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Postoperative intravenous morphine titration

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Editor's key points

- Titration of morphine i.v. is used widely for treatment of pain in post-anaesthesia care unit.
- The careful use of a protocol should minimize the adverse effects of morphine.
- Distinguishing between adequate pain relief and morphine-induced sedation can be difficult.
- It can be used with caution in the elderly, children, and obese patients.

Summary. Relief of acute pain during the immediate postoperative period is an important task for anaesthetists. Morphine is widely used to control moderate-to-severe postoperative pain and the use of small i.v. boluses of morphine in the post-anaesthesia care unit allows a rapid titration of the dose needed for adequate pain relief. The essential principle of a titration regimen must be to adapt the morphine dose to the pain level. Although morphine would not appear to be the most appropriate choice for achieving rapid pain relief, this is the sole opioid assessed in many studies of immediate postoperative pain management using titration. More than 90% of the patients have pain relief using a protocol of morphine titration and the mean dose required to obtain pain relief is 12 (7) mg, after a median of four boluses. Sedation is frequent during i.v. morphine titration and should be considered as a morphine-related adverse event and not evidence of pain relief. The incidence of ventilatory depression is very low when the criteria to limit the dose of i.v. morphine are enforced. Morphine titration can be used with caution in elderly patients, in children, or in obese patients. In practice, i.v. morphine titration allows the physician to meet the needs of individual patients rapidly and limits the risk of overdose making this method the first step in postoperative pain management.

Keywords: analgesia, postoperative, analgesic techniques, i.v., analgesics opioid, morphine, pain, acute, titration

Pain control after surgery remains a challenge.[1] Despite the development of multimodal strategies and evidence-based recommendations regarding the use of non-opioid analgesics, opioids are often required in the postoperative period.[1–3] In the majority of patients requiring potent analgesics in the postoperative period, morphine is both efficacious and acceptable. Morphine is a non-selective μ-opioid receptor agonist that acts directly on the spinal cord and via the descending projections of the periaqueductal grey matter to the rostral ventromedial medulla and to the dorsal horn of the spinal cord.[4]

However, clinical studies of morphine for postoperative analgesia have shown wide intra- and inter-individual variability in morphine plasma concentration and a wide range of morphine requirements for postoperative pain. The use of i.m. or s.c. morphine in the immediate postoperative period is usually not appropriate because of the time delay between morphine administration, morphine absorption, blood concentration, and analgesic effect (Fig. 1).[5] I.V. administration ensures complete bioavailability and high drug concentrations can be achieved promptly. Bolus doses given i.v. at fixed time intervals will result in drug accumulation but also achieves an efficient therapeutic concentration. A titration regimen must avoid both over- and under-dosing. Although morphine would not appear to be the most obvious choice for achieving rapid pain relief, it has been assessed in many studies of immediate postoperative pain management using titration.[6–10]

Lipophilic opioids such as fentanyl, alfentanil, or sufentanil are more potent than morphine and have a more rapid onset of action but the duration of analgesia of these drugs is shorter.[5] This review focuses on the i.v. titration of morphine in the immediate postoperative period. It addresses the pharmacological basis of i.v. morphine, clinical use in the post-anaesthesia care unit (PACU), the relationship between pain scores and morphine requirements, adverse effects, and limitations of the technique.

The search strategy used involved two electronic databases [PubMed® (MEDLINE/Index Medicus) and the Cochrane Controlled Trials Register] which were searched for studies published between 1966 and June 2010. The medical subject heading terms used for the search were 'postoperative opioid titration' (including morphine or other opioids), 'postanaesthesia care unit', or both. Studies were identified from databases and by hand-searching reference lists from review articles and original published articles to

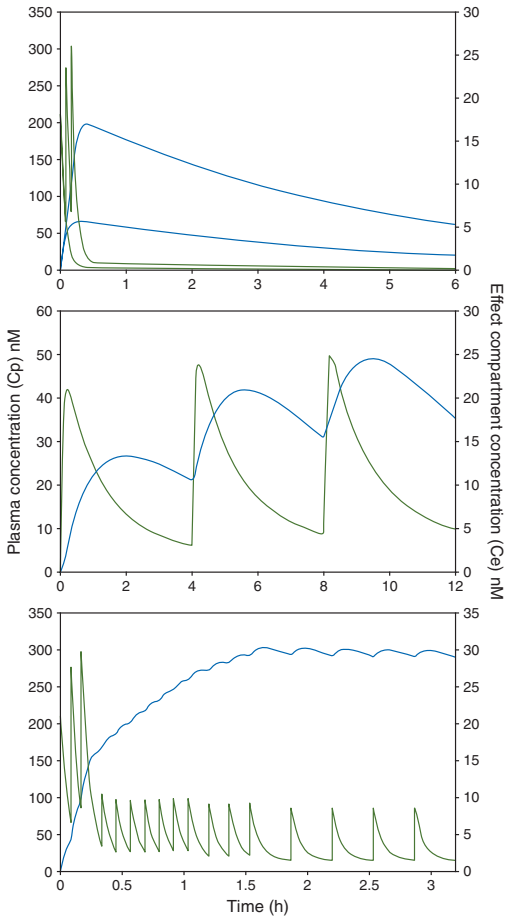

Fig 1 Simulations of morphine concentration in the central plasma compartment (Cp, green) and in the effect compartment (Ce, blue) after various schemes of administration (A–C). (A) Because morphine kinetics are linear, three successive i.v. boluses of 3 mg at 5 min interval lead to a three times higher Ce when compared with a single 3 mg injection. (B) Cp and Ce after i.m. injections of 10 mg morphine every 4 h. Because the kinetics are linear, steady state is not attained before the third injection. In addition, the delay of action after injection is important (time to maximum Ce=2 h) and the peak-and-valley phenomenon of large magnitude. (C) The administration of three titration doses of 3 mg at 5 min interval, followed by 1 mg by patient-controlled analgesia every 10 min from 20 to 90 min after initiation of titration and every 20 min after the 90th min. Ce 5 min after the third i.v. injection (15 min after initiation) is the same as Ce obtained 4.5 h after the first i.m. injection. Note the different time scale. Simulations have been performed with the data from Mazoit and colleagues.[13]

answer the questions. The following key words were included: 'intravenous morphine titration', 'morphine titration in elderly, children, obese patients', and 'adverse events and morphine in the PACU'.

Pharmacology

Morphine is a hydrophilic molecule with a clearance exceeding hepatic blood flow and a half-life of about 1.5 h.

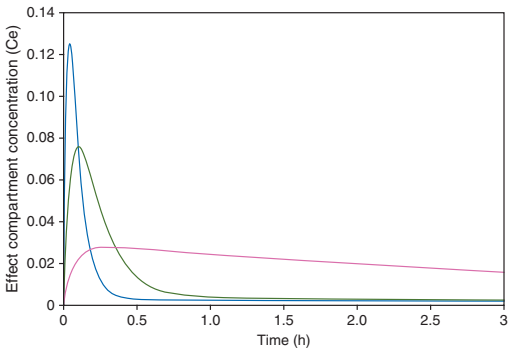

Fig 2 Simulations of Ce obtained after i.v. injection of alfentanil/remifentanil (blue), sufentanil/fentanyl (green), and morphine (pink). Units are arbitrarily normalized by the area under the Ce–time curve. The time to Ce_{max}, the peak concentration in the effect compartment, is 2, 6, and 20 min, respectively, for alfentanil/remifentanil, sufentanil/fentanyl, and morphine, respectively. The relative duration of analgesia, the time for which Ce exceeds 80% of its maximum value,[5] is 2.5, 7.5, and 78 min for alfentanil/remifentanil, sufentanil/fentanyl, and morphine, respectively. Simulations have been performed with the data from Mazoit and colleagues[13] and Lötsch and colleagues.[12] $t_{1/2ke0}$=1.65 h, k_a=1 h^{-1} for morphine, and $t_{1/2ke0}$=1 min for alfentanil/remifentanil and 6 min for sufentanil/fentanyl.

Morphine undergoes Phase II metabolism mainly by the 2B7 isoform of the UDP-glucuronosyltransferase (UGT2B7).[11] Because morphine is hydrophilic, its penetration into the central nervous system is delayed and does not parallel its disappearance from plasma. High hydrophobicity[1] facilitates opioid transport to the site of action and then confers a rapid onset of action. Short-acting drugs (such as alfentanil, fentanyl, or sufentanil) produce not only rapid onset but also short duration of action because plasma and brain concentrations remain above the threshold for therapeutic action for only a brief period as the drugs rapidly redistribute from the site of action to other tissues. The delay between plasma and effect-site drug transfer is usually estimated by $t_{1/2ke0}$, the half-life of transfer from central to effect compartment (Ce). Morphine $t_{1/2ke0}$ ranges from 1.6 to 3.9 h in volunteers and 1.7 h in postoperative patients.[12 13] In comparison, $t_{1/2ke0}$ of alfentanil and fentanyl are ≈1 and 6 min, respectively.[12] Thus, morphine concentration in the Ce peaks 20 min after a single i.v. injection.[5 13] The relative duration of action, that is, the time for which Ce exceeds 80% of its maximum value (Fig. 2), is much longer for morphine than for alfentanil or for fentanyl (78–96 *vs* 2, *vs* 7 min, respectively; Table 1).[5 13] The time to relative onset, defined as the time taken initially to reach 80% of Ce_{max}, the maximum concentration in the effect compartment after a single i.v. injection (Table 1), is between 5 and 6 min. This provides some insight into the lockout period used for patient-controlled analgesia and also the time before the administration of a second dose using a titration method.[5 13]

Table 1 Pharmacology of commonly used opioids and relative CNS concentration profiles after i.v. administration.[4–6] Relative duration of action, time for which the relative CNS concentration exceeded 80% of its maximum value; time to relative onset, time taken to initially reach 80% of the maximum concentration. Data are from Mazoit and colleagues[13]

	Morphine	Fentanyl	Alfentanil
Potency (*vs* morphine)	1	100	10–20
pK_a	8.0	8.4	6.5
Plasma protein bound (%)	30–35	84	90
Volume of distribution (litre kg^{-1})	2–4	3–5	0.4–1.0
Blood–brain equilibration rate (min)	120–180	6	1
Terminal half life (h)	2–3	3.5	1.6
Relative hydrophobicity	1	580	90
Time to relative onset (min)	6	2	1
$t_{1/2ke0}$ (min)	100	6	1
Time to maximum concentration (min)	19	4	2
Relative duration of action (min)	78–96	7	2
Benefits	Long-lasting duration of analgesia; cheapest opioid	Short time to efficacy; better benefit/risk ratio in the elderly	Very short time to efficacy
Disadvantages	Long time to action; peak effect and adverse events may occur 40–60 min after the last administration	Short duration of action; increased risk of accumulation in the obese patient	Very short duration of action

The morphine metabolite, morphine-6 glucuronide (M6G), is about 1–8 times the potency of morphine with a longer elimination half-life.[13 14] This water-soluble molecule has a delayed action ($t_{1/2ke0}$=3–8 h) and may accumulate in renal impairment.[13 14] Although unlikely in the postoperative period, late ventilatory depression due to accumulation of M6G may occur in patients with end-stage renal failure.[11 12]

There is a great inter-individual variability in the requirements for morphine in the postoperative period. Possible explanations include morphine metabolism, transfer across the blood–brain barrier, binding to the μ-receptor, or the patient's intrinsic sensitivity to pain. Several genetic polymorphisms have been reported for metabolism, P-glycoprotein substrates, and the μ-receptor. Single-nucleotide polymorphisms (A118G) in the μ-receptor gene are associated with decreased potency of morphine and M6G, with increasing morphine dosage requirements, and altered efficacy of μ-opioid agonists and antagonists.[15 16] However, pharmacogenetics may explain <50% of the observed inter-individual variability and major differences in the sensitivity to pain seem to be the major factor.[14]

A pharmacokinetic–pharmacodynamic study[6] showed that the inter-subject variability in the dose required for half an initial visual analogue scale (VAS) was >300%. Thus, patient sensitivity to pain remains the most important cause of variability. This is the major justification for using titration to achieve adequate analgesia in each patient. A study of morphine titration in the postoperative period attempted to identify the covariates significantly affecting the dose leading to analgesia and to sedation.[6] The morphine ED_{50} for analgesia was about 10.2 mg, which agrees well with previously reported values.[17] The factors which decreased ED_{50} included: a low VAS upon arrival in the PACU, a short delay between awakening and first titration dose, and the administration of non-steroidal anti-inflammatory drugs (NSAIDs) at the end of surgery. The ED_{50} for sedation was close to 15 mg and a dose of 20 mg was associated with sedation in more than 90% of the patients. As would be expected, the ED_{50} for morphine was nearly 1.5 times less in patients with moderate postoperative pain than those with severe pain. In addition, simulations[6] showed that an initial VAS-based titration regimen using an increased volume of bolus, rather than a shorter interval between boluses, may be appropriate for patients with severe pain. However, an increased volume of titrated bolus may increase the incidence of adverse effects and decreased safety.[18]

Indeed, although a loading dose concept has been suggested in pre-hospital care and in the PACU to improve analgesia and decrease the time to achieve pain relief,[19] this must be used cautiously, as the loading dose may be too great and thus increase the risk of dose-related adverse effects. A study using a standard anaesthetic procedure found that a loading dose of 0.15 mg kg^{-1} morphine given intraoperatively (moderate pain surgery) slightly decreased the postoperative pain scale but did not significantly reduce the time to achieve pain relief in the PACU or the morphine consumption over 24 h.[18] However, there was a trend towards an increase in the incidence of morphine-related adverse effects.[18]

I.V. opioid titration that allows the requirements of individual patients to be met rapidly while limiting the risk of overdose should be the first step in postoperative pain management.[20] The optimal regimen in the postoperative setting could be administration of both a lipid soluble opioid such as fentanyl to gain fast pain control, and morphine for a longer lasting action. However, there are studies of this combination and its benefit/risk ratio remains a matter of debate.[21] Any titration protocol should define the pain score threshold required to administer morphine, the dose of i.v. boluses of morphine administered,

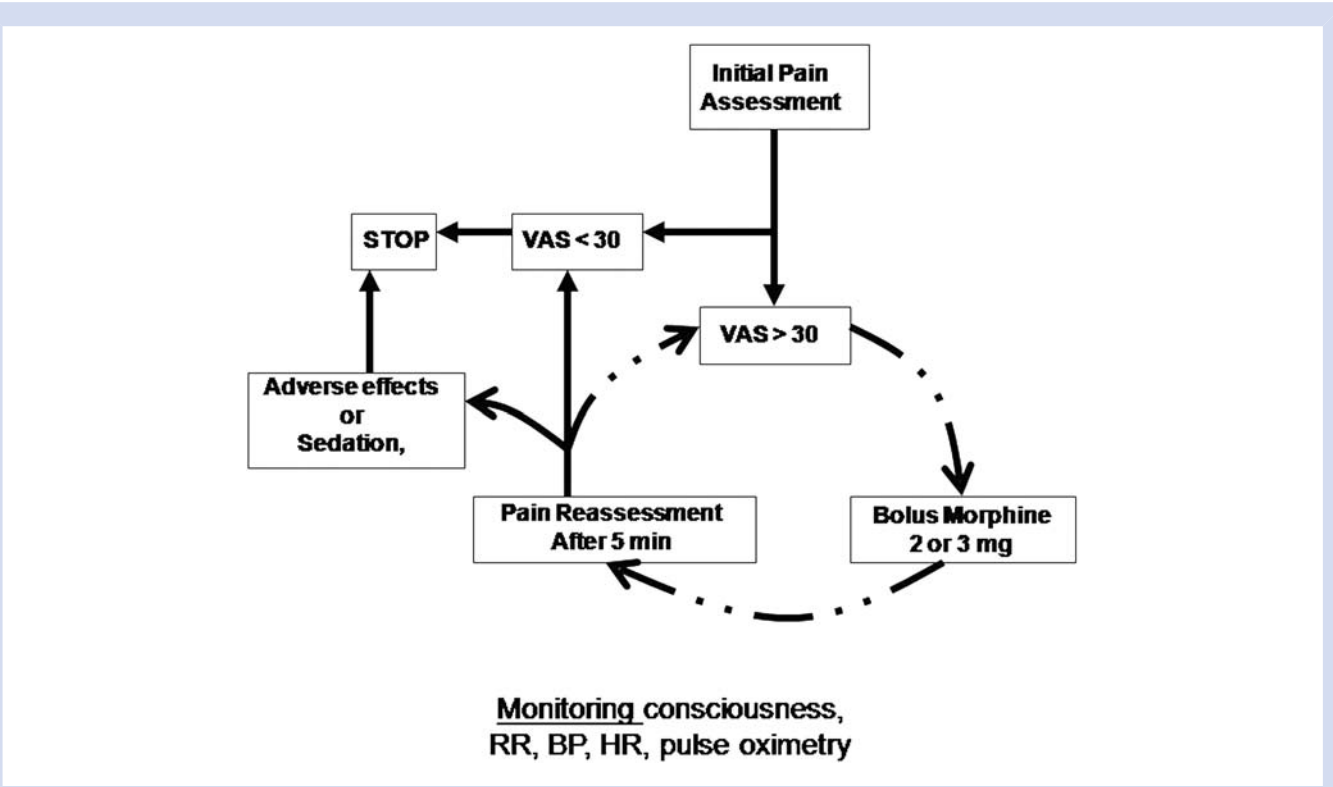

Fig 3 Protocol for i.v. morphine titration in adults. VAS, visual analogue scale; RR, respiratory rate; AP, arterial pressure; HR, heart rate.

the interval between boluses, the limitation (or not) of the total dose of morphine i.v. injected, and the criteria to stop titration.

Clinical use in the PACU

I.V. administration of opioids is usually recommended for acute pain relief in the immediate postoperative period and the use of small i.v. doses of morphine (<5 mg) allows rapid titration to adequate pain relief. The challenge is to administer the second and subsequent doses in a manner that takes account of the residual effects of the first dose. An important consideration is factors which may predict morphine requirements in the PACU. A study of 149 patients undergoing various non-cardiac surgical procedures identified that ethnicity (Caucasians), emergency surgery, major surgery, surgery exceeding 100 min, and pain score on arrival in the PACU (moderate-to-severe pain) were independent predictive factors of early morphine requirements in the PACU.[22]

In a patient who was awake in the PACU, the presence of pain can be assessed using a VAS or a numerical rating scale. Pain relief is usually defined as a VAS score of ≤30 mm. An example of an i.v. morphine titration protocol would be when pain increases to >30 mm, i.v. morphine is titrated i.v. until pain relief is achieved using a short interval between boluses (5 min) and no upper limit for the total administered dose (Fig. 3).[10 18] If the patient is asleep, no attempt is made to awaken him/her and the patient should be considered to have pain relief or morphine-related sedation. In the protocol proposed, morphine titration is stopped if the patient becomes sedated (Ramsay score >2), has a ventilatory rate of <12 bpm, or an oxygen saturation of <95%, or has a serious adverse event (allergy, hypotension, severe vomiting). Using this titration protocol, the percentage of patients with pain relief (defined as a pain level ≤30 mm) may be up to 98% with a very low incidence of severe adverse events such as severe ventilatory depression (<1%).[7–10 18] The administration of small boluses of morphine probably increases the time to pain relief but decreases the risk of adverse events related to morphine dose accumulation. Repeat i.v. doses of 5 or 10 mg, rather than doses of 2 or 3 mg, is inappropriate in an opioid-naive patient.[7 21 23]

The relationship between pain score and morphine requirements

For i.v. morphine titration, the relationship between the pain relief, as reflected by the VAS, and time is important. When the pain relief process is analysed globally, it appears to be linear (Fig. 4A).[8 10 18] A study of more than 3000 postoperative patients in the PACU found that patients with higher initial VAS required more incremental doses of morphine to reach an acceptable level. The mean (SD) dose for pain relief was 0.17 (0.10) mg kg^{-1} with a median of four boluses (range: 1–20).[9] Nevertheless, when patients were grouped according to the number of boluses required, each curve was sigmoid (Fig. 4B).[9] In the same way, the

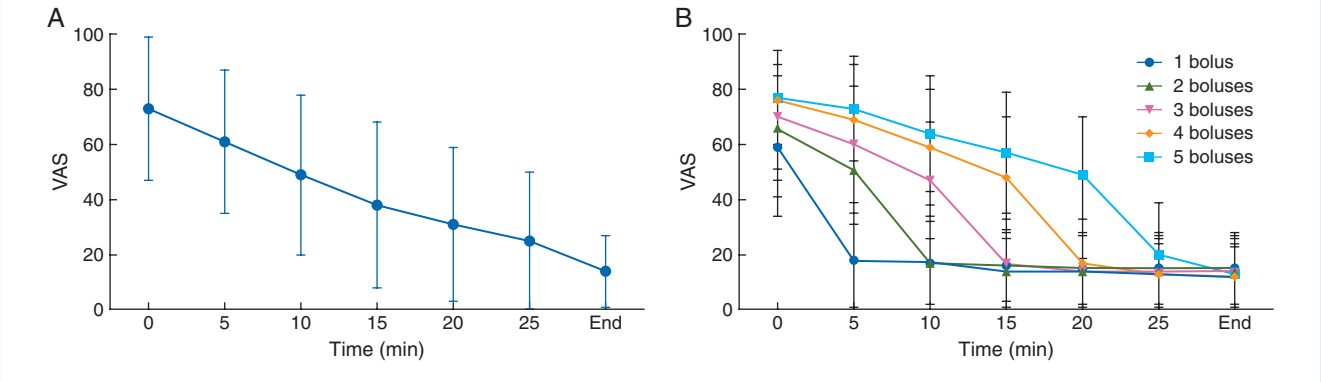

Fig 4 Relationship between the VAS score [mean (SD)] and time (interval between two boluses was 5 min) during morphine titration and thus pain relief. (A) Global population. (B) Patients separated into groups according to the number of boluses needed to obtain pain relief.[9]

relationship between the initial VAS score and subsequent morphine requirement was depicted by a sigmoid curve.[9] This relationship may have important consequences as VAS scores changed little with the initial incremental doses and then decreased rapidly to a value of 30 mm or less with the final incremental dose. These curves first suggest that the initial VAS score should be taken as an important covariate for pain relief when comparing the morphine-sparing effect of an analgesic drug to increase the power and limit the consequences of heterogeneity. Linearity of the time-course VAS during morphine titration is probably the result of the addition of several sigmoid curves. It is important to note that during i.v. morphine titration, the VAS score does not markedly change until the morphine dose approaches that dose ultimately needed to obtain pain relief (threshold dose) and then it abruptly decreases. Moreover, a VAS score of <60 is associated with a the subsequent requirement of only one bolus of morphine.[9] The use of i.v. titration is aided by an understanding of the time course of VAS scores during the pain relief process and the pharmacokinetic properties of i.v. morphine.

Morphine-related adverse effects

Patient satisfaction is, in part, related to pain management but also to their overall comfort in the PACU.

Nausea and vomiting

The most frequent adverse effect encountered in the PACU is postoperative nausea and vomiting (PONV) which occurs with an incidence of 8–15% (Table 2).[7–10 18] There are predictive risks for PONV related to personal history of the patient, the anaesthetic, and surgical risk.[24] No study has yet assessed if PONV in the PACU was strongly influenced by postoperative opioid use in a dose-related manner. In the same way, there have been no studies specifically assessing frequency (number of nausea episodes and times vomited), duration (minutes of nausea), and severity of PONV in the immediate postoperative period.

Table 2 Comparison of adverse effects in the PACU and in the ED with a morphine titration regimen. Data are mean (SD) or numbers (percentage). *$P<0.05$ *vs* PACU

	PACU ($n=1050$), Aubrun and colleagues[7]	ED ($n=621$), Lvovschi and colleagues[25]
Morphine dose (mg)	10.3 (6.1)	10.5 (6.4)
Morphine dose (mg kg^{-1})	0.15 (0.09)	0.15 (0.10)
Adverse events	141 (13.5)	67 (10.8)
Nausea and vomiting	109 (11.5)	26 (4.2)*
Urinary retention	27 (2.6)	17 (2.7)
Respiratory depression	4 (0.4)	16 (2.6)*
Severe respiratory depression	0	0
Pruritus	3 (0.3)	4 (0.6)
Allergy	4 (0.4)	1 (0.2)
Sedation	628 (59.8)	60 (9.6)*

The incidence of nausea and vomiting differs in the PACU and the Emergency department (ED), despite using a similar protocol.[25] In the postoperative period, anaesthetic and surgical procedures may be a risk factor for PONV.[24 25] The higher incidence of PONV in the PACU may also be related to anaesthetic drugs given before morphine titration, indicating that opioid adverse effects in the postoperative period should not be linked only to their postoperative administration.

Ventilatory depression

The most serious adverse effect of morphine is ventilatory depression and this needs to be clearly defined.[26] In the PACU, pulse oximetry ($S\,p_{O_2}$), ventilatory rate, and sedation (using a simplified version of Ramsay scale) are the main variables assessed and recorded in patients.[7–22 27 28] $S\,p_{O_2}$

values ranging from '≤85% to 94%' have been used to define respiratory depression.[26] As most patients in the PACU receive supplemental oxygen, an S_{pO_2} <95% may be considered as an index of ventilatory depression limiting morphine titration.[7–10 18] Ventilatory rate is considered a more reliable and adequate index of hypoventilation in most studies.[7 9 10] The threshold value used to define ventilatory depression and to discontinue morphine titration is usually taken as ≤10 or 12 bpm.[23 26 28] This threshold is used in many studies for safety reasons.[7–10 18] Severe postoperative ventilatory depression (<10 bpm) associated with an impairment of consciousness level requires reversal with naloxone until the ventilatory rate is >12 bpm in a patient who is awake. The incidence of severe ventilatory depression is low if a strict protocol for titration is used, particularly with a sedation scale; when the level on the Ramsay scale is >2, morphine titration is stopped.[7–10]

Sedation

In most studies, sedation occurs in up to 60% of the cases and represents a common cause of discontinuation of titration for safety reasons.[8–10 18] Studies of the relationship between sedation and morphine titration have attempted to explain whether it is a sign of pain relief or an adverse effect of morphine. There was a poor relationship between an increasing incidence of sedation during morphine titration, and an unchanged incidence of ventilatory depression.[7] A prospective assessment of a temporal relationship between morphine titration, analgesia, and sedation[29] used three tools: the VAS to assess immediate postoperative pain, and the Ramsay scale and the bispectral index to assess sedation and its depth. In this study, a group of patients who slept during morphine titration was compared with a group of patients who were awake. The changes in the Ramsay scale and the bispectral index were significantly different in the 'sleep group' compared with the 'awake group', whereas the time course of VAS for pain was comparable. However, at the time of sleep in the first group, VAS was still 47/100.[29] Moreover, among patients in whom titration was discontinued because of sedation, 25% still had a high level of pain (VAS≥50) while only 50% had satisfactory pain relief (VAS≤30). Thus, morphine titration was stopped before patients had complete pain relief. However, if sedation is a predictive factor for the need for rescue analgesia after i.v. morphine titration, it should be noted that stopping morphine titration as soon as the patients become drowsy is probably a good way to avoid morphine overdose.[29–31] Patients with Ramsay scores >3 and pain scores ≥3/10 in the PACU reported moderate-to-severe pain more frequently in the immediate postoperative period, poorer quality of sleep the night after surgery, and higher pain scores at 24 h.[31] In addition, the overall satisfaction with pain control during the first 24 h in the 'sedated group' was lower.

These studies suggest that:

(i) Morphine-induced sedation should not be systematically considered as an indicator of a correct level of analgesia during i.v. morphine titration.[30 31] Supporting this are the initiation of pain prevention during surgery and the use of multimodal analgesia in the PACU.

(ii) Stopping morphine titration when the Ramsay score is above 2 limits the risk of ventilatory depression, even if the causation of sedation is unclear.[7–10 18]

In conclusion, sedation is frequent during i.v. morphine titration even if this effect is often related to pain relief (Table 2). The incidence of ventilatory depression is low when the criteria to stop i.v. morphine administration are enforced.

Morphine titration in the elderly

In elderly patients, a reduced dose of opioids is usually recommended because of changes in pharmacokinetics and pharmacodynamics. There is a 50% reduction in clearance, and a reduction in protein binding,[32] and increased brain sensitivity to the effects of opioids.[33] However, because of the variability in dose requirements and as a titration adapts the dose to the pain, there is no evidence that a titration protocol should also take into account the age of the patients. On the assumption that titration is performed over a short period in which age-related changes in pharmacokinetics and pharmacodynamics might be less important, studies using the same protocol of i.v. morphine titration in young and elderly patients (≥70 yr) have been done.[7–10] The VAS scores were not significantly different in the two groups before, during, and at the end of morphine titration, and the number of patients with pain relief was also equivalent.[9] When the dose of titrated morphine was normalized for body weight (lower in elderly patients), no significant difference was observed between groups (Fig. 5). The number of morphine-related adverse effects, the number of sedated patients, and the number of patients requiring termination of morphine titration were not different.[10] A study after hip

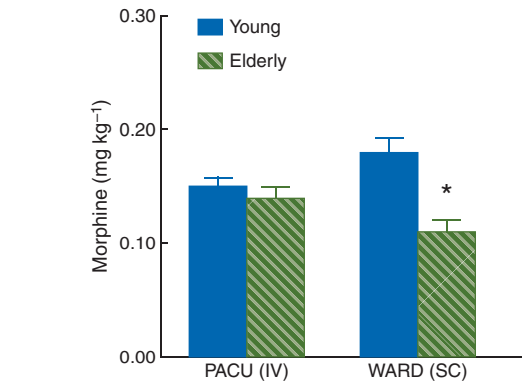

Fig 5 Comparison of postoperative morphine requirement in young (n=224) and elderly (n=105, ≥70 yr) patients in the PACU (i.v. morphine titration) and in the ward (s.c. administration). Data are mean (SEM). *P<0.05 *vs* young patients. From Aubrun and colleagues.[32]

surgery confirmed that the dose of morphine (normalized for body weight) was not significantly modified in elderly patients.[34] In contrast, on the ward after i.v. morphine titration, there was a significant reduction in the dose of s.c. morphine over the first 24 h (−36%) and the dose of s.c. morphine was significantly correlated with age ($R=-0.15$, $P<0.009$).[34] Thus, the dose of i.v. morphine during 'acute' postoperative titration is not significantly modified in elderly patients, but the dose of morphine given over the first 24 h is reduced by 40%.[10 34] Previous studies of the elderly in the postoperative period have assessed the variables influencing morphine requirements over a longer time period using patient-controlled analgesia and not in the immediate postoperative period using i.v. morphine titration. However, further studies are required comparing morphine requirements in the elderly and frail elderly patients. Patients >90 yr represented <2% of the elderly population in a previous study.[10] A protocol using small boluses of 1–2 mg with a greater time interval between boluses and a limitation in the total dose of morphine should be studied in the PACU in these patients.[35]

Morphine titration in children

Morphine undergoes a Phase II metabolism, which is immature at birth, as are opioid receptors, and both slowly mature during the first 1–6 months of life.[36–38] Thus, morphine dosing is different in those <6 months old when compared with older children. Postoperative pain in children is frequently undertreated because of the reluctance of clinicians to administer opioid analgesics, known for their attendant risk of ventilatory depression, and because of the difficulty of assessing pain level and the response of children to pain medication.[39] Morphine titration is appropriate for pain management in paediatric practice because of the limitation in dose and thus the incidence of adverse events. Unfortunately, there are few studies of morphine titration in the postoperative period in children. Pain relief after non-cardiac surgery was compared using a continuous i.v. infusion targeted to not exceed a steady-state serum morphine concentration of 20 ng ml^{-1}, or an intermittent bolus dosage of 0.05 mg kg^{-1} every 1 or 2 h as required found poorer pain relief with the bolus dose but a comparable incidence of ventilatory depression.[36] This study used morphine titration over a longer period and not with the short interval between boluses used in the PACU. In a study of pain management by nurses after major paediatric surgery, patients received i.v. opioids, oral analgesics, or a combination of both drugs.[40] Fentanyl and morphine were rarely given outside the PACU. Of the 45 of the 92 patients who received morphine, 40% received one dose, 38% received two doses, 18% received three doses, and 2% received four doses. In this study, only children who verbally reported pain (pain score of 1–5) received the recommended opioid dose of 0.1 mg kg^{-1} i.v. morphine equivalents during their 2–4 h PACU stay. Patients who reported no pain received a median dose of 0.084 mg kg^{-1}. However, despite the variation in the analgesics and the amount of analgesics administered in mg kg^{-1} morphine equivalents, patients in this study received adequate pain treatment in the recovery period.[41]

Most data support the use of titration and confirm that the amount required to relieve pain differs from child to child. Opioid infusions in children are useful but their dosing and titration require expertise and vigilance. Nevertheless, there are limitations to the use of morphine titration in paediatrics: pain scores are not always obtainable in the PACU,[36] and the validity of self-reported pain intensity scores may be unreliable making dose adjustment difficult.[36–41] The correct bolus dose adjusted to body weight is not established. However, several authors recommend an initial bolus of 100 μg kg^{-1} followed by additional doses of 20–25 μg kg^{-1} every 5 min until pain relief or sedation occurs.[37–41] Nevertheless, more studies are required to establish a consensus protocol for morphine titration in young children.

Morphine titration in obese patients

Obese patients with obstructive sleep apnoea have an increased risk of opioid-induced upper airway obstruction and require close monitoring.[42] There is limited information available regarding morphine administration in obese patients in the immediate postoperative period.[42 43] Intermittent i.v. injections of morphine boluses can be used, although the altered pharmacokinetics of this drug should be taken into account. Obesity significantly prolongs the elimination half-life of lipophilic drugs such as fentanyl and sufentanil.[43] Morphine should be used with caution in patients with obstructive sleep apnoea without non-invasive positive pressure ventilation[42 43].

Limitations of morphine titration

I.V. morphine titration is a simple, efficient, and safe method for pain relief in the PACU. However, the initial VAS in the PACU, before morphine titration, is often high (>70)[7–9] indicating severe pain,[9] and complete pain relief may take time. Despite a short time interval between boluses during titration (5 min), the mean time to achieve complete pain relief is 15 min (range: 5–60 min).[7 18] However, few studies have tested the use of other opioids such as fentanyl but the short duration of action may be an issue. The technique is time-consuming.[9 10] Although morphine titration is a useful method for pain relief, additional studies are required to analyse titration failure, to improve the timescale of pain relief, and to assess the implications of a titration regimen for nursing practice.

The use of VAS assumes that pain is a unidimensional experience, but pain refers to a variety of sensations not only intensity. However, VAS is widely accepted, because of its ease and brevity of administration, its minimal intrusiveness, and its conceptual simplicity. It is worth noting that in a study, nurses used the recommended VAS in only 53% of pain assessments, preferring to use a numerical rating scale as it was quicker and easier to use.[44] It would be

useful to study morphine titration using a VAS and a numerical rating scale, which is a validated tool in acute and chronic pain and well correlated with the VAS scale.[45]

Most authors agree that morphine titration should not be limited to three or four doses. However, it is appropriate to define a dose of morphine that triggers an 'alert' and also define failure of morphine titration. For an 'alert', when a locally agreed total dose is reached (e.g. 20 mg morphine) the nurse should seek advice as to whether it is appropriate to continue titration or to use an alternative analgesic drug or procedure. Failure can occur when adverse effects require discontinuation of morphine titration before sufficient pain relief is obtained.[28] I.V. administration of alternative analgesic drugs, such as nefopam or a small dose of ketamine, may improve the effects of subsequent morphine titration.[46] Indeed, benefits can be achieved by the combined use of opioids along with non-opioid analgesics, NSAIDs, and local anaesthetics. Further studies are required to find the best combination for different procedures which would minimize the morphine requirement in the PACU. The endpoint of this may be that morphine titration is used only as a rescue treatment.

In conclusion, it is important to emphasize the role of i.v. morphine titration in pain management, particularly when the pain is severe. Lack of pain relief increases the risk of adverse effects and of developing chronic postoperative pain. I.V. morphine titration allows adaptation of the dose to the patients' needs and can provide reliable immediate relief of postoperative pain after a wide range of surgical interventions in both young and elderly patients. Pharmacokinetic and pharmacogenetic studies have provided a better understanding of the relationship between morphine efficacy, morphine-related adverse events, and morphine concentration and mechanisms underlying individual differences in opioid action.

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