reported value in humans [28], and further confirms the efficacy of the mean dose to obtain analgesia in this study.

The observed increasing morphine potency with decreased DEL may be explained by the multimodal analgesic effects of the non-opioid analgesics (NSAIDs and/or acetaminophen) administered at the end of surgery. This may suggest that earlier administration of such analgesics during surgery may be more efficient for improving postoperative analgesia. This finding is in accordance with the reported synergistic effect of NSAIDs on reducing morphine dose and providing better postoperative analgesia [1,17,21,26]. As expected, morphine potency decreases as long as postoperative pain increases reflecting the increasing need of the receptor–ligand complex to produce an adequate analgesia. This finding may have important clinical implications in improving postoperative pain management; hence, it may suggest a VASi-based titration regimen in which an increase in titrated boluses, rather than a shorter interval between boluses (for practical reasons), may be proposed for patients with severe pain. However it should be pointed out that an increase in the titrated boluses as well as loading initial dose may increase the incidence of side effects and thus may decrease the safety of i.v. morphine titration [7]. The lack of significant influence of titrated boluses (2 or 3 mg) on model parameters provides an indirect validation of the correct adjustment of the titration procedure.

According to the morphine administration regimen as well as to the study population contradictory results, the influence of the

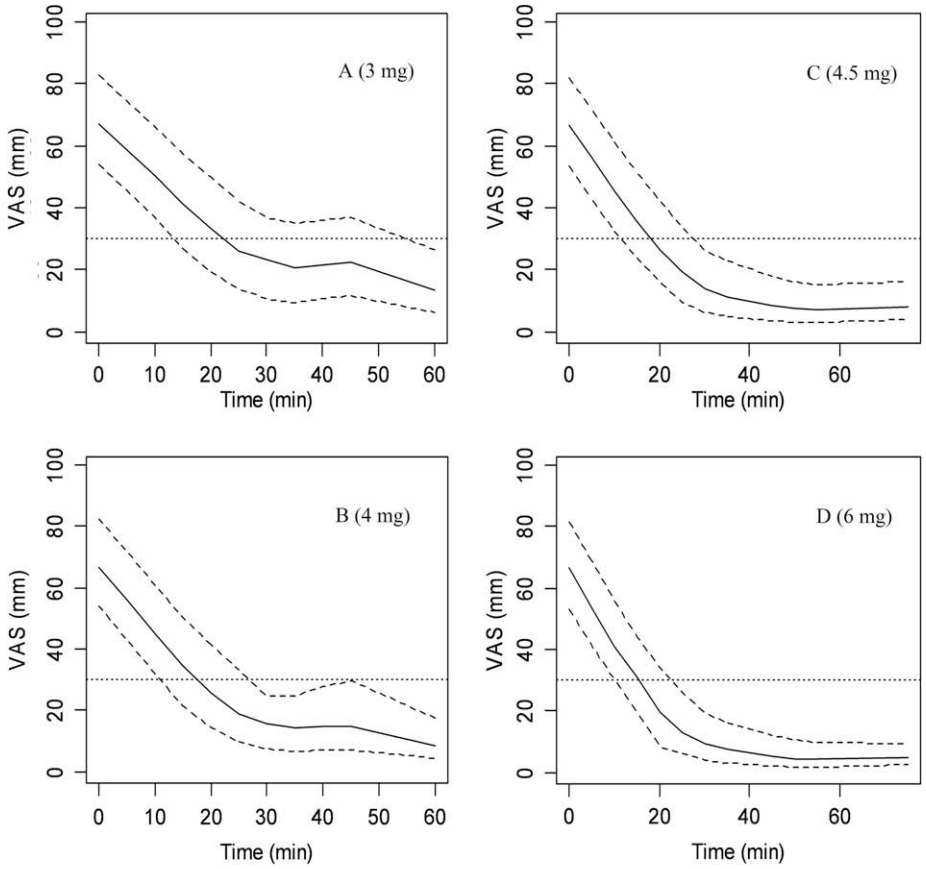

Fig. 4. Morphine simulated pharmacodynamic profiles during i.v. morphine titration using greater boluses of (A) 3 mg, (C) 4.5 mg, and of (B) 4 mg, (D) 6 mg instead of the usually used 2 mg and 3 mg, respectively.

Table 3
The sensitivity of the population model to the fixed pharmacokinetic parameter (morphine elimination half-life, $t_{1/2}$).

$t_{1/2}$ (min)	*BASE* (mm)	ED_{50} (mg)	K_{out} (min^{-1})	*GAM*	ISV (*BASE*)	ISV (ED_{50})	RV	OFV
180	67	10.2	0.26	1.9	22.0	64.8	25.0	8239
135 (−25%)	67	10.0	0.25	1.9	22.1	64.7	25.1	8240
225 (+25%)	67	10.4	0.26	1.9	22.3	65.0	25.1	8238

$t_{1/2}$, morphine elimination half-life; *BASE*, pain baseline; ED_{50}, morphine dose that produces 50% of the maximum analgesia; K_{out}, first-order dissipation rate of pain; *GAM*, sigmoidicity coefficient; ISV, inter-subject variability; RV, residual variability; OFV, objective function value.
Variabilities are expressed as square root of variance.

Table 4
Parameter estimates for the sedation effect as a function of morphine dose.

Parameter	Mean	SE
b_0	−19.1	5.73
b_1 (mg^{-1})	1.88	0.55
b_2 (mg^{-2})	−0.042	0.013
η_y	8.5	NE

The occurrence of sedation (y) was modeled in relation to the morphine amount in the virtual kinetic compartment (A_t) as follows: $y = b_0 + b_1A_t + b_2A_t^2 + \eta_y$ where $b_{0,1,2}$ are the regression coefficients and η_y is an inter-subject variability.
SE, standard error; NE, not estimated.

covariates on the pharmacodynamics of morphine has been reported.

In the same way, it was previously found that the duration of surgery, and the VASi are predictive factors of morphine requirements [11]. Controversial findings relating to sex influence were recorded [6,8,36]. However, the study of Aubrun et al. [6] showed that such differences disappeared in elderly patients, perhaps as a result of hormonal status changes. This could explain our finding of the absence of such effect with regard to the age of females included (mean age was 62 years). Further developments to the model include investigation of factors not considered in this study which could affect morphine-induced analgesia such as ethnicity, type of surgery, and particularly the genetic factor as shown in the recent studies [20,32,38].

Simulations based upon the final model showed that greater titrated boluses significantly reduced the time to achieve analgesia in patients usually requiring a prolonged time in the PACU. However, the safety of such regimen regarding the incidence of morphine-related adverse effects should be investigated in further studies. As these patients usually recorded significantly higher VASi than other patients, this further supports our proposition to adjust titration regimen according to VASi.

The incidence of sedation and adverse side effects during morphine titration in our study is in agreement with those previously published [2].

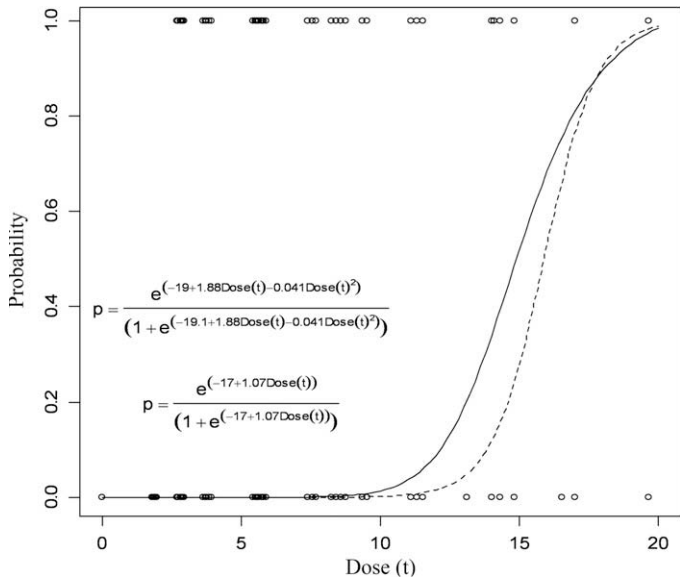

Fig. 5. Probability of sedation occurrence versus morphine dose (mg) during i.v. titration, where (o) are observed data and the line represents the results of logistic regression analysis of data, according to model with *b*0,1,2 coefficients (solid line) and model with *b*0,1 ones (dashed line). Sedation coded as 0 or 1.

The relationship between morphine dose and sedation occurrence was evaluated by logistic regression analysis. Sedation is considered as an early warning of morphine overdose rather than as an indicator of appropriate analgesia, leading to interruption of morphine titration [2,5,10,30,37]. A high likelihood of sedation occurrence resulted from morphine doses of 20 mg, thus alternative strategies, such as multimodal analgesia, to decrease postoperative morphine consumption are highly needed. However, except for the NSAIDs, most studies did not detect a similar decrease in morphine sedation with the other proposed combinations [29], which require further studies to evaluate their effect on the incidence of sedation [9,14,35].

The use of the Ramsay score to assess the sedation is a validated and widely used technique but its accuracy is questionable in the PACU. Therefore it was decided, in this study, to avoid the observer interpretation of Ramsay score and of the patient's behaviour.

Some remarks are necessary concerning the limitations of this study. First, because only assessments of pain intensity during morphine titration were normally recorded, the recovery from analgesia to baseline conditions could not be achieved. Therefore, studies including assessments of pain intensity for a longer period are required to better understand the time course of morphine-induced analgesia in the immediate postoperative period. Second, since the VAS scores incorporate a large subjective and emotional component of pain; a part of the variability in morphine analgesia could be explained by the variability in the placebo component. However, placebo analgesia was not considered in the present study, as it is not possible to include a placebo group to determine the size of the placebo effect for ethical reasons. Third, our model applies only to the immediate and short postoperative period of i.v. morphine titration and therefore later postoperative period and cancer patients were not considered in this study as well as emergency conditions in which the incidence of sedation has been recently shown to be markedly reduced [33].

In conclusion, a kinetic–pharmacodynamic model to characterize the time course of morphine-induced analgesia in the immediate postoperative period has been developed. Three factors associated with increased morphine potency were identified: a short delay between extubation and titration, intra-operative NSAIDs and a low initial VAS. On the other hand, a morphine dose of 20 mg was found to be associated with high likelihood of sedation occurrence. Although the current data suggest that larger titrated boluses are necessary to quickly reach adequate analgesia in patients with severe pain the safety of such a regimen cannot, as yet, be guaranteed.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pain.2009.03.029.

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