Fentanyl versus morphine for analgo-sedation in mechanically ventilated adult ICU patients

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Pain and discomfort are common in mechanically ventilated intensive care unit (ICU) patients.[1,2] Modern ICU practice focuses on managing the "ICU triad" of agitation or unpleasant awareness, delirium and pain[3,4] with sedative agents (propofol, midazolam and dexmedetomidine[5]), antipsychotic agents (haloperidol and quetiapine), and analgesic agents.

Despite the potential usefulness of short-acting analgesic agents such as remifentanil and alfentanil,[6-9] their use in ICU is potentially limited by cost (Table 1). Currently, the two most commonly used analgesic agents in Australian and New Zealand ICUs for analgo-sedation are morphine and fentanyl. This notion is supported by a survey of intensive care physicians and nurses,[10] which showed that morphine and fentanyl are the most observed prescribed analgesics, and by an international prospective observational study of 703 mechanically ventilated patients in 51 ICUs, including 251 patients from Australia and New Zealand, in which 55% were prescribed morphine and 61% were prescribed fentanyl during their ICU stay.[11] This equates to about 29 000 and 32 000 mechanically ventilated patients prescribed these two agents, respectively, per year in Australia and New Zealand.[12]

Despite such vast use of these agents, there are few publications comparing morphine and fentanyl for analgo-sedation in mechanically ventilated adult ICU patients. Clinical practice guidelines state, "All available [intravenous] opioids, when titrated to similar pain intensity endpoints, are equally effective", but the evidence for such a statement is rated as low quality.[4] Particular knowledge gaps, which have not been subject to robust clinical trials, include effectiveness, dose equivalency, cost, and use in special groups of patients, including those with acute kidney injury or liver failure. In this review, we aim to describe the pharmacology of both agents, the evidence on their effectiveness and adverse effects, and future research possibilities.

Morphine

Morphine was first marketed in the early 19th century, after being isolated from the opium poppy.[13] It is the prototype opioid agonist and is a phenanthrene alkaloid. Following intravenous administration, morphine is rapidly metabolised primarily by conjugation with glucuronic acid to morphine-3-glucuronide (M3G; 75–85%) and morphine-6-glucuronide (M6G; 5–10%).[14,15] The pharmacology of morphine is described in Table 2.

Unlike M3G, M6G is pharmacologically active and has an affinity for μ-opioid receptors comparable to that of morphine, with analgesic potency 650-fold higher when injected intrathecally than morphine.[24] M6G undergoes renal clearance and accumulates in patients with renal failure, with clinical effects including prolonged sedation and respiratory depression.[25,26] The clinical relevance of this in intubated, mechanically ventilated ICU patients in whom morphine is titrated to clinical effect is uncertain.

Table 1. Cost of narcotic drugs used

Product	Cost per unit
Morphine 10 mg	A$0.52
Morphine 30 mg	A$1.47
Morphine 100 mg/100 mL pre-made for infusion*	A$11.74
Fentanyl 100 μg	A$0.35
Fentanyl 500 μg	A$0.61
Fentanyl 1000 μg/100 mL pre-made for infusion*	A$27.50
Morphine 100 mg/100 mL for infusion	A$6.32†
Fentanyl 1000 μg/100 mL for infusion	A$2.61‡
Alfentanil 1 mg	A$3.60
Alfentanil 5 mg	A$18.00
Remifentanil 1 mg	A$2.31
Remifentanil 2 mg	A$3.48
Remifentanil 5 mg	A$4.78

* Pre-made bags for infusion have a longer half-life. † Cost of 1 × 10 mg vial + 3 × 30 mg vials + 1 × 100 mL normal saline prepared as required. ‡ Cost of 2 × 500 μg vials + 100 mL normal saline prepared as required.

Table 2: Pharmacology of fentanyl and morphine

	Morphine	Fentanyl
Structure	Phenanthrene alkaloid	Synthetic phenylpiperidine derivative
Absorption[16-18]	Oral bioavailability, 24%	Oral bioavailability, 31%; intranasal bioavailability, 89%
pKa[19]	7.9	8.4
Percentage non-ionised at pH 7.4[19]	23%	8.5%
Percentage of protein binding[19]	35%	84%
Volume of distribution[14,20]	192 litres	312 litres
Time to analgesia (after intravenous dose)[19,21,22]	10–40 minutes	6–15 minutes
Metabolism	Metabolised by conjugation with glucuronic acid in hepatic and extrahepatic sites, especially the kidneys; major metabolites are morphine-3-glucuronide (75–85%), morphine-6-glucuronide (5–10%); other metabolites are normorphine and a small amount to codeine	Metabolised by N-demethylation in the liver, catalysed by the cytochrome p450 system; major metabolite is norfentanyl and other metabolites are hydroxyproprionyl-fentanyl and hydroxyproprionyl-norfentanyl (all these metabolites have minimal pharmacologic activity)
Active metabolites	Morphine-6-glucuronide	Minimal
Excretion	Metabolites are renally excreted with 7–10% undergoing biliary excretion	Metabolites are renally excreted and < 10% of fentanyl is excreted unchanged in the urine
Elimination half life[14,20]	1.7–2.3 hours	3.1–6.6 hours
Context-sensitive half-time for a 4-hour infusion[23]	Not applicable	200 minutes
Specific reported adverse effects	Histamine release (see main text); decreased systemic vascular resistance; hypotension	Generalised skeletal muscle rigidity (uncommon, noted in case reports)

M6G has an elimination half-life of about 1.4 hours, but this is increased in patients with renal failure.[15]

Morphine has a similar adverse effect profile to other opioid medications. This includes nausea, vomiting, delayed gastric emptying, constipation, bowel distension, paralytic ileus, sphincter of Oddi spasm, urinary retention, miosis, and diffuse central nervous system effects (dizziness, light-headedness, sedation, drowsiness and euphoria).

In addition, morphine contains a tertiary amine group, which causes non-immune-mediated release of histamine and can lead to skin rashes, itchiness and hypotension. However, the increase in histamine and resultant clinical effects varies markedly among patients. One study showed an average peak increase in histamine of 750% in eight cardiac surgical patients receiving morphine,[27] while a later study with a different histamine testing assay showed no increase in histamine levels in ten cardiac surgical patients receiving morphine.[28] In addition, a study of 15 healthy volunteers showed 13 patients (86%) had an increase in histamine following injection of 0.15 mg/kg intravenous morphine.[29] It is not clear what the clinical significance of this is in mechanically ventilated ICU patients.

Fentanyl

Fentanyl is a phenylpiperidine-derivative synthetic opioid first synthesised in 1960.[30] The pharmacology of fentanyl is described in Table 2. Fentanyl has a more rapid onset of action than morphine, which reflects its greater lipid solubility and consequent increased ability to cross the blood–brain barrier. The relatively short duration of action of fentanyl compared with morphine reflects its rapid redistribution to inactive tissue sites such as fat and skeletal muscle, with an associated decrease in plasma

Table 3. Studies comparing morphine and fentanyl

Study	Patient group	Type of study	Intervention	Number of patients	Summary of results
Pre-hospital					
Galinski et al, 2005[37]	Pre-hospital patients with severe pain	Prospective randomised, double-blind controlled trial	Physician-initiated morphine *v* fentanyl	54	No difference in pain score reduction or adverse effects
Smith et al, 2012[39]	Pre-hospital trauma patients transported by helicopter	Prospective non-randomised, double-blind comparison trial	Physician-initiated morphine *v* fentanyl	200	No difference in pain score reduction or adverse effects
Weldon et al, 2016[38]	Pre-hospital patients with ischaemic sounding chest pain	Prospective randomised, double-blind controlled trial	Physician-initiated morphine *v* fentanyl	187	No difference in pain score reduction or adverse effects
Scharonow et al, 2017[40]	Pre-hospital patients with severe pain	Retrospective observational study	Physician-initiated morphine *v* fentanyl	77	No difference in pain score reduction or adverse effects
Non-cardiac surgical					
Howell et al, 1995[36]	Post-caesarean section patients	Prospective, randomised, double-blind controlled trial	Morphine *v* fentanyl PCA	37	No difference in pain scores between the two groups. Fentanyl group had more requirements for added analgesia and dose adjustments. No difference in nausea, itch, sleepiness or patient satisfaction
Woodhouse et al, 1996[41]	Post-operative patients	Prospective, randomised, double-blind controlled trial	Morphine *v* fentanyl (*v* pethidine) PCA	55	No difference in pain scores or patient satisfaction between groups. More pruritus in the morphine group
Claxton et al, 1997[42]	Ambulatory surgical patients due for same-day discharge	Prospective, randomised, double-blind controlled trial	Physician-initiated morphine *v* fentanyl in the post-anaesthesia care unit	58	No difference in initial reduction in pain scores but morphine had more prolonged analgesia with fewer requirements for supplemental oral analgesia. No difference in any adverse effects measured in hospital. Increased nausea and vomiting in the morphine group after hospital discharge
Woodhouse et al, 1999[43]	Post-operative patients	Prospective, randomised, double-blind, three-way crossover trial	Morphine *v* fentanyl (*v* pethidine) PCA	82	No difference in pain scores, patient satisfaction or adverse effects except for decreased measured sedation in the fentanyl group
Wheeler et al, 2002[44]	Post-operative patients	Systematic review	Studies that analysed post-operative adverse events	Varied	Morphine associated with more gastrointestinal symptoms, urinary retention and central nervous system effects
Hutchison et al, 2006[45]	Post-operative patients	Retrospective observational study	Morphine *v* fentanyl PCA (included hydromorphone)	165	Morphine associated with more nausea and vomiting, pruritus, urinary retention, sedation, respiratory depression, headache and confusion
Kim et al, 2008[46]	Post-uterine fibroid arterial embolisation	Prospective, non-randomised unblinded trial	Morphine *v* fentanyl PCA	200	Overall, morphine had more significantly reduced pain scores than fentanyl, with fentanyl having lower scores in first 2.5 hours but morphine having lower scores over the remainder of the 24 hours. No statistical difference in adverse effects

(*Continues*)

Table 3. Continued

Study	Patient group	Type of study	Intervention	Number of patients	Summary of results
Russo et al, 2017[47]	Post-open oncologic gynaecological surgery	Observational cohort study	Morphine *v* fentanyl infusion	60	More patients in the morphine group required rescue medication for pain with pain scores lower in the first 6 hours after surgery. Lower diastolic blood pressure with fentanyl and more intravenous fluids. More sedation in patients treated with fentanyl at 1 hour. Improved gastrointestinal recovery and shorter hospital length of stay in the fentanyl group
Nada et al, 2018[48]	Post-liver resection	Retrospective observational study	Morphine *v* fentanyl PCA	40	No differences in pain scores after controlling for sex, weight and type of incision. Fentanyl had increased morphine equivalent doses and demands for PCA. More patients in the morphine group were lightly to deeply sedated in the first 12 hours. No difference in any other adverse effects
Cardiac surgical					
Sanford et al, 1986[35]	Cardiac surgical patients	Prospective, randomised, unblinded trial	Morphine only *v* fentanyl only for cardiac anaesthesia (*v* sufentanil)	19	No difference in duration of anaesthesia. Shorter induction of anaesthesia times with fentanyl. No difference in return to consciousness, spontaneous ventilation, return of adequate ventilation, return of acceptable cardiovascular status or time to extubation
Yukioka et al, 1990[49]	Cardiac surgical patients	Prospective, randomised, unblinded trial	Morphine *v* fentanyl for anaesthesia	24	Shorter duration of anaesthesia with fentanyl. Shorter time from ICU admission to passage of flatus with morphine
Gurbet et al, 2004[50]	Off-pump cardiac surgical patients	Prospective, randomised, double-blind controlled trial	Morphine *v* fentanyl PCA (*v* remifentanil)	75	No difference in pain scores, adverse effect profile or time to extubation between groups
Murphy et al, 2007[51]	Primary coronary bypass graft patients	Prospective, randomised, double-blind controlled trial	Morphine *v* fentanyl as part of combined anaesthetic	30	Smaller increase in interleukin-6 production with morphine, and greater reduction in CD11b and CD18 expression with morphine. Less hyperthermia in the morphine group in first 12 hours after surgery. No difference in intubation times, ICU or hospital length of stay, or intraoperative haemodynamics
Murphy et al, 2009[52]	Cardiac surgical patients	Prospective, randomised, double-blind controlled trial	Morphine *v* fentanyl as part of combined anaesthetic	84	Lower pain scores after extubation with morphine. Lower QoR-40 scores with morphine on Days 1–3. No difference in intraoperative haemodynamics, intubation times, or ICU or hospital length of stay. Decrease in ICU temperature > 38°C in the morphine group

ICU = intensive care unit. PCA = patient-controlled analgesia. QoR-40 = Quality of Recovery – 40 Items.[53]

concentration.[31] Furthermore, fentanyl has been reported to have 75% first-pass uptake into the lungs,[32] thus the amount of fentanyl that reaches the systemic circulation is limited. In contrast, morphine's first-pass pulmonary uptake is extremely small.

Fentanyl is hepatically metabolised. Medications that inhibit or induce the cytochrome p450 system can interfere with fentanyl metabolism and therefore increase or decrease its effects respectively. Fentanyl has a high hepatic extraction ratio with clearance approaching liver blood flow. It undergoes N-demethylation and less than 10% of fentanyl is excreted unchanged in the urine. Norfentanyl is the principal metabolite and, like all metabolites of fentanyl, is believed to have minimal pharmacological activity. Despite being metabolised by the liver, fentanyl clearance was unchanged when eight patients with cirrhosis were compared with 13 patients who had normal liver function.[33]

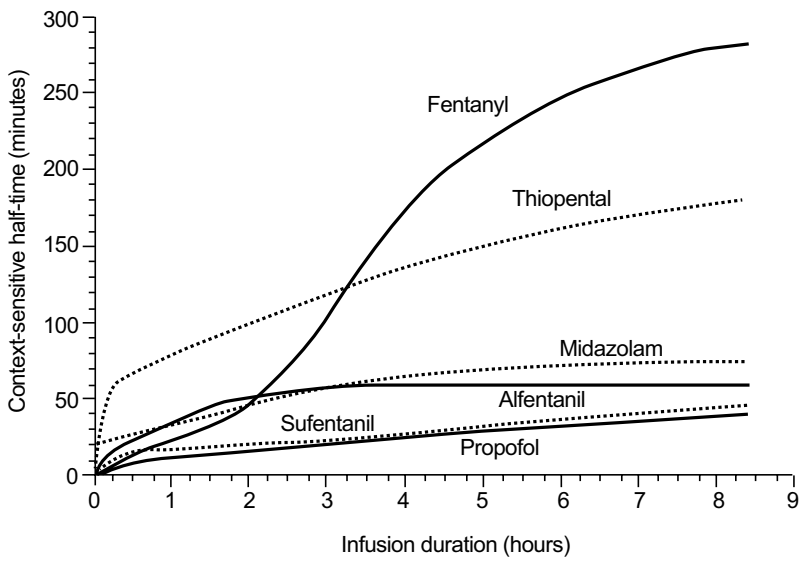
Despite fentanyl being a more attractive option than morphine for analgo-sedation, because of its potentially shorter duration of action, other pharmacokinetic properties may limit its usefulness. After initial redistribution, fentanyl's plasma concentrations are maintained by slow reuptake from the tissues across a concentration gradient. Consequently, following infusion, the clinical effects of fentanyl become increasingly prolonged owing to its long "context-sensitive half-time" (Figure 1). This has been reported to be 200 minutes with an infusion longer than 4 hours, 300 minutes with an infusion longer than 8 hours, and unpredictable with longer durations of infusion.[23] In contrast, morphine has no such pharmacokinetic properties. Following long term infusion, fentanyl's effects may be as prolonged as morphine, even when allowing for potential accumulation of metabolically active metabolites of morphine in renal failure. However, this has not been studied in mechanically ventilated ICU patients.

Dose equivalence and cost

Fentanyl is reportedly 75–125 times more potent than morphine, implying that about 10 µg of fentanyl will give a similar analgesic effect to 1 mg of morphine. Despite this commonly held belief, clinical data suggest that the relative potency is varied. Relative potency varies from 40 times for effectiveness on intraoperative evoked potentials and 46 times for anaesthesia to a range of 22 to 100 times for relief of pain.[34-38]

The costs of both agents are presented in Table 1. The costs vary depending on whether analgesic bags are pre-made (which have a longer shelf-life) or prepared in-house. An example of the cost of in-house preparation of an infusion bag of 1000 µg fentanyl in 100 mL normal saline for infusion is A$2.61; an example of the cost of in-house preparation of an infusion bag of 100 mg morphine in 100 mL normal saline is A$6.32. If fentanyl were 100 times more potent than morphine, it would clearly be more cost-effective to prescribe fentanyl for infusion rather than morphine. However, the true potency and dose equivalence in ICU patients has not been studied and is unclear.

Figure 1. Fentanyl context-sensitive half-time as a function of infusion duration



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Clinical studies of effectiveness

Several studies have compared the effectiveness and adverse effects of intravenous morphine and fentanyl in the prehospital setting,[37-40] for non-cardiac surgical post-operative analgesia,[36,41-48] and in cardiac surgery.[35,49-52] These are summarised in Table 3. In

the pre-hospital setting, three double-blind randomised controlled trials[37-39] and one retrospective observational study[40] showed no differences in terms of pain scores or adverse effects. In post-operative surgical patients, most studies showed no differences in pain scores, with slight variations in duration of analgesia and need for rescue medications. However, there were varied results with regards to adverse-effect profiles. Some studies revealed no difference in adverse-effect profile,[36,46] while others showed that morphine use was associated with more pruritus, nausea and vomiting (in hospital or after discharge), urinary retention, sedation, respiratory depression, headache and confusion.[41-45,48] In contrast, one study showed more sedation with fentanyl at 1 hour.[47] In post-cardiac surgical patients, results were varied with regards to duration of anaesthesia, pain scores and some adverse effects — one study showed no difference,[50] whereas others detected differences between morphine and fentanyl.[49,51,52]

ICU patients

To our knowledge, no randomised controlled trials have directly compared morphine and fentanyl infusions in mechanically ventilated adult ICU patients. It is possible that, if used appropriately and titrated to effect, neither analgesic agent will provide benefit over the other in any meaningful aspect of care. However, there is evidence that sedation prescription and assessment is varied and inconsistent. Shehabi and colleagues[54] reported that clinicians prescribed sedation targets only 24.9% of the time and that in only 34.7% of these patients did the actual sedation fall within the prescribed range. In addition, assessment of pain is difficult in sedated, mechanically ventilated ICU patients. Adult-specific pain assessment tools are available,[55,56] yet in a study of 1360 mechanically ventilated patients receiving analgesia, Day 2 pain was assessed in only 47% of patients, and both sedation and pain assessment tools were used in only 28% of patients.[57] It is unclear how intensive care physicians and nursing staff are titrating these analgesic agents. Unchecked overuse of morphine and fentanyl can have additional adverse effects (such as prolonging sedation, intubation, mechanical ventilation and ICU stay) and can increase the risk of associated complications (eg, delirium, weakness, pressure areas, and delayed long term recovery).

Potential research

Morphine and fentanyl are prescribed in thousands of mechanically ventilated adult ICU patients each year. Thus, there appears to be a need to compare these agents in clinical trials. Issues that need to be studied include comparative pharmacokinetics in ICU patients, comparable effectiveness with regards to duration of mechanical ventilation, ICU and hospital length of stay, delirium, additional sedative requirements, haemodynamic effects, gastrointestinal effects, tolerance, patient satisfaction, cost, and long term outcomes such as narcotic dependence, cognition and motor performance. Pilot studies are required to determine current trends in prescribing, sedation assessment and pain assessment, to establish dose relationships for each agent when used as an infusion for analgo-sedation, to determine feasibility of conducting comparative trials, whether there is any signal of difference of effect between the two agents, and to determine whether these drugs should be avoided in certain conditions (eg, morphine in patients with acute kidney injury and fentanyl in patients with impaired liver function). Following such research, studies that directly compare the two agents (either blinded randomised controlled trials or cluster controlled trials) could be undertaken to help clinicians determine the best agent to prescribe for individual patients.

Conclusion

Despite morphine and fentanyl being the two most commonly prescribed analgesics in Australian and New Zealand ICUs, no ICU studies have investigated whether one agent is superior to the other in mechanically ventilated adult ICU patients. Recent focus on sedation practices and long term outcomes after ICU stay should stimulate intensive care physicians to compare these two agents in robust clinical ICU trials.

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