

Remifentanil_{Ultiva}

Remifentanil: Predictable control in the ICU



ULT/SLK/06/24993/3
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Remifentanil Ultiva

Analgesia and sedation in the ICU – the challenges and goals



GlaxoSmithKline

What are the current challenges with analgesia and sedation in the ICU?

Half of patients cannot sleep,¹ with the major reason being pain²

PAIN

About 60% of patients suffer pain²



Over-sedation impedes efforts to perform daily neurological examinations⁵

PATIENT INTERACTION

Over-sedated patients are unable to co-operate⁶

WEANING AND LENGTH OF STAY

Over-sedation delays weaning and increases associated morbidity⁴

41% of ventilation time is spent trying to wean a patient³

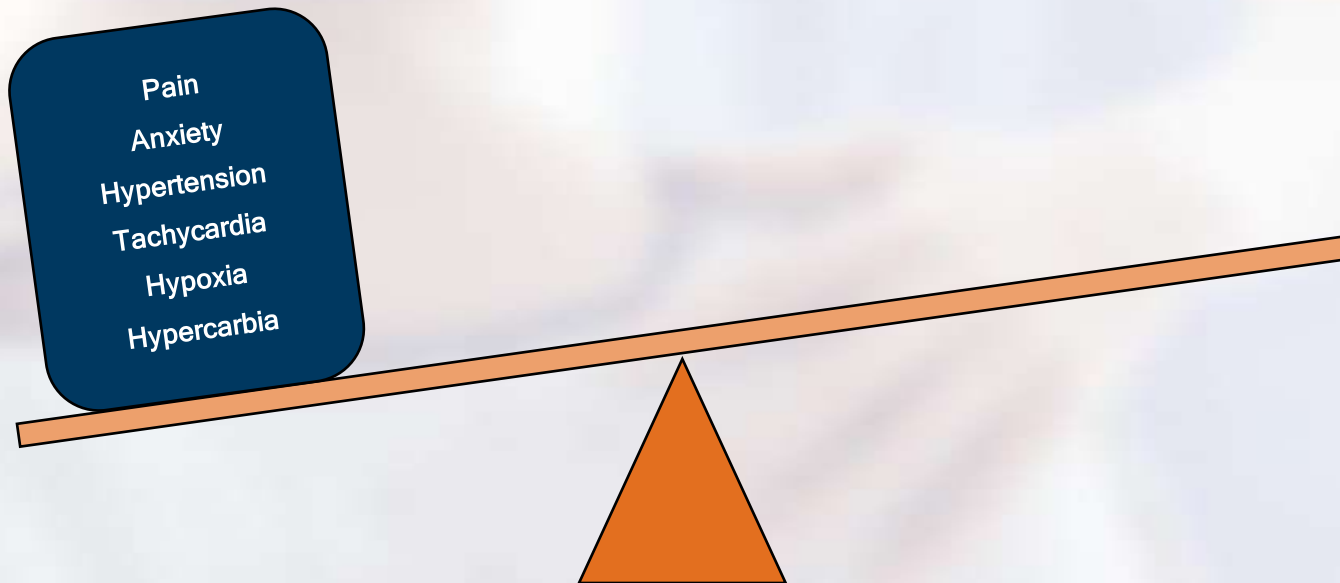
Over-sedation can also prolong duration of mechanical ventilation⁵ and ICU and hospital stay^{4,5}

1. Aurell J *et al. BMJ* 1985; **290**: 1029–32.
2. Park G. *Minerva Anesthesiol* 2002; **68**: 505–12.
3. Esteban A *et al. Chest* 1994; **106**: 1188–93.

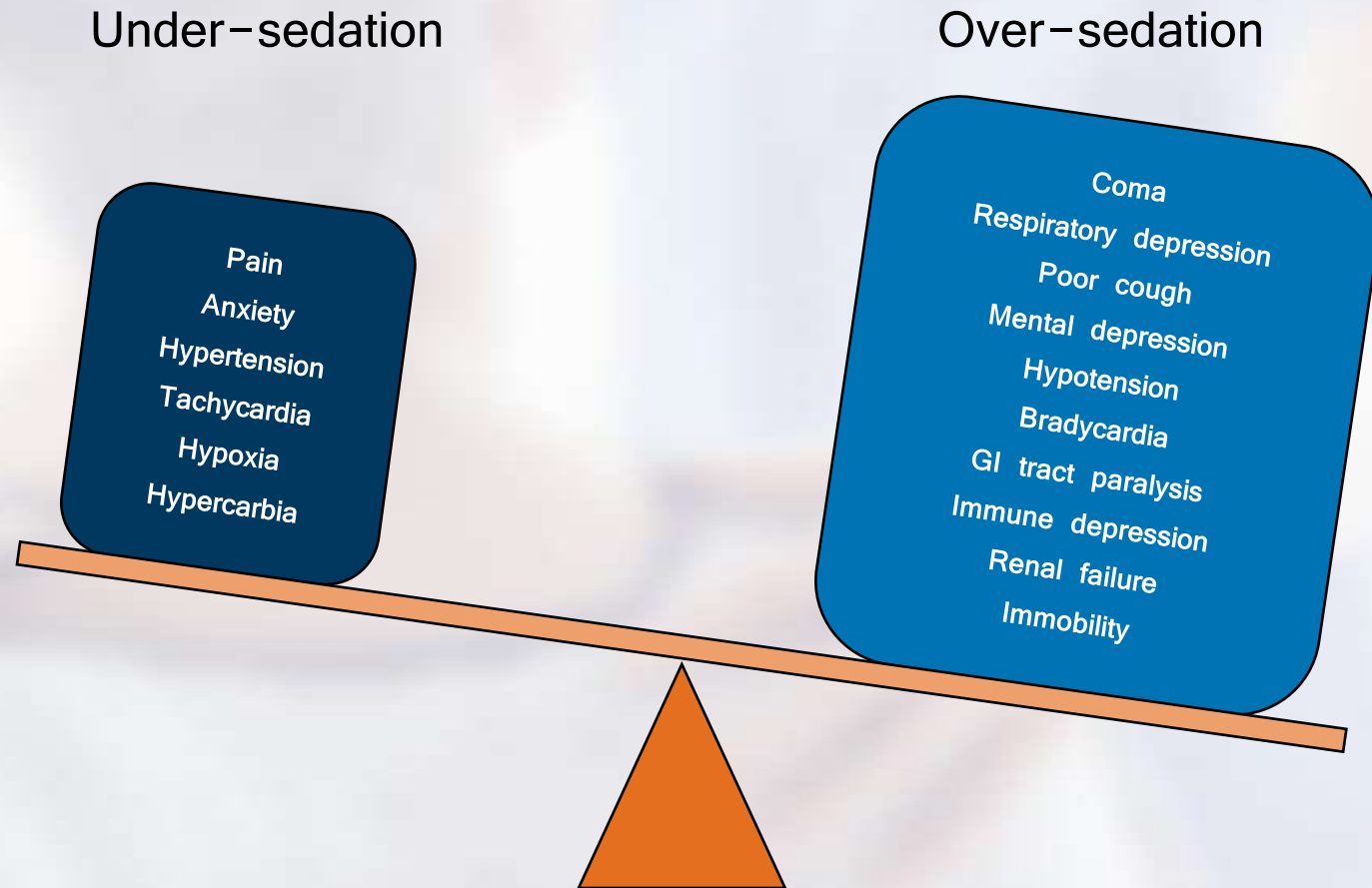
4. Ramsay M. *Bailliere's Clinical Anaesthesiology* 2000; **14**: 419–32.
5. Kress JP *et al. NEJM* 2000; **342**: 1471–7.
6. Park G. *Curr Anaesth Crit Care* 2002; **13**: 313–20.

The balance of over- versus under-sedation

Under-sedation



The balance of over- versus under-sedation



What are the goals of sedation in the ICU?

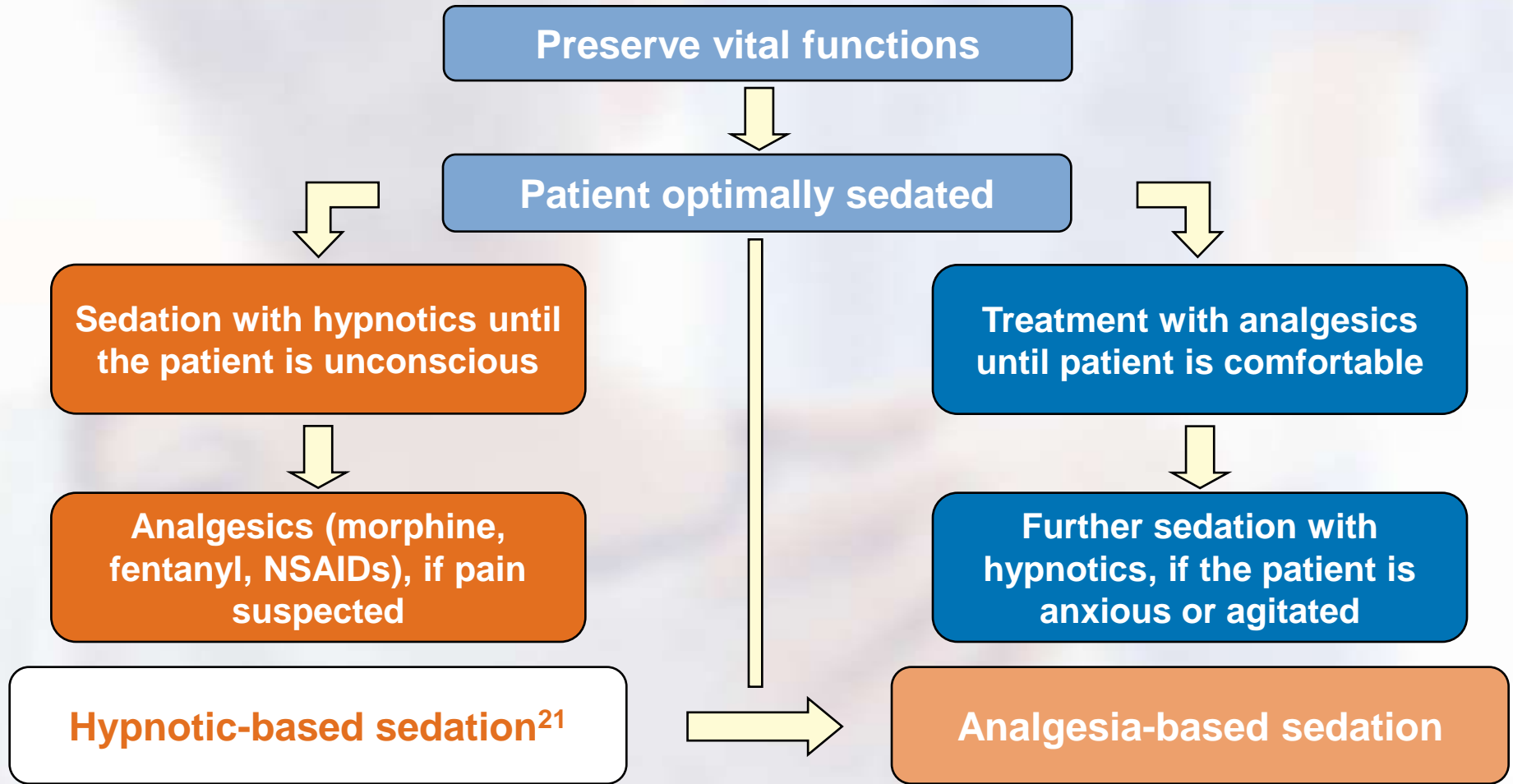
- The objective of sedation is to have patients that are optimally sedated, which means that patients are:¹
 - Calm
 - Co-operative
 - Comfortable
 - Communicative
- An analgesia-based approach focuses on patient comfort by effectively managing their pain,² adding a sedative only when necessary.³

1. Ramsay M. *Bailliere's Clinical Anaesthesiology* 2000; **14**: 419–32.

2. Dahaba AA *et al. Anesthesiol* 2004; **101**: 640–6.

3. Muellejans B *et al. Crit Care* 2004; **8**: R1–R11.

Possible ICU sedation regimens



Hypnotic versus analgesic approach

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

1. Soltesz S *et al.* *Br J Anaesth* 2001; **86**: 763–8.

2. Park G. *Curr Anaesth Crit Care* 2002; **13**: 313–20.

3. Evans TN *et al.* *Anaesthesia* 1997; **52**: 800–1.

4. Park G. *Minerva Anestesiologica* 2002; **68**: 505–12.

5. Breen D *et al.* *Crit Care* 2004; **8**: R21–30.

6. Lane M *et al.* *Care Crit Ill* 2002; **18**: 140–3.

Remifentanil^{Ultiva}

Remifentanil: A unique opioid for analgesia and sedation in the ICU



GlaxoSmithKline

Remifentanil – key pharmacokinetic and pharmacodynamic advantages

- Remifentanil is a unique, short-acting opioid receptor agonist:
 - Rapid onset of effect: $t_{1/2k_{e0}} = 1.3$ minutes¹
 - 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 discontinuation³
 - 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 drug³

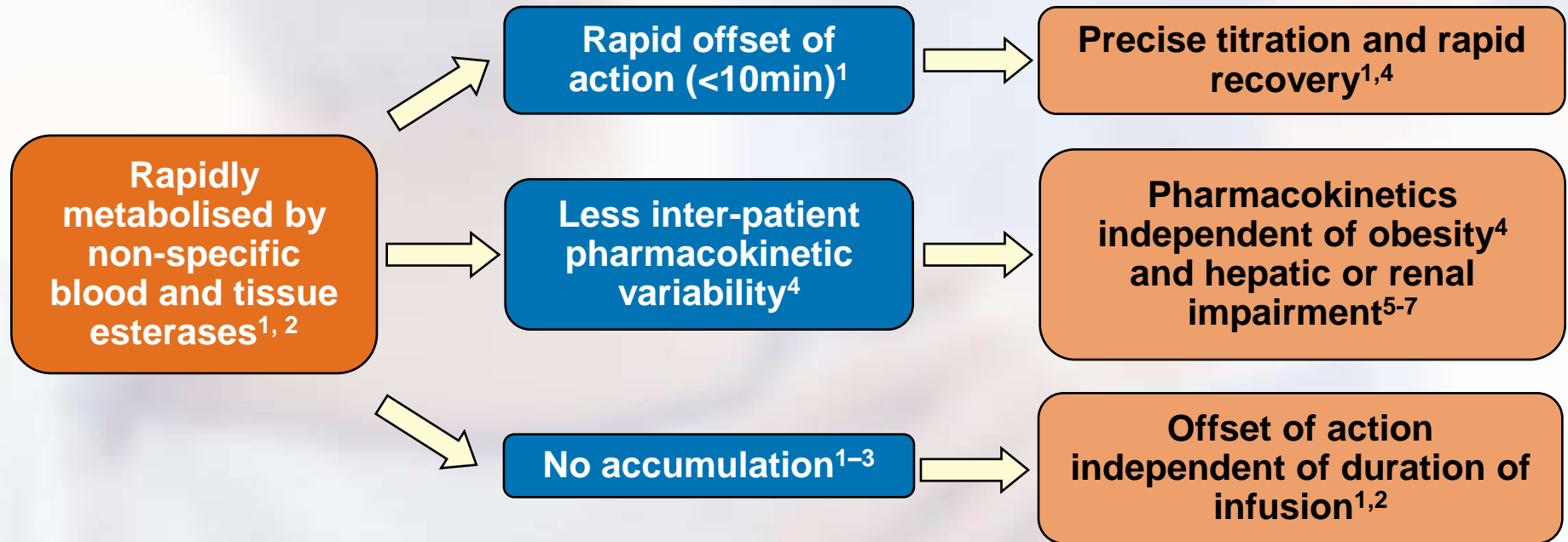
1. Egan TD. *Clin Pharmacokinet* 1995; **29**: 80–94.

2. Westmoreland CL *et al.* *Anesthesiology* 1993; **79**: 893–903.

3. GlaxoSmithKline. Remifentanil HCl (Ultiva) SPC, June 2005.

4. Beers R *et al.* *CNS Drugs* 2004; **18**:1085-104.

Unique metabolism amongst opioids



1. Egan TD. *Clin Pharmacokinet* 1995; **29**: 80–94.

2. Beers R, Camporesi E. *CNS Drugs* 2004; **18**: 085–104.

3. Schüttler J *et al. Anaesthesia* 1997; **52**: 307–17.

4. Glass PSA. *J Clin Anesth* 1995; **7**: 558–63.

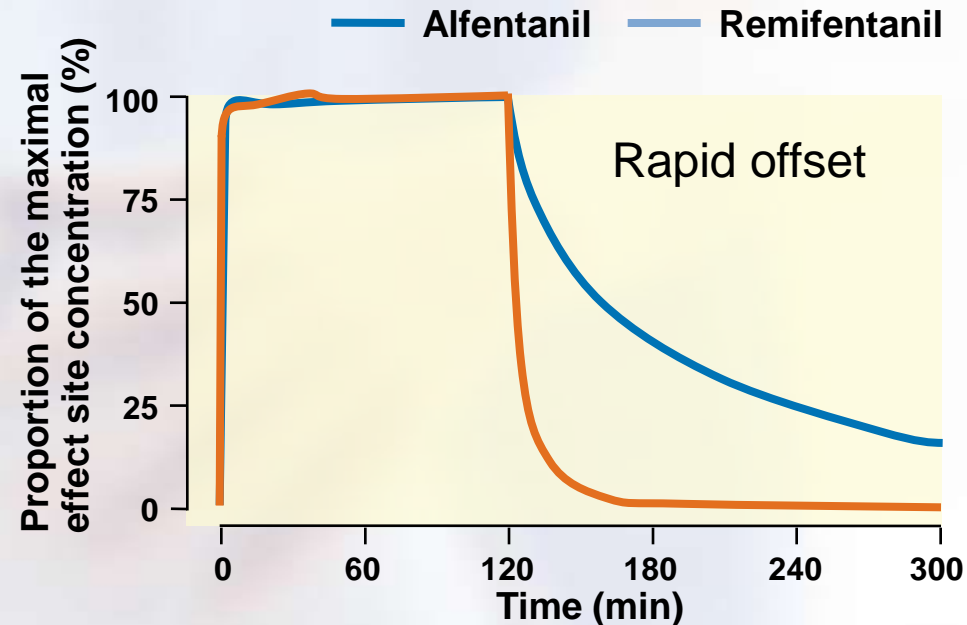
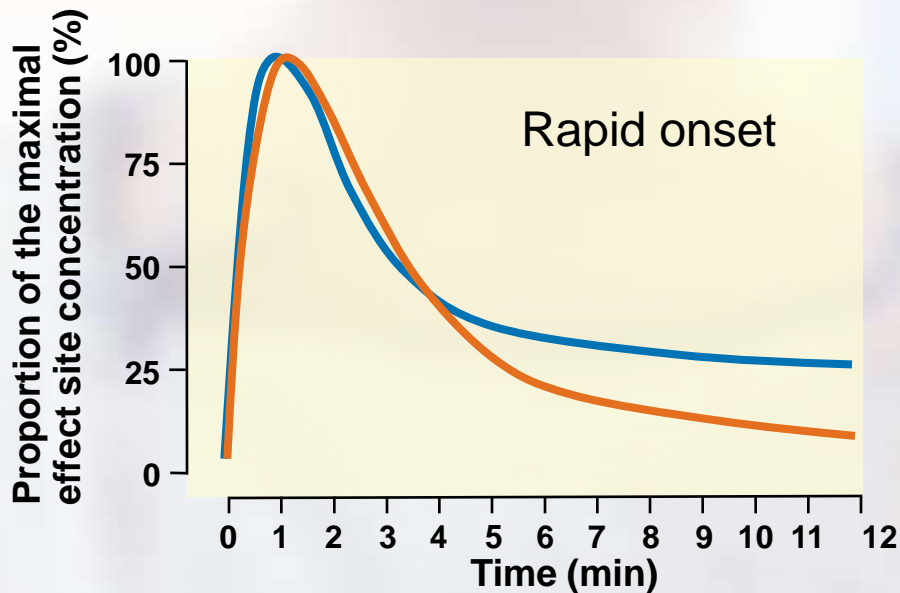
5. Westmoreland CL *et al. Anesthesiology* 1993; **79**: 893–903.

6. Dershwitz M *et al. Anesthesiology* 1996; **84**: 812–20.

7. Dershwitz M *et al. J Clin Anesthesia* 1996; **8**: 88S–90S.

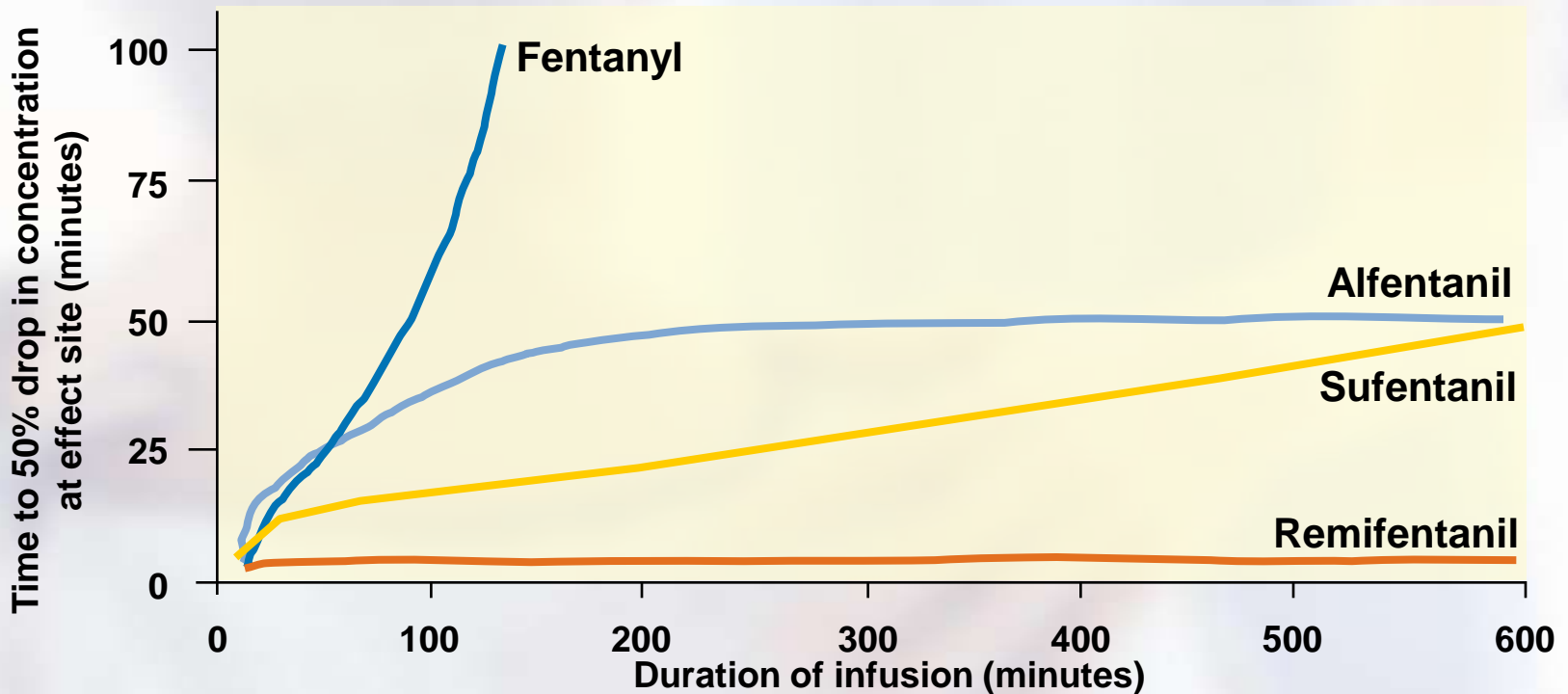
Quick response to changes in infusion rate

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



Lack of accumulation after use

- Remifentanyl'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

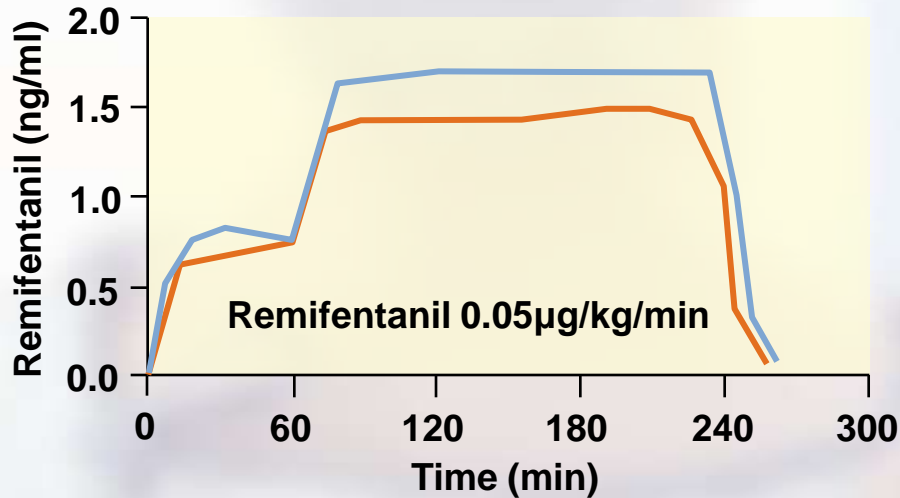
Sufentanil is not licensed in the UK

Egan TD *et al.* *Anesthesiology* 1993; **79**: 881–92.

Remifentanil in organ-impaired patients

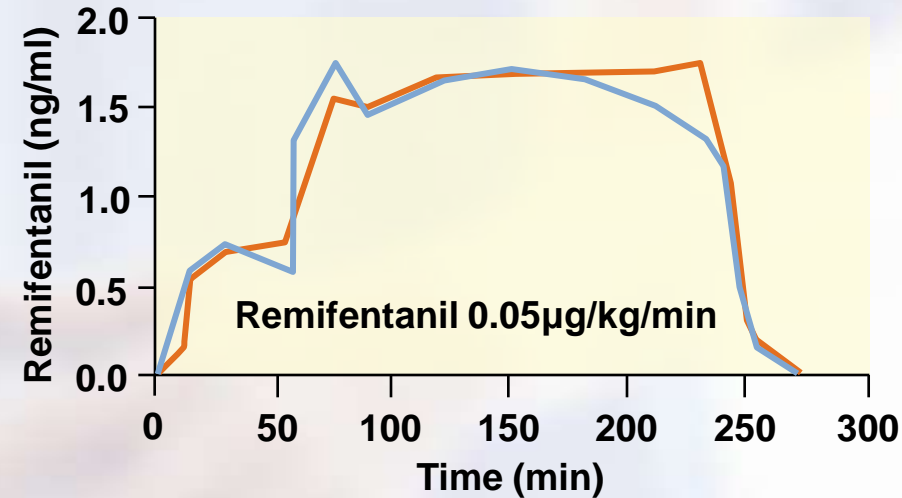
- There is no significant difference in Remifentanil clearance between healthy control subjects and patients with kidney failure¹ or liver disease²

Kidney failure¹



— Renal failure (CrCl 9ml/min, n=15)
— Control subjects (CrCl 88ml/min, n=8)

Liver disease²



— Hepatic impairment (n=5)
— Healthy subjects (n=5)

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

1. Hoke JF *et al.* *Anesthesiol* 1997; **87**: 533–41.
2. Dershwitz M *et al.* *Anesthesiology* 1996; **84**: 812–20.
3. GlaxoSmithKline. Remifentanil HCL (Ultiva) SPC. June 2005.

Remifentanil^{Ultiva}

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}

1. Soltesz S *et al.* *Br J Anaesth* 2001; **86**: 763–8.

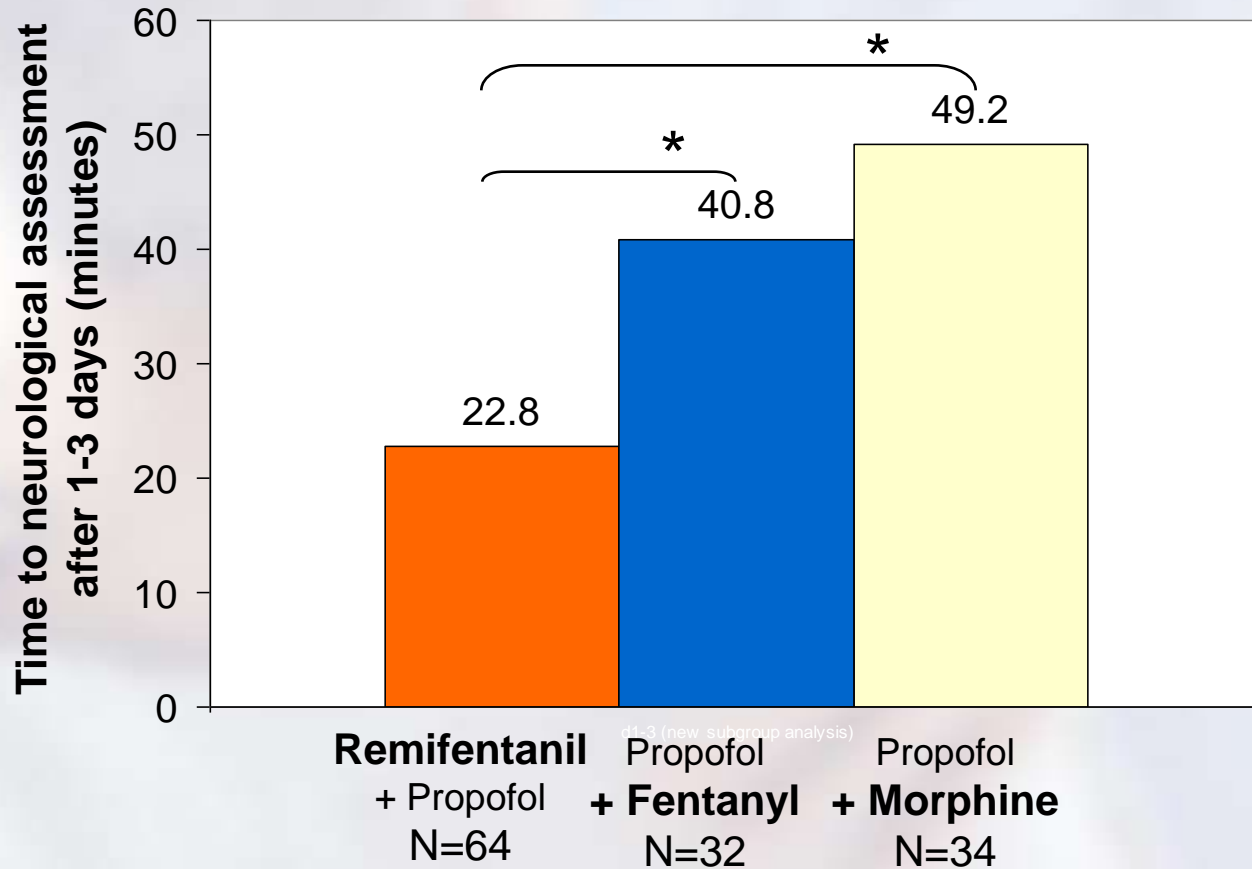
2. Muellejans B *et al.* *Crit Care* 2004; **8**: R1–R11.

3. Wilhelm W *et al.* *Eur J Anaesth* 2004; **21**(Suppl): A-705

4. Dahaba AA *et al.* *Anesthesiol* 2004; **101**: 640–6.

5. Matthey T *et al.* *Intens Care Med* 2004; **30**(Suppl): S409 and poster.

Reduced time to neurological examination compared to hypnotic-led regimes



*p < 0.05

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 scans²



1. Soltesz S *et al.* *Br J Anaesth* 2001; **86**: 763–8.
2. Wilhelm W *et al.* *Eur J Anaesth* 2004; **21**(Suppl): A-705.
3. Glass PSA. *J Clin Anesth* 1995; **7**: 558–63.

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 accumulation⁴

1. Muellejans B *et al. Crit Care* 2004; **8**: R1–R11.

2. Dahaba A *et al. Anesthesiology* 2004; **101**: 640–6.

3. Engelhard K *et al. Acta Anaesthesiol Scand* 2004; **48**: 396–9.

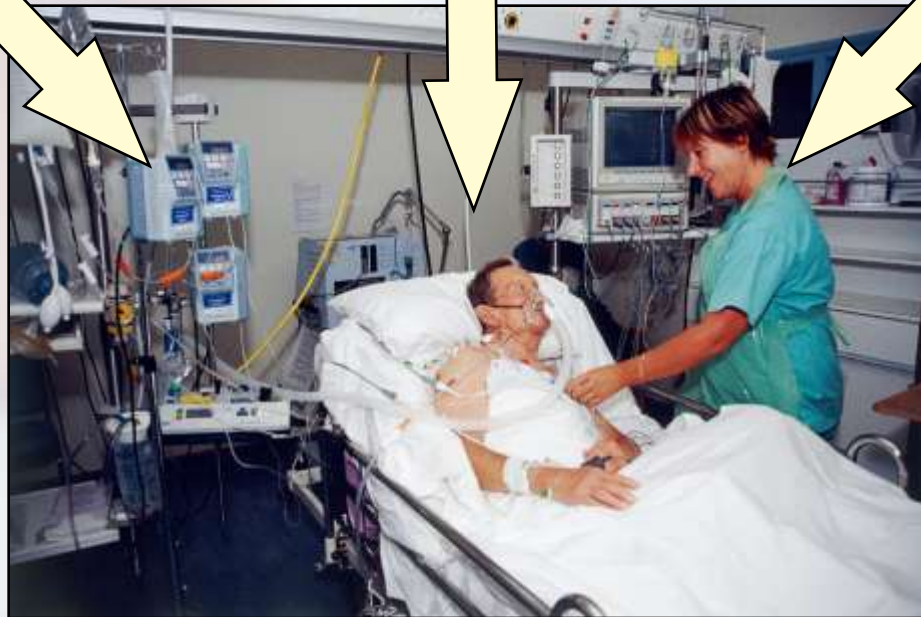
4. Soltesz S *et al. Br J Anaesth* 2001; **86**: 763–8.

Remifentanil improves patient comfort

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

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

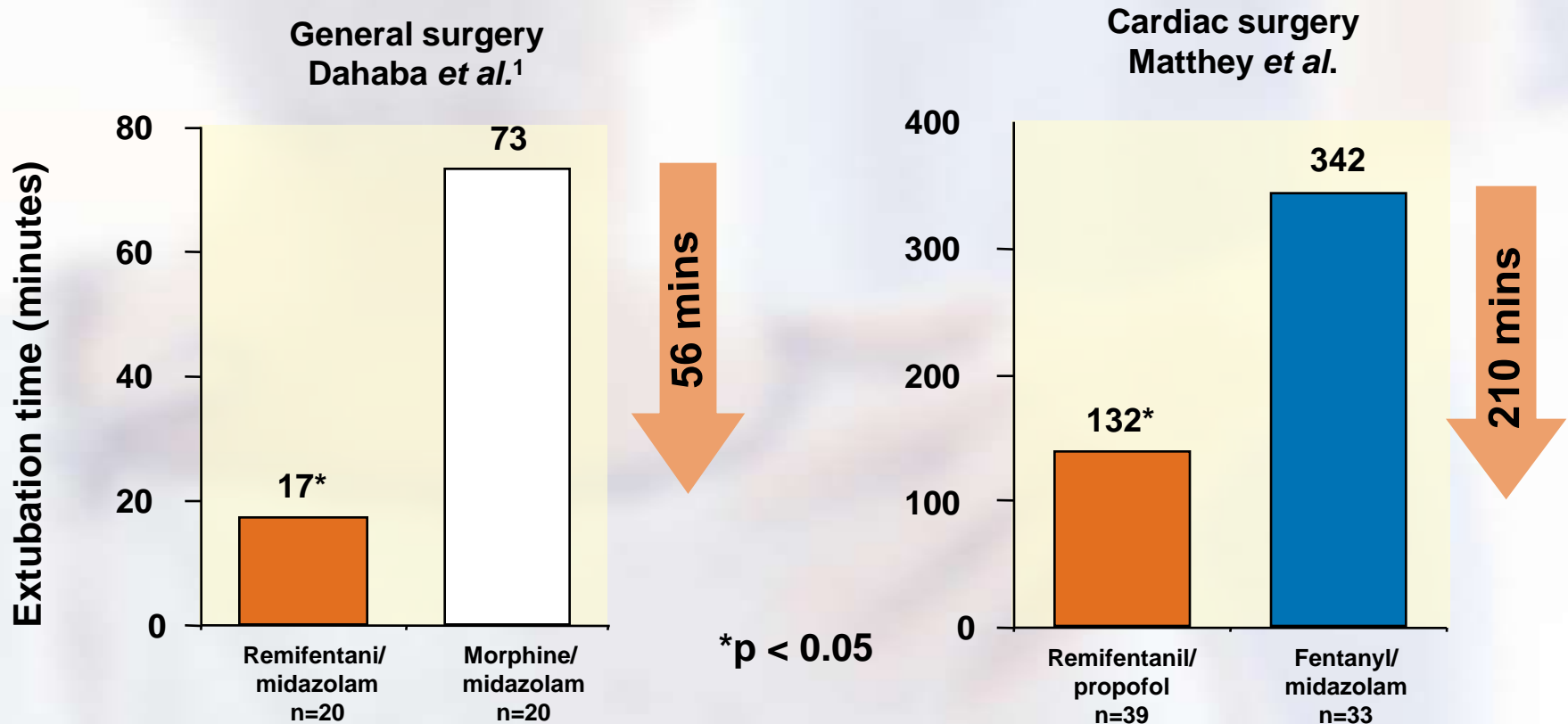
Allows for better interaction with family and carers²¹



1. Lane M *et al.* *Care Crit Ill* 2002; **18**: 140–3.
2. Park G. *Curr Anaesth Crit Care* 2002; **13**: 313–20.
3. Lane M *et al.* *Care Crit Ill* 2002; **18**: 146–7.

Remifentanil facilitates rapid weaning

- Remifentanil enables a shorter time to extubation compared with traditional opioid regimens^{1,2}



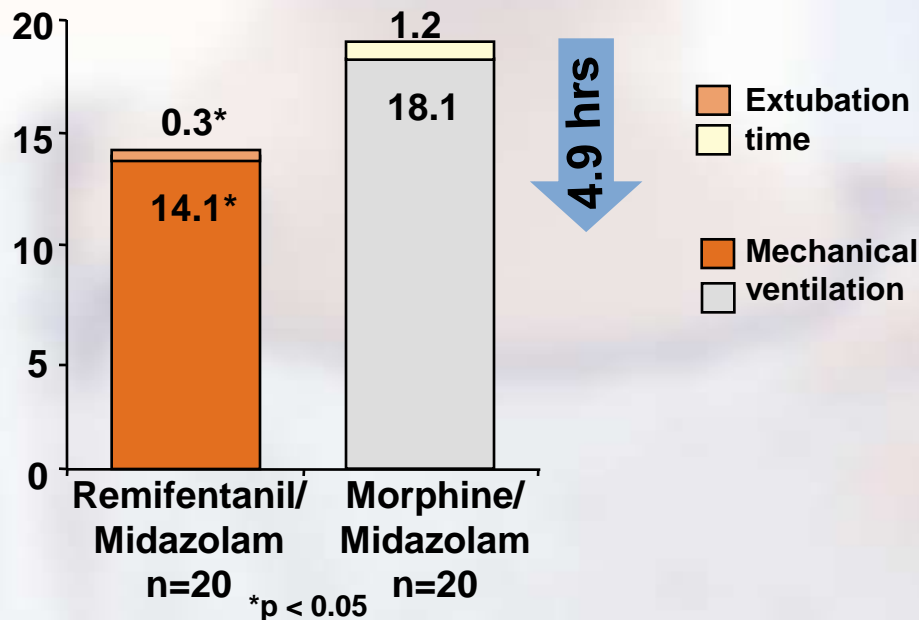
1. Dahaba AA *et al.* *Anesthesiol* 2004; **101**: 640–6.

2. Matthey T *et al.* *Intens Care Med* 2004; **30**(Suppl): S409 and poster.

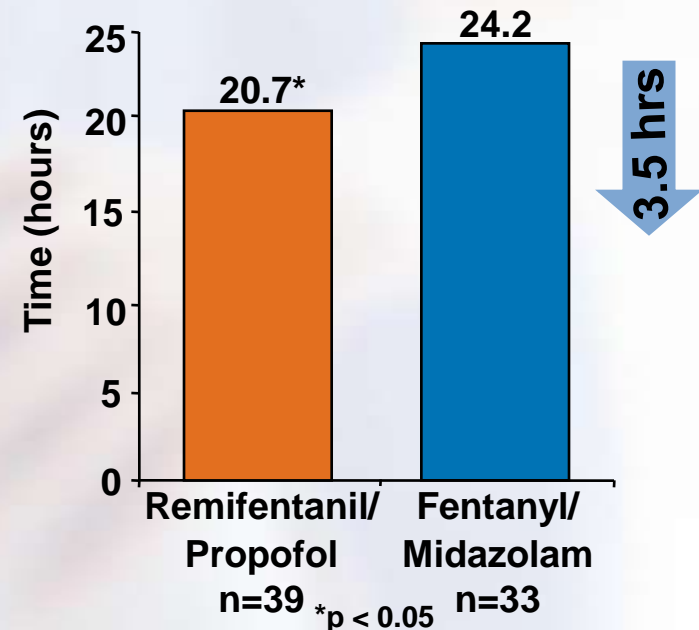
Remifentanil reduces time spent on mechanical ventilation

- ▶ 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.



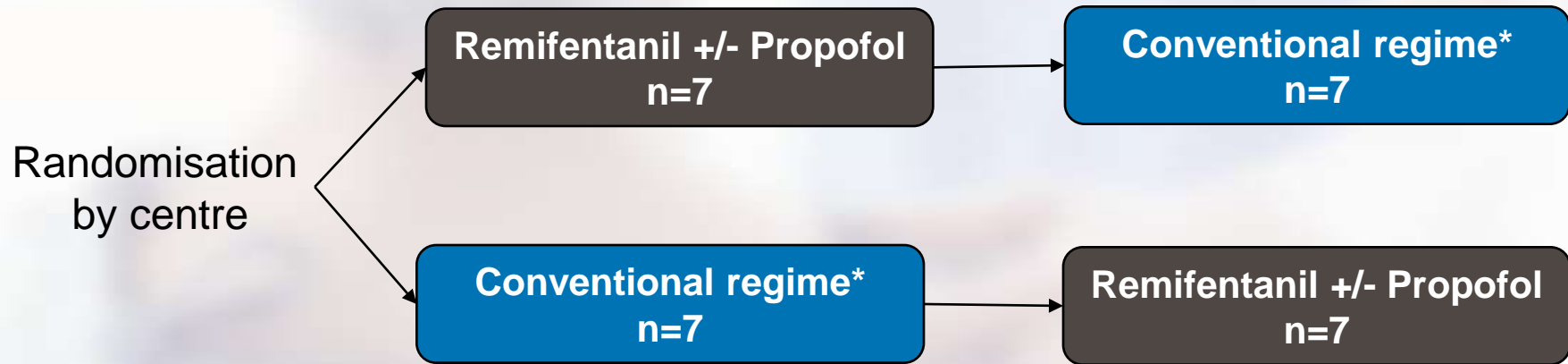
Cardiac surgery
Matthey et al.



1. Dahaba AA et al. *Anesthesiol* 2004; **101**: 640–6.
2. Matthey T et al. *Intens Care Med* 2004; **30**(Suppl. 1); S409 and poster .
3. Vincent J et al. *JAMA* 1995; **274**: 639–44.
4. Dasta J et al. *Crit Care Med* 2005; **33**: 1266–71.

The UltiSAFE study

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



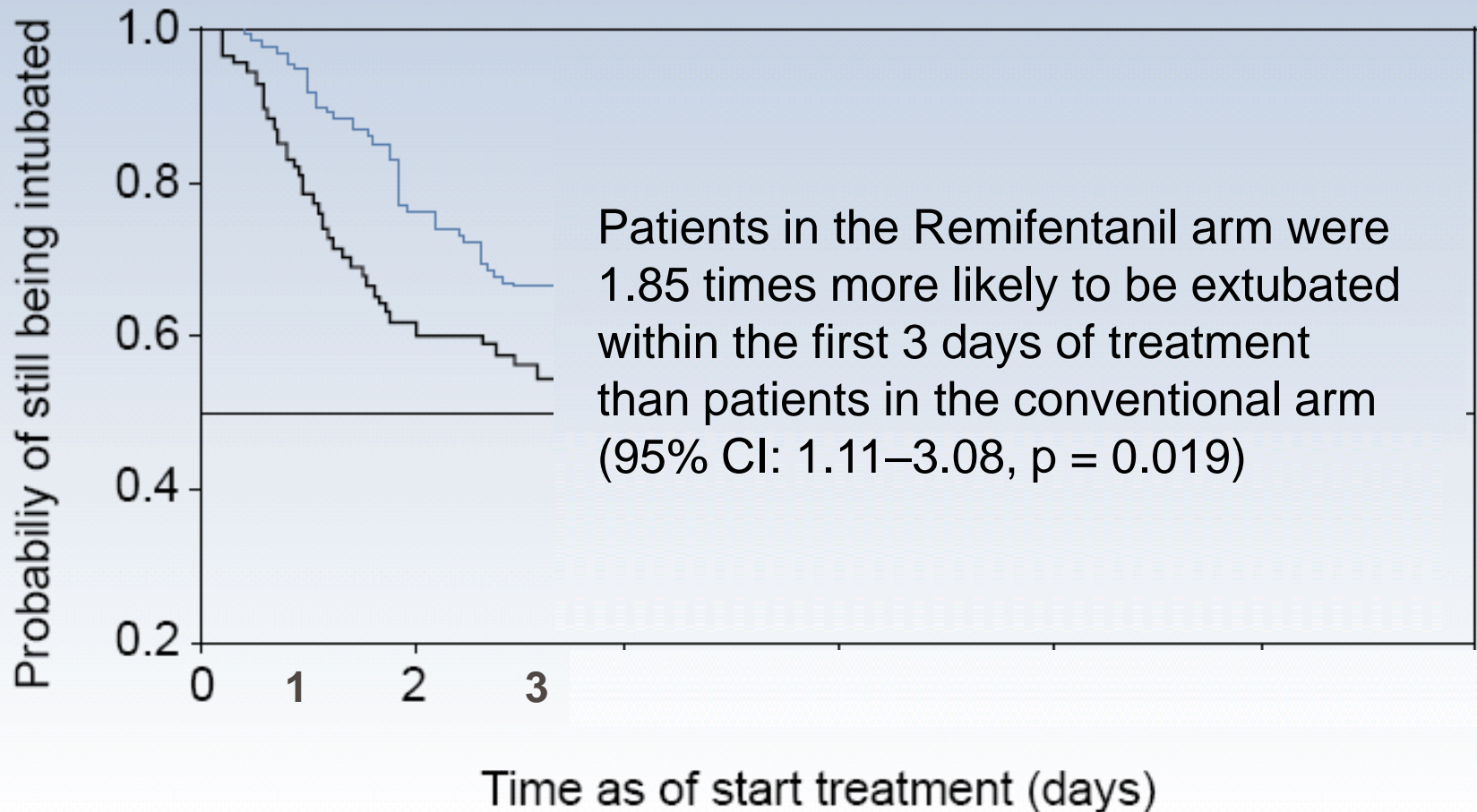
- **Primary Endpoint:** duration of mechanical ventilation

*Propofol/ Midazolam/ Lorazepam + Fentanyl/ Morphine
According to Dutch Society of Intensive Care guidelines

Kaplan—Meier plot of the duration of mechanical ventilation

KM-plot raw data

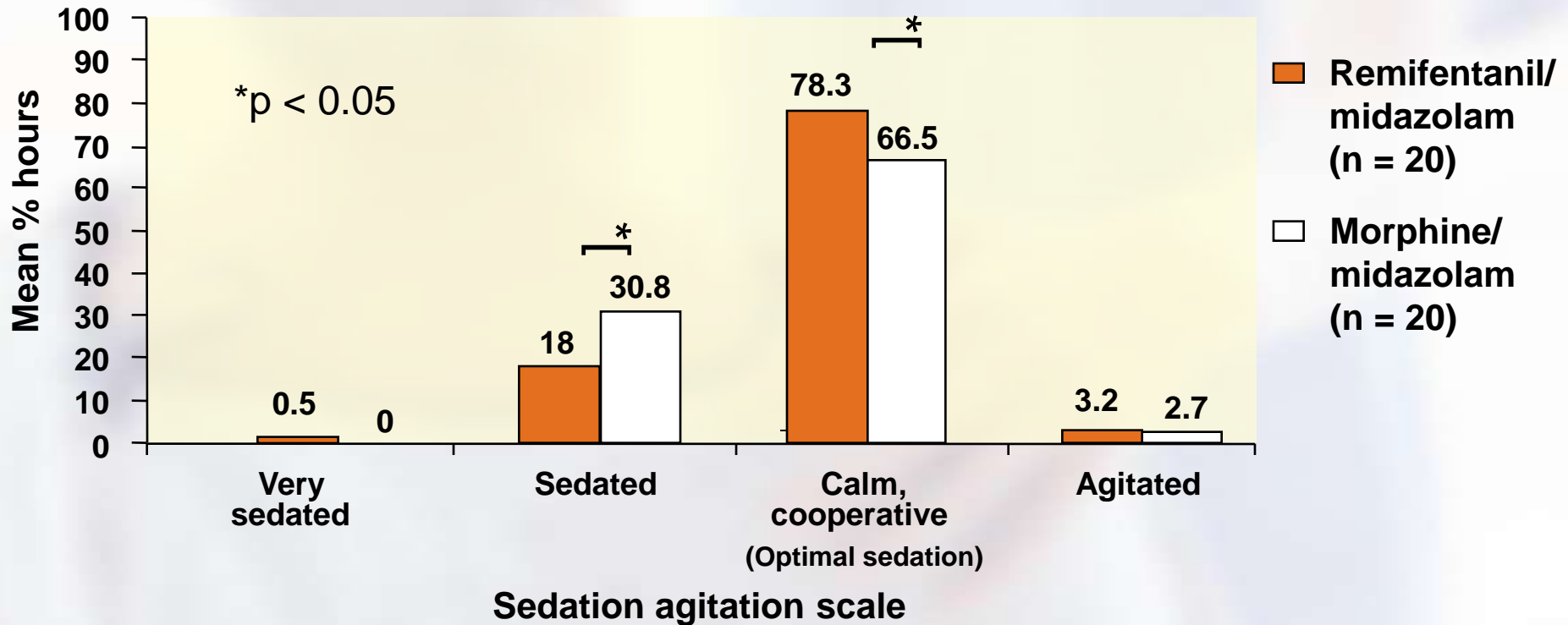
— Conventional regimen
— Remifentanil-based regimen



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, $p = 0.019$)

Optimal analgesia and sedation

- Analgesia and sedation with Remifentanyl provides significantly longer percentage hours of optimal sedation than with morphine



Remifentanil^{Ultiva}

**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 days¹
 - Have hepatic or renal impairment¹
 - Require dose titration (e.g. for neurological assessment or painful procedures)²⁻⁵

1. GlaxoSmithKline. Remifentanil HCl (Ultiva) SPC, June 2005.

2. Soltesz S *et al.* *Br J Anaesth* 2001; **86**: 763–8.

3. Dahaba AA *et al.* *Anesthesiol* 2004; **101**: 640–6.

4. Muellejans B *et al.* *Crit Care* 2004; **8**: R1–R11.

5. Engelhard K *et al.* *Acta Anaesthesiol Scand* 2004; **48**: 396–9.

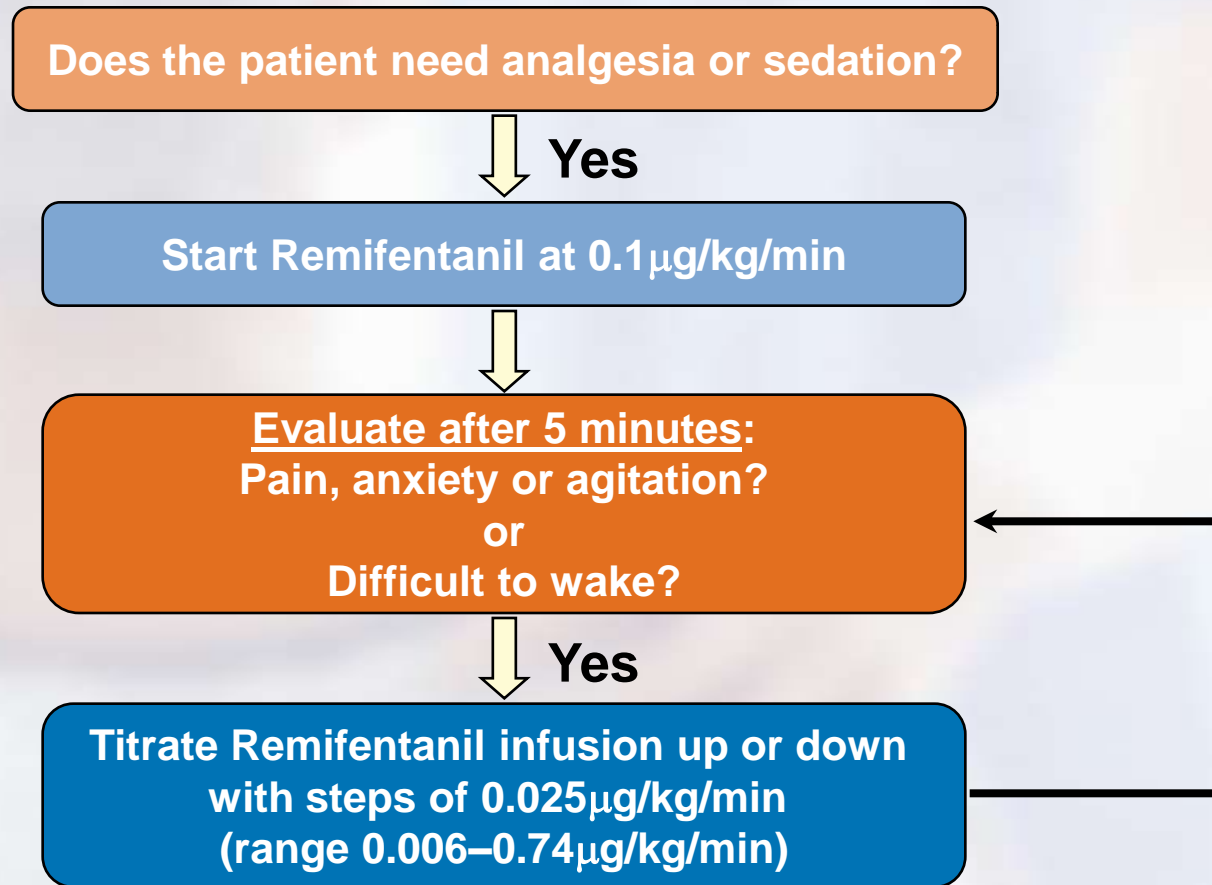
Therapeutic indication

*Remifentanil is indicated
for the provision of analgesia and sedation in
mechanically ventilated intensive care patients
18 years of age and over*

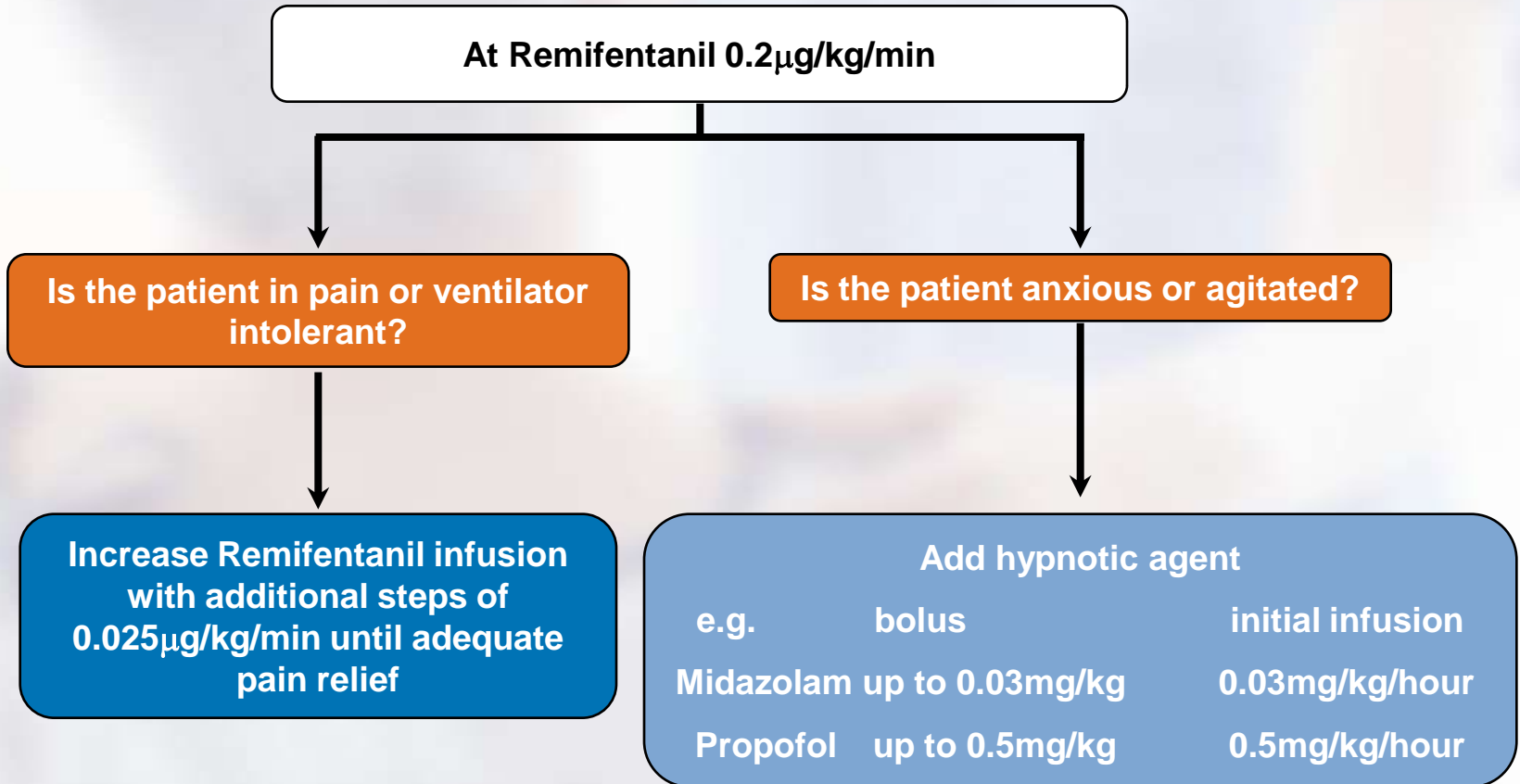
Remifentanil^{Ultiva}

How should Remifentanil be used in the ICU?

Dosing protocol for the ICU



Dosing protocol for the ICU

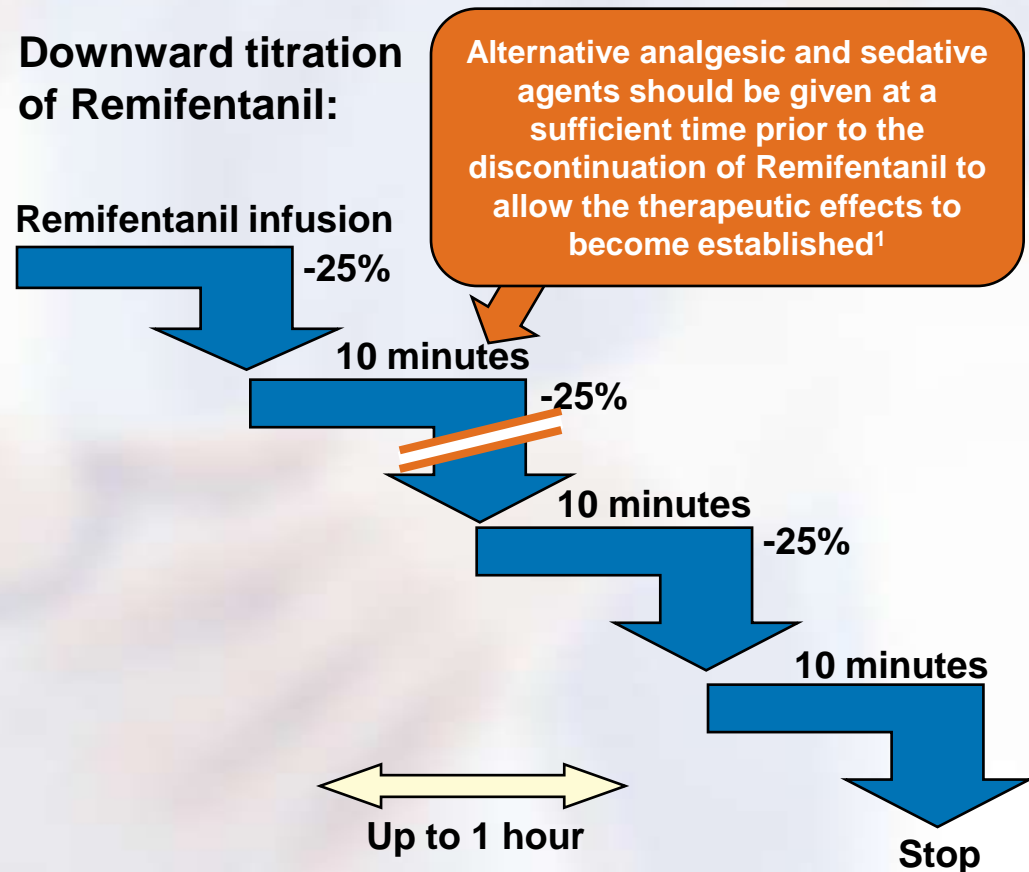


Remifentanil in special patient populations

- **Renally impaired patients:** no dose adjustments necessary for renally impaired patients, including those undergoing renal replacement therapy¹
- **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 population¹
- **Obese patients:** base Remifentanil dose on ideal body weight rather than actual body weight¹

Extubation and discontinuation of Remifentanil

- Titrate Remifentanil infusion in stages to $0.1\mu\text{g}/\text{kg}/\text{min}$ ($6\mu\text{g}/\text{kg}/\text{hr}$) 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



1. GlaxoSmithKline. Remifentanil HCl (Ultiva) SPC, June 2005.

What is Remi in Practice?

Resource pack

Factsheets, Case studies, CD-ROM on how to use remifentanyl

SIM Centres

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

Remi
in practice

Increasing knowledge, experience and confidence

A range of offerings on how to use remifentanyl, tailoring practical support to your individual needs

Online Web Forums

Interactive online presentation and discussion on topical remifentanyl 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

Remifentanil Ultiva

What are the cost implications of Remifentanil?

Potential for cost savings



Potential for cost savings

- **Compared to traditional opioids:**
 - Reduced need for hypnotic agents¹⁻²



1. Muellejans B *et al. Crit Care* 2004; **8**: R1–11.
2. Dahaba AA *et al. Anesthesiol* 2004; **101**: 640–6.

Potential for cost savings

- **Compared to traditional opioids:**
 - Reduced need for hypnotic agents¹⁻²
 - Reduced time spent on mechanical ventilation^{2,3}



1. Muellejans B *et al. Crit Care* 2004; **8**: R1–11.

2. Dahaba AA *et al. Anesthesiol* 2004; **101**: 640–6.

3. Matthey T *et al. Intens Care Med* 2004; 30(Suppl): S409 and poster.

Potential for cost savings

- **Compared to traditional opioids:**
 - Reduced need for hypnotic agents¹⁻²
 - Reduced time spent on mechanical ventilation^{2,3}
 - Reduced time to neurological assessment^{1,2,4}
 - Potentially reducing the necessity for expensive diagnostic investigations⁵



1. Muellejans B *et al. Crit Care* 2004; **8**: R1–11.

2. Dahaba AA *et al. Anesthesiol* 2004; **101**: 640–6.

3. Matthey T *et al. Intens Care Med* 2004; **30**(Suppl): S409 and poster.

4. Soltesz S *et al. Br J Anaesth* 2001; **86**: 763–8.

5. Wilhelm W *et al. Eur J Anaesth* 2004; **21**(Suppl): A-705.

Potential for cost savings

- **Compared to traditional opioids:**
 - Reduced need for hypnotic agents¹⁻²
 - Reduced time spent on mechanical ventilation^{2,3}
 - Reduced time to neurological assessment^{1,2,4}
 - Potentially reducing the necessity for expensive diagnostic investigations⁵
 - Reduced time spent in the ICU^{2,3,5}



1. Muellejans B *et al. Crit Care* 2004; **8**: R1–11.

2. Dahaba AA *et al. Anesthesiol* 2004; **101**: 640–6.

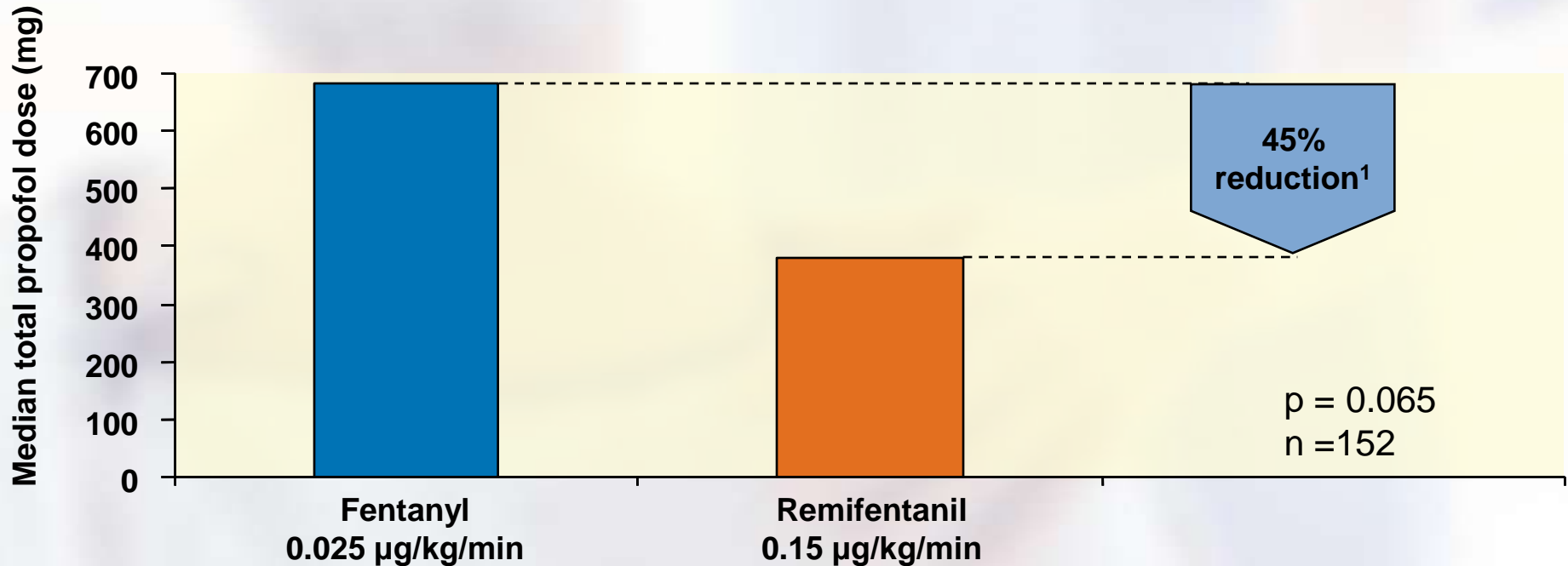
3. Matthey T *et al. Intens Care Med* 2004; **30**(Suppl): S409 and poster.

4. Soltesz S *et al. Br J Anaesth* 2001; **86**: 763–8.

5. Wilhelm W *et al. Eur J Anaesth* 2004; **21**(Suppl): A-705.

Reduced need for additional sedative agents

- Remifentanyl reduces the need for additional sedative agents,^{1,2} which are associated with delayed neurological assessment, prolonged weaning and increased duration of mechanical ventilation.²⁻⁵



1. Muellejans B *et al.* *Crit Care* 2004; **8**: R1–R11.

2. Dahaba AA *et al.* *Anesthesiol* 2004; **101**: 640–6.

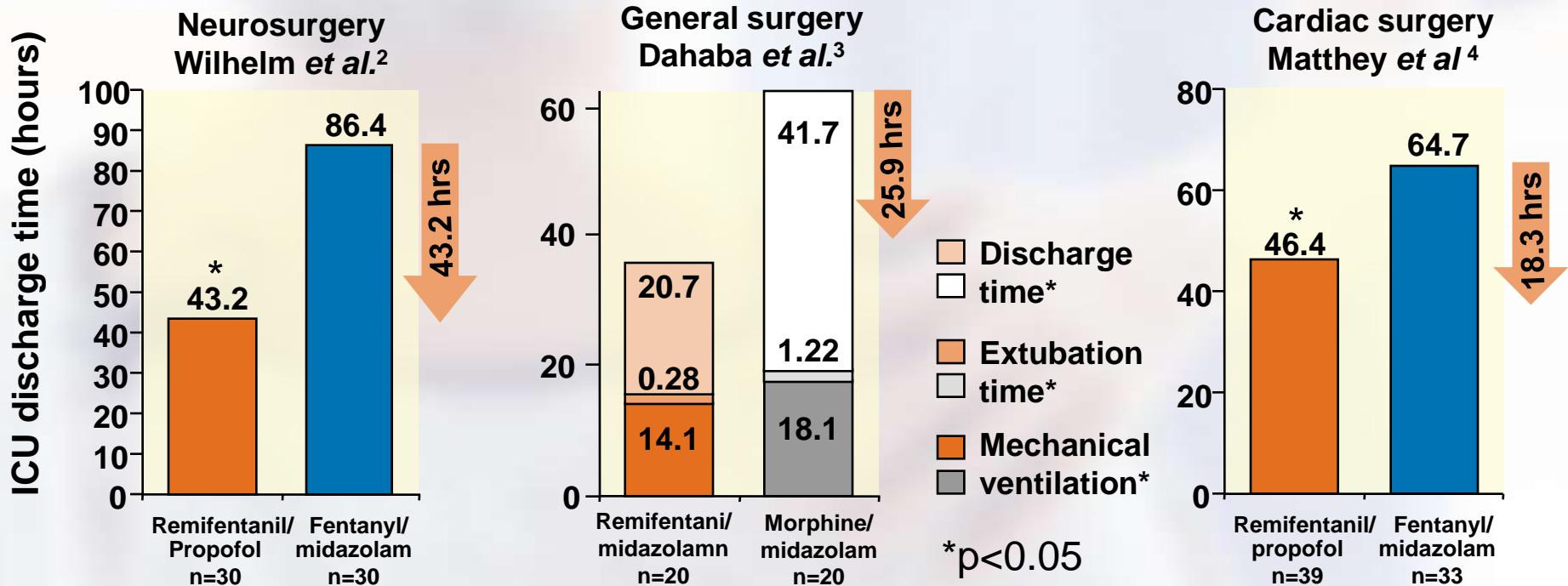
3. Park G. *Curr Anaesth Crit Care* 2003; **13**: 313–20.

4. Wilhelm W *et al.* *Eur J Anaesth* 2004; **21**(Suppl): A-705.

5. Matthey T *et al.* *Intens Care Med* 2004; **30**(Suppl): S409 and poster.

Reduced time spent in the ICU

- Due to its rapid offset of action, Remifentanyl facilitates the ability to plan and control the period of recovery, reducing the time spent in ICU¹
- This enables patients to be discharged from the ICU as soon as they are ready.



1. Royston D. *J Cardiothorac Vasc Anaesth* 1998; **12**: 11–9
 2. Wilhelm W *et al. Eur J Anaesth* 2004; **21**(Suppl): A-705.

3. Dahaba AA *et al. Anesthesiol* 2004; **101**: 640–6.
 4. Matthey T *et al. Intens Care Med* 2004; **30**(Suppl): S409 and poster.

Remifentanil accounts for a fraction of the total ICU costs

- The cost of an ICU stay is estimated at £1,328/day¹
- Interventions that result in even nominal decreases in length of time spent in the ICU have the opportunity to significantly reduce hospitalisation costs²
- 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}

1. Department of Health. Reference costs 2004. March 2005.
2. Shorr AF. *Curr Opin Crit Care* 2002; **8**: 337–43.

3. Wilhelm W *et al. Eur J Anaesth* 2004; **21**(Suppl): A-705.
4. Dahaba A *et al. Anesthesiology* 2004; **101**: 640–6.
5. Matthey T *et al. Intens Care Med* 2004; **30**(Suppl): S409 and poster.

Remifentanil^{Ultiva}

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 communicative¹
- **Remifentanil can be precisely titrated facilitating patient interaction and assessment²⁻⁴**
- **Remifentanil enables a shorter weaning time and a reduction in the time spent on mechanical ventilation compared with traditional opioid analgesics⁴⁻⁶**
- 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 savings⁴

1. Ramsay M. *Bailliere's Clinical Anaesthesiology* 2000; **14**: 419–32.

2. Soltész S *et al. Br J Anaesth* 2001; **86**: 763-8.

3. Muellejans B *et al. Crit Care* 2004; **8**: R1–R11.

4. Wilhelm W *et al. Eur J Anaesth* 2004; 21(Suppl): A-705.

5. Dahaba A *et al. Anesthesiology* 2004; **101**: 640–6.

6. Matthey T *et al. Intens Care Med* 2004; 30(Suppl): S409 and poster.

7. Park G. *Curr Anaesthesia & Crit Care* 2002; **13**: 313–20.

8. Royston D. *J Cardiothorac Vasc Anesth* 1998; **12**: 11–9.

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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.

Remi *in practice*

is now available online at
www.doctors.net/Remi

- 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**

Remi

in practice online





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Should Remifentanyl be used with total intravenous or volatile anaesthesia?

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[Volatile anaesthesia](#)

[view results](#)

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[Business Case \(553 PDF\)](#)

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[Doctors.net.uk will soon be hosting some new modules on anaesthesia](#) [↘](#)

[Personal Excellence Tracker \(PET\)](#) [↘](#)

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