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Remifentanil Update
Clinical Science and Utility

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Contents

Abstract

The anilidopiperidine opioid remifentanil has pharmacodynamic properties similar to all opioids; however, its pharmacokinetic characteristics are unique. Favourable pharmacokinetic properties, minimally altered by extremes of age or renal or hepatic dysfunction, enable easy titration and rapid dissipation of clinical effect of this agent, even after prolonged infusion.

Remifentanil is metabolised by esterases that are widespread throughout the plasma, red blood cells, and interstitial tissues, whereas other anilidopiperidine opioids (e.g. fentanyl, alfentanil and sufentanil) depend upon hepatic biotrans-

formation and renal excretion for elimination. Consequently, remifentanil is cleared considerably more rapidly than other anilidopiperidine opioids. In addition, its pK_a (the pH at which the drug is 50% ionised **((Author: is this definition OK instead?))**) is less than physiological pH; thus, remifentanil circulates primarily in the non-ionised moiety, which quickly penetrates the lipid blood-brain barrier and rapidly equilibrates across the plasma/effect site interface. By virtue of these distinctive pharmacokinetic properties, the context-sensitive half-time (i.e. the time required for the drug's plasma concentration to decrease by 50% after cessation of an infusion) of remifentanil remains consistently short (3.2 minutes), even following an infusion of long duration (≥8 hours).

Remifentanil, a clinically versatile opioid, is useful for intravenous analgesia and sedation in spontaneously breathing patients undergoing painful procedures. Profound analgesia may be achieved with minimal effect upon cognitive function. Remifentanil may also provide sedation and analgesia during placement of regional anaesthetic blocks, and in conjunction with topical anaesthesia and airway nerve blocks, it may be useful for blunting reflex responses and facilitating 'awake' fibreoptic intubation.

Compared with fentanyl and alfentanil in a day-surgery setting, remifentanil supplementation of general anaesthesia may improve intraoperative haemodynamic control. Both emergence time and the incidence of respiratory depression during post-anaesthetic recovery may be reduced. However, outcomes such as home discharge time, post-emergence adverse effect profile, and patient and provider satisfaction were not significantly improved, and the incidence of intraoperative hypotension and bradycardia was greater. In addition, drug acquisition costs for remifentanil were higher and clinicians may need extra time to familiarise themselves with the drug's unique pharmacokinetics.

Ironically, the quick dissipation of opioid analgesic effect following remifentanil discontinuation may be a significant clinical disadvantage. Unless little or no postoperative pain is anticipated, the clinician may wish to treat prospectively using local or regional anaesthesia, non-opioid analgesics, or longer-acting opioid analgesics.

Remifentanil is an opioid of the 4-anilidopiperidine class, with a chemical structure similar to that of fentanyl, alfentanil and sufentanil. It is pharmacodynamically similar to all selective mu opioid agonists, but possesses unique pharmacokinetic properties.

Remifentanil has a methyl ester at the N-acyl moiety. This site is cleaved by widespread nonspecific esterases, present ubiquitously in tissues and plasma; the parent drug is metabolised to its carboxylic acid metabolite, remifentanil acid. Remifentanil acid, which is approximately 800- to 2000-fold less potent than the parent drug, has an elimination half-time of 90–120 minutes and is excreted unchanged in the urine.[1] The metabolism of remifentanil is not affected by congenital and acquired conditions that cause abnormal plasma pseudocholinesterase activity. Cholinesterase inhibitors such as neostigmine do not alter remifentanil metabolism, and concomitant administration of remifentanil does not alter the breakdown of other esterase-metabolised drugs, such as esmolol and succinylcholine.[1]

The steady-state volume of distribution (30L) for remifentanil is similar to that of alfentanil (28L).[1] In comparison, the volume of distribution for fentanyl is 280L, almost 10-fold that of remifentanil and

Table I. Comparison of the pharmacokinetics of remifentanil, alfentanil, fentanyl and sufentanil**((Author: please provide a reference))**

Variable	Remifentanil	Alfentanil	Fentanyl	Sufentanil
Vd steady-state (L/kg)	0.3–0.4	0.25–0.75	3.2–5.9	2.86
Vd steady-state (L)[a]	30	28	335	200
Vd central compartment (L/kg)	0.1-0.2	0.1–0.4	0.5–1.0	0.7
Clearance (mL/min/kg)	40-60	3–8	20	10–15
Clearance (L/min)	4	0.24	1.5	0.9
Terminal elimination half-time (min)	9	90	260	150
$t_{1/2}k_{e0}$ (min)	1.0–1.5	0.6–1.2	6.2	6.4
pk_a	7.26	6.5	8.4	8.0
% non-ionised at pH 7.4	58	89	9	20
% protein bound at physiological pH	89–92	92	80–85	92
Context-sensitive half-time after 3-hour infusion (min)	3	50–55	>100	25

a For a 70kg adult patient.

pK_a = pH at which the drug is 50% ionised **((Author: is this definition OK?))**; **$t_{1/2}k_{e0}$** = half-time for equilibration across the plasma/effect compartment interface; **Vd** = volume of distribution.

alfentanil. Furthermore, like alfentanil, the pK_a (the pH at which the drug is 50% ionised **((Author: is this definition OK?))**) of remifentanil is lower than physiological pH. For this reason, >50% of remifentanil (pK_a 7.26) and alfentanil (pK_a 6.5) molecules are present in their non-ionised form upon entering the circulation. Non-ionised drugs are 1000- to 10 000-fold more lipid soluble than ionised drugs. Consequently, alfentanil and remifentanil will quickly penetrate the lipid blood-brain barrier; equilibration across the plasma/effect site interface occurs rapidly.[1]

Since the metabolism of remifentanil is widespread, its clearance is rapid (3–4 L/min, or about 3–4 times hepatic blood flow). In contrast, the terminal elimination of alfentanil, fentanyl or sufentanil is dependent upon hepatic biotransformation and renal excretion. Despite their similar distribution volumes, clearance of alfentanil is 0.2–0.5 L/min, one-tenth that of remifentanil. As a consequence, the terminal elimination half-times of alfentanil and remifentanil are 90 minutes and 9 minutes, respectively.[1] For a comparison of the pharmacokinetic properties of remifentanil and other anilidopiperidine-class opioids, please refer to table I.

The context-sensitive half-time of a drug is a pharmacokinetic measure of the time required for the drug's plasma concentration to decrease by 50% after cessation of an infusion. This statement assumes that a steady-state plasma concentration has been established before the infusion is stopped. Context-sensitive half-time is determined by measurement of blood concentration versus time; the 'context' is the duration of the infusion.

The context-sensitive half-time of remifentanil remains consistently short (3.2 minutes), even following an infusion of long duration (≥8 hours).[2] This clinically important feature distinguishes remifentanil from other anilidopiperidine opioids, the context-sensitive half-times of which are highly dependent upon the duration of the infusion. For example, following a 3-hour infusion, the context-sensitive half-times of alfentanil and fentanyl are 47.3 minutes and 180 minutes, respectively.[3]

The short, consistent context-sensitive half-time of remifentanil is a result of its unique pharmacokinetic properties. By virtue of its relatively small volume of distribution and widespread metabolism by nonspecific esterases, accumulation of remifentanil in the periphery is limited, and its clearance is rapid. In contrast, the volume of distribution for fentanyl is 10-fold and its clearance about one-third that of remifentanil. Fentanyl accumulates to a greater extent in the peripheral compartment, increasingly so as the infusion duration increases, and upon infusion cessation, the periphery serves as a reservoir from which fentanyl re-enters the central compartment. Sufentanil also undergoes significant distribution

within the peripheral compartment and depends upon hepatic biotransformation for its elimination.[4] For a comparison of the context-sensitive half-times for alfentanil, sufentanil, fentanyl and remifentanil, please refer to figure 1.

The pharmacokinetic characteristics of remifentanil have been found to be largely independent of the degree of impairment of hepatic[6] and renal[7] function. Although the pharmacokinetic properties of remifentanil are similar in both healthy subjects and those with severe hepatic disease, the latter population may be more sensitive to the respiratory depressant effects of opioids.[1]

The pharmacokinetic profile of remifentanil is relatively unaltered by extremes of age (neonates and patients aged ≥65 years) and the presence of coexisting conditions, such as obesity. In elderly patients (aged ≥65 years), remifentanil clearance is reduced by approximately 25%. In addition, equilibration between the plasma and effect site is slower in the elderly population.[8]

In neonates, fentanyl, alfentanil and sufentanil exhibit an increased volume of distribution and decreased clearance. In effect, loading dosage requirements are higher, but elimination half-life is prolonged. However, in neonates, remifentanil exhibits an increase in both volume of distribution and clearance. Consequently, elimination half-life remains unchanged in this patient population.[9]

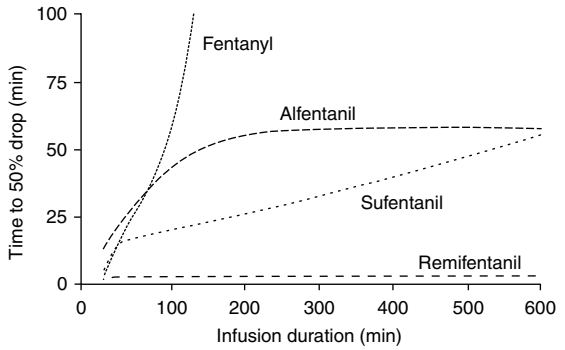

Fig. 1. Computer simulation of the context-sensitive half-times (i.e. the times required for a drug's plasma concentration to decrease by 50% after cessation of an infusion) for remifentanil, alfentanil, sufentanil and fentanyl (reproduced from Egan et al.,[5] with permission).

In morbidly obese patients, Egan et al.[10] found that a remifentanil dosage regimen based upon ideal body weight may be more clinically useful than one based upon actual body weight.

Remifentanil, like other anilidopiperidine-class opioids, readily crosses the placenta, but its pharmacokinetic profile is unaltered in the fetal circulation. Because the drug formulation presently contains glycine, the epidural or intrathecal administration of the drug is contraindicated for all patients.[1]

Although remifentanil has unique pharmacokinetic properties, its pharmacodynamic effects parallel those of other opioids. Remifentanil has dose-dependent analgesic, sedative and respiratory depressant effects, all of which are readily reversed by the mu receptor-specific opioid antagonist naloxone. The adverse-effect profile of remifentanil is similar to other opioids. Like many opioids, remifentanil has intense vagotonic and sympatholytic effects, as evidenced by its common adverse effects, bradycardia (heart rate <50 beats/min) and hypotension (systolic blood pressure <80mm Hg). Chest wall rigidity, especially after bolus administration, is common, as are the adverse effects of pruritus and nausea and vomiting.[1]

As mentioned previously, the time constant for equilibration across the plasma/effect site interface for remifentanil is short. Consequently, its onset of clinical effect is rapid (about 1.5 minutes). In contrast, the onset of clinical effect for fentanyl occurs after 3–5 minutes.[11]

Pharmacodynamic offset time is a measure of clinical effect versus time following cessation of an infusion that has established a steady-state plasma concentration of a given drug. Using respiratory depression as an endpoint, the pharmacodynamic offset time is the time required for patient recovery to baseline minute ventilation following cessation of drug infusion. Following a 3-hour infusion, the pharmacodynamic offset time of remifentanil is 5.4 minutes, whereas that of alfentanil is 54 minutes.[12] These pharmacodynamic properties are consistent with the context-sensitive half-times of these opioids.

In addition to the pharmacokinetic differences seen in the elderly population, elderly patients may be more sensitive to the opioid effects of remifentanil. The pharmacodynamic effects of opioids upon the cerebral cortex may be noted by the appearance of delta waves on the EEG. Opioid effects may be compared between groups by determination of the steady-state plasma opioid concentration at which delta waves are seen in 50% of subjects. Compared with younger patients, the effect site concentration at which delta waves are seen is reduced by 50% in the elderly, indicating that pharmacodynamic sensitivity to opioids is doubled in this population.[13] Furthermore, the onset of clinical effect is delayed, most likely due to slower equilibration between the plasma and effect site.[13] Consequently, it may be prudent to reduce remifentanil dosage for elderly patients by one-half and extend the anticipated time to clinical effect by 50–100%.

Because the clearance of remifentanil is unaltered in the placental and fetal circulations, its respiratory-depressant effects upon the fetus are short-lived, with little potential for recrudescence following delivery. For this reason, remifentanil may be a useful agent in the provision of patient-controlled analgesia (PCA) to women in labour.[14]

Minimal alveolar concentration (MAC) is the alveolar concentration of an inhalation anaesthetic required to prevent movement in response to noxious stimuli in 50% of subjects. Originally defined by Eger et al.,[15] it has become the standard measure of volatile anaesthetic potency. Inadequate analgesia during general anaesthesia is also detected by noting a response, whether autonomic (e.g. tachycardia and tearing) or somatic (e.g. movement). Therefore, MAC is, in effect, a measure of analgesia. Unlike the hypnotic effects of anaesthetic agents, which can be monitored by clinical sedation measures (e.g. Ramsay sedation score) and/or real-time processing of EEG signals (e.g. Bispectral Index), analgesic effects and MAC can be measured only by eliciting a response.

Opioids modulate the response to noxious stimuli, primarily at the level of the brain stem and spinal cord. Hence, all opioids, in a dose-dependent manner, reduce the dosage of hypnotics required to maintain anaesthesia. The degree to which the hypnotic anaesthetic dosage is reduced is known as the MAC-suppressing effect of an opioid, typically expressed as the percentage by which the baseline MAC (without the presence of opioid) is reduced.[16]

When defining drug effect and drug interactions, it is critical that each drug has reached a steady-state effect compartment concentration. After a bolus administration of an opioid, the plasma concentration is continuously changing because of drug distribution kinetics, and there is disequilibrium (hysteresis) between the plasma drug concentration and its effect. For this reason, investigators use computer-assisted continuous infusion devices to achieve a given steady-state plasma concentration. The user inputs the central compartment equilibration constant for the opioid administered and the weight and height of the patient.

The results from studies of the MAC-suppression properties of opioids are often reported as the opioid plasma concentration (ng/mL) required to reduce the MAC by a given percentage. To apply MAC-suppression data to clinical practice, it is necessary to know the infusion rate (μg/kg/min) and the infusion time necessary to establish a given opioid blood concentration. Remifentanil blood concentration has been found to be proportional to the dose administered throughout the recommended dose range. Data from Glass et al.[1] indicate that a remifentanil infusion rate of 0.1 μg/kg/min yields a blood concentration of 2.0–2.5 ng/mL, and that an incremental increase in the infusion rate of 0.1 μg/kg/min will raise the remifentanil blood concentration by an additional 2.0–2.5 ng/mL. A change in the infusion rate will be quickly translated at the effect site; once a change of infusion rate is made, 5 minutes are required to establish a new equilibrium at the effect site.

Lang et al.[17] found that a 50% reduction in isoflurane MAC may be achieved at a remifentanil whole blood concentration of 1.37 ng/mL. Using data from the previous paragraph, this blood concentration may be established by infusing remifentanil 0.05–0.07 μg/kg/min for 5 minutes. Remifentanil exerts a similar MAC-suppressant effect

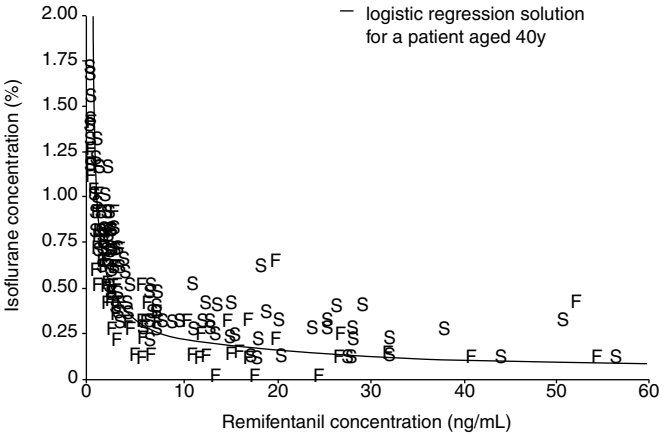

Fig. 2. The effect of increasing remifentanil whole-blood concentration on the isoflurane alveolar concentration necessary to prevent movement in response to skin incision in 50% of patients (reproduced from Lang et al.,[17] with permission). **F** represents a patient who moved; **S** represents a patient who did not move.

upon all volatile anaesthetic agents. For example, Song and White[18] found that a remifentanil infusion of 0.07 ± 0.03 μg/kg/min was associated with a 42% reduction in the desflurane anaesthetic requirement.

The MAC-suppression effect of opioids may be used to compare their potency. Katoh and Kazuyuki[19] found that sevoflurane MAC was reduced by 50% by a fentanyl plasma concentration of 1.8 ng/mL. McEwan et al.[20] found that isoflurane MAC was reduced by 50% by a fentanyl plasma concentration of 1.67 ng/mL. These data indicate that the relative potency of remifentanil is slightly greater than that of fentanyl. For reference, a fentanyl 1 ng/mL plasma concentration, which reduces sevoflurane MAC by 37% and isoflurane MAC by 40%, may be achieved within 15 minutes by administration of fentanyl 3 μg/kg followed by an infusion of 1 μg/kg/hour.

As with all opioids, an initial small increase in remifentanil plasma concentration produces a relatively large reduction in MAC. However, as the opioid plasma concentration increases, the MAC-reduction effect of remifentanil diminishes, and the curve describing the relation between opioid concentration and MAC displays a 'ceiling effect' (see figure 2). For example, an increase in the plasma concentration of remifentanil from 0 to 3 ng/mL decreases isoflurane MAC by about 66%, whereas doubling the plasma concentration from 3 ng/mL to 6 ng/mL produces only a further 11% reduction in MAC.[17] A remifentanil blood concentration as great as 32 ng/mL achieves only a 91% reduction in the MAC of isoflurane.[17] Data such as these support the concept that opioids may greatly diminish hypnotic dosage requirements, but opioids alone cannot produce a complete anaesthetic state without supplementation with a hypnotic agent (e.g. propofol, barbiturate, benzodiazepine, volatile anaesthetics or nitrous oxide).

Using loss of consciousness as an endpoint rather than movement in response to a surgical incision (MAC), Wilhelm et al.[21] found that the dosages of hypnotics required to induce loss of consciousness were reduced when remifentanil 0.5 μg/kg/min was administered concomitantly. Remifentanil 0.5 μg/kg/min reduced the induction dosages of propofol, thiopental and etomidate by 29%, 25% and 32%, respectively. Using a remifentanil infusion targeted to deliver a plasma concentration of 3 ng/mL (approximately 0.12–0.15 μg/kg/min), Conway et al.[22] found that the induction dosage of propofol was reduced by 29%; the dosage was reduced by 72% after midazolam 0.03 mg/kg was given 4 minutes prior to induction. The latter result demonstrates synergy between hypnotics (e.g. midazolam and

propofol); the former shows synergy between opioids and hypnotics. Similarly, remifentanil decreases the propofol concentration associated with the return of consciousness in a synergistic manner.[23]

The Bispectral Index, derived from processing the EEG signals obtained from superficial cortical cells, is a measure of the direct effect of hypnotics on cerebrocortical electrophysiology. The Bispectral Index has been shown to correlate with the sedative, amnesic and hypnotic effects of these agents.[24]

The Bispectral Index may be used to demonstrate the synergy between hypnotics and opioids. Conway et al.[22] titrated hypnotic dosage to loss of consciousness with or without remifentanil infusion, monitoring the Bispectral Index. The Bispectral Index at which 50% of patients lost consciousness was found to be higher when remifentanil was administered. Remifentanil amplified the cortical hypnotic effects of propofol, but these effects were not detected by the Bispectral Index. This may be explained by the fact that opioid effects are primarily subcortical.

Koitabashi et al.,[25] after establishing a Bispectral Index between 60 and 70 using a propofol infusion, identified a significant, dose-dependent decrease in Bispectral Index with increasing remifentanil dose. Again, this demonstrates enhancement of the cortical effects of hypnotics by opioids.

Opioids have also been shown to suppress increases in the Bispectral Index in response to noxious stimuli such as surgical incision and manipulation.[24] Although manifested by a different mechanism, the effect of opioids upon sedation and hypnosis is similar to that of central neuraxial sensory blockade by local anaesthetics. Like opioids, epidural anaesthesia has been shown to decrease the Bispectral Index-titrated dosage of hypnotics. For example, Hodgson and Liu[26] found that the sevoflurane dose required to maintain the Bispectral Index at 50 was significantly reduced (34%) by epidural anaesthesia with lidocaine; these effects could not be reproduced in a control group receiving intravenous lidocaine.

Short-term infusion of potent opioids, including remifentanil, may exacerbate postoperative pain or mechanical hyperalgesia after opioids are discontinued.[27] This effect, termed withdrawal hyperalgesia, may be relatively long lasting and associated with increased postoperative pain and analgesic requirement for hours after opioid cessation.[28,29] This finding is not consistently reported, as other investigators have found contradictory results.[30]

1. Clinical Utility

1.1 Sedation and Analgesia

1.1.1 Advantages and Disadvantages

Remifentanil may be used to provide sedation and analgesia (monitored anaesthesia care) for a wide variety of patients and procedures; it has several advantages over other hypnotics and opioids utilised for this purpose.

Firstly, remifentanil has little or no direct action on cerebral cortical cells and therefore exerts little effect upon cognitive function.[24] Compared with hypnotics such as propofol, remifentanil is less likely to cause startle and disorientation during a procedure.[24] The sedative effects of remifentanil arise indirectly by inhibition of ascending cortical activation from the reticular activating system.

Secondly, remifentanil infusion rate may be effectively titrated to respiratory rate (target range 8–12 breaths/min). Opioid-induced respiratory depression is observed at a lower plasma concentration than EEG changes. As a consequence, patients may be apnoeic, yet continue to respond to commands such as "take a deep breath." During remifentanil administration to a spontaneously breathing patient, preservation of responsiveness may be necessary to maintain normoxia.

Thirdly, remifentanil infusion has been shown to be useful for sedation and analgesia during painful procedures after which little or no pain is anticipated. Remifentanil infusion has been shown to be safe and effective during extracorporeal shock wave lithotripsy (ESWL),[31] minor gynaecological surgery,[32] and prostatic and bladder biopsies.[33]

Smith et al.[34] compared propofol (25–75 μg/kg/min) and remifentanil (0.05–0.15 μg/kg/min) infusion for sedation and analgesia during ambulatory surgery. Intraoperative rescue analgesia was necessary less often in the remifentanil group, although patients reported equivalent levels of intraoperative comfort. Remifentanil patients were less sedated, but experienced greater respiratory depression. According to the investigators, hypoxia secondary to hypoventilation was satisfactorily managed with supplemental oxygen. During the study, a 50-year-old patient transiently experienced a decline in SpO_2 (oxygen saturation as measured by pulse oximetry) to <80%, but correction was rapid following tactile stimulation, verbal instruction and a decrease in the opioid infusion rate.

Despite the aforementioned advantages, the use of remifentanil for sedation and analgesics has several drawbacks. Bowdle et al.[35] and Schüttler et al.[36] demonstrated the hazards of administering remifentanil bolus doses to spontaneously breathing patients. These investigators found that bolus doses given for analgesia during immediate postoperative recovery resulted in a significantly high incidence of muscle rigidity, respiratory depression and apnoea. It may be safest to avoid bolus administration of remifentanil when the patient is not directly under the observation of an anaesthesiologist or an appropriately trained provider, especially when the patient is breathing spontaneously or airway access is compromised. In addition, since a change in the infusion rate of remifentanil is rapidly translated at the effect site, the benefit of bolus administration is reduced. This fact further alters the cost-to-benefit ratio in favour of administration by infusion rather than bolus. Nonetheless, bolus administration of remifentanil has been shown to be safe and effective when an anaesthesiologist is in attendance, breathing is controlled or assisted, and the noxious stimulus occurs during a well circumscribed period of time (e.g. laryngoscopy and intubation).[37]

Compared with propofol infusion for sedation and analgesia, the disadvantages of remifentanil included mild pruritus (which was easily managed, according to the investigators), chest wall rigidity, and postoperative nausea and vomiting (PONV).[38]

1.1.2 Interactions with Benzodiazepines

Opioids do not provide adequate treatment for anxiety. Nonetheless, benzodiazepines such as midazolam have been shown to potentiate the adverse respiratory effects of fentanyl.[39] Avramov et al.[40] investigated this interaction by administering a bolus dose of midazolam 2, 4 or 8mg immediately preoperatively, then titrating the remifentanil infusion (commenced at 0.1 μg/kg/min), during breast biopsy surgery. As expected, remifentanil dose requirements decreased when the corresponding midazolam dose increased. In comparison with larger pre-induction midazolam doses, midazolam 2mg provided adequate anxiolysis and amnesia while minimising adverse effects.

1.1.3 Regional Block

Remifentanil has been shown to be useful for the initial placement of ophthalmic blocks (e.g. retrobulbar and peribulbar).[41] Remifentanil bolus (1 μg/kg) was compared with the same bolus dose followed by an infusion (0.2 μg/kg/min) and to alfentanil bolus 7 μg/kg. Patients receiving remifentanil patients experienced fewer instances of pain, as might have been predicted given that the analgesic potency of remifentanil is 20- to 30-fold that of alfentanil.[42] However, respiratory depression (respiratory rate [RR] <8 breaths/min) was experienced by 15–20% of patients following remifentanil administered as a bolus.

The efficacy and safety of remifentanil infusion have been compared with those of propofol infusion for sedation and analgesia during and after the placement of a regional block (axillary, ankle or spinal block).[43] Comparing the beneficial and adverse effects of various remifentanil dosages, these investigators found that optimal results were obtained at an infusion rate of 0.1 μg/kg/min. Remifentanil provided more effective analgesia without excessive sedation.

Holas et al.[44] compared continuous infusions of propofol or remifentanil or both for sedation and analgesia during cataract surgery under retrobulbar block. The greatest benefit with the least adverse

effects was found with a combination of the two drugs at reduced dosages (remifentanil 0.025 μg/kg/min and propofol 16.7 μg/kg/min).

1.1.4 Subarachnoid Block

In the presence of a successful subarachnoid block, remifentanil may exacerbate the vagotonic effects of a mid- or upper thoracic block level. In the authors' opinion, it may be prudent to avoid remifentanil infusion in this clinical setting. However, remifentanil may be useful, albeit in a reduced dosage (0.025 μg/kg/min), if the patient experiences a partial or 'patchy' block, early block regression, or musculoskeletal discomfort associated with prolonged recumbency.

1.1.5 'Awake' Fibreoptic Intubation

Remifentanil may be useful for the spontaneously breathing patient undergoing 'awake' fibreoptic intubation. Puchner et al.[45] reported on the use of remifentanil infusion to facilitate nasal fibreoptic intubation of a morbidly obese man with an odontogenic abscess and marked facial and cervical swelling. The authors chose to use remifentanil because it enabled them to relieve pain and suppress laryngeal reflexes, while maintaining responsiveness to commands and spontaneous breathing. According to the authors, opioids were less likely to produce a restless, over-sedated and uncooperative patient.

Machata et al.[46] investigated the optimal remifentanil dosage regimen required for awake nasotracheal fibreoptic intubation. The optimal dosage regimen would (i) provide patient comfort, sedation and amnesia; (ii) suppress airway reflexes; (iii) allow sufficient spontaneous ventilation and haemodynamic stability; and (iv) provide adequate intubating conditions. Optimal conditions were approximated by administering a remifentanil bolus 0.75 μg/kg (over 30 seconds) followed by a continuous infusion of 0.075 μg/kg/min. These authors recommended pretreatment with glycopyrrolate 0.2mg and midazolam 0.05 mg/kg.

1.1.6 'Awake' Craniotomy

Hans et al.[47] described the use of remifentanil infusion in combination with propofol infusion for sedation and analgesia in a 61-year-old man undergoing an 'awake' temporal-parietal craniotomy for tumour resection. Patient responsiveness was necessary to assess the patient's speech functionality during surgery. The unique ease of titration of remifentanil enabled effective analgesia during painful events (e.g. application of the head clamp) and sufficient responsiveness during speech mapping.

1.2 Supplementation of General Anaesthesia

1.2.1 Advantages

Remifentanil is used clinically as a supplement to general anaesthesia either combined with either volatile hypnotics such as sevoflurane, isoflurane or desflurane, or intravenous hypnotics such as propofol.

Remifentanil supplementation of general anaesthesia may be useful for several reasons. Firstly, its use may effectively attenuate autonomic, somatic and adrenocortical responses to noxious stimuli (e.g. laryngoscopy and intubation, surgical intervention). Secondly, the MAC-reducing effects of remifentanil may reduce the dose-dependent negative inotropic and/or vasodilatory effects of the hypnotic agent. Like all opioids, remifentanil has minimal effects on myocardial contractility even at high dosages. Thirdly, respiratory depression following discontinuation of remifentanil infusion is reliably brief, and recrudescence of opioid effects after return of adequate respiratory drive is unlikely. Respiratory adverse events in the acute recovery unit may be minimised compared with other opioids. Fourthly, the more rapid and improved cognitive recovery that follows remifentanil supplementation may be beneficial when early assessment of postoperative neurologic function is imperative.[24]

1.2.2 Disadvantages

Supplementation of general anaesthesia with remifentanil is not without drawbacks. Firstly, the dose-dependent vagotonic and sympatholytic effects of remifentanil may cause haemodynamic perturbation, especially when the patient is highly dependent upon sympathetic tone to maintain central perfusion

(e.g. hypovolaemic shock).[48] Secondly, intraoperative spontaneous ventilation may be difficult to achieve during anaesthetic maintenance. In a study using propofol supplemented with remifentanil for general anaesthesia for patients undergoing outpatient surgery, Murdoch et al.[49] recommended controlled ventilation because of the difficulties of maintaining both adequate anaesthesia and spontaneous ventilation. Thirdly, remifentanil, like any mu opioid agonist, is associated with PONV. Dershwitz et al.[50] found no difference in the incidence of PONV between patients receiving total intravenous anaesthesia (TIVA) with propofol supplemented by either remifentanil or alfentanil. Joshi et al.[51] found similar results comparing remifentanil and fentanyl after general anaesthesia supplemented with either sevoflurane or propofol.

In addition to these drawbacks, economic factors must be considered in relation to the clinical use of remifentanil. Although the superior pharmacokinetics of remifentanil may reduce, in comparison with other opioids, the costs of recovery personnel and adverse-effect management, its use entails higher overall costs.[52,53] Costs associated with remifentanil use include both the acquisition cost and the cost of equipment and supplies needed to administer the drug.

In addition, there may be a significant learning curve associated with the introduction of remifentanil and its unique pharmacokinetic qualities to anaesthesia clinical practice. Most notably, as clinicians acquired greater experience using this drug to supplement general anaesthesia in an outpatient surgery setting, the need for 'rescue analgesia' after emergence was reduced.[54] The investigators postulated that a better understanding of the evanescent nature of the analgesic effect of remifentanil may not only reduce the incidence of pain, but may also reduce the incidence of PONV. In this learning curve study, many of the clinician subjects received 5 hours of training prior to their clinical use of remifentanil. This suggests that the learning curve may have been even broader without prior instruction.

1.2.3 Blunt Responses to Laryngoscopy and Intubation

Remifentanil, administered by bolus, infusion or a combination thereof, has been shown to blunt the haemodynamic response to laryngoscopy and intubation effectively, with low incidence of bradycardia and hypotension. This has been demonstrated in both normal and treated hypertensive patients.

Using propofol for induction and rocuronium for muscle relaxation, Hall et al.[37] found that remifentanil 0.5 μg/kg followed by 0.25 μg/kg/min for 3 minutes most effectively blunted the cardiovascular response to laryngoscopy and intubation and had the least adverse effects of any of the dosages of remifentanil studied. These authors also found that the incidence of bradycardia was significantly reduced when glycopyrrolate 0.2mg was administered prior to induction. In treated hypertensive patients induced with propofol and relaxed with rocuronium, Maguire et al.[55] found similar results in patients receiving remifentanil (bolus 0.5 mg/kg followed by an infusion of 0.1 μg/kg/min) versus alfentanil 10 μg/kg bolus.

In a study of 40 elderly (aged >65 years) patients induced with propofol and relaxed with rocuronium, Habib et al.[56] compared remifentanil bolus (0.5 μg/kg over 30 seconds) followed by an infusion (0.1 μg/kg/min) with alfentanil bolus (10 μg/kg over 30 seconds). Both regimens effectively blunted the response to laryngoscopy and intubation. Although the incidence of hypotension was similar between groups, mild hypotension (systolic blood pressure <100mm Hg) occurred in 50% of study patients and marked hypotension (systolic blood pressure <80mm Hg) occurred in 3 of 40 patients (8%). These findings may highlight the greater sensitivity of elderly patients to the haemodynamic effects of opioids.

The combination of remifentanil and propofol for induction has been shown to provide adequate conditions for laryngoscopy and intubation without concomitant muscle relaxants. Alexander et al.[57] reported excellent intubating conditions in 95% of adult patients within 60 seconds following administration of remifentanil 4 μg/kg or 5 μg/kg and propofol 2 mg/kg. Klemola et al.[58] compared intubat-

ing conditions in 60 atropine-pretreated patients after administration of remifentanil 3 μg/kg, remifentanil 4 μg/kg or alfentanil 30 μg/kg over 30 seconds immediately followed by propofol 2.5 mg/kg. Remifentanil 4μg/kg blunted cardiovascular responses and provided satisfactory intubating conditions in 93% of patients. The decreases in blood pressure following study drug administration (systolic and diastolic blood pressure reductions of 20% and 25%, respectively) were deemed clinically acceptable. Without glycopyrrolate pretreatment, McNeil et al.[59] compared remifentanil 2 μg/kg or 4 μg/kg with succinylcholine 1 mg/kg immediately following induction with propofol 2 mg/kg in 60 healthy patients aged 18–65 years. Equally satisfactory intubating conditions were found within 30 seconds. However, the authors noted a significant, dose-related incidence of hypotension and bradycardia in the remifentanil group. Two patients receiving remifentanil experienced chest wall rigidity that was easily managed.

1.2.4 Outpatient Procedures

Breslin et al.[60] investigated the recovery profile following outpatient surgery under general anaesthesia using sevoflurane and nitrous oxide with or without remifentanil supplementation. Patients who received remifentanil supplementation had a faster immediate postoperative recovery, but had no reduction in the time to home discharge and a greater incidence of adverse effects (e.g. chest wall rigidity). In a multicentre investigation, patients receiving general anaesthesia supplemented by remifentanil infusion were found to have similar intraoperative and recovery profiles regardless of whether the hypnotic agent was propofol infusion or isoflurane.[61] In the ambulatory anaesthesia setting, similar results have been reported by other investigators.[62-65] As might be expected, patients receiving propofol as a supplement to remifentanil had a lower incidence of PONV.

1.2.5 Comparison with Fentanyl

Several investigators have compared the intraoperative responses, recovery profile, postoperative adverse effects and costs associated with general anaesthesia supplemented by remifentanil versus fentanyl. Montes et al.[66] found similar recovery profiles between patients who received TIVA with propofol and remifentanil and those who received treatment with a conventional technique using fentanyl 2 μg/kg pre-induction (plus 1 μg/kg as needed intraoperatively) with propofol for induction and sevoflurane for maintenance. During outpatient suspension laryngoscopy, Mackey et al.[67] compared remifentanil infusion 0.25 μg/kg/min with fentanyl boluses at doses (up to 250μg) for supplementation of general anaesthesia maintained with propofol. This procedure is generally undertaken for patients with a history of tobacco abuse and cardiovascular disease, and intraoperative surgical stimulation may be intense and episodic. Furthermore, patients typically experience little or no postoperative pain. Remifentanil provided excellent intraoperative haemodynamic control, as shown by the lower incidence of tachycardia and hypertension in the remifentanil group. Nonetheless, recovery profiles were similar between groups.

In a study comparing intraoperative responses, recovery profile, postoperative adverse effects, and patient and provider satisfaction, Beers et al.[52] found no differences between patients who received general anaesthesia (sevoflurane and nitrous oxide) supplemented with fentanyl 3 μg/kg (pre-induction bolus) versus remifentanil 0.5 μg/kg/min (reduced to 0.2 μg/kg/min after laryngoscopy and intubation) during outpatient gynaecological surgery. The perioperative drug costs were $US17.72 higher in the remifentanil group. In a multicentre study of 2438 patients, Joshi et al.[54] found a similar perioperative adverse-effect profile between patients who received fentanyl boluses versus remifentanil 0.25 μg/kg/min to supplement general anaesthesia maintained with propofol or isoflurane. Patients receiving remifentanil had a significantly higher incidence of intraoperative hypotension, and a slightly but not significantly higher incidence of bradycardia and chest wall muscular rigidity. The authors commented that the dosage of remifentanil (0.25 μg/kg/min) may have been too high, and recommended using lower doses with titration to effect.

1.2.6 Comparison with Alfentanil

Investigators have compared remifentanil with alfentanil as opioid supplements to general anaesthesia. Ozkose et al.[68] compared remifentanil 0.1 μg/kg/min and alfentanil 0.5 μg/kg/min as supplements to general anaesthesia maintained with propofol. Better control of hypertensive and tachycardic responses was achieved in the remifentanil patients. Because two remifentanil patients experienced intraoperative recall, the authors recommended Bispectral Index monitoring to titrate the propofol dosage. Remifentanil TIVA patients incurred a higher intraoperative drug cost and required earlier administration of postoperative analgesia. Nonetheless, remifentanil patients recovered more rapidly from opioid-induced respiratory depression. Unlike patients taking alfentanil, remifentanil patients had no occurrences of clinically significant respiratory depression or hypoxaemia (RR <10 breaths/min or SpO_2 <90%) during postanaesthesia recovery. Song et al.[18] reported similar findings. These findings demonstrate the potential safety advantage of intraoperative supplementation with remifentanil vis-à-vis other opioids, especially if the patient may be 'fast-tracked' (i.e. bypassing the post-analgesia care unit [PACU] and transported directly to second stage recovery). Importantly, the clinician must be certain that the intravenous tubing is thoroughly flushed to assure that all residual remifentanil is eliminated prior to transport to the PACU.

1.2.7 Comparison with Sufentanil

Casati et al.[69] compared recovery profile and respiratory complications between patients receiving sevoflurane general anaesthesia supplemented with remifentanil (0.15 μg/kg/min) and those receiving sufentanil (0.01 μg/kg/min) for upper abdominal surgery. Despite discontinuation of the sufentanil infusion 30 minutes prior to procedure completion, remifentanil patients were extubated earlier following surgery and experienced fewer respiratory complications.

1.3 Clinical Use in Special Situations

1.3.1 Electroconvulsive Therapy

Remifentanil supplementation of general anaesthesia has been useful as a means to reduce barbiturate induction dosage and prolong seizure duration following electroconvulsive therapy. Andersen et al.[70] found the combination of low-dose methohexital (0.5 mg/kg) and remifentanil 1.0 μg/kg resulted in a longer seizure duration following electroconvulsive therapy compared with methohexital alone at a dose of 0.75 mg/kg.

1.3.2 Carotid Endarterectomy

Remifentanil has been shown to be useful for procedures requiring intraoperative haemodynamic stability and prompt neurological examination after emergence from general anaesthesia (e.g. carotid endarterectomy). Since the incidence of coronary artery disease in patients undergoing carotid endarterectomy is high, intraoperative or postoperative haemodynamic disturbances, particularly tachycardia, may be associated with a higher risk for myocardial ischaemia. Furthermore, prompt postoperative neurological assessment may detect focal or global neurological deficits indicative of cerebral ischaemia that is potentially reversible with immediate reoperation (e.g. carotid artery dissection, acute thrombosis or haemorrhage).

In a comparison of remifentanil and sufentanil for supplementation of general anaesthesia during carotid endarterectomy, Mouren et al.[71] found that each opioid provided equivalent intraoperative haemodynamic stability without an increased risk for intraoperative hypotension or postoperative hypertension or tachycardia. Remifentanil was more effective than sufentanil at suppressing responses to episodes of intense intraoperative stimulation (e.g. laryngoscopy and intubation). Remifentanil provided the additional benefit of facilitating rapid awakening and earlier neurological examination. Similar results were reported by Doyle et al.[72] and Wilhelm et al.,[73] who compared remifentanil with fentanyl for supplementation of general anaesthesia for carotid endarterectomy. In a case report, Gerhardt and Grichnik[74] described the use of remi-

fentanil infusion to supplement general anaesthesia for a combined carotid endarterectomy and coronary artery bypass grafting (CABG) procedure. Use of remifentanil allowed early postoperative neurological evaluation of the patient and excellent haemodynamic control typical of a high-dose opioid anaesthetic technique.

When remifentanil was compared with propofol for sedation during carotid endarterectomy under cervical plexus block, the drawbacks were found to outweigh the advantages. Krenn et al.[75] found a higher incidence of bradycardia (heart rate 30–35 beats/min) and respiratory depression (<6 breaths/min) in patients receiving remifentanil 0.05 μg/kg/min versus propofol 16.7 μg/kg/min. Because of the difficulty accessing the airway and the elderly patient population that usually requires this procedure, these adverse effects may be more problematic than they would be if encountered in other clinical circumstances.

1.3.3 Craniotomy Under General Anaesthesia

Prompt neurological examination after emergence from general anaesthesia is also desirable following craniotomy. Because they have minimal effect upon the cerebrovascular response to changes in cerebral perfusion pressure,[76] opioids such as remifentanil are commonly utilised to supplement general anaesthesia for neurosurgical procedures.

1.3.4 Intraoperative Somatosensory and Motor-Evoked Potential Monitoring

The spinal pathway associated with motor-evoked potentials (MEPs) receives its blood supply from the anterior spinal artery; conversely, the spinal pathway associated with somatosensory-evoked potentials (SSEPs) receives its blood supply from the posterior spinal artery. As a consequence, spinal cord integrity during spinal surgery may be more completely assessed by monitoring SSEPs and MEPs simultaneously. Optimising conditions during MEP monitoring is particularly challenging because these potentials are extremely sensitive to interference by anaesthetic agents. MEPs are often unrecordable in the presence of halogenated volatile anaesthetics, even in low concentrations (e.g. 0.2–0.5% isoflurane). Opioids, however, have comparatively little effect upon SSEPs and MEPs, and are important components of anaesthetic techniques designed to optimise the conditions under which these potentials are monitored.[77] Propofol, in low dosages, also has relatively little effect upon MEPs. TIVA techniques combining propofol and opioid infusions have been shown to produce acceptable conditions for monitoring MEPs.[78]

When MEPs are monitored intraoperatively, general anaesthesia is maintained without the use of neuromuscular blocking agents. Somatic responses to surgical stimuli may be undesirable because of the delicate nature of the surgery and the fact that patients may be immobilised in a head clamp or similar device. In addition, spinal procedures during which SSEPs and MEPs are monitored are often of long duration (>3 hours). Given these clinical circumstances, the use of intraoperative remifentanil infusion may be especially advantageous because it enables the use of relatively high opioid dosages for long time periods without undue concern for delayed emergence. The use of the bispectral monitor enables the clinician to titrate the propofol infusion to the appropriate hypnotic depth and avoid delayed emergence and intraoperative awareness.

1.3.5 Epilepsy Surgery

During temporal lobe epilepsy surgery, localisation of the epileptogenic zone is critical in order to minimise resection of non-epileptogenic eloquent brain tissue. Wass et al.[79] found remifentanil a useful supplement to general anaesthesia for epilepsy surgery because it reduced isoflurane dosage, and like all opioids, induced epileptiform activity in a dose-related manner. Even after administration of the high dosages necessary to induce epileptiform activity, use of remifentanil facilitated a rapid, predictable emergence that is essential to the early postoperative neurological assessment of patients undergoing intracranial surgery.

1.3.6 Cardiac Procedures with Cardiopulmonary Bypass

Recent trends in cardiac anaesthesia have focused upon early weaning from ventilation and tracheal extubation within 4–6 hours of surgery. This strategy may reduce length of stay in the inten-

sive care unit (ICU) and reduce the morbidity associated with tracheal intubation and mechanical ventilation.[80] Remifentanil may be useful to maintain haemodynamic stability during periods of intense stimulation and to minimise opiate-induced respiratory depression during immediate postoperative recovery.

Nonetheless, two studies suggest that remifentanil is an unsuitable drug for bolus administration in patients with coronary artery disease, especially those receiving β-adrenoceptor antagonists, calcium channel antagonists, and/or ACE inhibitors. After induction of anaesthesia with propofol, Elliott et al.[48] found that a remifentanil bolus injection of 1 mcg/kg **((Author: mcg/kg or mg/kg?))**resulted in severe hypotension and markedly reduced systemic vascular resistance in three subjects, one of whom developed bradycardia and transient ST segment changes. Wang et al.[81] found that remifentanil, administered as a bolus of 0.5 mg/kg following sevoflurane inhalation induction, produced significantly greater bradycardia and reduction in mean systemic blood pressure than a technique using fentanyl, etomidate and isoflurane in patients scheduled for coronary artery surgery and receiving routine anti-anginal therapy (excluding ACE inhibitors). Severe perturbations included one patient who developed asystole for 24 seconds and two who showed ECG evidence of acute myocardial ischaemia during a hypotensive episode. Both authors attributed these adverse events to the central vagotonic and sympatholytic effects of remifentanil.

Remifentanil continuous infusion has been compared with low- (10–20 μg/kg) and medium- (20–30 μg/kg) dose fentanyl administration for supplementation of general anaesthesia for CABG. In 321 patients undergoing CABG, Mollhoff et al.[82] compared remifentanil (mean intraoperative infusion rate 1.25 μg/kg/min) with fentanyl (mean intraoperative dose 12 μg/kg) as a supplement to propofol administered at 50 μg/kg/min. Although intraoperative haemodynamic responses to surgical manipulation were better controlled in patients receiving remifentanil infusion, remifentanil patients needed a longer median time to meet postoperative eligibility criteria for extubation. According to the authors, the rapid offset of clinical effect for remifentanil made for a problematic transition to an alternate analgesic regimen. More patients in the remifentanil group experienced postoperative shivering and hypertension. However, the incidences of ischaemia and adverse cardiac outcomes were not different between groups, and the length of ICU stay was also similar. Myles et al.[83] compared low-dose fentanyl (12 μg/kg), moderate-dose fentanyl (24 μg/kg) and remifentanil infusion (0.83 μg/kg/min) as supplements to propofol infusion in 77 patients undergoing CABG. Interestingly, Bispectral Index monitoring was utilised to titrate the intraoperative hypnotic (propofol) dose. The intraoperative incidence of hypertension and rate of cortisol excretion were significantly reduced in the patients receiving remifentanil. However, the incidence of intraoperative hypotension and the need for vasopressor support were higher in the remifentanil group, and times to extubation and ICU discharge were similar between groups. In a multicentre study of 304 patients undergoing coronary bypass surgery, Cheng et al.[84] compared remifentanil 1 μg/kg/min and fentanyl administered by intermittent boluses (total intraoperative doses 10–15 μg/kg). Perioperative complications (stratified by age and preoperative risk score), times to extubation, ICU and home discharge, and resource utilisation (determined by nursing ratios) were all similar between groups.

In the study by Michelson et al.,[85] initiation of cardiopulmonary bypass (CPB) increased the steady-state volume of distribution of remifentanil by 86%. However, hypothermia during bypass decreased the clearance rate of remifentanil by approximately 6% for every degree that body temperature was reduced below 37ºC.[85] Therefore, the clinician may continue the infusion at normothermic rates until plasma concentration is restored following initiation of bypass, then reduce the rate as determined by the extent of hypothermia. For the hypothetical 70kg patient receiving remifentanil 1 μg/kg/min for 60 minutes prior to initiation of CPB with core temperature reduction to 27°C, the authors recommended that the remifentanil infusion rate may be

reduced by 60% to reflect the hypothermic conditions within 5–10 minutes after initiation of CPB. For milder hypothermia (e.g. cooling to 32ºC), remifentanil infusion should be maintained at the normothermic rate for 25 minutes to compensate for the increase in the volume of distribution prior to reducing the rate by 30% to reflect hypothermia.

1.3.7 Obstetric Analgesia

Remifentanil administered by a PCA device has been studied as an analgesic during labour and delivery.[14,86-88] Blair et al.[86] found that PCA remifentanil provided effective analgesia, with incidences of emesis and pruritus comparable to those of other perinatally-administered opioids. Fetal heart rates, Apgar scores, and fetal cord pH values were all satisfactory; no baby required naloxone to establish spontaneous respiration. Optimal analgesia was obtained with a demand PCA bolus dose of 0.25–0.5 μg/kg, a lockout time of 2 minutes, and no continuous infusion. When administered as a continuous infusion to labouring patients, neither neonatal respiratory depression nor a decrease in Apgar scores was reported following delivery.[14]

In contrast, Olufolabi et al.[88] found that remifentanil PCA for labour analgesia was both ineffective and associated with significant adverse effects, and suggested that remifentanil is unsuitable as a systemic analgesic for labour. In addition, all the investigators cited in this section emphasised caution and the importance of continuous respiratory rate and oxygen saturation monitoring of labouring patients receiving remifentanil PCA.[14,86-88]

Thurlow et al.[14] compared remifentanil PCA (demand dose 20μg, lockout interval 3 minutes, and no background infusion) with intramuscular meperidine 100mg for treatment of pain during labour. Remifentanil PCA was found to be an acceptable alternative when epidural analgesia was contraindicated. Reduced fetal heart rate variability may be anticipated during the period of remifentanil peak effect (1.5 minutes following a bolus); however, the rapid pharmacodynamic offset of remifentanil allows the clinician to distinguish between opioid-induced fetal heart rate variability and that resulting from adverse fetal circumstances.

1.3.8 Postoperative Pain Management

The rapid dissipation of opioid effects following remifentanil infusion creates challenges in postoperative pain control. Bowdle et al.[35] and Schütter et al.[36] recommended against providing analgesia after remifentanil-supplemented general anaesthesia by reducing the remifentanil dosage to 0.05–0.15 μg/kg/min and extending the infusion into the postoperative recovery phase. These investigators found a 29% incidence of adverse respiratory events (RR <12 breaths/min, SpO_2< 90%, and apnoea). The incidence of apnoea was 7%, with 9 of 11 apnoeic episodes occurring following administration of remifentanil by bolus. The noncontinuous presence of an anaesthesiologist, the need for additional infusion equipment, and the potential for life-threatening consequences due to dosage errors or equipment malfunction decrease the appeal of this postoperative analgesia strategy.

Postoperative pain control may be best undertaken by pre-emptive measures. An alternative strategy may be to administer (a) longer-acting analgesic(s) intraoperatively with the goal of achieving maximal analgesic effect shortly after emergence. In 80 patients undergoing major abdominal surgery, Albrecht et al.[89] compared pain control and recovery profile following fentanyl 150μg, morphine 15mg, piritramide 15mg, or buprenorphine 300μg given 20 minutes before emergence from general anaesthesia supplemented with remifentanil infusion. Each of the longer-acting opioid regimens provided effective and comparable postoperative analgesia without adversely affecting recovery parameters and facilitated the smooth transition to standard PCA analgesia prior to the PACU discharge. In a study of 553 patients undergoing elective major abdominal surgery under remifentanil-supplemented general anaesthesia, Kochs et al.[90] compared pain control and recovery profile between fentanyl 150μg and morphine 15mg given 25 minutes before the end of surgery. A second dose of either morphine 7mg or fentanyl 50μg was given if patients reported moderate-to-severe pain after emergence; 90–96% of patients requested the second analgesic dose within 20–30 minutes after emergence. Although analgesic efficacy and recov-

ery profiles were similar between patients who received either morphine or fentanyl, a significantly greater proportion of patients receiving morphine reported no pain or mild pain during the recovery period. Muñoz et al.[91] demonstrated a 50% reduction in the need for opioid analgesia in the PACU if morphine was given >40 minutes before emergence from anaesthesia.

1.3.9 Paediatric Anaesthesia and Analgesia

Safe and effective use of remifentanil in preterm infants has been reported.[92] In children aged 2–12 years, Muñoz et al.[93] found that the remifentanil dosage required to suppress haemodynamic and somatic responses to skin incision is 2-fold that required for adults (see figure 3). The authors indicated that their work does not examine whether pharmacokinetic or pharmacodynamic differences explain this disparity.

Remifentanil in paediatric patients has been shown to blunt the stress response to noxious surgical stimuli effectively. In 62 children undergoing general anaesthesia for ventriculoperitoneal shunt insertion, Chambers et al.[94] found that the stress response (as measured by plasma norepinephrine and changes in heart rate and blood pressure) was significantly less in patients who received intraoperative remifentanil supplementation. In children aged 1–12 years undergoing major abdominal, orthopaedic or urological surgery under general anaesthesia with nitrous oxide and isoflurane, Prys-Roberts et al.[95] found that remifentanil supplementation was as effective as epidural bupivacaine for suppression of the haemodynamic response to surgical stimuli.

As a supplement to general anaesthesia for paediatric patients, remifentanil has been used for procedures such as cardiac catheterisation[96] and bone marrow aspiration.[97] In spontaneously breathing paediatric patients, remifentanil 0.5 μg/kg/min in conjunction with intermittent propofol boluses (0.5–1.0 mg/kg) has been found to provide safe and effective sedation and analgesia during flexible bronchoscopy with topical local anaesthetics.[98]

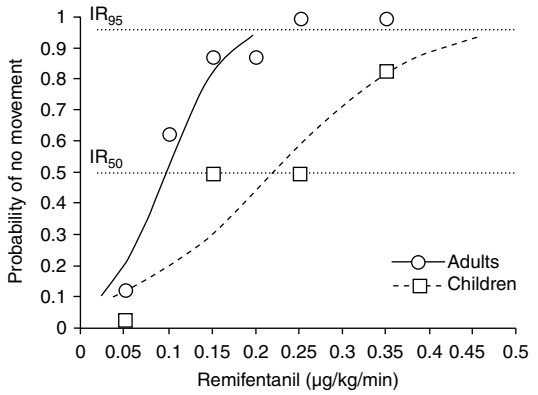

Fig. 3. The percentage of patients with no somatic response to skin incision compared with the infusion rate (IR) of remifentanil. The individual data points show the real percentage of nonresponders at each dose. The solid and dashed lines indicate the dose-response relationships predicted by logistic regression in both groups. The two dotted lines show the IR needed to prevent response in 50% and 95% of patients (reproduced from Muñoz et al.,[93] with permission).

2. Summary and Conclusion

In summary, remifentanil produces intense opioid effects that, by virtue of the drug's unique pharmacokinetic profile, are highly titratable and dissipate rapidly, enabling a predictable wake-up even after a prolonged infusion. Its favourable pharmacokinetic characteristics are minimally altered by extremes of age or renal or hepatic dysfunction.

Remifentanil is a clinically versatile opioid. Table II outlines its myriad clinical applications and their associated dosage recommendations and administration modes. Remifentanil is useful for spontaneously breathing patients undergoing painful procedures under intravenous analgesia and sedation. Profound analgesia may be provided with minimal effect upon the cognitive function. Remifentanil may be useful for sedation and analgesia during placement of regional anaesthetic blocks. In conjunction with topical anaesthesia and airway nerve blocks, it may also be useful to blunt reflex responses and facilitate 'awake' fibreoptic intubation. When combined with a hypnotic agent, remifentanil may be used to supplement general anaesthesia. Remifentanil may effectively attenuate autonomic and somatic responses to noxious anaesthetic procedures (e.g. laryngoscopy and intubation) and surgical stimuli for a circumscribed period of time. By reducing the hypnotic dosage during general anaes-

Table II. The recommended doses and modes of administration of remifentanil for various clinical applications

Clinical application	Remifentanil infusion (μg/kg/min)	Remifentanil bolus (μg/kg)	Comments
Sedation and analgesia	0.05–0.15	NR	If clinically appropriate, consider pre-procedure anxiolysis with midazolam 2mg IV
Sedation and analgesia for regional blockade	0.1	NR	Alternatively, remifentanil 0.025 μg/kg/min + propofol 16.7 μg/kg/min
Sedation and analgesia for subarachnoid block	NR	NR	Remifentanil 0.025 μg/kg/min for analgesia for 'breakthrough' pain
Sedation and analgesia for fibreoptic intubation	0.075	0.75 (over 30 seconds)	Pre-procedure treatment with glycopyrrolate 0.2mg IV + midazolam up to 2mg IV
Supplementation of inhalation or IV general anaesthesia	0.1–0.25	≤1	Glycopyrrolate 0.2mg prior to induction
Blunting response to laryngoscopy and intubation with muscle relaxation	0.1–0.25	0.5	Glycopyrrolate 0.2mg prior to induction
Blunting response to laryngoscopy and intubation without muscle relaxant	None	4	Glycopyrrolate 0.2mg prior to induction
Analgesia for labour and delivery via patient-controlled analgesia	NR	0.25–0.5	Continuous monitoring of pulse oximetry and respiratory rate recommended
Cardiac procedures with cardiopulmonary bypass	0.83–1.0	NR	Glycopyrrolate 0.2mg prior to induction
Postoperative analgesia	NR	NR	Use of remifentanil is not recommended in this setting
Elderly patients	See comments	See comments	Reduce dosages by one-half and double anticipated time to peak effect
Paediatric patients (2–12 years old)	See comments	See comments	May require as much as twice the dosage required for patients of other ages

IV = intravenous; **NR** = not recommended.

thesia, the undesirable effects of these agents (e.g. dose-dependent negative inotropy, vasodilatation, and impairment of MEP and SSEP monitoring) may be minimised. More rapid and improved cognitive recovery may facilitate early assessment of postoperative neurologic function.

When remifentanil is used to supplement general anaesthesia in the ambulatory surgery setting, advantages include improved intraoperative haemodynamic control, reduced emergence time, and fewer incidences of respiratory depression during postanaesthetic recovery. However, remifentanil provided no benefit with regard to home discharge time, incidence of adverse effects, or patient and provider satisfaction. Intraoperative drug costs were higher and clinicians required time to become familiar with the unique pharmacokinetics of the drug before its clinical utility was optimised.

Ironically, the quick dissipation of opioid analgesic effect following remifentanil discontinuation may be a significant clinical disadvantage. Unless little or no postoperative pain is anticipated, the clinician may wish to treat prospectively using local or regional anaesthesia, non-opioid analgesics, or longer-acting opioid analgesics.

The clinical advantages of remifentanil may be maximised and its disadvantages reduced by acquiring a firm understanding of the properties of this agent.

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References

1. Glass PSA, Gan TJ, Howell S. A review of the pharmacokinetics and pharmacodynamics of remifentanil. Anesth Analg 1999; 89 (4 Suppl.): S7-14
2. Kapila A, Glass PSA, Jacobs JR, et al. Measured context-sensitive half-times of remifentanil and alfentanil. Anesthesiology 1995; 83: 968-75
3. Michelsen LG, Hug CC. The pharmacokinetics of remifentanil. J Clin Anesthesia 1996; 8: 679-82

4. Bailey JM. Context-sensitive half-times: what they are and how valuable are they to anesthesiologists? Clin Pharmacokinet 2002; 41: 793-9
5. Egan TD, Lemmens HJ, Fiset P, et al. The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anesthesiology 1993; 79: 881-92
6. Dershwitz M, Hoke JF, Rosow CE, et al. Pharmacokinetics and pharmacodynamics of remifentanil in volunteer subjects with severe liver disease. Anesthesiology 1996; 84: 812-20
7. Hoke JF, Shulgman D, Dershwitz M, et al. Pharmacokinetics and pharmacodynamics of remifentanil in persons with renal failure compared with healthy volunteers. Anesthesiology 1997; 87: 533-41
8. Minto CF, Schnider TW, Egan TD. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I: model development. Anesthesiology 1997; 86: 10-23
9. Ross AK, Davis PJ, Dear Gd GL, et al. Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery of diagnostic procedures. Anesth Analg 2001; 93: 1393-401
10. Egan TD, Huizinga B, Gupta SK, et al. Remifentanil pharmacokinetics in obese versus lean patients. Anesthesiology 1998; 89: 562-73
11. Bovill JG. Targeting the effect site. In: Vuyk J, Engbers F, Groen-Mulder S, editors. On the study and practice of intravenous anaesthesia. Dordrect: Kluwer, 2000: 17-26
12. Kapila A, Glass PSA, Jacobs JR, et al. Measured context-sensitive half-times of remifentanil and alfentanil. Anesthesiology 1995; 83: 968-75
13. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II: model application. Anesthesiology 1997; 86: 24-33
14. Thurlow JA, Laxton CH, Dick A, et al. Remifentanil by patient-controlled analgesia compared with intramuscular meperidine for pain relief in labour. Br J Anaesth 2002; 88: 374-8
15. Eger EI, Saidman LJ, Brandstater B, et al. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. Anesthesiology 1965; 26: 756-63
16. Selbel PS, Glass PSA, Fletcher JE, et al. Reduction of the MAC of desflurane with fentanyl. Anesthesiology 1992; 76: 52-9
17. Lang E, Kapila A, Shlugman D, et al. Reduction of isoflurane minimal alveolar concentration by remifentanil. Anesthesiology 1996; 85: 721-8
18. Song D, White PF. Remifentanil as an adjuvant during desflurane anesthesia facilitates early recovery after ambulatory surgery. J Clin Anesth 1999; 11: 364-7
19. Katoh T, Kazuyuki I. The effects of fentanyl on sevoflurane requirements for loss of consciousness and skin incision. Anesthesiology 1998; 88: 18-24
20. McEwan AI, Smith C, Dyar O, et al. Isoflurane minimum alveolar concentration reduction by fentanyl. Anesthesiology 1993; 78: 864-9
21. Wilhelm W, Biedler A, Huppert A, et al. Comparison of the effects of remifentanil or fentanyl on anaesthetic induction characteristics of propofol, thiopental or etomidate. Eur J Anaesthesiol 2002; 19: 350-6
22. Conway DH, Hasan SK, Simpson ME. Target-controlled propofol requirements at induction of anaesthesia: effect of remifentanil and midazolam. Eur J Anaesthesiol 2002; 19: 580-4
23. Mertens MJ, Olofsen E, Engbers FHM, et al. Propofol reduces perioperative remifentanil requirements in a synergistic manner. Anesthesiology 2003; 99: 347-59
24. Johansen JW, Sebel PS. Development and clinical application of EEG bispectrum monitoring. Anesthesiology 2000; 92: 1336-44
25. Koitabashi T, Johansen JW, Sebel PS. Remifentanil dose/electroencephalogram bispectral response during combined propofol/regional anesthesia. Anesth Analg 2002; 94: 1530-3
26. Hodgson PS, Liu SS. Epidural lidocaine decreases sevoflurane requirement for adequate depth of anesthesia as measured by the bispectral index monitor. Anesthesiology 2001; 94: 799-803
27. Petersen KL, Jones B, Segredo V, et al. Effect of remifentanil on pain and secondary hyperalgesia associated with the heat-capsaicin sensitization model in healthy volunteers. Anesthesiology 2001; 94: 15-20
28. Guignard B, Bossard AE, Coste C, et al. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology 2000; 93: 409-17
29. Hood DD, Curry R, Eisenach JC. Intravenous remifentanil produces withdrawal hyperalgesia in volunteers with capsaicin-induced hyperalgesia. Anesth Analg 2003; 97: 810-5
30. Cortínez LI, Brandes V, Muñoz HR, et al. No clinical evidence of acute tolerance after remifentanil-based anaesthesia. Br J Anaesth 2001; 87: 866-9
31. Beloeil H, Corsia G, Coriat P, et al. Remifentanil compared with sufentanil during extracorporeal shock wave lithotripsy with spontaneous ventilation: a double-blind, randomized study. Br J Anaesth 2002; 89: 567-70
32. Tablov V, Tablov B, Partenov P. Analgesia with remifentanil or remifentanil / midazolam for minor gynecologic surgery: efficacy and patient comfort [abstract]. Eur J Anaesthesiol 2001; 18: 14
33. Drogheti L, Zopellari R, Morghen I, et al. Remifentanil in pump versus alfentanil in bolus in outpatient anaesthesia [abstract]. Eur J Anaesthesiol 2001; 18: 14
34. Smith I, Avramov MN, White PF. A comparison of propofol and remifentanil during monitored anesthesia care. J Clin Anesth 1997; 9: 148-54
35. Bowdle TA, Camporesi EM, Maysick L, et al. A multi-center evaluation of remifentanil for early postoperative analgesia. Anesth Analg 1996; 83: 1292-7
36. Schüttler J, Albrecht S, Breivik H, et al. A comparison of remifentanil and alfentanil in patients undergoing major abdominal surgery. Anaesthesia 1997; 52: 307-17
37. Hall AP, Thompson JP, Leslie NAP, et al. Comparison of different doses of remifentanil on the cardiovascular response to laryngoscopy and tracheal intubation. Br J Anaesth 2000; 84: 100-2
38. Servin FS, Raeder JC, Merle JC, et al. Remifentanil sedation compared with propofol during regional anaesthesia. Acta Anaesthesiol Scand 2002; 46: 309-15
39. Bailey PI, Pace NL, Ashburn MA, et al. Frequent hypoxemia and apnea after sedation with midazolam and fentanyl. Anesthesiology 1990; 73: 826-30
40. Avramov MN, Smith I, White PF. Interactions between midazolam and remifentanil during monitored anesthesia care. Anesthesiology 1996; 85: 1283-9
41. Ahmad S, Leavell M, Fragen RJ, et al. Use of remifentanil for analgesia during placement of ophthalmologic nerve blocks [abstract]. Anesth Analg 1996; 82: S3

42. Egan TD, Minto CF, Hermann DJ. Remifentanil versus alfentanil: comparative pharmacokinetics and pharmacodynamics in healthy adult male volunteers. Anesthesiology 1996; 84: 821-33
43. Mingus ML, Monk TG, Gold MI, et al. Remifentanil versus propofol as adjuncts to regional anesthesia. J Clin Anesth 1998; 10: 46-53
44. Holas A, Krafft P, Marcovic M, et al. Remifentanil, propofol, or both for conscious sedation during eye surgery under regional anaesthesia. Eur J Anaesthesiol 1999; 16: 741-8
45. Puchner W, Obwegeser J, Puhringer FK. Use of remifentanil for awake fiberoptic intubation in a morbidly obese patient with severe inflammation of the neck. Acta Anaesthesiol Scand 2002; 46: 473-6
46. Machata AM, Gonano C, Holzer A, et al. Awake nasotracheal fiberoptic intubation: patient comfort, intubating conditions, and hemodynamic stability during conscious sedation with remifentanil. Anesth Analg 2003; 97: 904-8
47. Hans P, Bonhomme V, Born JD, et al. Target-controlled infusion of propofol and remifentanil combined with bispectral index monitoring for awake craniotomy. Anaesthesia 2000; 55: 255-9
48. Elliott P, O'Hare R, Bill KM, et al. Severe cardiovascular depression with remifentanil. Anesth Analg 2000; 91: 58-61
49. Murdoch JAC, Hyde RA, Kenny GNC. Target-controlled remifentanil in combination with propofol for spontaneously breathing day-case patients. Anaesthesia 1999; 54: 1028-31
50. Dershwitz M, Michalowski P, Chang YC, et al. Postoperative nausea and vomiting after total intravenous anesthesia with propofol and remifentanil or alfentanil: how important is the opioid? J Clin Anesth 2002; 14: 275-8
51. Joshi GP, Warner DS, Twersky RS, et al. A comparison of the remifentanil and fentanyl adverse effect profile in a multicenter phase IV study. J Clin Anesth 2002; 14: 494-9
52. Beers RA, Calimlim JR, et al. A comparison of the cost-effectiveness of remifentanil versus fentanyl as an adjuvant to general anesthesia for outpatient gynecologic surgery. Anesth Analg 2000; 91: 1420-5
53. Suttner S, Boldt J, Schmidt C, et al. Cost analysis of target-controlled infusion-based anesthesia compared with standard anesthesia regimens. Anesth Analg 1999; 88: 77-82
54. Joshi GP, Jamerson BD, Roizen MF, et al. Is there a learning curve associated with the use of remifentanil? Anesth Analg 2000; 91: 1049-55
55. Maguire AM, Kumar N, Parker JL, et al. Comparison of the effects of remifentanil and alfentanil on cardiovascular response to tracheal intubation in hypertensive patients. Br J Anaesth 2001; 86: 90-3
56. Habib AS, Parker JL, Maguire AM, et al. effects of remifentanil and alfentanil on the cardiovascular responses to the induction of anaesthesia and tracheal intubation on the elderly. Br J Anaesth 2002; 88: 430-2
57. Alexander R, Olufolabi AJ, Booth J, et al. Dosing study of remifentanil and propofol for tracheal intubation without the use of muscle relaxants. Anaesthesia 1999; 54: 1037-40
58. Klemola UM, Mennander S, Saarnivaara L. Tracheal intubation without the use of muscle relaxants: remifentanil or alfentanil in combination with propofol. Acta Anaesthesiol Scand 2000; 44: 465-9
59. McNeil IA, Culbert B, Russell I. Comparison of intubating conditions following propofol and succinylcholine with propofol and remifentanil 2μg/kg or 4μg/kg. Br J Anaesth 2000; 85: 623-5
60. Breslin DS, Reid JE, Mirakhur RK, et al. Sevoflurane nitrous oxide anaesthesia supplemented with remifentanil: effect on recovery and cognitive function. Anaesthesia 2001; 56: 11-9
61. Wilhelm W, Grundmann U, van Aken H, et al. A multi-center comparison of isoflurane and propofol as adjuncts to remifentanil-based anesthesia. J Clin Anesth 2000; 12: 129-35
62. Grundmann U, Silomon M, Bach F, et al. Recovery profile and side effects of remifentanil-based anaesthesia with desflurane or propofol for laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2001; 45: 320-6
63. Chung F, Mulier JP, Scholz J, et al. A comparison of anaesthesia using remifentanil combined with either propofol, enflurane, or isoflurane in patients undergoing gynaecological laparoscopy, varicose vein or arthroscopic surgery. Acta Anaesthesiol Scand 2000; 44: 790-8
64. O'Hare RA, Mirakhur RK, Reid JE, et al. Recovery from propofol anesthesia supplemented with remifentanil. Br J Anaesth 2001; 86: 361-5
65. Van Delden PG, Houweling PL, Bencini AF, et al. Remifentanil-sevoflurane anaesthesia for laparoscopic cholecystectomy: comparison of three dose regimens. Anaesthesia 2002; 57: 212-7
66. Montes FR, Trillos JE, Rincon IE, et al. Comparison of total intravenous anesthesia and sevoflurane: fentanyl anesthesia for outpatient otorhinolaryngeal surgery. J Clin Anesth 2002; 14: 324-8
67. Mackey JJ, Parker SD, Nass CM, et al. Effectiveness of remifentanil versus traditional fentanyl-based anesthetic in high-risk outpatient surgery. J Clin Anesth 2000; 12: 427-32
68. Ozkose Z, Cok OY, Tuncer B, et al. Comparison of hemodynamics, recovery profile, and early postoperative pain control and costs of remifentanil versus alfentanil-based total intravenous anesthesia (TIVA). J Clin Anesth 2002; 14: 161-8
69. Casati A, Albertin A, Fanelli G, et al. A comparison of remifentanil and sufentanil as adjuvants during sevoflurane anesthesia with epidural analgesia for upper abdominal surgery: effects on postoperative recovery and respiratory function. Anesth Analg 2000; 91: 1269-73
70. Andersen FA, Arsland D, Holst-Larsen H. Effects of combined methohexitone-remifentanil anaesthesia in electroconvulsive therapy. Acta Anaesthesiol Scand 2001; 45: 830-3
71. Mouren S, De Winter G, Guerrero SP, et al. The continuous recording of blood pressure in patients undergoing carotid surgery under remifentanil versus sufentanil analgesia. Anesth Analg 2001; 93: 1402-9
72. Doyle PW, Coles JP, Leary TM, et al. A comparison of remifentanil and fentanyl in patients undergoing carotid endarterectomy. Eur J Anaesthesiol 2001; 18: 13-9
73. Wilhelm W, Schlaich N, Harrer J, et al. Recovery and neurologic examination after remifentanil-desflurane or fentanyl-desflurane anesthesia for carotid artery surgery. Br J Anaesth 2001; 86: 44-9
74. Gerhardt MA, Grichnik KP. Early extubation and neurologic examination following combined carotid endarterectomy and coronary artery bypass grafting using remifentanil. J Clin Anesth 1998; 10: 249-52
75. Krenn H, Deusch E, Jellinek H, et al. Remifentanil or propofol for sedation during carotid endarterectomy under cervical plexus block. Br J Anaesth 2002; 87: 637-40
76. Engelhard K, Werner C, Mollenberg O, et al. Effects of remifentanil/propofol in comparison with isoflurane on dynamic cerebrovascular autoregulation in humans. Acta Anaesthesiol Scand 2001; 45: 971-6

77. Sloan TB, Heyer EJ. Anesthesia for intraoperative neurophysiologic monitoring of the spinal cord. J Clin Neurophysiol 2002; 19: 430-43

78. Pechstein U, Nadstawek J, Zentner J, et al. Isoflurane plus nitrous oxide versus propofol for recording of motor evoked potentials after high frequency repetitive electrical stimulation. Electroencephalogr Clin Neurophysiol 1998; 108: 175-81

79. Wass CT, Grady RE, Fessler AJ, et al. The effects of remifentanil on epileptiform discharges during intraoperative electrocorticography in patients undergoing epilepsy surgery. Epilepsia 2001; 42: 1340-4

80. Bacon R, Chandrasekan V, Haigh A, et al. Early extubation after open heart surgery with total intravenous anaesthetic technique [letter]. Lancet 1995; 345: 133-4

81. Wang JYY, Winship SM, Thomas SD, et al. Induction of anaesthesia in patients with coronary artery disease: a comparison between sevoflurane-remifentanil and fentanyl-etomidate. Anaesth Intensive Care 1999; 27: 363-8

82. Mollhoff T, Herregods L, Moerman A, et al. Comparative efficacy and safety of remifentanil and fentanyl in "fast-track" coronary artery bypass graft surgery: a randomized, double-blind study. Br J Anaesth 2001; 87: 718-26

83. Myles PS, Hunt JO, Fletcher H, et al. Remifentanil, fentanyl, and cardiac surgery: a double-blinded, randomized, controlled trial of costs and outcomes. Anesth Analg 2002; 95: 805-12

84. Cheng DCH, Newman MF, Duke P, et al. The efficacy and resource utilization of remifentanil and fentanyl in fast-track coronary artery bypass graft surgery: a prospective randomized, double-blinded controlled, multi-center trial. Anesth Analg 2001; 92: 1094-102

85. Michelsen LG, Holford NHG, Lu W, et al. The pharmacokinetics of remifentanil in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. Anesth Analg 2001; 93: 1100-5

86. Blair JM, Hill DA, Fee JPH. Patient-controlled analgesia for labour using remifentanil: a feasibility study. Br J Anaesth 2001; 87: 415-20

87. Volmanen P, Akural EI, Raudaskoski T, et al. Remifentanil in obstetric analgesia: a dose-finding study. Anesth Analg 2002; 94: 913-7

88. Olufolabi AJ, Booth JV, Wakeling HG, et al. A preliminary investigation of remifentanil as a labor analgesic. Anesth Analg 2000; 91: 60-8

89. Albrecht S, Fechner J, Geisslinger G, et al. Postoperative pain control following remifentanil-based anesthesia for major abdominal surgery. Anaesthesia 2000; 55: 315-22

90. Kochs E, Cote D, Deruyck L, et al. Postoperative pain management and recovery after remifentanil-based anesthesia with isoflurane or propofol for major abdominal surgery. Br J Anaesth 2000; 84: 169-73

91. Muñoz HR, Guerrero ME, Brandes V, et al. Effect of timing of morphine administration during remifentanil-based anaesthesia on early recovery from anaesthesia and postoperative pain. Br J Anaesth 2002; 88: 814-8

92. Sommer M, Riedel J, Fusch C, et al. Intravenous anaesthesia with remifentanil in a preterm infant. Paediatr Anaesth 2001; 11: 252-3

93. Muñoz HR, Cortĩnez LI, Altermatt FR, et al. Remifentanil requirements during sevoflurane administration to block somatic and cardiovascular responses to skin incision in children and adults. Anesthesiology 2002; 97: 1142-5

94. Chambers N, Lopez T, Thomas J, et al. Remifentanil and the tunneling phase of paediatric ventriculoperitoneal shunt insertion: a double-blind, randomized, prospective study. Anaesthesia 2002; 57: 133-9

95. Prys-Roberts C, Lerman J, Murat I, et al. Comparison of remifentanil versus regional anaesthesia in children anaesthetized with isoflurane/nitrous oxide. International Remifentanil Paediatric Anaesthesia Study group. Anaesthesia 2000; 55: 870-6

96. Foubert L, Reyntjens K, DeWolf D, et al. Remifentanil infusion for cardiac catheterization in children with congenital heart disease. Acta Anaethesiol Scand 2002; 46: 355-60

97. Keidan I, Berkenstadt H, Sidi A, et al. Propofol/remifentanil versus propofol alone for bone marrow aspiration in paediatric haemato-oncological patients. Paediatr Anaesth 2001; 11: 297-301

98. Reyle-Hahn M, Niggemann B, Max M, et al. Remifentanil and propofol for sedation in children and young adolescents undergoing diagnostic flexible bronchoscopy. Paediatr Anaesth 2000; 10: 59-63

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