How to use remifentanil in general anaesthesia

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How to use remifentanil in general anaesthesia

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Properties of remifentanil

- Unique, very short-acting opioid, rapidly cleared by blood and tissue esterases[1]
  - Rapid onset of action: $t^1/_2k_{e0}$ = 1.3 minutes[1]
  - Rapid offset of action: context-sensitive half-time = 3.65 minutes[1]

- Predictable offset of action, independent of duration of infusion[1]

- Pharmacokinetics are unaltered by obesity and renal or hepatic function[1,2]

- Precise intra-operative control and fast, clear-headed recovery[1]

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1. Egan TD. *Clin Pharmacokinet* 1995; **29**: 80–94.
2. GlaxoSmithKline. Remifentanil HCl (Ultiva) Summary of Product Characteristics, June 2005.

Intra-operative control

- Remifentanil is suitable for use in many different types of surgery[1–5]
- Remifentanil's fast onset and short duration of action enables rapid titration to effect[6]
- Remifentanil offers a unique approach to the management of surgical patients by providing:
  - More effective control of intra-operative responses than alfentanil or fentanyl[7,8]
  - More effective at maintaining haemodynamic stability than alfentanil or fentanyl[5,9]
  - Control in difficult-to-treat patients with renal or hepatic impairment, with no initial dose adjustment needed[10-12]

1. Sneyd J *et al. Br J Anaesth* 2005; **94**: 778–83.
2. Demirbilek *et al. J Clin Anesth* 2004; **16**: 358–63.
3. Howie MB *et al.* Anesth Analg 2001; **92**: 1084–93.
4. Fish W. *Anaesthesiology* 1999; **54**: 1002–6.
5. Mackey J. *et al. J Clin Anesth* 2000; **12**: 427–32.
6. Egan T. *Pharmacokinet* 1995; **29**: 80–94.
7. Schuttler J *et al. Anaesthesia* 1997; **52**: 307–317.
8. Sneyd J *et al. Eur J Anaesthesiol* 2001; **18**: 605–14.
9. Kallar SK *et al Anesthesiol* 1994; **81**: A32.
10. Dershwitz M *et al. Anesthesiology* 1996; **84**: 812–20.
11. Dershwitz M *et al. J Clin Anesthesia* 1996; **8**: 88S–90S
12. GlaxoSmithKline. Remifentanil HCl (Ultiva) SPC, June 2005.

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Recovery

- Remifentanil provides fast, clear-headed recovery[1–3]
- Recovery with remifentanil is more rapid than with fentanyl or alfentanil[2,3]
- Remifentanil facilitates rapid extubation and reduces the need for ICU admission[1–5]
- Remifentanil enables early post-operative neurological assessment[1–3]
- Post-operative pain can be effectively managed[6]

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1. Wilhelm W *et al. Br J Anaesth* 2001; **86**: 44–9.
2. Kovac A *et al. J Clin Anesth* 1997; **9**: 532–41.
3. Bekker A *et al. Anesth Analg* 2000; **91**: 117–22.
4. Park G *et al. Eur J Anaes* 2000; **17**: 111–19.
5. Eberhart L *et al. Eur J Anaesthesiol* 2004; **21**: 107–14.
6. Minkowitz H. *Can J Anesth* 2000; **47**: 522–28.

See factsheet: Reconstitution Guidelines

Reconstitution

- Available as lyophilised powder for reconstitution in 1mg, 2mg and 5mg vials
- To reconstitute add recommended diluent to powder in vial and shake well
- After reconstitution, further dilute to recommended dilution
- 50µg/ml is the recommended dilution for adults

Target concentration	Remifentanil vial size	Total volume of recommended diluent required	Volume of diluent required for reconstitution	Volume of diluent required for dilution
50µg/ml	1mg	20ml	3ml	17ml
	2mg	40ml	5ml	35ml
	5mg	100ml	10ml	90ml

- 20–25µg/ml is recommended for paediatric patients aged 1 year and over

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GlaxoSmithKline. Remifentanil HCl (Ultiva) Summary of Product Characteristics, June 2005.

See factsheet: Dosing Protocol for General Anaesthesia

Dosing protocol for general anaesthesia – induction

- Remifentanil is indicated as an analgesic agent for use during induction and/or maintenance of general anaesthesia under close supervision[1]
- Induction of anaesthesia in adults:*
  - Remifentanil: continuous infusion 0.5–1µg/kg/min[1]
  - Mackey *et al* used an infusion rate of 0.5µg/kg/min for 2 minutes prior to intubation[2]
  - Warner *et al* used an infusion rate of 0.5–1µg/kg/min for 1 minute prior to intubation[3]
  - Isoflurane: starting dose 0.5 MAC[1]
  - Propofol: starting dose 100µg/kg/min[1]

Details of infusion rates required for target dosages according to patient weight are supplied in the corresponding factsheet

*When given by bolus injection at induction remifentanil should be administered over not less than 30 seconds[1]

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1. GlaxoSmithKline. Remifentanil HCl (Ultiva) Summary of Product Characteristics, June 2005.
2. Mackey J. *et al. J Clin Anesth* 2000; **12**: 427–32.
3. Warner DS. *Anesth Analg* 1999; **89**: S33–39.

See factsheet: Dosing Protocol for General Anaesthesia

Dosing protocol for general anaesthesia – maintenance

Maintenance of anaesthesia in adult ventilated patients:

- The administration of remifentanil should be individualised based on the patient's response
  - During anaesthesia, the rate of administration can be titrated:
    - upward in 25–100% increments every 2–5 minutes
    - downward in 25–50% decrements every 2–5 minutes
  - When used with isoflurane: starting rate 0.25µg/kg/min (range 0.05–2µg/kg/min)*
  - When used with propofol: starting rate 0.25µg/kg/min (range 0.05–2µg/kg/min)*

*For cardiac patients refer to the Summary of Product Characteristics

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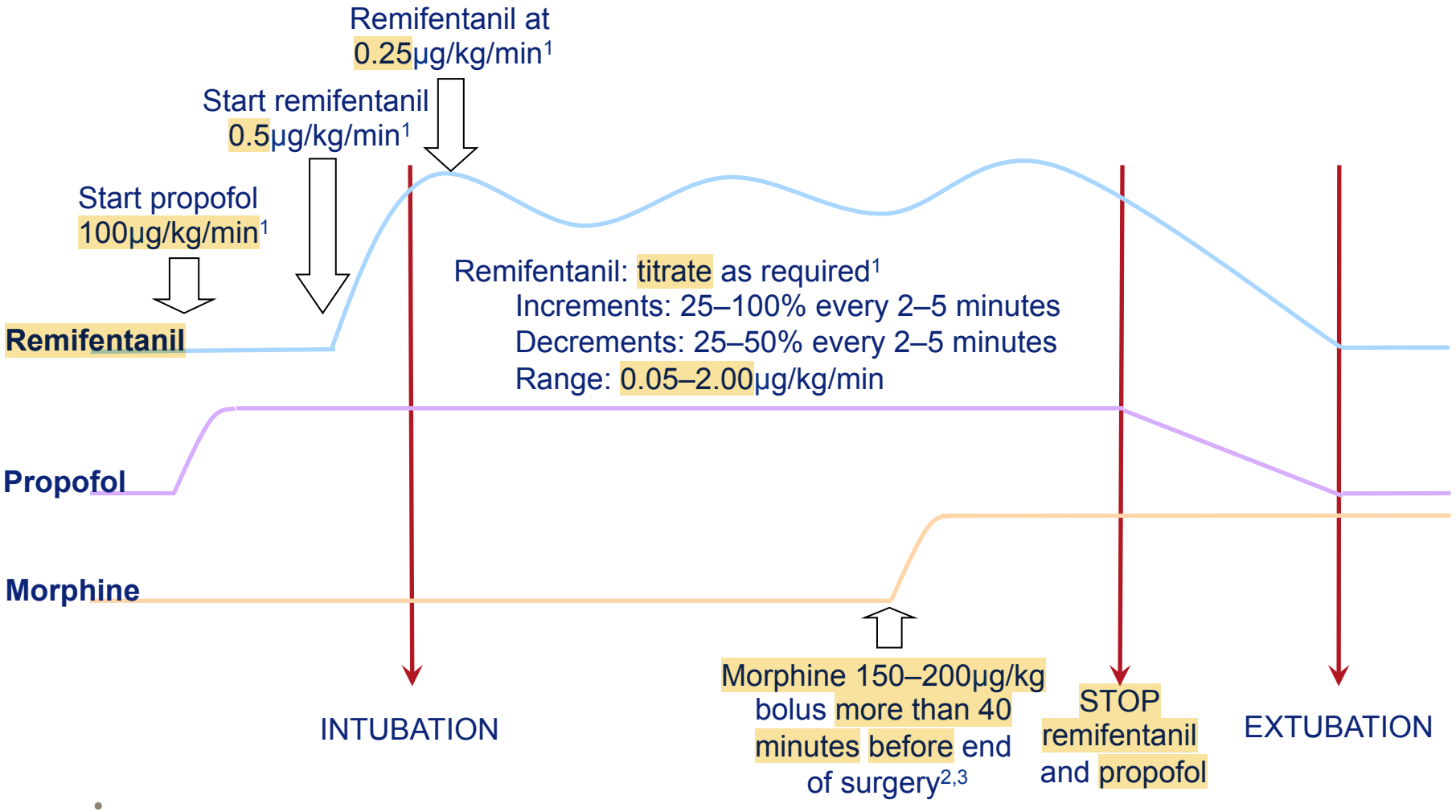
GlaxoSmithKline. Remifentanil HCl (Ultiva) Summary of Product Characteristics, June 2005.

See factsheet: Dosing Protocol for General Anaesthesia

Dosing protocol for general anaesthesia – summary

SCHEMATIC REPRESENTATION ONLY



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1. GlaxoSmithKline. Remifentanil HCl (Ultiva) Summary of Product Characteristics, June 2005.
2. Muñoz HR *et al. Br J Anaesth* 2002; **88**: 814–18.
3. Minkowitz H. *Can J Anesth* 2000; **47**: 522–28.

See factsheet: Hypnotic Sparing Effects in General Anaesthesia

Hypnotic sparing effects in general anaesthesia

- Remifentanil significantly reduces the amount of hypnotic agent required to maintain anaesthesia[1]
- The doses of the following agents used in anaesthesia have been reduced by up to 75% when used concurrently with remifentanil:
  - Isoflurane[1]
  - Thiopentone[1]
  - Propofol[1]
  - Temazepam[1]
  - Sevoflurane[2]

Starting doses of hypnotics are detailed on the corresponding factsheet

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1. GlaxoSmithKline. Remifentanil HCl (Ultiva) Summary of Product Characteristics, June 2005.
2. Breslin DS *et al. Anaesthesia* 2001; **56**: 114–19.

See factsheet: Hypnotic Sparing Effects in General Anaesthesia

Hypnotic sparing effects in general anaesthesia

Combining remifentanil with		
Isoflurane[1]	**Sevoflurane[2]**	**Propofol[3]**
0.05 µg/kg/min remifentanil is associated with a 50% reduction in isoflurane MAC	Use of remifentantanil (0.34µg/kg/min) with low concentrations of sevoflurane (0.5 MAC) facilitates early recovery	Increasing remifentanil concentrations produces a dose-dependent reduction in propofol requirements

- It is appropriate to maintain a low concentration of hypnotic agent and titrate remifentanil to produce adequate anaesthesia[1-3]

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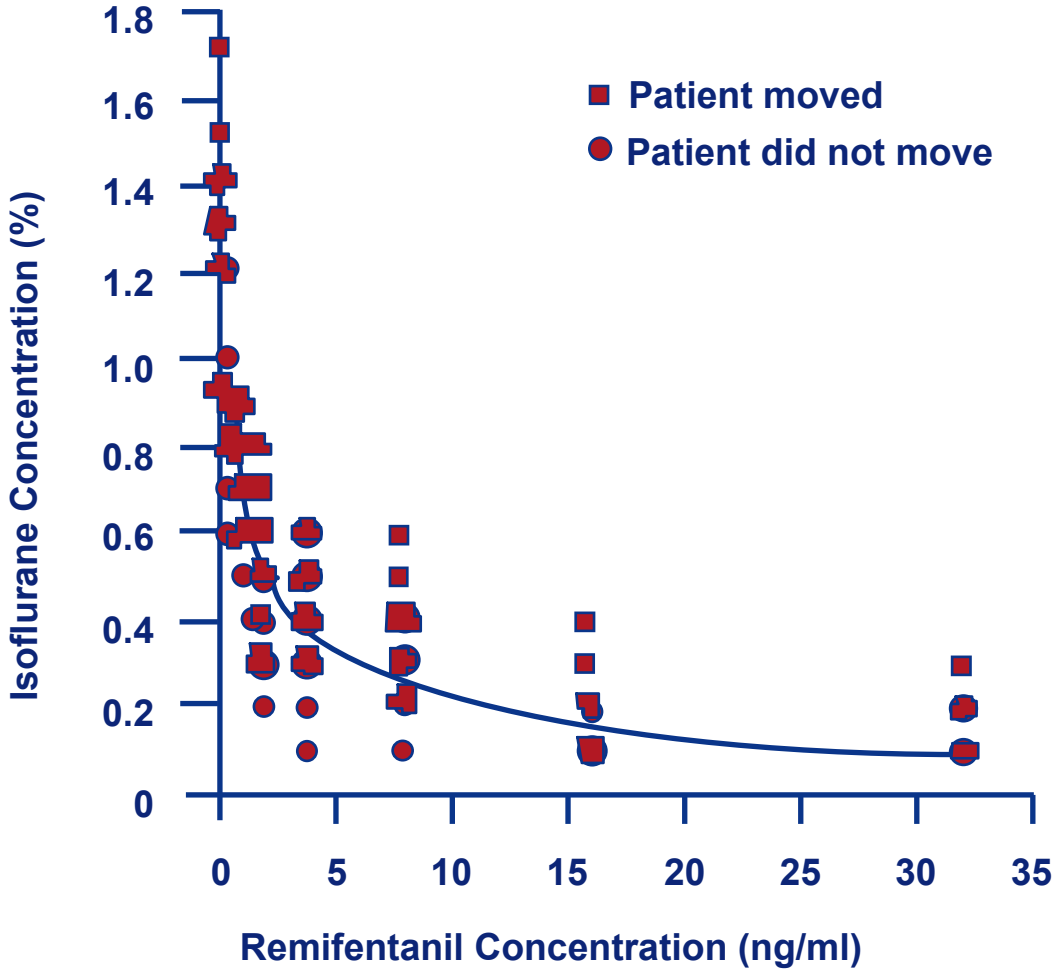
1. Lang E *et al. Anesthesiology* 1996; **85**: 721–28.
2. Breslin DS *et al. Anaesthesia* 2001; **56**: 114–19.
3. Milne S *et al. Br J Anaesth* 2003; **90**: 623–29.

See factsheet: Hypnotic Sparing Effects in General Anaesthesia

MAC Reduction of Isoflurane with Remifentanil

- Figure showing the reduction in isoflurane concentration to prevent movement at skin incision in 50% of patients by increasing measured remifentanil concentrations.
- The solid line is a logistic regression line for a patient aged 40 years.



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Adapted from Lang E *et al.*, Anesthesiol 1996; 85: 721–28.

See factsheet: Post-operative Pain Management

Post-operative pain management

- Due to the very rapid offset of action of remifentanil, no residual opioid activity will be present within 5–10 minutes after discontinuation, regardless of duration of infusion
- Post-operative analgesia, including choice of agent, dose and time of administration must be planned well in advance of remifentanil discontinuation
  - Analgesics should be administered prior to discontinuation of remifentanil
  - Sufficient time must be allowed to reach the maximum effect of the longer-acting analgesic
  - The choice of analgesic should be appropriate for the patient's surgical procedure and the level of post-operative care

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GlaxoSmithKline. Remifentanil HCl (Ultiva) Summary of Product Characteristics, June 2005.

See factsheet: Post-operative Pain Management

Post-operative pain management

- The dosage and timing of administration of the alternative long-acting analgesic agent should be considered to allow therapeutic effects to become established[1]
- Minkowitz *et al.* achieved adequate post-operative pain management with a 150 or 200µg/kg bolus of morphine sulphate administered 30 minutes before the end of surgery[2]
- Muñoz *et al.* used 150µg/kg morphine and showed a reduction in the number of patients requiring morphine in the post-anaesthesia care unit, when morphine had been given more than 40 minutes before the end of surgery[3]

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1. Lane M *et al. Care Crit Ill* 2002: **18**: 144-45.
2. Minkowitz H. *Can J Anesth* 2000; **47**: 522–28.
3. Muñoz HR *et al. Br J Anaesth* 2002; **88**: 814–18.

Special precautions for use

- Due to the very rapid offset of action of remifentanil, post-operative analgesia must be planned well in advance of remifentanil discontinuation
- Care should be taken to avoid inadvertent administration of remifentanil remaining in IV lines and cannulae
- Muscle rigidity induced by remifentanil must be treated in the context of the patient's clinical condition with appropriate supporting measures including ventilatory support.
- Remifentanil should only be used in areas where facilities for monitoring and dealing with respiratory depression are available
- Hypotension and bradycardia may be managed by reducing the rate of infusion of remifentanil or the dose of concurrent anaesthetics or by using IV fluids, vasopressor or anticholinergic agents as appropriate

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GlaxoSmithKline. Remifentanil HCl (Ultiva) Summary of Product Characteristics, June 2005.

Summary

- Rapid and easy titration to effect - titrate remifentanil rather than hypnotic
- Substantial hypnotic sparing effects
- The rapid offset of action of remifentanil is independent of dose and duration
- The pharmacokinetic profile of remifentanil offers precise intra-operative control of anaesthesia and fast, clear headed recovery
- Post-operative pain is easily managed if planned in advance

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References

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Prescribing information

PRESCRIBING INFORMATION: Ultiva (remifentanil hydrochloride). The following is for guidance only. **Refer to Summary of Product Characteristics (SmPC) before prescribing.** Ultiva is a very short acting opioid for injection/infusion. **Indications**: General Anaesthesia. Analgesia/sedation in ICU. **Dosage**: tailor to individual. Anaesthesia: *Adults*: Dilute to e.g. 50mcg/ml (2mg in 40 ml). Induction (not sole agent): 1mcg/kg bolus administered over not less than 30 seconds then 0.5 –1 mcg/kg/min. Reduce to 0.25mcg/kg/min (using e.g. propofol or isoflurane). Maintenance: 0.05 – 2 mcg/kg/min with 0.5 – 1mcg/kg bolus or alter infusion rate as needed. Due to rapid metabolism, no residual opioid activity will be present 5 - 10 minutes after discontinuation. Where post-operative pain anticipated, analgesics should be administered prior to discontinuation of Ultiva. *Spontaneous ventilation:* Respiratory depression likely; ventilatory support may be required. Avoid inadvertent administration of Ultiva remaining in IV lines and cannulae. *Elderly (over 65 years):* initiate half adult dose. *Children*: see SmPC. *Cardiac surgery*: See SmPC. Intensive Care: *Adults:* 0.1 to 0.15mcg/kg/min. Increase by 0.025mcg/kg/min. If inadequate sedation at 0.2mcg/kg/hr add sedative. *Elderly (over 65 years):* No initial dose reduction required. *Children:* not recommended. *Renal/hepatic impairment*: No dosage adjustment necessary. Severe hepatic impairment may be slightly more sensitive to respiratory depressant effects. **Contraindications**: Epidural and intrathecal use. Known hypersensitivity to any ingredient or other fentanyl analogues. Not for use as sole induction agent. **Warnings and Precautions**: Administer only in appropriate setting. **Interactions**: As with other opioids, remifentanil decreases the requirements for inhaled and IV anaesthetics and benzodiazepines. **Pregnancy and lactation**: No adequate and well-controlled studies. Use only if potential benefit justifies potential risk to the foetus. Caution in nursing mothers. Insufficient evidence to recommend use during labour or Caesarean section. May cause respiratory depression in neonate. **Undesirable effects**: Acute respiratory depression, bradycardia, hypotension and/or skeletal muscle rigidity all resolve within minutes of discontinuation or decrease in the administration rate. Post-operative shivering, apnoea, hypertension, hypoxia, pruritus, constipation, aches, sedation, nausea and vomiting have also been reported. Very rarely, allergic reactions and bradycardia leading to asystole. As with other opioids remifentanil may produce dependency. **Basic NHS Costs**: Available as 1mg, 2mg and 5mg vials containing white/off-white powder for reconstitution to provide 1mg/ml remifentanil hydrochloride. 1mg vial x 5, £25.58, 2mg vial x 5, £51.15, 5mg vial x 5, £127.88. **Legal category**: CD POM. **Product Licence numbers**: Ultiva 1mg PL19494/0026, Ultiva 2mg PL19494/0027, Ultiva 5mg PL19494/0028. **Marketing Authorisation holder**: GlaxoSmithKline UK Ltd, 980 Great West Road, Brentford, Middlesex TW8 9GS. Prescribing Information updated: February 2005.

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