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Remifentanil

A Review of its Analgesic and Sedative Use in the Intensive Care Unit

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Data Selection

Sources: Medical literature published in any language since 1980 on 'remifentanil', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE search terms were 'remifentanil' and ('intensive care' or 'intensive care units' or 'ICU' or 'critical care') and ('sedation' or 'analgesia'). EMBASE search terms were 'remifentanil' or ('intensive care' or 'intensive care units' or 'ICU' or 'critical care') and ('sedation' or 'analgesia'). AdisBase search terms were 'remifentanil' or ('intensive-care-units' or 'intensive care' or 'ICU' or 'critical care') and ('sedation' or 'analgesia'). Searches were last updated 23 January 2006.

Selection: Studies in patients admitted to the intensive care unit who received remifentanil. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Remifentanil, analgesia, sedation, intensive care, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

Remifentanil (Ultiva™), a 4-anilidopiperidine derivative of fentanyl, is an ultra-short-acting μ-opioid receptor agonist indicated to provide analgesia and sedation in mechanically ventilated intensive care unit (ICU) patients.

Analgesia-based sedation with remifentanil is a useful option for mechanically ventilated patients in the ICU setting. Its unique properties (e.g. organ-independent metabolism, lack of accumulation, rapid offset of action) set it apart from other opioid agents. Remifentanil is at least as effective as comparator opioids such as fentanyl, morphine and sufentanil in providing pain relief and sedation in mechanically ventilated ICU patients. Moreover, it allows fast and predictable extubation, as well as being associated with a shorter duration of mechanical ventilation and quicker ICU discharge than comparators in some studies. In addition, remifentanil is generally well tolerated in this patient population. Thus, remifentanil is a welcome addition to the currently available pharmacological agents employed in the management of mechanically ventilated ICU patients.

Pharmacological Properties

Remifentanil is a 4-anilidopiperidine derivative of fentanyl containing an ester linkage to propanoic acid. It is ultra-short acting and displays analgesic effects, consistent with its agonist activity at the μ-receptor. The primary metabolite, remifentanil acid, has negligible activity compared with remifentanil. Remifentanil has a rapid onset of action (≈1 minute) and a rapid offset of action following discontinuation (≈3–10 minutes). The time to offset of action was not prolonged to a clinically significant extent by renal impairment or prolonged infusion in post-surgical or medical ICU patients who received remifentanil for up to 72 hours. In mechanically ventilated ICU patients, the median time to offset of action was significantly shorter with remifentanil than with morphine or fentanyl after 10 days' treatment.

The effect of remifentanil on haemodynamics is typical of opioids (e.g. decreased blood pressure and heart rate). In ICU patients, remifentanil was generally associated with an acceptable degree of haemodynamic stability. There were no significant differences between remifentanil, fentanyl and morphine recipients in mean intracranial pressure (ICP) or cerebral perfusion pressure in mechanically ventilated ICU patients with acute brain injury or who had undergone neurosurgery. However, compared with baseline, ICP was significantly increased and cerebral perfusion pressure was significantly reduced with remifentanil in mechanically ventilated patients with severe traumatic brain injury in another study.

Remifentanil is rapidly distributed throughout the body and demonstrates linear, dose-dependent, multicompartmental pharmacokinetics. The drug undergoes widespread extravascular metabolism and is rapidly metabolised via extrahepatic, nonspecific blood and tissue esterases to remifentanil acid. The

pharmacokinetics of remifentanil were not altered to a clinically significant extent in ICU patients with moderate to severe renal impairment who received the drug for up to 72 hours, compared with ICU patients with normal renal function or mild renal impairment. The pharmacokinetics of remifentanil were also not altered to a clinically significant extent in patients with severe chronic liver disease. Remifentanil has a context-sensitive half-time of ≈3–4 minutes, irrespective of the duration of infusion. Age-related changes in clearance and volume of distribution occurred in paediatric patients receiving remifentanil.

Therapeutic Efficacy

A number of well designed trials have compared the use of analgesia-based sedation with remifentanil with that of morphine, fentanyl or sufentanil in post-surgical, trauma and/or medical patients ($n \geq 20$) who were being mechanically ventilated in an ICU setting.

Remifentanil provided effective analgesia-based sedation in mechanically ventilated patients in the ICU setting. Optimal sedation was achieved for ≥78% of the time with remifentanil. Moreover, with remifentanil, the duration of optimal sedation and the percentage of hours during which patients had no or mild pain was generally similar to that with fentanyl or morphine. In addition, compared with remifentanil, the need for additional sedation generally appeared greater with fentanyl and morphine regimens, but not with sufentanil regimens.

Remifentanil was at least as effective as fentanyl, morphine and sufentanil in terms of recovery parameters. In some studies, including a study examining longer-term mechanical ventilation, remifentanil was associated with a significantly shorter duration of mechanical ventilation than fentanyl or morphine. In addition, remifentanil was associated with a significantly shorter extubation time than fentanyl, morphine or sufentanil and a shorter time to ICU discharge than fentanyl or morphine in some studies. Two studies noted an absence of tolerance to remifentanil, although tolerance was seen in 29% of remifentanil recipients in another study. A remifentanil-based regimen may also be associated with savings in staff costs, according to the results of a prospective cost-consequence analysis.

Remifentanil was associated with rapid and predictable emergence from sedation in mechanically ventilated ICU patients with acute brain injury or who had undergone neurosurgery in a randomised, nonblind study. Significantly less between-patient variability in the time to neurological assessment occurred in patients receiving analgesia-based sedation with remifentanil than in those receiving hypnotic-based sedation incorporating fentanyl or morphine. Remifentanil patients requiring mechanical ventilation were extubated significantly earlier than patients receiving the morphine-based regimen. The extubation time and time until ICU discharge were also significantly shorter with remifentanil plus propofol than with fentanyl plus midazolam in mechanically ventilated ICU patients who had undergone supratentorial brain surgery in a retrospective study.

Remifentanil provided similar analgesia-based sedation to fentanyl in paediatric patients aged 3–16 years who were being mechanically ventilated following orthopaedic spinal surgery. Remifentanil also demonstrated efficacy in mechanically ventilated newborns.

Remifentanil provided adequate analgesia in ICU patients with severe burns during dressing changes, and an intravenous infusion of remifentanil effectively

reduced stress during endotracheal suctioning in mechanically ventilated post-surgical ICU patients sedated with sufentanil.

Tolerability

Remifentanil was generally well tolerated in ICU patients requiring mechanical ventilation. The most commonly occurring adverse events in remifentanil recipients relate to its μ-opioid agonist properties (e.g. bradycardia, hypotension).

The tolerability of remifentanil was generally similar to that of fentanyl or morphine in ICU patients requiring short-term mechanical ventilation for up to ≈3 days. In terms of the proportion of patients experiencing drug-related adverse effects, there was no significant difference between remifentanil and morphine recipients (22% vs 16%), or between remifentanil and fentanyl recipients (23% vs 17%). Moreover, there was no significant difference between remifentanil and fentanyl recipients in the incidence of hypotension, nausea, fever or vomiting.

In critically ill patients mechanically ventilated for up to 10 days, drug-related adverse events occurred in 11% of recipients and in 8% of patients receiving a comparator regimen (midazolam with fentanyl or morphine). The most commonly occurring adverse events in remifentanil recipients (occurring in ≥5% of patients, not necessarily drug related) included hypotension, atrial fibrillation and vomiting. Muscle rigidity did not occur in either treatment group.

Remifentanil was also generally well tolerated in mechanically ventilated paediatric patients in the ICU setting.

1. Introduction

For most patients admitted to the intensive care unit (ICU), analgesia and sedation will be required at some time throughout their hospital stay.[1] Inadequate or inappropriate use of sedation or analgesia may result in unnecessary pain, disturbed sleep and anxiety, and may potentially exacerbate confusion and delirium.[1,2]

Therefore, one of the primary challenges for clinicians in the ICU setting is to provide and maintain patient comfort. The broad spectrum of patients and conditions managed within the ICU calls for an individualised treatment approach which takes into consideration inter-individual variations and illness-induced alterations in the pharmacodynamics and pharmacokinetics of different agents.[1]

Opioids are a commonly used form of analgesia following major surgery and in patients who are critically ill.[1] Remifentanil (Ultiva™)[1] is a selective, ultra-short-acting μ-opioid receptor agonist.[2] The efficacy and tolerability of adjunctive intravenous remifentanil in general anaesthesia has been well documented in a broad spectrum of patients undergoing surgical procedures.[3] This article reviews the efficacy of intravenous remifentanil in patients requiring sedation and analgesia within the ICU, focusing mainly on its use in patients requiring mechanical ventilation.

2. Pharmacodynamic Properties

The pharmacodynamic properties of remifentanil have been reviewed previously[3] and are summarised in table I; this section focuses on the properties of the drug most relevant to the ICU setting.

Remifentanil is a 4-anilidopiperidine derivative of fentanyl containing an ester linkage to propanoic acid.[3] It is highly active and ultra-short acting and, consistent with its agonist activity at the μ-receptor, displays analgesic effects (table I).[3] The primary metabolite of remifentanil, remifentanil acid (GR90291) [see section 3], has negligible pharmacological activity compared with the parent drug.[4-6]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table I. Overview of the *in vitro* and *in vivo* pharmacodynamic characteristics of remifentanil (REM) in animal models, healthy volunteers, patients (pts) undergoing surgery or other procedures and intensive care unit (ICU) pts

Analgesic effects
Similar potency to that of FEN and ≈16- to 70-fold more potent than ALF based on analgesia testing as well as on EEG and MAC reduction studies in adults[7,20,21] (reviewed by Egan[4,22])
Competitively inhibited by the μ-receptor antagonist naloxone[23,24] but not by the κ-receptor antagonist norbinaltorphimine[23]
Analgesic efficacy in healthy volunteers using various pain models[25-28]
Rapid onset of action (≈1 min) and rapid offset of action following discontinuation of a continuous infusion (≈3–10 min)[7-9]
Offset of action not altered to a clinically significant extent by renal impairment or prolonged infusion in ICU pts.[10] Shorter median time to offset of action than with MOR or FEN at day 10 in mechanically ventilated ICU pts (15 vs 70 min; $p < 0.001$)[11]
Haemodynamic effects
Displays typically dose-dependent inhibition of HR and MAP in animal models[9,29,30]
Dose-dependent haemodynamic responses that were similar in nature to those observed with ALF, but of shorter duration, in an animal model (10–20 vs ≥60 min recovery time)[9,30]
Significant reductions ($p < 0.001$ vs baseline) in systolic and diastolic BP and HR in healthy volunteers with bolus doses of REM 2–30μg[31]
In pts with coronary artery disease, high-dose REM 2.0 μg/kg/min significantly reduced stroke volume index, HR, MAP, myocardial blood flow and MV_{O2} (all $p < 0.05$ vs awake state)[32]
Generally associated with an acceptable degree of haemodynamic stability (e.g. MAP and HR) in ICU pts,[10,12-15] including during procedures such as endotracheal suctioning.[16] However, associated with clinically significant reductions in heart rate and BP at infusion rates ≥0.1 μg/kg/min in a dose-ranging study in mechanically ventilated ICU pts[17] and a significantly ($p < 0.05$) lower MAP than that seen with MOR in another study[18]
Respiratory effects
Dose-dependently decreased respiratory rate and increased ET_{CO2} in healthy volunteers (both $p < 0.05$ vs placebo)[33]
Caused dose-dependent respiratory depression (like alfentanil); nadir occurred 2.5–5 min after a single bolus dose of REM in healthy volunteers[7,33,34]
Respiratory drive depression occurred with infusion rates of >0.05 μg/kg/min in critically ill pts[17]
Following extubation of mechanically ventilated ICU pts, fewer REM than MOR recipients had a respiratory rate of <10 breaths/min (4% vs 13%; $p = 0.042$)[13] and the respiratory rate was higher with REM than with MOR (14 vs 11 breaths/min; $p = 0.03$)[18]
CNS effects
Generally, no clinically relevant effect on cerebral blood flow,[35,36] cerebrovascular CO_2 reactivity[37-39] or cerebral capacity[40] in healthy adult volunteers[35,37,40] or surgical pts[36,38,39]
No significant differences between REM, FEN and MOR recipients in mean ICP (12.0 vs 13.9 vs 10.3mm Hg) or CPP (68.8 vs 75.6 vs 77.0mm Hg) in mechanically ventilated ICU pts with acute brain injury or who had undergone neurosurgery[14]
No significant effect on ICP, CPP or cerebral blood flow velocity in mechanically ventilated ICU pts with traumatic brain injury[15]
Increased mean ICP from baseline (from 17 to 19–22mm Hg; $p < 0.05$) and decreased mean CPP (from 74 to 59–63mm Hg; $p < 0.05$) in mechanically ventilated pts with severe traumatic brain injury.[19] ICP also increased to 20–22mm Hg ($p < 0.05$ vs baseline) following endotracheal suctioning
Interactions with hypnotic agents
Synergistic actions when coadministered with propofol in terms of cardiorespiratory[41] and hypnotic[42] responses

ALF = alfentanil; **BP** = blood pressure; **CPP** = cerebral perfusion pressure; **EEG** = electroencephalogram; **ET_{CO2}** = end-tidal carbon dioxide levels; **FEN** = fentanyl; **HR** = heart rate; **ICP** = intracranial pressure; **MAC** = minimum alveolar concentration; **MAP** = mean arterial pressure; **MOR** = morphine; **MV_{O2}** = myocardial oxygen uptake.

Remifentanil has a rapid onset of action (≈1 minute) and a rapid offset of action following discontinuation (≈3–10 minutes) [table I].[7-9] The time to offset of action was not prolonged to a clinically significant extent by renal impairment or prolonged infusion, according to the results of a study in 40 post-surgical or medical ICU patients who had normal renal function or mild renal impairment (creatinine clearance [CL_{CR}] ≥3 L/h [≥50 mL/min]) versus moderate to severe renal impairment (CL_{CR} <3 L/h [<50 mL/min]).[10] Patients received an intravenous infusion of remifentanil (initial infusion rate 0.1–0.15 μg/kg/min, titrated to effect) for up to 72 hours. An increase, and greater variability, in time to offset was observed in patients with moderate to severe renal impairment at 24 and 72 hours; these

differences were statistically ($p < 0.05$ vs normal renal function/mild renal impairment group) but not clinically significant. At 72 hours, the difference between the two groups in the mean time to offset was 16.5 minutes.

Remifentanil displays a shorter duration of action following discontinuation (3–10 min) than alfentanil (5–20 min), fentanyl (20–30 min) or morphine (180–240 min) [reviewed by Mason[8]]. Moreover, in a study in mechanically ventilated ICU patients, the median time to offset of action was significantly shorter with remifentanil than with morphine or fentanyl after 10 days' treatment (table I).[11]

The effect of remifentanil on haemodynamics is typical of opioids (e.g. decreased blood pressure and heart rate) [table I]. In ICU patients, remifentanil was generally associated with an acceptable degree of haemodynamic stability,[10,12-15] including during procedures such as endotracheal suctioning[16] (table I). For example, no significant differences between mechanically ventilated ICU patients receiving remifentanil or fentanyl were reported in terms of weighted mean heart rate (88.3 vs 88.6 beats/min) or mean arterial pressure (80.9 vs 79.6mm Hg).[12] However, remifentanil was associated with clinically significant reductions in heart rate and blood pressure at infusion rates of ≥0.1 μg/kg/min in a dose-ranging study[17] and mean arterial pressure was significantly lower with remifentanil than with morphine in another study[18] (see section 4.1 for study design details).

In critically ill patients, respiratory drive suppression occurred at remifentanil infusion rates of >0.05 μg/kg/min in a dose-ranging study[17] (table I). Among mechanically ventilated ICU patients, recovery of spontaneous respiration was significantly better with remifentanil than with morphine following extubation[13,18] (table I).

There were no significant differences between remifentanil, fentanyl and morphine recipients in mean intracranial pressure (ICP) or cerebral perfusion pressure in mechanically ventilated ICU patients with acute brain injury or who had undergone neurosurgery[14] (table I). In addition, remifentanil infusion had no significant effect on ICP, cerebral perfusion pressure or cerebral blood flow velocity in mechanically ventilated ICU patients with traumatic brain injury (table I).[15] However, compared with baseline, ICP was significantly increased and cerebral perfusion pressure was significantly reduced with remifentanil in mechanically ventilated patients with severe traumatic brain injury in another study[19] (table I). A significant increase from baseline in ICP was also seen following endotracheal suctioning.[19]

3. Pharmacokinetic Properties

The pharmacokinetics of remifentanil have been reviewed previously by Scott and Perry[3] (including data on healthy volunteers and patients undergoing surgery). This section provides a brief overview of the pharmacokinetics of the drug, as relevant to the ICU setting. Remifentanil pharmacokinetics were assessed using arterial blood samples.

Remifentanil is rapidly distributed throughout the body and demonstrates linear, dose-dependent, multicompartmental pharmacokinetics.[3] The drug is approximately 70% bound to plasma proteins and rapidly equalises across the blood-brain barrier.[3] Remifentanil also crosses the placenta but no clinically relevant effects on the neonate have been reported.[43]

Remifentanil undergoes widespread extravascular metabolism, and is rapidly metabolised via extrahepatic, nonspecific blood and tissue esterases to its main metabolite, the essentially inactive carboxylic acid metabolite remifentanil acid.[4,44] This organ-independent elimination makes the drug particularly useful in the ICU setting given that critically ill ICU patients often have a degree of organ dysfunction.[44] Indeed, the pharmacokinetics of remifentanil were not altered to a clinically significant extent in ICU patients with moderate to severe renal impairment (CL_{CR} <3 L/h [<50 mL/min]) who received the drug for up to 72 hours, compared with ICU patients with normal renal function or mild renal impairment (CL_{CR} ≥3 L/h [≥50 mL/min]) [table II].[44] There was high interindividual variability in volume of distribution (Vd) and clearance values

Table II. Pharmacokinetics of remifentanil and remifentanil acid in intensive care unit (ICU) patients (pts). In this study, post-surgical or medical ICU pts requiring mechanical ventilation received continuous intravenous infusion of remifentanil for up to 72h.[44] [a] Pts had normal renal function or varying degrees of renal impairment. Mean values are reported

	Normal renal function or mild renal impairment (n = 10)	Moderate to severe renal impairment[b] (n = 30)
CL_{CR} (mL/min)	62.9	14.7
Remifentanil		
CL (mL/kg/min)	44.3	59.0
Vd (L/kg)	0.737	1.76
$t_{1/2}$ (min)	11.4	20.5
Remifentanil acid		
CL (mL/kg/h)	176	41.4*
V_c (L/kg)	0.719	0.768
Q (mL/kg/h)	125	
V_p (L/kg)	0.685	
$t_{1/2}$ (h)	2.48	18.5*
$t_{1/2\beta}$ (h)	16.6	

a Initial remifentanil infusion rate of 0.1–0.15 μg/kg/min, titrated to effect. If required, propofol 0.5 mg/kg/h was started and titrated to effect.

b Pts were receiving no renal replacement therapy (n = 16), intermittent renal replacement therapy (n = 9) or continuous renal replacement therapy (n = 5).

CL = clearance; **CL_{CR}** = creatinine CL; **Q** = intercompartmental clearance; **$t_{1/2}$** = elimination half-life; **$t_{1/2\beta}$** = terminal $t_{1/2}$; **V_c** = volume of the central compartment; **Vd** = volume of distribution; **V_p** = volume of the peripheral compartment; * $p < 0.0001$ vs normal renal function/mild renal impairment.

for remifentanil; however, there were no significant differences between groups.[44]

The majority of remifentanil acid (≥88%) is eliminated by the kidneys[7,45] and this metabolite accumulated in ICU patients with moderate to severe renal impairment.[44] However, this accumulation is unlikely to be clinically relevant due to the low potency of remifentanil acid versus remifentanil. The metabolic ratio (reflecting the ratio of remifentanil acid : remifentanil concentrations at steady state) in patients with moderate to severe renal impairment was ≈8-fold higher than that in patients with normal renal function or mild impairment (116 vs 15.1; $p < 0.0001$). Mean remifentanil acid clearance showed a linear decline which corresponded to a decline in CL_{CR}; clearance was significantly decreased by ≈75% in patients with moderate-to-severe renal impairment compared with the normal renal function/mild renal impairment group (table II).

Remifentanil and remifentanil acid displayed three-compartment model pharmacokinetics in patients with normal renal function or mild renal impairment, whereas a two-compartment model was adequate for most patients with moderate-to-severe renal impairment.[44]

In patients with renal failure, pharmacokinetic modelling predicted that remifentanil acid concentrations would reach steady state after a continuous infusion of remifentanil 0.15 μg/kg/min over 6 days; these concentrations are not likely to exceed those observed in patients with moderate-to-severe renal impairment.[44]

A significant ($p < 0.05$) reduction in clearance and prolongation of terminal elimination half-life ($t_{1/2\beta}$) have been reported in patients with end-stage renal failure who had undergone haemodialysis in the past 24 hours compared with healthy controls in a non-ICU setting.[46] However, these reductions were clinically modest and could be explained by a reduction in Vd shortly after haemodialysis. Moreover, the pharmacokinetics of remifentanil were not altered to a clinically significant extent in patients with severe chronic liver disease (n = 10) compared with healthy controls (n = 10).[47]

The context-sensitive half-time (i.e. the time required for a 50% reduction in the effect site concentration after a continuous infusion designed to maintain a constant effect site concentration) is ≈3–4 minutes, irrespective of the duration of remifentanil infusion.[7,48] Context-sensitive half-time may be a more appropriate measure of the elimination rate of remifentanil than $t_{1/2\beta}$.[7] By contrast, context-sensitive half-times following infusion of sufentanil, alfentanil and fentanyl were 33.9, 58.5 and 262.5 minutes, respectively; study drugs were infused for up to 4 hours.[48]

Based on a non-steady-state population modelling analysis, the concomitant administration of intravenous remifentanil and propofol resulted in a significant reduction in remifentanil central Vd (V_c) and distribution clearance of 41% and 41%, respec-

tively ($p < 0.05$ for both), in 20 healthy volunteers.[49] Propofol pharmacokinetics were unaffected.

3.1 Special Patient Populations

Age-related changes in clearance and Vd at steady state (Vd_{ss}) were seen in paediatric patients (n = 34) undergoing surgical procedures (non-ICU setting) who received a single intravenous dose of remifentanil 5 μg/kg.[50] Mean remifentanil clearance was significantly ($p < 0.05$) increased in patients aged 0–2 months (90.5 mL/min/kg) and >2 months to <2 years (92.1 mL/min/kg) compared with patients aged 2–18 years (46.5–76.0 mL/min/kg). Mean Vd_{ss} was significantly ($p < 0.05$) higher in paediatric patients aged 0–2 months (452.8 mL/kg) than in older patients (223.2–307.9 mL/kg). There were no significant age-related changes in $t_{1/2}\beta$ (3.4–5.7 min), reflecting the inverse relationship of age with clearance.

In healthy adult volunteers, V_c and clearance showed approximate reductions of 25% and 33% from the ages of 20 to 85 years.[51] For use in general anaesthesia, the prescribing information therefore recommends that the initial remifentanil dose be reduced by 50% in those aged >65 years.[45] However, because of the lower initial dosages, no initial dosage reduction is required in the elderly in the intensive care setting (section 7).[45]

4. Therapeutic Efficacy

4.1 Efficacy in Mechanically Ventilated Intensive Care Unit (ICU) Patients

The efficacy of intravenous remifentanil in providing analgesia-based sedation in adults admitted to the ICU who require mechanical ventilation has been examined in early trials (section 4.1.1) and in trials comparing remifentanil with other opioids (section 4.1.2). Trials have also examined the analgesic efficacy of remifentanil in paediatric ICU patients requiring mechanical ventilation (section 4.1.3).

4.1.1 Early Trials

The efficacy of remifentanil in mechanically ventilated ICU patients was first evaluated in noncomparative trials (n = 46,[52] n = 10[17] and n = 132[53]). Patients in these trials had undergone major noncardiac surgery or needed mechanical ventilation because of respiratory insufficiency,[52] were critically ill,[17] or had undergone coronary artery bypass graft (CABG) surgery.[53] Where specified, mean patient age was 63[52] or 68[17] years and patients received remifentanil for up to 78 hours (mean duration 9.8 hours)[52] or a median 4.8 hours (postoperative infusion time).[53] One study assessed sedation using the Ramsay Sedation Scale (RSS: 1 = patient anxious and/or agitated, to 6 = no response) and the respiratory response subscore of the comfort scale (CSRR: 1 = no coughing or spontaneous respiration, to 5 = fights ventilator, coughing or choking).[17] One study is available as an abstract.[53]

Mechanically ventilated ICU patients recovered rapidly following sedation with remifentanil, with 31 of 46 patients (67%) extubated within 15 minutes of discontinuing the drug and 40 (87%) extubated within 45 minutes.[52] Remifentanil was commenced at an infusion rate of 0.15 μg/kg/min and was titrated in 0.05 μg/kg/min increments (mean infusion rate 0.14 μg/kg/min). Bolus midazolam 1–3mg could be administered for insufficient sedation and clonidine 0.5 μg/kg/h could be administered for shivering or hypertension. Remifentanil monotherapy provided adequate analgesia and sedation in 17 of 46 (37%) patients.

Low-dose remifentanil (≤0.05 μg/kg/min) provided effective sedation in critically ill patients receiving mechanical ventilation in pressure support mode in a dose-ranging study.[17] A remifentanil infusion of 0.02 μg/kg/min was initiated and increased to 0.05, 0.1, 0.15, 0.2 and 0.25 μg/kg/min every 30 minutes. At a dosage of 0.05 μg/kg/min, remifentanil improved patient adaptation to mechanical ventilation and provided sedation (RSS ≥2; $p < 0.05$ vs baseline) without loss of consciousness. At this dosage, the CSRR score was 3, the same as at baseline. The bispectral index (BIS; an electroencephalographic index of the level of consciousness) was significantly ($p < 0.05$) reduced

from baseline with remifentanil dosages ≥0.05 μg/kg/min. However, tracheal mucosal stimulation increased BIS up to values seen in awake patients.

Remifentanil facilitated early extubation in patients who had undergone CABG surgery in a multicentre study.[53] Recipients of remifentanil 1 μg/kg/min were able to obey a command a median 4 hours after the end of surgery, had adequate respiration a median 5.2 hours after the end of surgery and could be extubated a median 6.1 hours after the end of surgery. A significantly shorter mean time to ICU discharge was reported in patients eligible for early extubation than in those extubated later (18.5 vs 43.8 hours; $p < 0.001$).

4.1.2 Comparisons with Other Opioids

This section mainly focuses on well designed, comparative trials in ≥20 patients (results of early, smaller trials[54,55] are not discussed). Studies compared the use of remifentanil in analgesia-based sedative regimens with that of morphine,[11,13,14,18] fentanyl,[11,12,14,56,57] or sufentanil[58,59] in mechanically ventilated ICU patients. Studies were randomised[11-14,18,56-59] and, where specified, of double-blind[12,13,18,56,58,59] or nonblind[11,14,57] and/or multicentre[11-14,56] or single-centre[18,57,58] design.

Trials included post-surgical, trauma and/or medical patients; a study in patients with acute brain injury or who had undergone neurosurgery is discussed separately.[14] Some studies only included patients with normal renal function[12,13,18,58] or mild renal impairment.[12,13] Where specified, mean patient age was 47–63 years.[11-14,18,56,58,59]

In most studies, remifentanil was titrated to achieve an optimal level of analgesia and midazolam[11,13,18] or propofol[12,14,57] were administered if additional sedation was required, although in two studies all patients received both remifentanil and either propofol[58] or midazolam.[59] Some studies also used initial titration of the comparator opioid followed by the administration of midazolam[13,18] or propofol[12] if required, and in some both the comparator opioid and midazolam[11,14,57,59] or propofol[14,58] were administered. Two of these latter studies used sedative-based regimens, in which the hypnotic component was used as the main variant for sedation.[11,14] One study compared the effect of fast-track cardiac anaesthesia with remifentanil with that of fentanyl (both in combination with isoflurane plus propofol) on early extubation time in patients undergoing CABG surgery.[56] Details of the drug dosages used in these trials are given in tables III and IV or discussed in subsequent text.

The duration of mechanical ventilation was <5 hours following CABG surgery[56] and up to ≈3 days in most other studies.[12,13,18,57] Patients with acute brain injury or who had undergone neurosurgery were mechanically ventilated for up to 5 days[14] and in two longer-term studies, patients were mechanically ventilated for up to ≈10 days.[11,59]

Where specified, primary endpoints included the time from arriving in the ICU until the discharge criteria were fulfilled,[57] the time from the start of study drug until extubation,[11] the mean percentage time of optimal sedation,[18] the between-patient variability in the percentage time of optimal sedation[12,13] and the between-patient variability in the mean time to neurological assessment.[14]

Sedation was evaluated using the Sedation-Agitation Scale (SAS; 1 = not rousable, to 7 = dangerous agitation)[11-13,18] or the RSS.[58] Optimal sedation was defined as an SAS score of 3–4,[11] 4[12,13,18] or 1–3,[14] or an RSS score of 2–5.[58] Analgesia was evaluated according to a 6-point Pain Intensity scale (1 = no pain, to 6 = worst possible pain).[11-14,18]

One study is only available as an abstract.[57]

Remifentanil provided effective analgesia-based sedation in mechanically ventilated patients in the ICU setting. Optimal sedation was achieved for ≥78% of the time with remifentanil (table III).[11-13,18] Moreover, the duration of optimal sedation provided by remifentanil was generally similar to that provided by fentanyl[11,12] or morphine,[11,13] although remifentanil provided optimal sedation for a significantly longer duration than morphine in one study (primary endpoint)[18] [table III]. In two studies, there were no significant differences between remifentanil and fentanyl[12] or morphine[13] recipients in between-patient variability for the optimal duration of sedation during the maintenance phase (primary endpoint). In one of these studies,[12] when

Table III. Efficacy of remifentanil (REM) in medical and post-surgical intensive care unit (ICU) patients (pts). Results of studies comparing REM-based analgesia with other opioids in pts requiring mechanical ventilation. All study drugs were administered intravenously

Study (design)	Pt group	Regimen[a]	No. of pts	Optimal sedation (% h)[b]	Extubation time[c] (h)	Duration of mechanical ventilation[d] (h)	Time to ICU discharge[e] (h)	Additional sedative requirements[f]
Comparisons with FEN								
Howie et al.[56] (r, db, mc)	CABG	REM[g]	150			3.6	16.8	
		FEN[g]	154			3.7	19.2	
Matthey et al.[57][h] (r, nb, sc)	Cardiac surgery	REM 0.1–1 μg/kg/min ± PRO 0.3–1 mg/kg bolus and/or infusion 0.5–4.0 mg/kg/h	80[i]			20.7*	46.1*[j]	
		FEN 1–2 μg/kg bolus then 1–7 μg/kg/h + MID 0.03–0.2 mg/kg bolus then 0.02–0.2 mg/kg/h				24.2	62.4[j]	
Muellejans et al.[12] (r, db, mc)	Cardiac/general surgery or medical	REM 0.15 μg/kg/min ± PRO ≤0.5 mg/kg bolus then 0.5 mg/kg/h	77	88.3	1.1		40.8	Total PRO 378mg
		FEN 1 μg/kg bolus then 1.5 μg/kg/h ± PRO ≤0.5 mg/kg bolus then 0.5 mg/kg/h	75	89.3	1.3		39.5	Total PRO 683mg
Comparison with FEN or MOR								
Breen et al.[11] (r, nb, mc)	Medical and surgical	REM 0.1–0.15 μg/kg/min ± MID ≤2mg bolus	57	96.9	0.9**	94*[j]	187.3	Total MID 125mg[k]
		MID infusion and/or bolus + FEN or MOR[l]	48	97.8	27.5	147.5[j]	209.8	FEN: total MID 1100mg; MOR: total MID 525mg[k]
Comparisons with MOR								
Chinachoti et al.[13] (r, db)	Cardiac/general surgery or medical	REM 0.15 μg/kg/min ± MID 0.03 mg/kg/h	74	82.7	1.5			Total MID 15mg
		MOR 0.045 mg/kg/h ± MID 0.03 mg/kg/h	78	84.3	2.5			Total MID 28.4mg
Dahaba et al.[18] (r, db, sc)	Orthopaedic or general surgery	REM 0.15 μg/kg/min ± MID 0.03 mg/kg bolus then 0.03 μg/kg/h	20	78.3*[j]	0.3*	14.1*	20.7*	MID 0.2 μg/kg/min*
		MOR 0.045 mg/kg/h ± MID 0.03 mg/kg bolus then 0.03 mg/kg/h	20	66.5[j]	1.22	18.1	41.7	MID 0.5 μg/kg/min
Comparison with SUF								
Baillard et al.[59] (r, db)	Critically ill	REM ≈0.17 μg/kg/min + MID 0.1 mg/kg/h	21		22*	144	168	Total MID 14.5 mg/kg
		SUF 0.125 μg/kg/h + MID 0.1 mg/kg/h	20		96	144	252	Total MID 8.9 mg/kg

Continued next page

Table III. Contd

a Study drugs were titrated to effect.[11-13,18,57,59] In most studies, PRO[12,57] or MID[11,13,18] were added to REM only if required.

b Percentage of hours on study drug during which an SAS score of 3–4[11] or 4[12,13,18] was maintained.

c Defined as the time from discontinuation of study drug until extubation,[18,59] the time from the start of the extubation process until extubation[12,13] or the time from the start of weaning until extubation.[11] Values are means,[13,18] medians[12,59] or the 75th centile.[11]

d Defined as the time from entry to the ICU to extubation,[56,57] the time from initiation of study drug until extubation,[11] or the time from the start of study drug infusion until its discontinuation.[18,59] Values are means,[18,57] medians[56,59] or the 75th centile.[11]

e Where specified, defined as the time from ICU arrival until discharge criteria were fulfilled,[57] the time from the start of study drug until ICU discharge,[11,12] the time from interruption of sedation until ICU discharge[59] or the time from extubation until ICU discharge.[18] Values are means,[18,57] medians[12,56,59] or the 75th centile.[11]

f Means[11,18] or medians.[12,13,59]

g Pts received fast-track cardiac anaesthesia with a REM bolus of 1 μg/kg and infusion of 1 μg/kg/min or a FEN bolus of 10 μg/kg and placebo infusion; further boluses were given and the REM infusion adjusted as required. ISO was used for maintenance anaesthesia and discontinued just after rewarming, when PRO 2 mg/kg/h was commenced. On ICU admission, the PRO infusion was reduced to 0.5 mg/kg/h and adjusted as needed. 30 minutes after starting the extubation sequence, a bolus of FEN 2 μg/kg was given to REM recipients and FEN 1 μg/kg to FEN recipients.

h Abstract.

i Total number of pts. Number in each group not specified.

j Primary endpoint.

k Values estimated from graph.

l All pts received MID with either FEN or MOR. Mean infusion rates were 3.0 μg/kg/h for FEN and 0.042 mg/kg/h for MOR.

CABG = coronary artery bypass graft; **db** = double-blind; **FEN** = fentanyl; **ISO** = isoflurane; **mc** = multicentre; **MID** = midazolam; **MOR** = morphine; **nb** = nonblind; **PRO** = propofol; **r** = randomised; **SAS** = Sedation-Agitation Scale; **sc** = single-centre; **SUF** = sufentanil; * $p < 0.05$, ** $p < 0.001$ vs comparator.

a remifentanil recipient who did not achieve an SAS score of 4 (deemed unrelated to the study drug) was excluded from the analysis, there was significantly less variability with remifentanil than with fentanyl ($p = 0.009$).

The percentage of hours during which patients had no or mild pain (i.e. a Pain Intensity score of 1 or 2) was similar with remifentanil and morphine (94.5% vs 93.9%[13] and 95.6% vs 92.6%[18]). Patients had at least moderate pain for a mean 2.6% and 3.1% of the maintenance phase with remifentanil and fentanyl.[12] However, compared with fentanyl recipients, remifentanil recipients experienced at least moderate pain for significantly greater proportions of the extubation (1.4% vs 6.5%; $p = 0.013$), post-extubation (3.6% vs 10.2%; $p = 0.001$) and post-treatment (5.1% vs 13.5%; $p = 0.001$) periods, probably reflecting the rapid offset of action of remifentanil.[12]

The need for additional sedation generally appeared greater with fentanyl and morphine regimens than with remifentanil, although statistical analysis of this parameter was provided for only one trial[18] (table III).[11-13,18] A propofol infusion was added to remifentanil or fentanyl in 35% and 40% of patients[12] and midazolam was added to remifentanil or morphine in 22% and 27%[13] and 30% and 45%[18] of patients. In addition, midazolam was not required by 26% of remifentanil recipients in the longer-term study.[11]

Midazolam requirements appeared greater in remifentanil than sufentanil recipients in one study, although statistical analysis was not reported (table III).[59] In addition, remifentanil ≈0.18 μg/kg/min plus propofol 2.1 mg/kg/h and sufentanil 0.5 μg/kg/h plus propofol 1.3 mg/kg/h (mean dosages) provided effective sedation and analgesia (median RSS of 3) in 20 mechanically ventilated patients admitted to the ICU following either surgery or trauma in a randomised, double-blind trial; the propofol dosage was significantly higher in remifentanil than in sufentanil recipients ($p = 0.012$).[58] However, remifentanil was associated with a more rapid recovery from sedation than sufentanil; within 10 min-

Table IV. Efficacy of remifentanil (REM)-based analgesia in patients (pts) with acute brain injury[14] or who had undergone neurosurgery[14,60] and were being mechanically ventilated in the intensive care unit (ICU). Results of a randomised, nonblind, multicentre trial[14] and a retrospective analysis.[60] All study drugs were administered intravenously

Study	Regimen[a]	No. of pts	Optimal sedation (% h)[b]	Between-pt variability in mean time to neurological assessment	Mean time to neurological assessment (h)	Time to extubation[c] (h; median[14] or mean[60])	Median duration of mechanical ventilation (h)	Time to ICU discharge[d] (h; median[14] or mean[60]	Additional sedative requirements (median) [mg/kg/h]
Karabinis et al.[14]	REM 0.15 μg/kg/min ± PRO[e] ≤0.5 mg/kg bolus and/or 0.5 mg/kg/h infusion	87	95.6	0.44*†[f]	0.41**††	1.0††	24.8	43.5	PRO 1.93; MID 0.18
	PRO[e] + FEN	34	98.1‡	0.86[f]	0.71	0.7	24.1	42.9	PRO 2.49; MID 0.11
	PRO[e] + MOR	40	99.0‡	0.98[f]	0.82	1.9	37.0	49.6	PRO 2.30; MID 0.13
Wilhelm et al.[60] [g]	REM 0.1–0.2 μg/kg/min + PRO 0.5–3 mg/kg/h	30				0.8*		43.2*	
	FEN 0.03–0.2 mg/h + MID 2–12 mg/h	30				8.0		86.4	

a Study drugs were titrated to effect.[14,60] Starting dosages of study drugs in the FEN and MOR treatment arms were not specified in one study.[14]

b Median percentage of hours on study drug during which a Sedation-Agitation Scale score of 1–3[14] was maintained.

c Defined as the time from the start of the extubation process until extubation[14] or not specified.[60]

d Defined as the time from the start of extubation until ICU discharge[14] or not specified.[60]

e PRO was replaced by MID in pts requiring sedation for >3d.

f Primary endpoint.

g Abstract.

FEN = fentanyl; **MID** = midazolam; **MOR** = morphine; **PRO** = propofol; * $p < 0.05$, ** $p = 0.001$ vs FEN; † $p < 0.01$, †† $p \leq 0.001$ vs MOR; ‡ $p < 0.001$ vs REM.

utes of cessation of the opioid infusion, RSS scores were 1.5 versus 3 ($p = 0.015$).

Remifentanil was at least as effective as fentanyl, morphine and sufentanil in terms of recovery parameters (table III). In some studies, including a study[11] examining longer-term mechanical ventilation, remifentanil was associated with a significantly shorter duration of mechanical ventilation than fentanyl[11,57] or morphine[11,18] (primary endpoint in one study[11]) [table III]. Definitions for the duration of mechanical ventilation varied between studies (see table III for definitions).

In addition, the extubation time was generally <3 hours in remifentanil recipients[11-13,18] and was significantly shorter with remifentanil than with fentanyl,[11] morphine[11,18] or sufentanil[59] (table III). Remifentanil was also associated with a shorter time to ICU discharge than fentanyl[57] or morphine[18] in some studies (table III).

Both remifentanil- and fentanyl-based regimens allowed early extubation in patients who had undergone CABG surgery.[56] The median time from ICU admission until extubation was ≈3.5 hours and the median duration of ICU stay was <1 day (table III). A limitation of this study was that an infusion of remifentanil was compared with bolus doses of fentanyl; a *post hoc* analysis suggested that the dosing regimens were not equipotent.[56]

Two studies noted an absence of tolerance to remifentanil.[11,18] In a shorter-term study, mean remifentanil infusion rates were 0.14 μg/kg/min in the first hour of infusion and 0.11 μg/kg/min at the start of weaning[18] and in a longer-term study, the mean remifentanil infusion rate increased slightly up to day 3 and then was constant until day 10.[11] However, in another longer-term study, tolerance was seen in 6 of 21 (29%) remifentanil recipients after a median duration of sedation of 8.5 days.[59]

In ICU Patients with Brain Injuries

Remifentanil was associated with rapid and predictable emergence from sedation in mechanically ventilated ICU patients with acute brain injury or who had undergone neurosurgery, and was superior to fentanyl or morphine in this regard in a nonblind study.[14] Significantly less between-patient variability in the time to neurological assessment occurred in patients receiving analgesia-based sedation with remifentanil than in those receiving hypnotic-based sedation incorporating fentanyl or morphine (primary endpoint) [table IV]. In addition, the mean time to neurological assessment was significantly shorter with remifentanil than with fentanyl or morphine (table IV). The proportion of ICU staff rating the ability of the study drug to wake patients for neurological assessment as good or excellent was 78% for remifentanil, 25% for fentanyl and 8% for morphine.

The percentage of time on study drug with optimal sedation (defined as an SAS score of 1–3) was significantly lower with remifentanil than with fentanyl or morphine, although optimal sedation was maintained for >95% of the time in all three treatment groups (table IV). Across all three treatment arms, patients reported no or mild pain for >99% of the treatment period; >90% of patients in each treatment arm received propofol and ≥30% received midazolam.

Remifentanil recipients were extubated significantly earlier than patients receiving morphine (table IV).[14] However, there were no significant between-treatment differences in the duration of mechanical ventilation or time to ICU discharge (table IV). Results concerning the effect of remifentanil on ICP and cerebral perfusion pressure are discussed in section 2.

The extubation time and time until ICU discharge were significantly shorter with remifentanil plus propofol than with fentanyl plus midazolam in mechanically ventilated ICU patients who had undergone supratentorial brain surgery, according to the results of a retrospective analysis (table III).[60] The results of this study should be interpreted with caution given its retrospective design and the fact that it is only available as an abstract.

4.1.3 In Paediatric Patients

The analgesic efficacy of remifentanil in paediatric ICU patients requiring mechanical ventilation has been examined in two trials.[61,62] A randomised, double-blind study included 22 patients (mean age 13 years; range 3–16 years) undergoing orthopaedic

spinal surgery.[61] Patients received intravenous remifentanil 0.1 μg/kg/min or fentanyl 1.5 μg/kg/h, titrated to effect. If adequate sedation was not achieved, propofol 0.3 mg/kg/h was started and titrated to effect. The efficacy of remifentanil was also examined in 18 newborns requiring mechanical ventilation in a noncomparative study; newborns received remifentanil 0.25 μg/kg/min, titrated to effect (mean infusion rate 0.15 μg/kg/min; mean infusion time 66.9 hours).[62]

Remifentanil provided similar analgesia-based sedation to fentanyl in paediatric patients who were being mechanically ventilated postoperatively.[61] The median duration of the ICU stay was 3 days in remifentanil recipients and 2 days in fentanyl recipients and the median duration of mechanical ventilation was 19 and 18.5 hours in the corresponding treatment groups. There were no significant differences between remifentanil and fentanyl recipients in the time in which a behavioural pain scale score of 3 was achieved (5 vs 10 minutes) or the time from the end of infusion to extubation (5 vs 10 minutes). Propofol was administered to three remifentanil recipients and one fentanyl recipient (total propofol dose 11.5 vs 20mg).

In newborns, optimal analgesia was achieved with remifentanil in a mean 20 hours.[62] Following discontinuation of remifentanil, extubation occurred in a mean 18 minutes.

4.2 Efficacy During Other Painful Procedures in ICU Patients

Several studies have examined the efficacy of remifentanil in ICU patients undergoing painful procedures such as dressing changes[63] or endotracheal suctioning.[16,19,64]

Remifentanil provided adequate analgesia in ICU patients with severe burns (n = 31) during dressing changes, according to the results of a noncomparative study.[63] Over a 4-month period, patients received intravenous remifentanil 0.1–5 mg/h (mean 0.5 mg/h) in combination with midazolam, ketamine or propofol; the study included both intubated and nonintubated patients. The mean dosage necessary for the provision of analgesia was 0.3 mg/h in nonintubated patients and 0.88 mg/h in intubated patients. The overall mean cumulative dosage was 11.96 mg/day reaching a maximum of 153 mg/day. The basal dose of remifentanil was increased by ≈30% approximately 10 minutes prior to the inspection, cleaning and dressing of wounds.

An intravenous infusion of remifentanil effectively reduced stress during endotracheal suctioning in mechanically ventilated post-surgical ICU patients (n = 16) sedated with sufentanil, according to the results of a saline-controlled study (available as an abstract).[16] Sufentanil 15–150 μg/h was administered to maintain background sedation levels at RSS scores of 2–3. Prior to endotracheal suctioning, patients randomly received remifentanil 1 μg/kg or saline. For patients receiving remifentanil, the BIS index and systemic haemodynamic variables did not change in response to stimulation. Patients receiving a saline infusion displayed significant increases in heart rate and systolic blood pressure (indicating a stress response) compared with those administered remifentanil ($p < 0.05$).[16] RSS scores and responses to verbal commands were similar before and after administration of remifentanil or saline.[16]

The cough reflex was suppressed by remifentanil in a dose-dependent manner during endotracheal suctioning in mechanically ventilated patients with severe traumatic brain injury (n = 20). Patients received intravenous boluses of remifentanil 1, 2 or 4 μg/kg in a stepwise manner, followed by infusions of 0.25, 0.5 or 1 μg/kg/min, respectively.[19] With the corresponding treatment regimens, cough reflex was absent in 4 of 20 (20%), 5 of 20 (25%) and 15 of 20 (75%) patients. The effect of remifentanil on ICP and cerebral perfusion pressure is discussed in section 2.

Procedures such as endotracheal suctioning, postural drainage and bronchoscopy could be performed without any corresponding increase in ICP or decreases in mean arterial or cerebral perfusion pressures, according to case report data from six patients admitted to the ICU with either spontaneous intracranial bleeding (two cases of subarachnoid haemorrhage and one case of intraventricular haemorrhage) or severe traumatic subdural haemor-

rhage (two patients were not intubated).[64] These patients received remifentanil administered as a bolus 0.05–1 μg/kg then a continuous infusion of 0.03–0.26 μg/kg/min titrated to effect.

5. Tolerability

5.1 In Adult Patients

Tolerability data were obtained from the trials in adult ICU patients receiving mechanical ventilation discussed in section 4.1.[11-14,18,56]

Remifentanil was generally well tolerated in ICU patients requiring mechanical ventilation.[11-14,18,56] The most commonly occurring adverse events in remifentanil recipients were related to its μ-opioid agonist properties (e.g. bradycardia, hypotension).[12,13]

The tolerability of remifentanil was generally similar to that of fentanyl or morphine in ICU patients requiring short-term mechanical ventilation for up to ≈3 days.[12,13,18] In terms of the proportion of patients experiencing drug-related adverse events, there was no significant difference between remifentanil and morphine recipients (22% vs 16%),[13] or between remifentanil and fentanyl recipients (23% vs 17%).[12] Moreover, there was no significant difference between remifentanil and fentanyl recipients in the incidence of hypotension (10% vs 9%), nausea (9% vs 6%), fever (5% vs 9%) or vomiting (5% vs 6%).[12] A serious adverse event (hypotension) that was possibly related to the study drug was reported in a remifentanil recipient in one study.[13]

In patients who required mechanical ventilation following CABG surgery, the incidence of hypotension during the ICU stay was significantly higher in remifentanil than in fentanyl recipients (21% vs 6.5%; $p < 0.05$).[56] There was no significant between-group difference in the incidence of bradycardia.

In patients being mechanically ventilated in the ICU following acute brain injury or neurosurgery, drug-related adverse events were reported in 25% of remifentanil recipients, 8% of fentanyl recipients and 10% of morphine recipients.[14] There were no significant differences between remifentanil and fentanyl or morphine recipients in the incidence of hypotension (14% vs 11% and 5%), bradycardia (6% vs 5% or 5%) or polyuria (4% vs 5% and 0%). One remifentanil recipient experienced a serious drug-related adverse event (bradycardia).

In critically ill patients mechanically ventilated for up to 10 days, drug-related adverse events occurred in 11% of remifentanil recipients (74% of whom also received midazolam) and in 8% of patients receiving a comparator regimen (midazolam with fentanyl or morphine).[11] The most commonly occurring adverse events in remifentanil recipients (occurring in ≥5% of patients, not necessarily drug related) included hypotension, atrial fibrillation and vomiting (figure 1). One patient receiving fentanyl and midazolam experienced serious treatment-related hypotension which was considered to be life-threatening. Muscle rigidity did not occur in either treatment group. Mortality was 13% in remifentanil recipients and 10% in recipients of the comparator regimen. Liver function tests and creatinine clearance remained stable throughout the treatment period.[11]

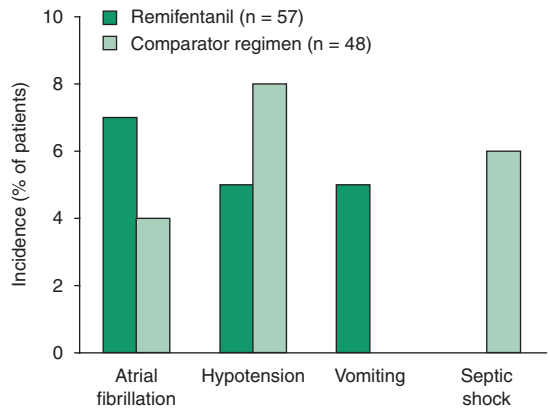

Fig. 1. Tolerability of remifentanil-based regimen in critically ill patients admitted to the intensive care unit requiring mechanical ventilation. Adverse events occurring with an incidence of ≥5% in patients mechanically ventilated for up to 10 days. Patients received remifentanil (0.1–0.15 μg/kg/min) plus boluses of midazolam ≤2mg if required (n = 57) or a comparator regimen comprising midazolam administered by bolus and/or infusion alone (n = 11) or in combination with fentanyl (n = 30) or morphine (n = 7).[11] Study drugs were titrated to effect.

5.2 In Paediatric Patients

Data concerning the tolerability of remifentanil in paediatric patients being mechanically ventilated in the ICU were obtained from the study discussed in section 4.1.3.[61] Remifentanil was generally well tolerated in this patient group. There were no significant differences between remifentanil and fentanyl recipients in terms of clinical adverse events. Nausea occurred in 8 of 11 remifentanil and 6 of 11 fentanyl recipients and vomiting was reported in 6 of 11 remifentanil and 5 of 11 fentanyl recipients. Chest wall rigidity did not occur in any patient.

6. Pharmacoeconomic Considerations

Infusion of remifentanil plus propofol was associated with significantly lower staff costs than fentanyl plus midazolam, according to the results of a prospective cost-consequence analysis (not yet fully published).[65] The study was conducted in a German ICU unit and involved patients who were being mechanically ventilated following cardiac surgery. The cost analysis was conducted from a hospital perspective and considered only direct costs (including drug costs, staff costs and the costs of materials). Details of the drug regimens used are discussed in section 4.1.2.[57] Nursing costs were significantly lower with remifentanil than with fentanyl (€869 vs €1131; $p < 0.05$), as were physician costs (€260 vs €352; $p < 0.05$) [2003 prices]. However, the cost of study drugs was significantly higher with remifentanil than with fentanyl (€353 vs €42; $p < 0.05$), and there was no significant difference between remifentanil and fentanyl in total costs (€1712 vs €1729).

Scenario analysis showed that a lower remifentanil infusion rate combined with a higher propofol infusion rate (corresponding to routine practice) would have rendered total cost savings compared with fentanyl plus midazolam. Univariate sensitivity analysis revealed that the pharmacoeconomic results were sensitive to changes in drug and nursing costs.[65]

The remifentanil regimen was also associated with clinical benefits, including a significantly shorter duration of mechanical ventilation and time in the ICU,[57] as also found in other studies[11,18] (see section 4.1.2). Although not investigated in this cost-consequence analysis,[65] a reduction in mechanical ventilation duration decreases the risk of ventilator-associated morbidity, such as pneumonia,[66] and associated costs.[67,68]

7. Dosage and Administration

In the EU, remifentanil is indicated to provide analgesia and sedation in mechanically ventilated ICU patients aged ≥18 years.[45]

Remifentanil may initially be administered alone to mechanically ventilated ICU patients.[45] Bolus injection of remifentanil is not recommended in the ICU setting. Rather, an intravenous infusion rate of 0.1–0.15 μg/kg/min (6–9 μg/kg/h) should initially be used and the dosages should subsequently be titrated in 0.025 μg/kg/min (1.5 μg/kg/h) increments (at intervals of ≥5 minutes) to achieve the required level of analgesia and sedation.

If sedation is not adequate at a remifentanil infusion rate of 0.2 μg/kg/min (12 μg/kg/h), it is recommended that an appropriate sedative agent (e.g. propofol or midazolam) be initiated and the dosage titrated to the desired level of sedation.[45] The use of remifentanil will reduce the dosage requirement of concomitantly administered sedative agents in adult ICU patients. Typical initial bolus doses and infusion rates are ≤0.5 mg/kg and 0.5 mg/kg/h for concomitant propofol, and ≤0.03 mg/kg and 0.03 mg/kg/h for concomitant midazolam. The remifentanil infusion rate can be further increased in increments of 0.025 μg/kg/min (1.5 μg/kg/h) if additional analgesia is needed. No adjustments to the above-mentioned dosages are necessary in patients with renal impairment, including those undergoing renal replacement therapy. In addition, no initial dose reduction is required in elderly patients aged >65 years who are receiving remifentanil in the intensive care setting.

The remifentanil infusion rate can be increased ≥5 minutes before a stimulating and/or painful procedure to provide additional analgesia.[45]

Prior to extubation, the remifentanil infusion rate should be gradually titrated down to 0.1 μg/kg/min

(6 μg/kg/h).[45] After extubation, the remifentanil infusion rate should be further decreased in 25% decrements at intervals of at least 10 minutes until the infusion is discontinued. Only down-titration should occur during weaning from ventilation. Transition to alternative analgesic and sedative drugs should be planned and initiated prior to discontinuation of remifentanil.

Formal dosage recommendations for the use of remifentanil in paediatric patients in the ICU setting are not available.

For further details regarding the use of remifentanil in special patient populations, and contraindications and precautions governing its use, the manufacturer's prescribing information should be consulted.

8. Place of Remifentanil When Used for Analgesia and Sedation in the ICU

Sedation and analgesia are core components of effective patient management in the ICU setting.[69] A combination of analgesia and sedation is necessary to relieve pain, agitation and anxiety, and to help adaptation to and compliance with procedures such as endotracheal intubation and mechanical ventilation.[69] Additional benefits of providing optimal sedation and analgesia in critically ill patients include ensuring adequate sleep and possibly reducing morbidity.[69] There is also the potential for cost savings associated with reduced ICU and hospital stays, which ultimately lead to more efficient use of resources.[2]

Within the ICU, the majority of patients receive an opioid to provide analgesia and a hypnotic agent such as midazolam or propofol for sedation.[12,70] Historically, these agents have often been administered using a sedative-based regimen which minimises the opioid dose while manipulating the sedative dose to provide optimal patient comfort.[11,14,71] This regimen is effective when traditional opioids are administered, since it minimises the potential for drug accumulation and the unpredictable recovery or weaning from mechanical ventilation associated with some of these agents.[11] Even though newer synthetic opioids such as fentanyl, sufentanil and alfentanil have shorter durations of action than morphine (reflecting rapid redistribution), they still have relatively long half-lives (≈70–90 min for alfentanil and ≈120–480 min for fentanyl and sufentanil), leading to accumulation and a prolonged duration of action with repeat bolus injection or infusion.[23] Moreover, these agents are eliminated via hepatic metabolism, with the potential for prolonged retention in patients with hepatic impairment.[23,71] The hypnotic component of sedative-based regimens may also be associated with problems. For example, the metabolism of midazolam may be unpredictable when the drug is administered by continuous infusion to critically ill patients.[2] Sedative-based regimens may also be associated with oversedation and its attendant complications (e.g. hypotension, increased time on the ventilator and in the ICU).[72]

An alternative to sedative-based regimens is analgesia-based sedative regimens (analgo-sedation) which provide pain relief with an opioid first and then a sedative agent is administered if and when required.[11,12] While this strategy may enhance patient comfort, concerns regarding opioid accumulation have, to date, limited its use.

Recent guidelines concerning the use of analgesics and sedatives in ICU patients state that the pain should be treated prior to the sedation of an agitated, critically ill patient.[69] When deciding on the most appropriate agent, consideration needs to be given to the patient's underlying medical condition, expected duration of sedation and the ease of administering a particular agent.[1] Drug choice is further complicated in critically ill patients who may have a systemic illness, multiple organ failure and haemodynamic instability.[73] Agents that can offer a clearly defined and predictable onset and offset of action, and that do not show any evidence of accumulation, are likely to be treatments of choice in the ICU setting.[73,74]

Remifentanil possesses a number of properties that support its use in the ICU setting.[1,74] It specifically targets the μ-opioid receptors that mediate pain and has a highly predictable onset and offset of action (section 2), allowing it to be easily titrated to

achieve effective analgesia.[2,11] In addition, remifentanil has a context-sensitive half-time of approximately 3–4 minutes irrespective of the duration of infusion (section 3).[74] Remifentanil does not accumulate and its organ-independent metabolism is not affected by renal or hepatic impairment; the accumulation associated with its metabolite, remifentanil acid, in renal impairment is not considered clinically significant (section 3).[1,2,44,74]

In addition to providing effective pain relief and sedation, remifentanil enhances patient comfort and allows fast and predictable extubation when administered to critically ill ICU patients requiring short-term mechanical ventilation (section 4.1). Remifentanil-based analgesia was also associated with sedative-sparing effects, with the majority of remifentanil recipients not requiring additional propofol or midazolam.[12,13,18] Shorter durations of mechanical ventilation and quicker ICU discharge times were seen with remifentanil than with comparator opioids in two shorter-term studies.[18,57] These findings were confirmed in longer-term studies; remifentanil was associated with a shorter weaning time than fentanyl, morphine or sufentanil in two studies[11,59] and a shorter duration of mechanical ventilation than fentanyl or morphine in one study.[11] A shorter duration of mechanical ventilation may help minimise the risk of complications (e.g. pneumonia, airway trauma) and reduce costs.[75] One of these longer-term studies also showed no evidence of remifentanil accumulation over time.[11]

The fact that remifentanil can be easily and rapidly titrated to effect may make it easier to maintain optimal levels of analgesia and sedation.[12] Moreover, it has been suggested that the rapid offset of action of remifentanil means that patient monitoring need not be as intensive as with fentanyl; if a patient becomes oversedated, this should be easily rectified by altering the infusion rate.[12] A drawback of its rapid offset of action is that patients may experience pain following discontinuation of remifentanil.[12] This highlights the need to consider analgesic requirements prior to discontinuing remifentanil, in order to ensure a smooth transition to alternative analgesia.[12,72]

In patients with neurological impairment, it is imperative that physicians are able to quickly assess neurological function and, therefore, rapid and predictable emergence from sedation is crucial.[14,74] Clinical trial data indicate that remifentanil-based analgesia allowed earlier neurological assessment than either fentanyl or morphine (administered in a hypnotic-based regimen; section 4.1). This suggests that remifentanil provides better sedation control and has greater predictability of the offset of effect.[14] In this study, remifentanil and fentanyl and morphine provided optimal sedation for >95% of the treatment period.

Remifentanil also appears to have potential in paediatric ICU patients requiring mechanical ventilation, as it had similar efficacy to fentanyl in post-operative paediatric patients in one small study (section 4.1.3). Remifentanil may have a particularly important role to play in paediatric patients given concerns over propofol infusion syndrome, which has been observed in critically ill children receiving long-term, high-dose propofol infusion.[76,77] More data concerning the use of remifentanil in this patient population are needed.

In addition to its use as an analgesic and sedative in mechanically ventilated ICU patients, remifentanil has also demonstrated efficacy in providing relief during painful procedures such as wound dressing in patients with severe burns or endotracheal suctioning in mechanically ventilated patients (section 4.2).

Remifentanil is generally well tolerated in a range of ICU patients requiring mechanical ventilation, including post-surgical and medical patients. A similar type and frequency of treatment-related adverse events were reported with remifentanil, fentanyl and morphine regimens (section 5). Remifentanil was generally considered to be associated with an acceptable degree of haemodynamic stability (section 2).

It would be of interest to have more data concerning the use of remifentanil in specific patient groups. For example, only one[59] of the trials discussed in

section 4.1.2 specifically noted the inclusion of patients with septic shock. Patients with septic shock are hypotensive and are usually receiving vasopressors,[78] and the use of analgesics and sedatives in such patients may aggravate hypotension.[79] Use of a shorter-acting agent such as remifentanil may be preferable as it allows for fast discontinuation in the event of poor haemodynamic tolerance. The rapid onset, easy titratability and lack of accumulation associated with remifentanil are important attributes in this patient group.[79]

Preliminary results of a cost-consequence analysis suggest that use of remifentanil in mechanically ventilated patients may be associated with savings in staff costs (section 6).[65] A reduction in the length of ICU and hospital stay may also yield savings, as well as decreasing the risk of costly complications, which may help to balance the high drug costs. Further economic evaluation is needed to corroborate these preliminary findings.

In conclusion, analgesia-based sedation with remifentanil is a useful option for mechanically ventilated patients in the ICU setting. Its unique properties (e.g. organ-independent metabolism, lack of accumulation, rapid offset of action) set it apart from other opioid agents. Remifentanil is at least as effective as comparator opioids such as fentanyl, morphine and sufentanil in providing pain relief and sedation in mechanically ventilated ICU patients. Moreover, it allows fast and predictable extubation, as well as being associated with a shorter duration of mechanical ventilation and quicker ICU discharge than comparators in some studies. In addition, remifentanil is generally well tolerated in this patient population. Thus, remifentanil is a welcome addition to the currently available pharmacological agents employed in the management of mechanically ventilated ICU patients.

Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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