Safety of pain control with morphine: new (and old) aspects of morphine pharmacokinetics and pharmacodynamics

Abstract
Background: A 26-year-old, 59 kg female was administered morphine 10 mg during tonsillectomy, and 5 mg in the recovery room. She died 5 hours after the operation. Hypoxic cerebral injury, arising from morphine side-effects, was pronounced the cause of death, in spite of morphine being undetectable in blood. Recent pharmacokinetic-pharmacodynamic modelling indicates that, after a single intravenous dose, maximum respiratory depression occurs after 1 hour and 40 minutes and persists for hours. Furthermore, respiratory depression is accompanied by airway obstruction, pain stimulates breathing and antagonises respiratory depression, pain relief unmasks respiratory depression, and a slow breathing rate is uncommon.

Methods: Pharmacokinetic-pharmacodynamic simulations were used to estimate the time course of morphine effect-site concentrations in an “average” 59 kg female, and to calculate the degree of resulting respiratory depression.

Results: Morphine effect-site concentrations approached dangerous levels for respiratory depression and persisted for hours, while plasma concentrations were undetectably low.

Discussion: Court testimony indicates that additional factors contributed to the patient’s demise. Respiratory depression was potentiated by pain relief following quinsy tonsillectomy, and by falling asleep. The airway was obstructed, as witnessed both by nurses and a fellow patient. In addition, nursing staff failed to recognise that snoring can indicate a dangerously obstructed airway.

Conclusions: Dangerous respiratory depression often goes unrecognised in surgical wards. Strategies for improved safety include education of nursing and other staff regarding the following aspects of respiratory depression: (i) recognition of delayed and prolonged respiratory depression; (ii) noisy breathing indicates obstructed breathing; (iii) respiratory rate is an unreliable monitor of respiratory depression; (iv) training in airway management should be compulsory; (v) sleeping patients should be administered oxygen, and pulse oximetry monitoring should be done (especially at night); (vi) more local anaesthesia should be administered for postoperative pain; (vii) combination analgesic therapy (NSAIDs, paracetamol, ketamine, dexmedetomidine, gabapentin) should be utilised to reduce morphine requirements; (viii) high risk patients (e.g. elderly, obese, sleep-apnoea syndrome) should be identified; (ix) sedation scores should be recorded to detect obtunded patients. Morphine plasma concentrations do not reflect pharmacological activity.

Introduction
First isolated in 1803 by the German pharmacist Friedrich Sert Turner, morphine was introduced into clinical practice at about the time of the development of the hypodermic needle in 1853. Since then, morphine has remained an important and widely used drug for the treatment of pain. The most feared adverse effect of all the opiates is major respiratory depression, leading to apnoea and death and, although theoretically preventable, the incidence of adverse effects related to respiratory depression remains an unacceptable 0,1% to 1,0% regardless of the route of administration. The purpose of this paper is to re-examine the known features of morphine-induced respiratory depression and to revise its characteristics in the light of newer pharmacokinetic-pharmacodynamic (PKPD) research. This will be done by means of a case presentation and applied PKPD modelling of a patient who died after a
tonsillectomy, and around whom the discussion will revolve.

Case presentation
A 26-year-old female patient, 157 cm in height and weighing 59 kg, was admitted to hospital with a sore throat that was not responding to antibiotics. She was not receiving any other medication and there was nothing of note in her medical history. She had mild trismus as well as pain on speaking. Her temperature was 36.7°C and her white cell count was 12 700/mm² with a neutrophilia. Swelling around the right upper tonsillar pole was noted. Flexible laryngoscopy was performed awake, and nothing further abnormal was detected. No pus was aspirated from the infected area. Treatment was begun with intravenous fluid and intravenous antibiotics (cefuroxime and metronidazole).

A tonsillectomy was performed the following morning, during which a pocket of pus was noted in the right upper tonsillar pole. No premedication was administered. Induction of anaesthesia was accomplished using sufentanil 10µg and propofol 150 mg, and maintained using desflurane and nitrous oxide in 50% oxygen. No muscle relaxant was administered. Morphine 10 mg (0.17 mg/kg of body weight) was administered intravenously soon after induction of anaesthesia.

The patient arrived in the recovery room about an hour after induction of anaesthesia. It was noted that she was awake and stable with an unobstructed airway, and that there was no bleeding. At this time, she complained of pain and the anesthesiologist administered a further 5 mg of morphine (0.085 mg/kg) approximately one hour and ten minutes after the first 10 mg dose. She was discharged to the ward approximately 20 minutes later. Three hours later she was seen by the surgeon, who noted that she was pain free and that her “vitals” were stable. Two hours later, the senior nurse was called by another patient who said that the patient was “breathing funny and now she is quiet”. She was found to have suffered a cardiac arrest from which she could not be resuscitated. The pathologist’s postmortem examination report stated that there was no abnormal swelling of the airway structures and that the findings were “strongly suggestive of a period of considerable cerebral hypoxia”. No drugs (including morphine) were detected in the blood. The inquest conclusion was that the cause of death was due to hypoxic cerebral injury arising from the side effects of morphine, and that no one was to blame.

Methods
Lötsch et al² used PKPD modelling of morphine during an inquest to determine the most likely cause of death of a young female patient who died after a knee operation in the Netherlands. She suffered respiratory and cardiac arrest in the postsurgical recovery unit after administration of repeated doses of morphine intravenously, to a total of 35 mg within 1 hour and 45 minutes. By means of simulation studies, the authors demonstrated that the morphine concentrations in the effect-site were probably very high. They compared their results with those of a previous study that they had performed on volunteers in whom they had administered large doses of morphine.³ Their findings were that the patient’s expected effect-site morphine concentrations at the time of her death corresponded closely with those of the volunteers at the stage when the latter suffered severe respiratory depression. They could, therefore, conclude that the cause of the patient’s death was most probably the result of severe respiratory depression and apnoea. Lötsch et al used pupil size as a surrogate measure of morphine effect, which does not necessarily parallel morphine’s effects on respiration.

For the purposes of this study, the integrated PKPD model of Dahan et al⁴ was considered appropriate, because they assessed morphine’s effects on pain responses and, in addition, measured the effects on ventilation directly by means of acute hypercapnic and hypoxic challenges. By means of frequent measurements of morphine plasma concentrations, they developed a pharmacodynamic model by which the relationship between morphine effect-site concentrations and drug effects could be expressed as a percentage of normal values in the average volunteer.

Morphine effects versus morphine effect-site concentrations

\[
E(t) = E_0 \cdot \left[ 1 + \left( \frac{C_{E}(t)}{C_{50}} \right) \right]^{-1}
\]

Equation - 1

\[C_{E}(t) = \text{effect-site concentration at time } t; \quad E(t) = \text{drug effect at time } t \text{ expressed as a } \% \text{ of the normal baseline value}; \quad E_0 = 100\%; \quad C_{50} = 9.13 \text{ ng/ml and } \gamma = 1.0 \text{ for respiratory depression and } 2.4 \text{ for analgesia.} \]
A graph of Equation-1 depicting morphine effect-site concentrations versus response with regard to both analgesic as well as respiratory depressant effects for the average subject in the study of Dahan et al is presented in figure 1. Some interesting observations can be made. The half maximal effective concentration (EC$_{50}$) of 9.1 ng/ml is the same for analgesia and respiratory depression. However, the slopes of the response curves differ, the slope for respiratory curve being greater at concentrations less than the EC$_{50}$ and lower at higher concentrations. Effective analgesic concentrations occur at values greater than 9 ng/ml. However, at an effect-site concentration of 14 ng/ml, there is depression of respiration to such an extent that there is a 40–50% decrease of alveolar ventilation and a similar increase in arteriolar carbon dioxide tension. This can be regarded as a demarcation for a serious degree of respiratory depression that is to be avoided. It is, therefore, possible to define a therapeutic window of 9–14 ng/ml for the average patient within which the concentration vs. response curve is, fortunately, steeper for analgesic effects than it is for depression of respiration. Effect-site concentrations between 14 ng/ml and 30 ng/ml can be regarded as a “danger-zone” for severe adverse effects that culminate in apnoea.

**Simulation studies**

Using pharmacokinetic simulation software (TIVA Trainer, StelSim) and employing the pharmacokinetic parameter set of Dahan et al, it was possible to simulate morphine effect-site concentrations that result from various dosage regimens. The data were then transferred to a spreadsheet (Microsoft Excel), which was used to calculate the effects on respiration using equation-1 and for graphing. The following simulation studies were performed:

1. The dosage regimen that had been administered to the patient who died as described by Lütsch et al as well as that of their volunteer study. Thereby it was possible to establish at what effect-site concentrations severe respiratory depression to the extent of probable apnoea can be expected to occur, using the Dahan et al PKPD model.

2. A single dose of morphine 10 mg administered intravenously to an “average” 59 kg person, in order to illustrate the pharmacokinetics of morphine and the expected effects on respiration.

3. Two doses of morphine, 10 mg and 5 mg, administered 70 minutes apart to an “average” 59 kg person.

4. Two doses of morphine, 10 mg and 5 mg, administered 70 minutes apart to two hypothetical individuals whose morphine total body clearance and EC$_{50}$ were at the lower and upper limits of the 95% confidence intervals of the volunteers in the study by Dahan et al. By this means, it was possible to simulate the effects of morphine on...
individuals who would be either particularly sensitive or particularly resistant to the effects of morphine.

**Results**

Simulations of the fatal case and of the volunteer dosage regimens reported by Lötsch et al.\(^2\)\(^3\) indicate that severe respiratory depression, to the point of apnoea, can be expected at morphine effect-site concentrations of about 30 ng/ml. This corresponds to depression of respiration by 77% (i.e. decreased to a value of 23% of normal responses to carbon dioxide and hypoxic challenges), as illustrated in Figure 1.

Figure 2 depicts a simulation of the concentration-time course after a single intravenous injection of morphine 10 mg administered to a 59 kg adult. Blood concentrations increase to very high values and remain elevated for about 60 minutes as a result of slow total body clearance, as well as slow intercompartmental clearances. Because of the initial high diffusion gradient, effect-site concentrations rise fairly rapidly at first, to reach the clinically important EC\(_{50}\) of 9 ng/ml after about 30 minutes. Effect-site concentrations then continue to increase more slowly to reach the maximum value 100 minutes after injection. Thereafter the concentrations decrease slowly, which is in contrast to the blood concentrations that decrease much more rapidly to very low levels by 6 hours after injection.

This illustrates that, although analgesic effects after a bolus dose of morphine are achieved fairly rapidly, maximum depression of respiration can be expected to occur much later, at approximately 1 hour and 40 minutes after a single intravenous injection. Furthermore, although blood concentrations may be low after several hours, morphine continues to

---

**Figure 2:** Simulation of the plasma and effect-site concentrations that result from intravenous administration of morphine 10 mg to a 59 kg adult. The theoretical therapeutic window and “danger zone” for severe respiratory depression are depicted by the light grey and dark grey areas respectively. Apnoea can be expected at about 30 ng/ml. Note the initial, prolonged high diffusion gradient between plasma and the effect-site. This results in clinically effective effect-site concentrations within 30 minutes, but the maximum concentration is achieved 100 minutes after injection. Six hours after injection, plasma concentrations are very low, while clinically important effect-site concentrations persist.

**Figure 3:** Simulation of the plasma and effect-site concentrations that result from intravenous administration of morphine 10 mg, followed by 5 mg 70 minutes later.
exert significant effects at the effect-site. Figure 2 also illustrates that, after a 10 mg dose, effect-site concentrations approach and enter the predefined “therapeutic window” for effective analgesia after about 40 minutes and remain in that vicinity for about 2½ hours. During this period, according to Equation-1, both pain responses and respiration will be depressed by about 50% without entering the “danger zone” where respiration is depressed by more than 60%.

The blood and effect-site concentrations resulting from of two doses of morphine, 10 mg and 5 mg, administered 70 minutes apart, are illustrated in Figure 3. In this instance, effect-site concentrations do reach the “danger zone” where respiration is depressed by 60%, and remain in that vicinity for several hours. Six hours after the initial injection (the time of the patient’s demise), blood concentrations are very low (and probably undetectable), while effect-site concentrations remain clinically significant.

Figure 4 depicts the corresponding effects on respiration as the effect-site concentrations increase and decrease.

Figure 5 depicts the severe depression of respiration if 10 mg and 5 mg of morphine are administered to an hypothetical patient who has a decreased clearance of morphine and, in addition, is particularly sensitive to morphine (total body clearance and EC50 at the lower limits of the 95% confidence interval for the group of volunteers in the study by Dahan et al4).

Discussion
These simulations illustrate what is well known about the clinical effects of morphine, namely that it takes a long time to achieve maximum effects although,
clinically, analgesic effects are discernible within minutes. The integrated PKPD model of Dahan et al.\(^4\) reveals that the maximum effect on breathing occurs much later than previously supposed. Furthermore, morphine’s exit from the effect-site occurs extremely slowly and repeated doses, albeit small, result in accumulation therein. The simulations are in agreement with the conclusion by Rigg et al. that plasma concentrations are not an objective indicator of morphine’s pharmacological activity.\(^7\) The unique pharmacokinetics of morphine are due to its physicochemical properties. Not only does morphine have low lipid solubility, but the high pKa of 8.0 ensures that only a small proportion (10–20%) is in the unionised form. This results in slow transfer between plasma and brain, corresponding with the long transfer halftime (\(t_{1/2}\)) of 4.4 hours.\(^4\) As a result, both brain penetration and brain egress are slow.

The generally recommended dose of morphine for an average adult is variously stated to be 10 mg for patients of greater than 50 kg body weight,\(^8,9\) or 10 mg per 70 kg body weight,\(^10\) and up to 15 mg for an adult.\(^11,12\) This may be expressed as doses of 0.14 to 0.2 mg/kg body weight. The dose of a total of 0.17 mg/kg, followed by 0.085 mg/kg, during the course of approximately one hour is therefore not considered to be excessive, albeit large. Patient responses to morphine are extremely variable and the patient may have been especially sensitive to its effects, considering the above simulations as well as the observable fact that women have been shown to be more susceptible.\(^11\) We can conclude from these simulations that it is likely that at the time of her death, five hours after the last morphine dose, there was clinically significant central depression of respiration. These speculations do not constitute sufficient evidence to conclude that morphine caused the patient’s demise. Nevertheless, there are additional features about the effects of morphine on breathing that may elucidate the cause of death. These include effects on airway patency, as well as the interaction with pain and sleep.

**Influence of sleep and effects on the airway**

Forrest and Bellville\(^14\) obtained respiratory carbon dioxide response curves in four healthy volunteers after 10–12 mg of morphine was administered. This was done while the volunteers were awake, asleep, awake after morphine and asleep after morphine. They demonstrated a substantial worsening of respiratory depression when the subjects who received morphine were asleep.

The potentiating effects of sleep were also demonstrated by Catley et al.\(^15\), who studied the respiratory effects of two postoperative analgesic regimens in two groups consisting of 16 adult patients each. One group received a pain-relieving dose of intravenous morphine (mean 18.1 mg), followed by the same dose administered as a continuous infusion during the next 24 hours. The other group received regional anaesthesia. During the first 16 hours after surgery, the two regimens provided patients with comparable analgesia, but the effects on breathing were different. Ten patients who were receiving morphine had a total of 456 episodes of pronounced oxygen desaturation (\(\text{SaO}_2 < 80\%\)). This occurred only while the patients were asleep, and all were associated with disturbances in ventilatory pattern, namely obstructive apnoea and paradoxical breathing. Oxygen saturation in the group who underwent regional anaesthesia never decreased below 87%. It is interesting to note that, of the ten patients who suffered severe respiratory depression, only one had a low respiratory rate.

**Influence of pain**

Patients who received morphine patient-controlled analgesia (PCA) after knee surgery, and whose pain was then completely abolished by a nerve block, subsequently manifested an increased incidence of oxygen desaturation and obstructed airway events.\(^16\) Borgbjerg et al.\(^17\) examined the effects of experimental pain stimulation on the ventilatory response to carbon dioxide- and morphine-induced (0.2 mg/kg IV) respiratory depression in 10 healthy volunteers. Experimental pain stimulated respiration and abolished morphine-induced respiratory depression. Respiratory depression was accompanied by decreased mouth occlusion pressure, indicating a tendency to tolerate an obstructed airway. No effect was observed on breathing rate. The antagonistic influence of pain is exemplified by two reports concerning patients with severe, morphine-resistant cancer pain.\(^16,15\) Upon undergoing either local anaesthesia or chordotomy that completely relieved their pain, these patients developed severe morphine-induced respiratory depression.

**Breathing rate and respiratory depression**

In addition to those already mentioned,\(^14,15\) there are a number of clinical\(^20\) and laboratory studies\(^21,22\) that document the occurrence of opioid-induced respiratory depression without concomitant reduction in breathing rate. It is important to appreciate that respiratory rate is a very unreliable index of impaired respiratory sensitivity.

In summary, considering the foregoing we can deduce the following characteristics concerning morphine-
induced respiratory depression:
• Significant respiratory depression lasts for hours after a single dose.
• Respiratory depression is accompanied by a tendency to tolerate airway obstruction.
• Sleep potentiates respiratory depression as well as airway obstruction.
• Pain stimulates breathing and antagonises the effects of morphine.
• Pain relief can unmask respiratory depression.
• A slow breathing rate is uncommon.
• Females are more vulnerable.

With regard to pain relief, it is noteworthy that a tonsillar abscess is a particularly painful condition and that performance of an immediate quinsy tonsillectomy (in contrast to conservative therapy prior to operation) rapidly leads to remarkable pain relief within hours.\textsuperscript{23,24}

We can now surmise further what happened to the patient under discussion. At the inquest, there was testimony by a fellow patient (who had drawn the nurse’s attention to the patient suffering from respiratory depression) that included the following statements: “…she was asleep and snoring all the time; …her mouth was half open and there were snoring sounds; … she lay on her back all the time”. The ward nursing notes recorded at regular intervals that her respiratory rate was between 18 and 20 breaths per minute, that she was snoring and that there was no bleeding. In addition, it was claimed that, for at least most of the time, the patient was nursed in the “tonsillar” position. Whereas the respiratory depression experienced by the patient was probably insufficient to cause apnoea per se, it is likely that it predisposed her to obstruction of the airway by decreasing her respiratory drive and obtunding her protective reflexes.

Respiratory depression was probably further potentiated by the fact that she was afforded rapid pain relief and that, being pain-free and possibly sleep deprived, fell asleep. The fact that, in the time period preceding her cardiac arrest, she was lying supine while deeply asleep, almost certainly aggravated her airway obstruction. She did not react and this probably eventually resulted in severe hypoxia that was sufficient to cause cardiac arrest.

Research into anaesthesia-related risk indicates that the most common cause of death and coma totally attributable to anaesthesia remains postoperative respiratory depression.\textsuperscript{25-28} Morphine is a frequent cause, whether it be by parenteral or epidural administration, or by PCA.\textsuperscript{29,30} Simulation of a PCA dosage regimen to an average adult (endorsed by the Pain Management Society of South Africa\textsuperscript{*}) reveals that, if such a regimen is followed to the letter, this would lead to dangerously high morphine effect-site concentrations after only five repeated doses of 1.5 mg at 15 minute intervals (Figure 6).

\textsuperscript{23} “The only patients who are immediately grateful postoperatively for the surgeon’s performing a tonsillectomy, are those who have undergone a quinsy tonsillectomy”: Personal communication by an ENT surgeon.

\textsuperscript{24} 10 mg loading dose followed one hour later by repeated 1.5 mg doses with 8-minute lockout intervals, to a maximum dose of 28 mg over a period of 4 hours.
The pharmacokinetics and pharmacodynamics of morphine vary widely, so that, in addition to the pharmacokinetic vagaries that result in diverse blood and effect-site concentrations in the population, it has been reported that the effect-site concentrations for effective analgesia may also vary between 9–25 ng/ml. Unfortunately, it is not possible to predict which patients will be particularly sensitive or resistant to a specific morphine dose. Taking the above considerations into account, it is important that the healthcare profession review and revise present practices with regard to pain control using morphine.31

The following remedial actions should be introduced into clinical practice:

• Surgical caregivers should be trained in basic airway management. The realisation that noisy breathing in an unconscious patient constitutes obstructed breathing, and that the exaggerated breathing movements of an obtunded and airway-obstructed patient may delude the observer into concluding that the patient is actually breathing, can be life saving. Such patients should be given close attention and be nursed scrupulously while lying on their sides.

• Nurses who work in surgical wards should be taught that counting the number of breaths per minute is an unreliable indicator of opioid-induced respiratory depression. Sedation-scoring at regular intervals utilising the Ramsay Sedation Scale,30 or the Observer’s Assessment of Awareness/Sedation (OAA/S) Scale32 will constitute a more effective method of identifying which patients are seriously obtunded and require extra attention34.

• The greater the morphine dose, the greater the danger of adverse effects resulting from respiratory depression. Therefore strategies to reduce opioid requirements using multimodal therapy should be implemented as a routine. These include continuous regional/epidural anaesthesia, as well combinations of morphine with other classes of analgesics such as nonsteroidal analgesics,35-40 intravenous paracetamol,41,42 ketamine,43-45 dexmedetomidine46 and gabapentin.47-51

• Patients who have been administered opioids, and are asleep, should be given supplemental oxygen by mask and be monitored by pulse oximetry, particularly at night.50,52 Any episode of desaturation should alert nursing staff to the possibility of a major adverse effect.

• Patients at high risk for respiratory depression and airway obstruction, such as the morbidly obese,53,54 the aged55-59 and those with a history of obstructive sleep apnoea,60 should preferably be administered postoperative analgesia in a high-care area.

• Considering the numerous reports of respiratory depression that occur during PCA, as well as the new information with regard to the PKPD of morphine that is emerging, the recommended dosage regimens for PCA should be reviewed and revised.31

Conclusion

The American Pain Society has declared pain to be the “fifth vital sign”31 and this has led to increased efforts to redefine and improve postoperative pain management.32 However, it appears that this has not been accompanied by an awareness of the greater potential for serious adverse effects.34,35 Morphine features extensively in pain management, as evidenced by the fact that, in South Africa alone, more than 1,8 million ampoules were sold by a single manufacturer during 2009 (personal communication).

Safe and effective care of postoperative surgical patients being administered morphine depends inevitably upon the knowledge, insight and vigilance of the nursing staff. It is our duty to empower them with that knowledge, and to assist them in defining and improving nursing policy and procedures. Healthcare workers have to live with the fact that morphine analgesia is inevitably accompanied by respiratory depression, and our patients need to live in spite of it.

Conflicts of interest: none

References


Carstensen PE and Jarvis DA. Age Is the Best Predictor of Postoperative Pain Requirements. Pain. 1996 Feb;64(2):357-64.


Other references not included due to formatting limitations.