Remifentanil: Predictable control in the ICU
Analgesia and sedation in the ICU – the challenges and goals
What are the current challenges with analgesia and sedation in the ICU?

**PAIN**
- Half of patients cannot sleep,\(^1\) with the major reason being pain\(^2\)
- About 60% of patients suffer pain\(^2\)

**PATIENT INTERACTION**
- Over-sedation impedes efforts to perform daily neurological examinations\(^5\)
- Over-sedated patients are unable to co-operate\(^6\)

**WEANING AND LENGTH OF STAY**
- Over-sedation delays weaning and increases associated morbidity\(^4\)
- 41% of ventilation time is spent trying to wean a patient\(^3\)
- Over-sedation can also prolong duration of mechanical ventilation\(^5\) and ICU and hospital stay\(^4,5\)

The balance of over- versus under-sedation

Under-sedation

- Pain
- Anxiety
- Hypertension
- Tachycardia
- Hypoxia
- Hypercarbia

The balance of over- versus under-sedation

Under-sedation
- Pain
- Anxiety
- Hypertension
- Tachycardia
- Hypoxia
- Hypercarbia

Over-sedation
- Coma
- Respiratory depression
- Poor cough
- Mental depression
- Hypotension
- Bradycardia
- GI tract paralysis
- Immune depression
- Renal failure
- Immobility

What are the goals of sedation in the ICU?

- The objective of sedation is to have patients that are optimally sedated, which means that patients are:
  - Calm
  - Co-operative
  - Comfortable
  - Communicative

- An analgesia-based approach focuses on patient comfort by effectively managing their pain, adding a sedative only when necessary.

Possible ICU sedation regimens

- Preserve vital functions

- Patient optimally sedated
  - Sedation with hypnotics until the patient is unconscious
    - Analgesics (morphine, fentanyl, NSAIDs), if pain suspected
    - Hypnotic-based sedation\(^{21}\)
  - Treatment with analgesics until patient is comfortable
    - Further sedation with hypnotics, if the patient is anxious or agitated
    - Analgesia-based sedation

Lane M et al. Care Crit Ill 2002; 18:146–7
## Hypnotic versus analgesic approach

<table>
<thead>
<tr>
<th>Hypnotic approach</th>
<th>Analgesic approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients are often difficult to wean (accumulation and over-sedation)(^1,2)</td>
<td>Enables a fast and predictable weaning / extubation(^3)</td>
</tr>
<tr>
<td>Patients may be difficult to assess(^1)</td>
<td>Allows intermittent assessment(^3)</td>
</tr>
<tr>
<td>Pain can be an issue(^4)</td>
<td>Ensures patient is more comfortable(^4)</td>
</tr>
<tr>
<td>Renal / hepatic impairment can be an issue(^1,5)</td>
<td>Not all analgesics are affected by renal / hepatic impairment(^2)</td>
</tr>
<tr>
<td>Patients less able to co-operate(^2,6)</td>
<td>Patient can co-operate with nursing staff(^2,6)</td>
</tr>
<tr>
<td>Patient is asleep and unaware of surroundings(^2)</td>
<td>Patient is more aware of surroundings and able to interact with relatives(^2)</td>
</tr>
</tbody>
</table>

Remifentanil: A unique opioid for analgesia and sedation in the ICU
Remifentanil – key pharmacokinetic and pharmacodynamic advantages

- Remifentanil is a unique, short-acting opioid receptor agonist:
  - Rapid onset of effect: $t^{1/2}k_{e0} = 1.3$ minutes$^1$
  - Rapid offset of action: context-sensitive half-time of 3.65 minutes, independent of duration of infusion (i.e. ‘context insensitive’)$^{1,2}$
  - Predictable offset with no residual opioid activity 5–10 minutes after discontinuation$^3$
  - Metabolised by non-specific blood and tissue esterases$^{1,4}$
  - Metabolism results in formation of remifentanil acid, which is 1/4600th as potent as its parent drug$^3$

Unique metabolism amongst opioids

- Rapid offset of action (<10 min)
- Less inter-patient pharmacokinetic variability
- No accumulation
- Precise titration and rapid recovery
- Pharmacokinetics independent of obesity and hepatic or renal impairment
- Offset of action independent of duration of infusion

Rapidly metabolised by non-specific blood and tissue esterases

References:
Quick response to changes in infusion rate

- Remifentanil and alfentanil have a similar time to peak effect in healthy volunteers.
- After a 2 hour infusion Remifentanil has a more rapid offset of effect than alfentanil.

**Graphs:**
- **Rapid onset:**
  - Proportion of the maximal effect site concentration (%).
  - Time (min) from 0 to 12.
- **Rapid offset:**
  - Proportion of the maximal effect site concentration (%).
  - Time (min) from 0 to 300.

Lack of accumulation after use

- Remifentanil’s short context-sensitive half-time results in an offset of action independent of the duration of infusion (context insensitive)

Simulation from a study in healthy volunteers (n=10) showing time necessary to achieve a 50% decrease in drug concentration in the blood (or plasma) after variable-length intravenous infusions.

**Sufentanil is not licensed in the UK**

Remifentanil in organ-impaired patients

- There is no significant difference in Remifentanil clearance between healthy control subjects and patients with kidney failure\(^1\) or liver disease\(^2\)

![Graphs showing Remifentanil concentration over time for kidney failure and liver disease](image)

Patients with severe hepatic impairment should be closely monitored and the dose of Remifentanil titrated to individual need,\(^3\) as these patients may be more sensitive to the respiratory depressant effects of Remifentanil.\(^2\)

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Why should Remifentanil be used in the ICU?
Remifentanil: why should it be used in the ICU?

- Remifentanil can be precisely titrated, facilitating patient interaction and assessment\(^1\)\(^-\)\(^3\)

- Remifentanil enables a shorter weaning time and a reduction in the time spent on mechanical ventilation compared with traditional opioid analgesics\(^3\)\(^-\)\(^5\)

Reduced time to neurological examination compared to hypnotic-led regimes

- Remifentanil + Propofol (N=64): 22.8 minutes
- Propofol + Fentanyl (N=32): 40.8 minutes
- Propofol + Morphine (N=34): 49.2 minutes

* p < 0.05

Data on File, 2007
Precise down-titration facilitating interaction and assessment

- Remifentanil facilitates rapid emergence from analgesia and sedation allowing patient interaction within 10 minutes (n=10)\(^1\)
- Faster recovery from analgesia and sedation with Remifentanil/propofol compared with fentanyl/midazolam facilitates neurological examination and potentially reduces the need for diagnostic investigations such as CT scans\(^2\)

Precise up-titration facilitating interaction and assessment

- Remifentanil can be easily titrated:
  - allowing painful, stimulating procedures to be performed\(^1\)\(^-\)\(^3\)
  - and can be administered at higher doses without concerns about accumulation\(^4\)

Remifentanil improves patient comfort

Effective analgesia reduces pain and resulting anxiety, decreasing the need for hypnotic agents$^{19,21,22}$

Ensures patient is pain-free, rather than over-sedated$^{19,21,22}$

Allows for better interaction with family and carers$^{21}$

Remifentanil facilitates rapid weaning

- Remifentanil enables a shorter time to extubation compared with traditional opioid regimens\(^1,2\)

**General surgery**
Dahaba *et al.*\(^1\)

<table>
<thead>
<tr>
<th>Remifentanil/midazolam</th>
<th>Extubation time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=20</td>
<td>17*</td>
</tr>
<tr>
<td>Morphine/midazolam</td>
<td>73</td>
</tr>
</tbody>
</table>

**Cardiac surgery**
Matthey *et al.*

<table>
<thead>
<tr>
<th>Remifentanil/propofol</th>
<th>Extubation time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=39</td>
<td>132*</td>
</tr>
<tr>
<td>Fentanyl/midazolam</td>
<td>342</td>
</tr>
</tbody>
</table>

\(p < 0.05\)

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Remifentanil reduces time spent on mechanical ventilation

- Remifentanil reduces the time spent on mechanical ventilation compared with traditional opioid regimens\(^1,2\)
- Reduced time on mechanical ventilation potentially reduces associated complications\(^3,4\)

**General surgery**

Dahaba *et al.*

\[\begin{array}{cc}
\text{Remifentanil/Midazolam} & 0.3^* \\
\text{Morphine/Midazolam} & 18.1 \\
\end{array}\]

\(\text{4.9 hrs}\)

\[\begin{array}{cc}
\text{Remifentanil/Midazolam} & 14.1^* \\
\text{Morphine/Midazolam} & 20.7^* \\
\end{array}\]

\(\text{3.5 hrs}\)

**Cardiac surgery**

Matthey *et al.*

\[\begin{array}{cc}
\text{Remifentanil/Propofol} & 20.7^* \\
\text{Fentanyl/Midazolam} & 24.2 \\
\end{array}\]

\(\text{3.5 hrs}\)

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2. Matthey T *et al.* *Intens Care Med* 2004; 30(Suppl. 1); S409 and poster.
The UltiSAFE study

- 16 Dutch ICUs
- 215 patients randomised - medical and post-surgical with an expected mechanical ventilation time of 2-3 days

**Primary Endpoint**: duration of mechanical ventilation

*Propofol/ Midazolam/ Lorazepam + Fentanyl/ Morphine*

According to Dutch Society of Intensive Care guidelines

Patients in the Remifentanil arm were 1.85 times more likely to be extubated within the first 3 days of treatment than patients in the conventional arm (95% CI: 1.11–3.08, p = 0.019).
Analgesia and sedation with Remifentanil provides significantly longer percentage hours of optimal sedation than with morphine.


Sedation agitation scale

- Remifentanil/midazolam (n = 20)
- Morphine/midazolam (n = 20)

* p < 0.05
When should Remifentanil be used in the ICU?
Remifentanil: when to use it in the ICU

- For analgesia and sedation in mechanically ventilated, critically ill patients aged 18 years or over who:
  - Are expected to have an overnight or short ICU stay (up to 3 days)\(^1\)
  - Need to be weaned and extubated within the next 3 days\(^1\)
  - Have hepatic or renal impairment\(^1\)
  - Require dose titration (e.g. for neurological assessment or painful procedures)\(^2-5\)

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Remifentanil is indicated for the provision of analgesia and sedation in mechanically ventilated intensive care patients 18 years of age and over.
How should Remifentanil be used in the ICU?
Dosing protocol for the ICU

Does the patient need analgesia or sedation?

Yes

Start Remifentanil at 0.1\(\mu\)g/kg/min

Evaluate after 5 minutes:
- Pain, anxiety or agitation?
- or
- Difficult to wake?

Yes

Titrate Remifentanil infusion up or down with steps of 0.025\(\mu\)g/kg/min (range 0.006–0.74\(\mu\)g/kg/min)

Dosing protocol for the ICU

At Remifentanil 0.2μg/kg/min

- Is the patient in pain or ventilator intolerant?
  - Increase Remifentanil infusion with additional steps of 0.025μg/kg/min until adequate pain relief

- Is the patient anxious or agitated?
  - Add hypnotic agent
    - e.g. bolus
    - Midazolam up to 0.03mg/kg 0.03mg/kg/hour
    - Propofol up to 0.5mg/kg 0.5mg/kg/hour

Remifentanil in special patient populations

- **Renally impaired patients:** no dose adjustments necessary for renally impaired patients, including those undergoing renal replacement therapy\(^1\)

- **Hepatically impaired patients:** no dose adjustment of initial dose, relative to that used in healthy adults, is necessary as the pharmacokinetic profile of Remifentanil is unchanged in this patient population\(^1\)

- **Obese patients:** base Remifentanil dose on ideal body weight rather than actual body weight\(^1\)

Extubation and discontinuation of Remifentanil

- Titrate Remifentanil infusion in stages to 0.1µg/kg/min (6µg/kg/hr) over a period of 1 hour prior to extubation.

- Following extubation, reduce infusion rate by 25% decrements in at least 10-minute intervals until the infusion is discontinued.

- During weaning from the ventilator only down titration of Remifentanil should occur, supplemented as required with alternative analgesics.

**Downward titration of Remifentanil:**

- Remifentanil infusion
- -25%
- 10 minutes
- -25%
- 10 minutes
- -25%
- 10 minutes
- Up to 1 hour
- Stop

Alternative analgesic and sedative agents should be given at a sufficient time prior to the discontinuation of Remifentanil to allow the therapeutic effects to become established.

What is Remi in Practice?

Resource pack
Factsheets, Case studies, CD-ROM on how to use remifentanil

SIM Centres
Hands-on nurse and consultant training for the ICU, using high fidelity mannequins with interactive, life-like scenarios

Increasing knowledge, experience and confidence
A range of offerings on how to use remifentanil, tailoring practical support to your individual needs

Online Web Forums
Interactive online presentation and discussion on topical remifentanil issues

Hands-on Workshops
1:1 or small groups following a theatre list for the day

Speaker Meetings
National meetings with key opinion leaders, for consultants, nurses and pharmacists
What are the cost implications of Remifentanil?
Potential for cost savings
Potential for cost savings

- Compared to traditional opioids:
  - Reduced need for hypnotic agents$^{1-2}$

Potential for cost savings

- Compared to traditional opioids:
  - Reduced need for hypnotic agents\(^1\)-\(^2\)
  - Reduced time spent on mechanical ventilation\(^2\),\(^3\)

Potential for cost savings

- **Compared to traditional opioids:**
  - Reduced need for hypnotic agents\(^1\text{-}^2\)
  - Reduced time spent on mechanical ventilation\(^2\text{-}^3\)
  - Reduced time to neurological assessment\(^1\text{-}^2\text{-}^4\)
    - Potentially reducing the necessity for expensive diagnostic investigations\(^5\)

Potential for cost savings

- Compared to traditional opioids:
  - Reduced need for hypnotic agents\(^1\)\(^-\)\(^2\)
  - Reduced time spent on mechanical ventilation\(^2\),\(^3\)
  - Reduced time to neurological assessment\(^1\),\(^2\),\(^4\)
    - Potentially reducing the necessity for expensive diagnostic investigations\(^5\)
  - Reduced time spent in the ICU\(^2\),\(^3\),\(^5\)

Reduced need for additional sedative agents

Remifentanil reduces the need for additional sedative agents,\textsuperscript{1,2} which are associated with delayed neurological assessment, prolonged weaning and increased duration of mechanical ventilation.\textsuperscript{2–5}

\begin{itemize}
  \item Fentanyl 0.025 $\mu$g/kg/min
  \item Remifentanil 0.15 $\mu$g/kg/min
\end{itemize}

\[\text{Median total propofol dose (mg)}\]

\begin{itemize}
  \item 45\% reduction\textsuperscript{1}
  \item \(p = 0.065\)
  \item \(n = 152\)
\end{itemize}

\textsuperscript{1} Muellejans B \textit{et al}. \textit{Crit Care} 2004; 8: R1–R11.
\textsuperscript{2} Dahaba AA \textit{et al}. \textit{Anesthesiol} 2004; 101: 640–6.
\textsuperscript{5} Matthey T \textit{et al}. \textit{Intens Care Med} 2004; 30(Suppl): S409 and poster.
Reduced time spent in the ICU

- Due to its rapid offset of action, Remifentanil facilitates the ability to plan and control the period of recovery, reducing the time spent in ICU\(^1\).
- This enables patients to be discharged from the ICU as soon as they are ready.

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Remifentanil accounts for a fraction of the total ICU costs

- The cost of an ICU stay is estimated at £1,328/day\(^1\)
- Interventions that result in even nominal decreases in length of time spent in the ICU have the opportunity to significantly reduce hospitalisation costs\(^2\)
- Estimated daily cost of Remifentanil = £77.52 (for infusion rate 0.15 μg/kg/min in 70kg patient)
- Remifentanil has the potential to reduce ICU stay and the need for diagnostic investigations\(^3\)–\(^5\)

Summary: Remifentanil in the ICU
Summary: Remifentanil in the ICU

- The objective of sedation is to have patients optimally sedated, which means that they are calm, co-operative, comfortable and communicative\(^1\)

- Remifentanil can be precisely titrated facilitating patient interaction and assessment\(^2-4\)

- Remifentanil enables a shorter weaning time and a reduction in the time spent on mechanical ventilation compared with traditional opioid analgesics\(^4-6\)

- An analgesic-based approach ensures that the patient is pain-free and reduces the time spent in ICU\(^7,8\)

- Rapid recovery with Remifentanil provides the potential for cost savings\(^4\)

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Additional Slides
UK and US Sedation Guidelines: Analgesia-based Sedation

- **Intensive Care Society Sedation Guideline (UK, 2001)**
  - All patients must be comfortable and pain free. Analgesia is thus the first aim.

- **Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult (US, 2002)**
  - Sedation of agitated critically ill patients should be started only after providing adequate analgesia and treating reversible physiological causes.

UK and US Sedation Guidelines: Optimal Sedation

- Intensive Care Society Sedation Guideline (UK, 2001)
  - Patients should be calm, co-operative and able to sleep when undisturbed. This does not mean that they must be asleep at all times.

GlaxoSmithKline (GSK) are looking to support clinicians who already use, or are looking to increase their use, of Remifentanil in their practice.

As such we have been working with doctors.net.uk to develop a Remi in Practice website: www.doctors.net.uk/Remi

If you are a member of doctors.net.uk, but have forgotten your details, simply telephone the helpdesk on 01235 828400 or e-mail help@doctors.org.uk

If you are not a member of doctors.net.uk you can still have access to the site. User name: guestaccess and Password: remi
Welcome to Remi in Practice Online: aiming to increase your knowledge, experience and confidence with each click...

Join the debate
Should Remifentanil be used with total intravenous or volatile anaesthesia?
Total intravenous
Volatile anaesthesia

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- Request a clinical summary

Remi in General Anaesthesia
Remi in Intensive Care

Business Case (553 PDF)

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Doctors.net.uk will soon be hosting some new modules on anaesthesia
Personal Excellence Tracker (PET)
Remi in Practice Online:
Aiming to increase your knowledge, experience and confidence with each click
References and prescribing information

Bakker et al. Remifentanil-based analgo-sedation shortens duration of ventilation, weaning time, and ICU length of stay compared to conventional sedation and analgesia. Results of a centre-randomised, open-label, crossover, ‘real-life’ study Intensive Care Medicine 2006; 32(Suppl 1): S0320


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Muellejans B et al. Remifentanil versus fentanyl for analgesia based sedation to provide patient comfort in the intensive care unit: a randomized, double-blind controlled trial [ISRCTN43744713]. Critical Care 2004; 8: R1-R11.
References

Ultiva is a registered trademark of the GlaxoSmithKline group of companies.

Further information is available on request from: GlaxoSmithKline UK Ltd, Stockley Park West, Uxbridge, Middlesex UB11 1BT