Can immediate opioid requirements in the post-anaesthesia care unit be used to determine analgesic requirements on the ward?

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The aim of this prospective study was to evaluate the efficacy of two dosage regimens of (im) morphine calculated from an initial (iv) titrated dose in the early postoperative period. Seventy ASA I-III patients who underwent general anaesthesia (GA) (n = 58), regional anaesthesia (RA) (n = 10) or GA + RA (n = 2) for orthopaedic (n = 54), urological (n = 11) or abdominal surgery (n = 5) received iv titrated morphine in the post-anaesthesia care unit (PACU). Titration consisted of 3 mg morphine iv every ten minutes until patients had a visual analogue pain scale (VAS) <3, without marked sedation. Seventeen patients did not complain at all or had good analgesia with an initial iv dose ≤6 mg of morphine followed by paracetamol only. Patients who needed more than 6 mg iv morphine were randomly assigned to a "high-dose" or a "low-dose" group and received a systematic im morphine regimen calculated from the initial titrated dose. Pain was assessed by VAS before each im injection and the next morning. One patient had respiratory depression and one marked sedation in the PACU. These patients were excluded from the rest of the study. Only 16 patients had a VAS >3 at least once during the study period and only three needed rescue analgesia which was avail-

able on request. We conclude that a systematic im morphine regimen adapted from an initial iv titration in the PACU provides efficacious and relatively inexpensive postoperative analgesia, applicable to a great majority of patients.

Ce travail prospectif avait pour objectif d'évaluer l'efficacité de deux posologies de morphine calculées à partir d'un titrage iv à la période postopératoire immédiate. Chez 70 patients ASA I-III soumis à une chirurgie orthopédique (n = 54), urologique (n = 11) ou abdominale (n = 5) sous anesthésie générale (n = 58), loco-régionale (n = 10) ou les deux (n = 2), on a titré la morphine iv à l'unité des soins postopératoires. Le titrage a consisté à injecter 3 mg de morphine iv toutes les dix minutes jusqu'à l'obtention d'un score <3 sur une échelle visuelle analogue (EVA) sans sédation importante. Dix-sept patients ne se sont plaints d'aucune douleur ou ont rapporté une bonne analgésie avec la dose initiale de morphine ≤6 mg suivie uniquement de paracétamol. Les patients qui ont eu besoin de plus de 6 mg de morphine iv ont été assignés au hasard à un groupe « forte dose » ou à un groupe « faible dose ». Ils ont reçu de la morphine im de façon systématique à la posologie calculée selon la dose initiale. La douleur était évaluée sur l'EVA avant chaque injection im et le lendemain matin. A la salle de réveil, un patient a présenté une dépression respiratoire précoce et un autre une sédation importante. Ces patients ont alors été exclus de l'étude. Seuls 16 patients ont révélé un EVA >3 au moins une fois pendant la période de l'étude et seulement trois ont demandé une analgésie supplémentaire. Nous pouvons conclure que la morphine im systématique administrée selon un titrage initial iv procure une analgésie efficace et peu coûteuse, applicable à la majorité des patients.

Key words

ANALGESIA: postoperative pain;
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morphine.

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In our institution, about 10,000 adult surgical procedures are performed each year. Of these, 5–10% require planned postoperative analgesia, either continuous regional anal-

gesia (most often epidural with a combination of local anaesthetics and opioids) or *iv* PCA with morphine. At the other extreme, 15–20% of the patients require little or no postoperative analgesia with paracetamol. We routinely use *im* morphine for the other 75% and, therefore, the problem of adequate postoperative analgesia for these 75% remains.

The institution of postoperative analgesia is often delayed until the patients are discharged from the post-anaesthesia care unit (PACU) and is often delegated to the nursing staff.¹ In several studies dealing with postoperative pain therapy, the beginning of treatment is either not specified, or delayed to the later postoperative period when the patient has recovered from anaesthesia.^{2–4} However, it is well established that pain therapy should begin as early as possible in the postoperative period, if not preemptively before surgery.^{5,6}

Morphine is widely used for postoperative pain relief. However, drug requirements to obtain analgesia show great interindividual variability.⁷ This variability in patient's needs may lead to insufficient analgesia or respiratory depression, when morphine is systematically administered by *im* injections.⁸ The poor results obtained by intermittent systematic *im* administration of morphine are due to inappropriate doses and/or intervals between injections.^{9–11} Previous studies have demonstrated indirectly that the dose of morphine needed by *iv* PCA to produce 24 hr analgesia is correlated with the initial titrated dose of morphine.^{8,12} However, there are no data on the use of an *im* morphine dose based upon the initial titrated dose.

We decided, in a prospective randomized study, to define a morphine dosage regimen that permits early and individually adapted postoperative analgesia established by the *iv* titration of small morphine boluses in the PACU. Maintenance of analgesia was provided by two different dosage regimens of *im* injections, according to the initially titrated dose.

Methods

Patients

After Ethics committee approval, ASA physical status I–III patients of either sex scheduled for planned orthopaedic, urological or abdominal surgery were studied. Patients usually scheduled for planned postoperative analgesia such as *iv* PCA or regional technique were not excluded from the study; patients with known painful procedures were included. All patients were informed and a written consent was obtained. Outpatients as well as patients with a history of drug abuse or known dependence on opioids were excluded from the study. With the exception of delayed postoperative tracheal extubation, no

patient was excluded for any other cause. General or regional anaesthesia was conducted by the usual anaesthetist with no change in our clinical practice. Patients were premedicated with oral hydroxyzine (100–150 mg). General anaesthesia was induced with thiopentone and fentanyl 1.5–2.5 $\mu\text{g} \cdot \text{kg}^{-1}$. Maintenance was performed with fentanyl 1.5–2.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ and halothane or isoflurane (0.4–1 MAC). Adequate relaxation was obtained with either pancuronium, vecuronium or atracurium. Regional anaesthesia techniques (spinal, epidural or interscalene bloc) used either lidocaine or bupivacaine. No NSAIDs were given.

Procedure

In the PACU, when complaining of pain, patients received morphine hydrochloride 3 mg *iv* every ten minutes until satisfactory analgesia was achieved (the criteria for satisfactory analgesia are defined below). If the total *iv* dose of morphine was >6 mg, analgesia was maintained with systematic intermittent *im* injections, otherwise only paracetamol (50 mg $\cdot \text{kg}^{-1} \cdot 24 \text{ hr}^{-1}$) was given. Patients who received an *iv* titrated dose >6 mg were randomly assigned to either a high- or a low-dose maintenance group. Only the person who recorded the data (KB) was aware of the patient's group. Patients in the high-dose group received $\frac{2}{3}$ of the total titrated dose three hours after the end of titration, followed by $\frac{1}{2}$ of the titrated dose every four hours, whereas patients in the low-dose group received $\frac{1}{2}$ of the total titrated dose three hours after the end of titration, followed by $\frac{1}{3}$ of the total titrated dose every four hours. Patients were discharged from the PACU 30–40 min after the first *im* injection. The patients were informed that supplemental analgesia was available if needed. In this case, the nurse sought the advice of an anaesthetist before giving additional analgesia.

Postoperative vital signs (ECG, heart rate, blood pressure, respiratory rate, SpO_2) were continuously monitored in the PACU. Pain was evaluated by visual analogue scale (VAS 0–10). Pain assessment was begun as soon as possible when the patients arrived in the PACU. Assessment of sedation was made by a simple numeric scale (0 = awake, 1 = asleep, easy to arouse, 2 = asleep, difficult to arouse). Criterion for satisfactory analgesia was: a pain score <3 on the VAS scale provided that sedation was <2 . Pain and sedation were recorded every ten minutes during the titration and before each *im* injection. Moreover, respiratory rate and the appearance of side effects were recorded when patients first complained in the PACU, at the end of titration, before the first *im* injection and the next morning, before morphine *im* injection. On the next morning, the quality of patients sleep was assessed with the following score: 0 = no sleep, 1 = intermittent sleep, 2 = good night with continuous

FIGURE 1 Correlation between titrated dose of morphine and VAS pain scale upon arrival in the PACU in the 58 patients who received morphine ($\rho = 0.756$, $P < 0.0001$). The area of the circles is proportional to the number of patients.

TABLE I Demographic data for the 70 patients who entered the study

	High-dose group 25	Low-dose group 28	Paracetamol group 17
Sex (M/F)	13/12	14/14	11/6
Age (yr)	52 $\pm$ 15 (25–81)	50 $\pm$ 16 (18–77)	49 $\pm$ 15 (23–69)
Weight (kg)	68 $\pm$ 15 (46–104)	69 $\pm$ 16 (41–100)	71 $\pm$ 16 (47–112)
Height (cm)	169 $\pm$ 11 (148–184)	163 $\pm$ 18 (110–186)	167 $\pm$ 7 (154–181)
ASA I	18	17	10
ASA II	6	10	5
ASA III	1	1	1

sleep. At this time, the recording chart was completed for side effects possibly unnoticed.

Statistics

The groups were compared for demographic data and respiratory rate by using Student's *t* test with the Bonferroni correction for continuous variables and a χ^2 -test for discrete variables. The VAS pain scores were compared between the two groups receiving morphine using the Mann-Whitney test. The sedation score was analysed using a χ^2 test. A Spearman rank test was used to

test the correlation between VAS on arrival in the PACU and the titrated dose of morphine. Data are presented as mean $\pm$ SD. $P < 0.05$ was considered to be significant.

Results

Of the 70 patients who entered the study (38 male and 32 female, aged 18 to 81 yr), 58 (83%) needed initial *iv* morphine. They received an initial titrated dose of 15.3 ± 6.8 mg (range 3–33 mg) which was correlated to the intensity of pain assessed by the VAS scale ($\rho = 0.756$, $P < 0.0001$) (Figure 1). Fifty-three of those 58 patients received more than 6 mg of morphine as PACU titration and were deemed to require *im* morphine for maintenance of analgesia: 25 patients in the high-dose group and 28 in the low-dose group. The ensuing *im* maintenance dose in the ward was 43.5 ± 15.2 mg $\cdot$ 24 hr⁻¹ for the high-dose group patients (range 27–81 mg) and 34.7 ± 14.7 mg $\cdot$ 24 hr⁻¹ for the low-dose group patients (range 18–66 mg). The five patients who received 6 mg or less of morphine as *iv* titration and the 12 patients who did not receive any morphine formed the paracetamol group. None required additional analgesia during the first postoperative day.

There was no difference regarding the demographic data between the groups (Tables I and II), but the VAS pain scale was higher before titration in the low-dose group ($P < 0.05$). After titration, the VAS score was <3 in 45 of the 53 patients who received >6 mg morphine *iv*. Titration was stopped in eight patients before they reached a VAS <3 because of a sedation score of 2. In this case, we calculated the maintenance *im* dose as a function of the *iv* dose received by the patient: Analgesia remained adequate during the first postoperative day (from arrival in the PACU until the next morning) with no difference between the two groups (Figure 2). A total of 16 patients (eight in the high-dose group and eight in the low-dose group) had a VAS score >3 at least once during the first postoperative day, but only three of them requested rescue analgesic (two in the high-dose group and one in the low-dose group) (Figure 2). Of these 16 patients, four had a VAS >3 twice and two had a VAS >3 three times during the study course. The two patients with a VAS ≥ 6 at the end of titration (Figure 2) had total hip arthroplasty and the four patients with a VAS >6 on the next morning had the following operations: one total hip arthroplasty, one elbow arthroplasty, one nephrectomy, and one shoulder arthroplasty. None of the patients who received only paracetamol had a VAS score >3 during the first postoperative day.

One patient had an episode of respiratory depression at the end of the titration which necessitated the injection of naloxone in the PACU and one patient exhibited an

TABLE II Detail of anaesthesia and surgery

<i>n</i>	High-dose group 25	Low-dose group 28	Paracetamol group 17
Anaesthesia			
General anaesthesia	20	24	14
Regional anaesthesia	3 (spinal)	4 (epidural)	3 (2 epidural, 1 spinal)
General + regional	2 (combined interscalene bloc + general anaesthesia)	0	0
Surgery			
Upper limb	<i>n</i> = 6 (24%) (shoulder arthroplasty <i>n</i> = 5, elbow arthroplasty <i>n</i> = 1)	<i>n</i> = 2 (7%) (shoulder arthroplasty)	<i>n</i> = 1 (6%) (shoulder arthroplasty)
Spine (removal of herniated disc)	<i>n</i> = 4 (16%)	<i>n</i> = 5 (18%)	<i>n</i> = 5 (29%)
Lower limb	<i>n</i> = 10 (40%) (total hip arthroplasty <i>n</i> = 5, knee arthroplasty <i>n</i> = 4, ankle arthroplasty <i>n</i> = 1)	<i>n</i> = 14 (50%) (total hip arthroplasty <i>n</i> = 4, knee arthroplasty <i>n</i> = 6, tibial arthrodesis <i>n</i> = 2, ankle arthrodesis <i>n</i> = 2)	<i>n</i> = 7 (41%) (total hip arthroplasty <i>n</i> = 3, tibial osteotomy <i>n</i> = 1, ankle arthrodesis <i>n</i> = 2)
Abdominal and urological surgery	<i>n</i> = 5 (20%) (nephrectomy <i>n</i> = 3, nephrostomy <i>n</i> = 1, cystectomy <i>n</i> = 1)	<i>n</i> = 7 (25%) (nephrectomy <i>n</i> = 4, cystectomy <i>n</i> = 2, hepatectomy <i>n</i> = 1)	<i>n</i> = 4 (24%) (incisional hernia <i>n</i> = 2, laparotomy <i>n</i> = 2)

FIGURE 2 Visual analogue pain scale in the 51 patients who completed the study in the high- and low-dose groups. The box display represents the 25, 50 (median) and 75 percentiles. Bars are respectively the 10 and 90 percentiles. Outliers are represented by open circles.

important sedation after the initial *iv* titration. These two patients did not receive the planned *im* morphine and have been excluded from the rest of the study. One patient did not receive one *im* injection in the night because of a sedation score > 1. Fourteen patients had a respiratory rate lower than 12 breaths $\cdot$ min⁻¹ at the end of the *iv* titration. Throughout the whole study period no difference was revealed between the groups concerning sedation and other side effects such as nausea, vomiting, urinary retention and pruritus (Table III). However, the

TABLE III Side effects observed in the two groups receiving *im* morphine. Respiratory depression and sedation are reported in the text

	High dose (<i>n</i> = 24)	Low dose (<i>n</i> = 27)
Nausea	4	2
Vomiting	3	4
Urinary retention	1	1
Pruritus	0	1

number of patients who exhibited a sedation score > 0 was greater after the titration and before the first *im* than before the titration and on the next morning ($p < 0.001$). Fifteen patients in the high-dose group (62%) and 18 patients in the low-dose group (67%) slept well with a score of 2.

Discussion

This study confirms the great variability of morphine dosage required to produce adequate postoperative analgesia. Despite this, a systematic *im* dose regimen may provide adequate postoperative analgesia after a wide variety of surgical procedures. This regimen is based on an initial *iv* titration performed in the PACU.

Although a close correlation between morphine dosage and the level of analgesia has been found in rats,¹³ great variability in analgesic needs is usually reported in humans.²⁻⁸ In the present study, there was a positive correlation between the intensity of pain measured by the VAS scale before titration and the titrated dose (Figure

1). Nevertheless, the variability was too wide and did not permit prediction of the dose to be given to a particular patient based on the VAS pain scale. We then used the initial *iv* titration to predict the patient's need instead of the VAS. The titration was performed in the immediate postoperative period in the PACU, despite the fact that it is often difficult to obtain a reliable assessment of analgesia (especially by the use of VAS scale) in a patient in pain but who has not totally recovered from anaesthesia. Thus, we performed the titration early in the PACU, but under close monitoring.

The great variability in analgesic needs reported in the literature²⁻⁸ can be explained by two different mechanisms: (1) a pharmacokinetic phenomenon leading to important variations in morphine and morphine-6-glucuronide concentrations in plasma as well as at the site of action,⁷ and (2) a pharmacodynamic phenomenon. Such a pharmacodynamic cause may explain the great variability in the intensity of pain in patients otherwise similar for demographic data and type of surgery. In the present study, 17 patients (24%) did not complain at all or had excellent analgesia with 3 or 6 mg morphine *iv* followed only by paracetamol. It is noteworthy that these patients had similar surgical procedures to patients who needed more than 30 mg morphine *iv* (Table II). Also, the same level of analgesia has been observed in patients who exhibited a three- to fourfold difference in plasma concentrations of morphine: the minimum effective analgesic concentration (MEAC) of morphine in the postoperative period has been found to vary from 9 to 23 ng · ml⁻¹.⁷ In our study, the initial *iv* dose of morphine needed to produce adequate analgesia (i.e., a VAS score <3) after the same surgical procedure (e.g., total hip arthroplasty) varied from 0 to 33 mg.

After titration, most of the patients had satisfactory analgesia (Figure 2). The *iv* titration was followed by systematic *im* administration of morphine with two different dosage regimens. These regimens led to a fixed daily *im* maintenance dose equal to 2.2 times the initial *iv* titrated dose for the low-dose regimen and to 3.2 times this dose for the high-dose regimen. Patients in the high-dose group received an average *im* dose of 7.25 mg every four hours and patients in the low-dose group received an average maintenance dose of 5.7 mg every four hours. Both regimens showed similar efficacy, with a median VAS <2 after the initial titration until the next morning (Figure 2). These results are comparable with those obtained by PCA techniques, except for the psychological aspect of PCA that is not taken into account in our study.¹⁴ The use of the high dosage did not show any advantage provided that the initial *iv* titration was performed in the PACU under close monitoring. Indeed, morphine injection early after the end of anaesthesia may lead to res-

piratory depression and one patient required the injection of naloxone in the PACU.

In conclusion, *im* morphine given systematically in the surgical ward at a dosage calculated from an *iv* titration performed early in the PACU is an efficient and relatively inexpensive method for providing postoperative analgesia during the first day after surgery. Intramuscular analgesics have shown their efficacy when given at regularly scheduled time intervals rather than on demand.^{8,15} We, then, propose an improvement of the systematic *im* morphine prescription with the calculation of the *im* regimen deduced from an initial *iv* titration. This technique is applicable to almost all patients and this has to be taken into account since it has been shown that sophisticated techniques are offered to fewer than 30% of patients either in North America or in Europe.¹⁶

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