



Original contribution

# Morphine and its metabolites after patient-controlled analgesia: considerations for respiratory depression<sup>☆</sup>

Wai Johnn Sam PhD (Research Fellow in Anesthesia)<sup>a</sup>,  
Sean C. MacKey MD, PhD (Associate Professor of Anesthesia)<sup>a</sup>,  
Jörn Lötsch MD (Professor of Clinical Pharmacology)<sup>b</sup>,  
David R. Drover MD (Associate Professor of Anesthesia)<sup>a,\*</sup>

<sup>a</sup>Department of Anesthesia, Stanford University, H3580, 300 Pasteur Dr., Stanford, CA 94305-5640

<sup>b</sup>Pharmazentrum Frankfurt/ZAFES, Institute of Clinical Pharmacology, Johann Wolfgang Goethe-University, 60590 Frankfurt am Main, Germany

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## Abstract

**Study Objective:** To assess concentrations of morphine and its metabolites after patient-controlled analgesia (PCA).

**Design:** Pilot pharmacokinetic study of morphine and pharmacokinetic simulation.

**Setting:** Post-anesthesia care room and ward of an academic teaching hospital.

**Patients:** 10 ASA physical status I, II, and III postoperative surgical patients.

**Interventions:** Patients received morphine via PCA by routine hospital protocols.

**Measurements:** The population mean plasma and effect-site concentrations of morphine, morphine-6-glucuronide (M6G), and morphine-3-glucuronide (M3G) was simulated in 4 patient group scenarios: morphine PCA used alone, morphine PCA used with continuous background morphine infusion of 0.5 mg/hr, morphine PCA used with continuous background morphine infusion of 1.0 mg/hr, and morphine PCA used with continuous background morphine infusion of 2.0 mg/hr.

**Main Results:** The 4 groups exhibited simulated peak morphine, M6G, and M3G effect-site concentrations at 8 to 24 hours post-infusion. The highest peak morphine, M6G, and M3G effect-site concentrations decreased in the following order by group: 2.0 mg/hr morphine infusion + PCA group, 1.0 mg/hr morphine infusion + PCA group, and 0.5 mg/hr morphine infusion + PCA group.

**Conclusions:** Patients receiving morphine PCA should be monitored closely from 8 to 24 hours postoperatively. Morphine PCA given with background infusion rates up to 1.0 mg/hr does not offer distinct pharmacokinetic advantages over morphine PCA alone. Morphine PCA with background infusion rate of 2.0 mg/hr is associated with the greatest risk of respiratory depression.

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\* Corresponding author. Tel.: +1 650 725 0364; fax: +1 650 725 8544.  
E-mail address: [ddrover@stanford.edu](mailto:ddrover@stanford.edu) (D.R. Drover).

## 1. Introduction

Patient-controlled analgesia (PCA) is purported to enable better pain management after surgery than other traditional

pain therapies [1,2]. Morphine is the most widely used medication in PCA devices.

Most studies have not shown that background opioid infusions combined with PCA techniques are more beneficial. Total opioid doses are increased when background infusions are used [3-5]. This increased dose of morphine may expose patients to a higher risk of respiratory depression, a source of patient morbidity and mortality [6]. Consequently, the risk of respiratory depression associated with a background infusion with morphine PCA is higher [7].

The ASA Closed-Claims Database does not collect information on the postoperative period after the Post-anesthesia Care Unit (PACU). Cases of respiratory depression related to the use of basal infusions with PCA use have been reported [8-11]. The risk of respiratory depression was studied by analyzing which background infusion rates were associated with the greatest risk. Four different scenarios were studied: morphine PCA used alone, morphine PCA used with a continuous background morphine infusion of 0.5 mg/hr, morphine PCA used with a continuous background morphine infusion of 1.0 mg/hr, and morphine PCA used with a continuous background morphine infusion of 2.0 mg/hr.

## 2. Materials and methods

This was a 2-step study. This first step characterized PCA use patterns and validated published morphine pharmacokinetic parameters. The second step was a simulation based on published PCA use and pharmacokinetic parameters. The goal of the second step was to predict the effects of morphine PCA use with and without a basal morphine infusion.

### 2.1. Patients

Ten patients were enrolled in a prospective, non-randomized fashion to establish common PCA dosing requirement and to validate subsequent pharmacokinetic models for simulation. The study was approved by the Stanford University Medical Center Institutional Review Board, and was conducted in accordance with the Declaration of Helsinki on Biomedical Research Involving Human Subjects (Somerset West Amendment). All patients gave written, informed consent. Inclusion criteria were patients undergoing a general anesthetic with planned use of postoperative morphine PCA without a basal infusion. Exclusion criteria were contraindication to the planned anesthetic, morphine allergy or intolerance, kidney or liver disease, or lack of informed consent.

The anesthesia plan included the attending anesthesiologist's choice of general anesthetic with volatile or intravenous (IV) anesthetic agents plus fentanyl, meperidine, or hydromorphone, but excluding morphine. After

patients emerged from anesthesia and were delivered to the PACU, they were treated with morphine for analgesia. The PACU nurse delivered the required morphine until the patient was alert enough to use the morphine PCA. The nurse delivered morphine boluses based on each patient's reported visual analog scale (VAS) score from 1 to 10. Morphine use was recorded in the PACU, and morphine PCA dosing was downloaded electronically from the PCA while the patient was receiving the PCA on the hospital ward.

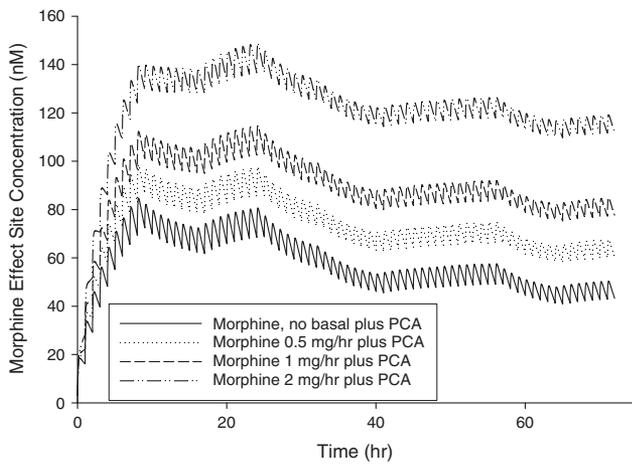
### 2.2. Pharmacokinetic simulation

Using parametric values from a previously published population pharmacokinetic-pharmacodynamic model of morphine and its metabolites in postoperative patients [12], the NONMEM V program (GloboMax, Hanover, MD, USA) [13] was used to simulate the population mean plasma and effect-site concentrations of morphine, morphine-6-glucuronide (M6G), and morphine-3-glucuronide (M3G) after morphine PCA administration alone, or with a background continuous infusion of 0.5 mg/hr, 1.0 mg/hr, and 2.0 mg/hr morphine. The morphine dosing used in the study resulted from a clinical study that investigated the influence of a continuous background morphine infusion as part of a PCA on postoperative analgesic requirements [5]. The data from that study [5] had been converted from graphical to numeric format with Digimatic software (DASTOR, Castiglione, Italy) for use in the simulation.

The input function (ie, dosing regimen) was derived from 4 groups of patients who underwent abdominal hysterectomy operations. The control group (no infusion) received 2.0 mg IV bolus doses of morphine "on demand," with a minimum lockout interval of 10 minutes. The second group received a continuous IV morphine infusion of 0.5 mg/hr, supplemented with 2.0 mg IV bolus doses at minimum intervals of 10 minutes. The third group received a continuous morphine infusion of 1.0 mg/hr, with supplemental IV bolus doses of 1.0 mg at a lockout interval of 10 minutes. The fourth group received continuous 2.0 mg/hr IV doses of morphine, supplemented with 1.0 mg IV bolus doses at minimum lockout intervals of 10 minutes.

## 3. Results

The pharmacokinetic simulation results of the effect-site concentrations of morphine, M6G, and M3G are shown in Figs. 1, 2, and 3. Table 1 shows that the effect-site concentration of morphine, M6G, and M3G increased as the basal infusion of morphine was increased. Table 1 also shows that the 4 groups exhibited peak morphine effect-site concentration at 8 to 24 hours after the start of the infusion: the highest peak occurred in the 2.0 mg/hr morphine infusion + PCA group (149 nM); the second highest peak

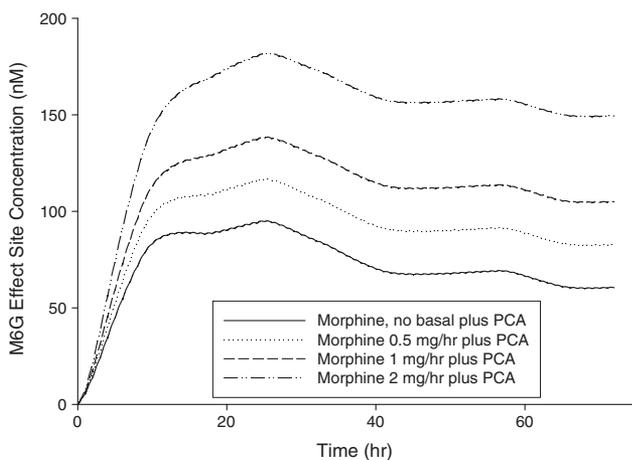


**Fig. 1** Simulated morphine effect-site concentration versus time profiles in the 4 groups: morphine PCA only, 0.5 mg/hr morphine infusion + PCA, 1.0 mg/hr morphine infusion + PCA, and 2.0 mg/hr morphine infusion + PCA.

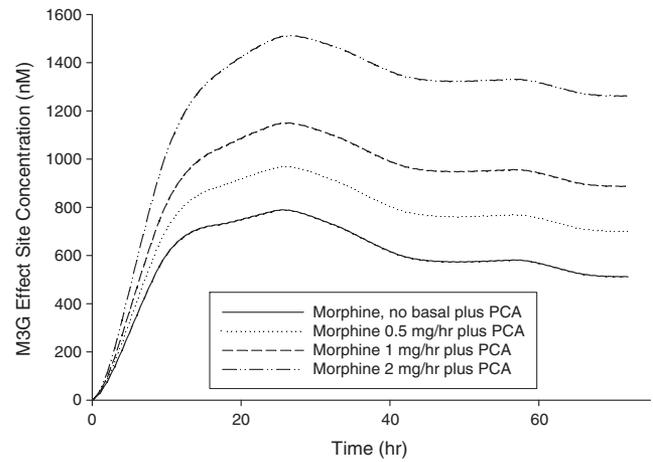
occurred in the 1.0 mg/hr morphine infusion + PCA group (115 nM); the third highest peak occurred in the 0.5 mg/hr morphine infusion + PCA group (97 nM); and the lowest peak occurred in the morphine PCA alone group (85 nM).

As noted in Table 1, the 4 groups exhibited peak M6G effect-site concentration at about 25 hours after the start of the infusion: the highest M6G peak occurred in the 2.0 mg/hr morphine infusion + PCA group (181 nM); the second highest peak occurred in the 1.0 mg/hr morphine infusion + PCA group (138 nM); the third highest peak occurred in the 0.5 mg/hr morphine infusion + PCA (117 nM); and the lowest peak occurred in the morphine PCA alone group (95 nM).

The 4 groups exhibited peak M3G effect-site concentration at 25 to 27 hours post-infusion: the highest M3G peak occurred in the 2.0 mg/hr morphine infusion + PCA



**Fig. 2** Simulated morphine-6-glucuronide effect-site concentration versus time profiles in the 4 groups: morphine PCA only, 0.5 mg/hr morphine infusion + PCA, 1.0 mg/hr morphine infusion + PCA, and 2.0 mg/hr morphine infusion + PCA.



**Fig. 3** Simulated morphine-3-glucuronide effect-site concentration versus time profiles in the 4 groups: morphine PCA only, 0.5 mg/hr morphine infusion + PCA, 1.0 mg/hr morphine infusion + PCA, and 2.0 mg/hr morphine infusion + PCA.

group (1510 nM); the second highest peak occurred in the 1.0 mg/hr morphine infusion + PCA group (1150 nM); the third highest peak occurred in the 0.5 mg/hr morphine infusion + PCA group (970 nM); and the lowest peak occurred in the morphine PCA alone group (790 nM) (Table 1).

#### 4. Discussion

Simulated peak effect-site concentration for morphine and its metabolites occurred between 8 and 24 hours after the start of the infusions. This early peak was due to a higher required total dose of PCA morphine during the first 8 hours after the start of PCA therapy, irrespective of the continuous infusion rate, compared with the PCA dose self-administered in the 9 to 72-hour period. As a consequence, the greatest risk of morphine-induced respiratory depression during morphine PCA therapy occurred between 8 and 24 hours post-infusion, the time during which the peak effect-site concentration occurred.

The simulated effect-site concentration profiles and peak concentrations of morphine, M6G, and M3G were similar for three of the 4 groups: the morphine PCA alone group, the 0.5 mg/hr morphine infusion + PCA group, and the 1.0 mg/hr morphine infusion + PCA group, because they required similar amounts of morphine throughout the study. However, in the fourth group – the 2.0 mg/hr morphine infusion + PCA group – the peak morphine, M6G, and M3G effect-site concentrations were higher because these patients received significantly more morphine between 9 and 72 hours after their operation than did those who did not receive a basal morphine infusion. This finding is consistent with a published study [5]. In the fourth group, the fact that the simulated morphine, M6G, and M3G effect-site pharmacokinetic profiles remained

**Table 1** Results of pharmacokinetic simulation of morphine and its metabolites after PCA at various basal infusion rates

	Group			
	Morphine PCA only	Morphine 0.5 mg/hr + PCA	Morphine 1 mg/hr + PCA	Morphine 2 mg/hr + PCA
Morphine effect-site concentration at end of 72 hrs (nM)	43	60	78	112
M6G effect-site concentration at end of 72 hrs (nM)	60	72	105	149
M3G effect-site concentration at end of 72 hrs (nM)	510	700	890	1,260
Peak morphine effect-site concentration (nM)	85	97	115	149
Peak M6G effect-site concentration (nM)	95	117	138	181
Peak M3G effect-site concentration (nM)	790	970	1,150	1,510
Time to peak morphine effect-site concentration (hrs)	8	8, 24	24	23
Time to peak M6G effect-site concentration (hrs)	25	25	25	25
Time to peak M3G effect-site concentration (hrs)	25	25	26	27

M3G = morphine-3-glucuronide, M6G = morphine-6-glucuronide, PCA = patient-controlled analgesia.

elevated after the peak concentration, indicates the greatest risk of morphine-induced respiratory depression among the 4 groups. These findings are consistent with the clinical findings of Flisberg et al. when examining morphine PCA plus basal infusions [11]. These authors reported that if respiratory depression occurred, it happened on the first postoperative day and not immediately after the start of the infusion [11].

Patients typically require more analgesic medication during the initial hours after completion of surgery. This fact is further emphasized by their increased use of PCA opioid during these initial hours. As the effect-site concentration of morphine and M6G reach their peak at 8 hours, patient-initiated dosing of morphine decreases. Commonly, at the same time morphine and M6G are peaking, an additional social factor occurs in many hospitals. The patient at that time is left comfortable in their hospital bed and visiting hours are ending. Family members go home and nursing interaction decreases. In addition, pain for many procedures may be diminishing; thus the patient requires less opioid for pain relief. If basal levels of morphine are continued, the patient may have sustained levels of morphine while the need for opioid may be decreasing. This combination of factors places these patients at increased risk of respiratory depression [14].

This study and simulation has its limitations. The dose of morphine was chosen based on previously published results. While a limited pilot study was performed to confirm that the dose previously published was consistent with current practice, this dose could be described as not consistent with expected clinical use. The use of more morphine from a PCA may vary for many reasons such as patient demographics and surgical procedure. The pharmacokinetic model used parameters from a study in volunteers. This pharmacokinetic model may not have reflected accurately the distribution of morphine in all patients. If patient variability, morphine dose, and the pharmacokinetic model are considered, it is possible to see many limitations to this analysis. Regardless of this variability, the simulation should accurately reflect the increasing concentrations of morphine and its metabolites during repeated dosing.

In conclusion, patients who are receiving morphine PCA should be monitored closely from 8 to 24 hours postoperatively for signs of morphine-induced respiratory depression. Morphine PCA used with background infusion rates up to 1.0 mg/hr did not offer distinct pharmacokinetic advantages compared with morphine PCA alone. Morphine PCA therapy with a background infusion is expected to be associated with the greatest risk of respiratory depression due to the higher accumulation of morphine and its metabolites at the effect site.

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