Remifentanil in the Intensive Care Unit (ICU)

Key messages

- Remifentanil enables predictable recovery, facilitating patient interaction and assessment.\(^1\)\(^-\)\(^4\)
- Remifentanil enables a shorter weaning time and a reduction in the time spent on mechanical ventilation compared with traditional opioid analgesics.\(^3\)\(^,\)\(^5\)\(^,\)\(^6\)

Summary

Remifentanil (Ultiva) has a number of benefits in the ICU:

- Remifentanil effectively controls analgesia/sedation in mechanically ventilated ICU patients\(^1\)\(^,\)\(^5\) and can reduce the time on mechanical ventilation and to extubation compared with traditional opioid analgesics\(^3\)\(^,\)\(^5\)\(^,\)\(^6\)
- Remifentanil offers precise control of analgesia for painful procedures in ICU patients and its rapid, predictable recovery facilitates neurological assessments\(^1\)\(^,\)\(^4\)\(^,\)\(^5\)\(^,\)\(^7\)\(^,\)\(^8\)
- Remifentanil offers control in special populations such as patients with hepatic and renal impairment so that there is no need for initial dose adjustment\(^9\)\(^-\)\(^12\)
- Remifentanil could help control ICU costs, by reducing the time spent in ICU and the need for other sedative agents.\(^3\)\(^,\)\(^5\)\(^,\)\(^6\)\(^,\)\(^13\)\(^,\)\(^14\)

Analgesia-based sedation versus hypnotic-based regimens

Most patients experience pain during their stay in the ICU, but with conventional regimens hypnotic agents are titrated to make the patient sleepy, with pain relief only being considered as adjunctive therapy. The consequence is that patients are often over-sedated but are not necessarily pain free.\(^2\)\(^,\)\(^15\)\(^,\)\(^16\)

Analgesia-based sedation involves focusing in the first instance on achieving effective analgesia, with a sedative agent (hypnotic or anxiolytic) being given only if the patient needs it (table 1). Analgesia itself should relieve much of the patient’s anxiety reducing the need for sedatives in many cases\(^2\)\(^,\)\(^15\)\(^,\)\(^16\) and in turn allowing for better interaction with family and carers.\(^2\)

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The adoption of this ‘pain relief first’ policy has been hampered in the past by the lack of suitable opioids, due to their unpredictable metabolism and their slow onset and offset of action.\(^15\)
Therapeutic indication
Remifentanil, a potent selective \(\mu\)-opioid agonist, is indicated for the provision of analgesia and sedation in the mechanically ventilated intensive care patients aged 18 years and over. It has a number of benefits making it suitable for use as the opioid component in combined analgesia and sedation in the ICU.

Control through easy titration
Remifentanil has a rapid onset of action of about one minute and quickly achieves steady state. Unlike traditional opioids, it is rapidly metabolised in an organ-independent manner by non-specific blood and tissue esterases into a clinically inactive metabolite. This gives it a short duration and predictable offset of action (<10 minutes), which is independent of the duration of infusion. These characteristics render remifentanil very easy to titrate according to individual requirements. They also allow it to be administered in higher doses than are normally used with traditional opioids without concerns about accumulation and the possibility of unpredictable and/or delayed recovery. This makes remifentanil ideally suited for use in analgesia-based sedation technique, reducing the need for sedative agents while maintaining the patient in a calm and easily rousable condition.

Effective provision of analgesia-based sedation in ICU patients
The inadequate treatment of pain can result in increased morbidity and mortality through long-lasting psychological effects together with adverse haemodynamic changes. Studies have demonstrated that analgesia-based sedation with remifentanil allows effective provision of optimal sedation in mechanically ventilated patients.

Muellejans et al compared the effectiveness of a remifentanil-based regimen versus a standard fentanyl-propofol regimen in providing analgesia/sedation in 152 ICU patients requiring mechanical ventilation. Patients were randomised to receive an initial infusion of either remifentanil (9 µg/kg/h) or fentanyl (1 µg/kg bolus + 1.5 µg/kg/h) titrated to provide ‘optimal sedation’ as defined by a Sedation Agitation Score (SAS) of 4 (i.e. patient was calm, cooperative and easily rousable). Propofol (0.5 mg/kg/h, titrated to effect) was given only if additional sedation was needed to treat agitation. Mean times of optimal sedation were similar between the two groups, although there was significantly less between-subject variability in the remifentanil group suggesting improved control of patient comfort (p=0.009). In the remifentanil group 27 out of 77 patients (35%) required propofol compared with 30 out of 75 (40%) patients in the fentanyl group and the median total propofol dose was also less in the remifentanil group (378.4 [range 15.8, 4690.8] mg vs. 683.0 [range 30.0, 11323.3] mg; p=0.065). The fentanyl results were similar probably because the dosing algorithm required frequent monitoring and adjustment thereby preventing over-sedation. The tolerability and safety profile was similar to fentanyl.

Dahaba et al compared the efficacy and safety of a remifentanil-midazolam regimen to a standard morphine-midazolam regimen in mechanically ventilated ICU patients. Forty postsurgery intubated patients admitted to the ICU for the short- or medium-term were randomised to receive either remifentanil (0.15 µg/kg/min) or morphine (0.75 µg/kg/min). The opioid infusion was titrated to achieve and maintain optimal sedation, as defined by an SAS of 4, without clinically significant pain (Pain Intensity scale score of 2 or less). If necessary, midazolam was added (0.5 µg/kg/min + 30 µg/kg bolus) and titrated to effect.
Optimal sedation was achieved for a significantly higher proportion of hours in the remifentanil group compared with the morphine group (78.3% vs 66.5%; p<0.05). In addition subjects in the remifentanil group required less frequent infusion rate adjustments (0.34 changes/hr) than did those in the morphine group (0.42 changes/hr). Midazolam requirements were also lower in the remifentanil group with only 6/20 requiring midazolam compared with 9/20 in the morphine group, and the mean midazolam infusion rate was lower in the remifentanil group (0.2 ± 0.1 µg/kg/min) than in the morphine group (0.5 ± 0.3 µg/kg/min) in those that required midazolam. The incidence of adverse events was low and comparable across the two treatment groups.5

**Sedative sparing effects reduces the need for other sedative agents**

The above studies demonstrate that remifentanil can reduce the need for concomitant sedative/hypnotic agents. In clinical studies, up to 70% of patients received adequate analgesia and sedation using remifentanil alone.1,5,10

The study by Muellejans et al1 in which patients received either a remifentanil-based regimen or a standard fentanyl-propofol regimen found that a 45% lower propofol dose was needed with remifentanil (p=0.065), and a smaller proportion of patients (35%) in the remifentanil group received a propofol infusion compared with the fentanyl group (40%).

**Rapid, predictable recovery facilitates neurological assessments**

The rapid offset of action of remifentanil provides many clinical advantages compared to other opioids.17 It enables predictable recovery and rapid emergence from sedation, facilitating rapid neurological assessment.1,4,5

Soltész et al4 investigated the use of remifentanil-based analgesia and sedation in 20 ICU patients following major surgery or trauma without intra-cranial pathology. Within 24 hours of arrival in the ICU patients were randomised to receive either remifentanil (5 µg/kg/h) or sufentanil* (0.5 µg/kg/h) both in combination with propofol (2 mg/kg/h). The drugs were titrated to achieve a Ramsay score between 2 (cooperative, orientated, tranquil) and 5 (sluggish response to a light glabellar tap or loud auditory stimulus) according to individual patient requirements, together with complete pain relief.

After 24 hours of infusion, both regimens were shown to provide adequate analgesia and sedation with no differences between the groups indicated by Ramsay score (median 3 in both groups). Ten minutes after stopping the infusions the median Ramsay score remained unchanged in the sufentanil group; however, in the remifentanil group there was a significant decrease in median Ramsay score from 3 to 1.5 (p=0.002). The decrease in the remifentanil group was also significantly greater when compared to the sufentanil group (p=0.015). After a further 20 minutes all but one patient in the remifentanil group had emerged from analgesia and sedation necessitating recommencement of the infusions before the 30 minute evaluation interval was complete. This only occurred in one patient in the sufentanil group and the median Ramsay score after 30 minutes was 2 (p<0.05 compared with baseline) in the sufentanil group. The authors conclude that the use of remifentanil may be particularly advantageous in patients suffering from severe intra-cranial disease or head trauma because it allows intermittent and rapid neurological assessment by clinical examination.4

A retrospective study by Wilhelm et al3 found that in 60 post-neurosurgery patients receiving fentanyl-midazolam sedation and analgesia, prolonged unconsciousness and the impossibility of neurological examination meant that CT scans were necessary in some patients to rule out neurosurgical complications. However this was not the case in similar patients receiving remifentanil-propofol analgesia and sedation.

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5 sufentanil is not licensed for use in the UK – chosen for use in this study as its pharmacokinetics mean it can be used in a continuous infusion.
**Rapid titration to respond to analgesic requirements for painful procedures**

Although patients may be adequately sedated while in an ICU, they may still mount a stress response to painful procedures (e.g. insertion of a venous line, chest drain etc.). Analgesia and sedation with remifentanil can be easily titrated to allow painful procedures to be performed in critically ill patients.1,5,7

A recent study by Engelhard et al7 investigated the use of remifentanil as an on-top analgesic in head trauma patients during transient painful procedures e.g. endotracheal suctioning or physiotherapy on the ICU. Remifentanil was administered as a bolus (0.5 µg/kg) followed by an infusion of 0.25 µg/kg/min for 20 minutes. There was no change in mean arterial blood pressure, intra-cranial pressure, or cerebral blood flow velocity in response to remifentanil infusion. The authors conclude that remifentanil is suitable for on-top analgesia during painful stimuli.

Gupta et al8 discussed the use of remifentanil in percutaneous tracheostomies in the ICU setting. In their ICU, after local infiltration of 2% lidocaine with adrenaline, a bolus of 1 µg/kg remifentanil followed by 0.25–1.0 µg/kg/min was given to control responses to this painful procedure. The authors found that remifentanil provided haemodynamic stability during this very short procedure and allowed rapid weaning from ventilatory support following the procedure.

**Remifentanil facilitates rapid weaning and extubation**

Because remifentanil does not accumulate and is rapidly metabolised, recovery is consistently rapid.9,17 This means that remifentanil enables a short and predictable time to extubation (figure 1), reducing the time spent on mechanical ventilation.3,5,6

In the study by Dahaba et al5 the extubation time (defined as time from discontinuation of opioid infusion until extubation) in patients receiving remifentanil-based analgesia and sedation was significantly shorter than in patients receiving morphine (17 ± 6 vs 73 ± 7 minutes; p=0.0149) following orthopaedic or general surgery.

The retrospective study by Wilhelm et al3 also showed a significant reduction in extubation time with remifentanil-propofol compared with fentanyl-midazolam (47 ± 34 vs 481 ± 47 minutes; p<0.05) in patients recovering from neurosurgery.
Remifentanil reduces the time spent on mechanical ventilation, enabling earlier discharge from the ICU

Prolonged ICU stay and mechanical ventilation, a significant predictor of less favourable outcome, predisposes patients to a greater risk of infection and death.\textsuperscript{19,20} Delirium is also associated with prolonged mechanical ventilation\textsuperscript{21} and has been shown to be a predictor of higher 6-month mortality and longer hospital stay.\textsuperscript{22} Remifentanil-based analgesia and sedation reduces the time spent on mechanical ventilation compared with morphine or fentanyl,\textsuperscript{5,6} potentially reducing the associated complications.\textsuperscript{19,20} The use of a remifentanil-based analgesia and sedation regimen can significantly reduce the amount of time spent in the ICU.\textsuperscript{3,5,6,14}

\textbf{Matthey et al}\textsuperscript{6} investigated the use of remifentanil-propofol compared with a conventional fentanyl-midazolam analgesia and sedation regimen in patients after cardiac surgery. On arrival in the ICU 72 patients were randomised to receive either remifentanil (0.1–1.0 µg/kg/min) titrated to effect and supplemented if required with propofol (0.3–1.0 mg/kg bolus and/or 0.5–4.0 mg/kg/h infusion), or fentanyl (1.0–2.0 µg/kg bolus; 1.0–7.0 µg/kg/h infusion) and midazolam (bolus 0.03–0.2 mg/kg; infusion 0.02–0.2 mg/kg/h) both titrated to effect. At the start of weaning, the remifentanil group received a morphine bolus (0.1–0.3 mg/kg).

In the group receiving remifentanil-based analgesia and sedation a significant reduction in the time spent on mechanical ventilation was apparent compared with the fentanyl-midazolam group: weaning time was only 2.2 hours compared with 5.7 hours (p<0.05) and time to extubation was 20.7 hours compared with 24.2 hours (p<0.05) in the remifentanil and fentanyl groups respectively (figure 2). The remifentanil group also experienced a significantly shorter stay in the ICU with time to ICU discharge reduced from 64.7 hours in the fentanyl group to 46.4 hours in the remifentanil group (p<0.05).\textsuperscript{6}
Dahaba et al\textsuperscript{5} reported that in short- to medium-term mechanically ventilated ICU patients, admitted following orthopaedic and general surgery, there was a significant reduction in time on mechanical ventilation with a remifentanil-based regimen compared with a morphine-based regimen: duration of mechanical ventilation 14.1 ± 2.8 hours with remifentanil versus 18.1 ± 3.4 hours with morphine (p=0.0433). The mean ICU discharge time was nearly 1 day (21 hours) longer in those treated with morphine-compared with remifentanil-based analgesia and sedation (p=0.0136).\textsuperscript{5}

Wilhelm et al\textsuperscript{3} also observed that for patients admitted to the ICU following surgery of supratentorial brain tumours, remifentanil, compared with fentanyl analgesia and sedation resulted in a significantly (p<0.05) shorter duration (1.8 days less) of ICU stay.

Royston\textsuperscript{14} evaluated remifentanil and propofol for early extubation in 132 patients following remifentanil-based total intravenous anaesthesia (TIVA) for coronary artery bypass graft (CABG) surgery. The author set a time of 3–5 hours for extubation, with all patients having a 3 hour post-op 1 µg/kg/h remifentanil infusion. 80% of patients were eligible for extubation during this time. The time to eligibility for ICU discharge was significantly shorter in those eligible for early extubation than those not eligible and extubated later that day (18.5 ± 6.5 hours vs 43.8 ± 38.8 hours after surgery, p<0.001). Time to return to adequate spontaneous respiration was not related to duration of remifentanil infusion, with over 90% of patients achieving this within 30 minutes of starting a controlled remifentanil weaning process.

It is important to note that when remifentanil is being reduced in preparation for extubation and immediately following its discontinuation, the provision of pre-emptive analgesia is required to ensure the patient remains pain free. In the above study, morphine 0.1–0.2 mg/kg was given 30 minutes before reducing the remifentanil infusion.\textsuperscript{14}

Well tolerated in ICU patients with good haemodynamic control
Remifentanil provides haemodynamic stability\textsuperscript{1,5,7} and is well tolerated.\textsuperscript{5}

In the study by Dahaba et al\textsuperscript{5} of ICU patients on remifentanil-based analgesia and sedation, the incidence of haemodynamic-related adverse events was low (2 of 20). The incidence of nausea (2 of 20) and vomiting (1 of 20) was also low.
Muellejans et al\(^1\) concluded that remifentanil is well tolerated and provided good haemodynamic stability similar to that observed in patients receiving fentanyl, which is the current ‘gold standard’ for the provision of haemodynamic stability in the ICU setting.

It has been reported that fentanyl and alfentanil can increase intra-cranial pressure.\(^2\) Engelhard et al\(^7\) reported that painful procedures could be carried out with remifentanil in ICU patients with head trauma without compromising cerebrovascular haemodynamics, cerebral perfusion pressure or intracranial pressure.

**No initial dose adjustment required in hepatic or renal impairment**
Elimination of traditional opioids is dependent on organ function and organ function is often abnormal in the critically ill.\(^1\) One of the most significant advantages of remifentanil is its organ-independent mode of metabolism, which makes it particularly valuable for use in patients with organ impairment.\(^1\)

Dershwitz et al\(^11\) studied 10 patients with hepatic impairment awaiting liver transplantation with 10 matched controls without liver impairment. The pharmacokinetics of remifentanil were not altered in those subjects with severe hepatic disease. Although levels of the main metabolite, remifentanil acid, were increased, this was not significant and as the potency of this compound is 1/4600\(^1\) that of remifentanil itself,\(^7\) it would not induce respiratory depression. The recovery of patients was similar in the two groups.

Another study by Dershwitz\(^12\) found similar results for renally impaired patients (n=15) i.e. clearance, volume of distribution and half-life were not significantly altered compared with control subjects (n=8) without renal impairment. Although there was substantial accumulation of the metabolite, remifentanil acid, the authors conclude that its contribution to the overall opioid effect is likely to be of little consequence, even in severe renal impairment.

A study by Breen et al\(^10\) assessed the offset times of the pharmacodynamic effects of remifentanil in ICU patients with varying degrees of renal impairment. Remifentanil was infused for up to 72 hours (initial rate 6–9 µg/kg/h) in 40 patients with normal/mild (n=10) or moderate/severe (n=30) renal dysfunction, and titrated to achieve an SAS of 2–4 with no or mild pain (propofol could be administered if required).

The time to offset of the effects of remifentanil (measured at 8, 24, 48 and 72 hours during scheduled down-titrations of the infusion) were more variable and were statistically significantly longer in the moderate/severe than in the normal/mild group at 24 and 72 hours (figure 3). However, these differences were not clinically significant: the difference in mean time to offset between the two groups after 72 hours of remifentanil administration was only 16.5 minutes. There was no evidence of increased offset time with increased duration of exposure to remifentanil in either group and no difference in incidence of adverse events between the groups. Remifentanil was an effective agent for analgesia and sedation in patients with renal impairment. Accumulation of remifentanil acid, the primary metabolite, in renal dysfunction was not associated with clinically significant prolonged opioid effects.\(^10\)
Figure 3: Time to offset of pharmacodynamic effects of remifentanil at scheduled down titrations in ICU patients with varying degrees of renal impairment.

Potential cost savings in the ICU
The estimated cost per bed day of an ICU stay is £1330. According to Therapeutic Intervention Scoring System (TISS) calculations, over 50% of ICU expenditure is on labour costs, particularly constant bedside nursing. Therefore the use of remifentanil only constitutes a small proportion of the overall ICU costs (£77.52 for a 0.15 µg/kg/min infusion in a 70 kg patient over 24 hours). The use of remifentanil also provides the opportunity to make substantial overall cost savings in the ICU setting.

Remifentanil reduces the need for hypnotic agents
The use of remifentanil for analgesia-based sedation in the ICU offers potential savings in drug costs through reduced need for and usage of other hypnotic/sedative agents. The study by Muellejans et al in which patients received either a remifentanil-based regimen or a standard fentanyl-propofol regimen found that a 45% lower propofol dose was needed with remifentanil (p=0.065).

Remifentanil may reduce costs by reducing the time spent in the ICU
The rapid and predictable recovery following discontinuation of remifentanil reduces the time spent on mechanical ventilation and allows for earlier and more predictable discharge of patients from the ICU. It has been shown that remifentanil has the potential to reduce ICU stay by at least 18 hours. Indeed Royston et al found that patients in the group eligible for early extubation had significantly shorter times to eligibility for ICU discharge than those extubated later (18.5 vs. 43.8 hrs, p<0.001). The author remarked that the potential cost savings of patient transfer from the ICU to a high-dependency environment require the patient to be extubated approximately 5 hours after cardiac surgery. Furthermore, the ability of remifentanil to allow controlled rapid extubation is reflected in reductions in ICU time and possibly overall hospital stay, which may have cost advantages in certain situations.

Remifentanil may be cost-effective by reducing the necessity for expensive diagnostic investigations
A reduced necessity for expensive diagnostic investigations may make remifentanil-based analgesia and sedation cost-effective. In the study by Wilhelm et al use of a fentanyl-midazolam analgesia and sedation resulted in prolonged unconsciousness and the impossibility of neurological examination, making a CT scan necessary in 3 (out of 30) patients in the ICU following neurosurgery. No CT scans were necessary in the 30 patients receiving a remifentanil-propofol analgesia and sedation regimen.
Dosage

It is recommended that remifentanil infusions in mechanically ventilated ICU patients should be started at 6–9 µg/kg/h (0.1–0.15 µg/kg/min) and then titrated in the range 0.36–44.4 µg/kg/h (0.006–0.74 µg/kg/min), depending on the levels of analgesia and sedation required, using titration increments of 1.5 µg/kg/h (0.025 µg/kg/min) with intervals of at least 5 minutes between dose adjustments. If the desired level of sedation is not reached with a remifentanil infusion level of 12 µg/kg/h (0.2 µg/kg/min), it is recommended that dosing with an appropriate sedative agent is initiated.9

For further information on the dosing and titration of remifentanil, please refer to the SPC.
References:

9. GSK. Ultiva (remifentanil HCl) for injection, 1mg, 2mg and 5mg. Summary of Product Characteristics, June 2005.