Research

Open Access

Safety and efficacy of analgesia-based sedation with remifentanil versus standard hypnotic-based regimens in intensive care unit patients with brain injuries: a randomised, controlled trial [ISRCTN50308308]

Andreas Karabinis[1], Kostas Mandragos[2], Spiros Stergiopoulos[3], Apostolos Komnos[4], Jens Soukup[5], Ben Speelberg[6] and Andrew JT Kirkham[7]

[1]Director of Intensive Care Unit, Genimatas General Hospital, Athens, Greece
[2]Director of Intensive Care Unit, Red Cross General Hospital of Athens, Korgialenio, Benakio, Athens, Greece
[3]Assistant Professor of Surgery, Head of SICU and Trauma Unit, 4th Surgical Department, Athens Health Science University, Athens, Greece
[4]Director of Department of Intensive Care, General Hospital of Larissa, Larissa, Greece
[5]Anesthesiologist, Department of Anesthesiology and Intensive Care Medicine, Martin-Luther-University Halle-Wittenberg, Ernst-Grube-Strasse 40, 06097 Halle, Germany
[6]Internist-Intensivist, Intensive Care, St Elisabeth Ziekenhuis, Tilburg, The Netherlands
[7]Anaesthesia Clinical Development, GlaxoSmithKline, Greenford, Middlesex, UK

Corresponding author: Andreas Karabinis, akarab@ath.forthnet.gr

Received: 8 April 2004

Revisions requested: 17 May 2004

Revisions received: 26 May 2004

Accepted: 28 May 2004

Published: 28 June 2004

Critical Care 2004, **8**:R268-R280 (DOI 10.1186/cc2896)

This article is online at: http://ccforum.com/content/8/4/R268

Abstract

Introduction This randomised, open-label, observational, multicentre, parallel group study assessed the safety and efficacy of analgesia-based sedation using remifentanil in the neuro-intensive care unit.

Methods Patients aged 18–80 years admitted to the intensive care unit within the previous 24 hours, with acute brain injury or after neurosurgery, intubated, expected to require mechanical ventilation for 1–5 days and requiring daily downward titration of sedation for assessment of neurological function were studied. Patients received one of two treatment regimens. Regimen one consisted of analgesia-based sedation, in which remifentanil (initial rate 9 μg kg^{-1} h^{-1}) was titrated *before* the addition of a hypnotic agent (propofol [0.5 mg kg^{-1} h^{-1}] during days 1–3, midazolam [0.03 mg kg^{-1} h^{-1}] during days 4 and 5) ($n = 84$). Regimen two consisted of hypnotic-based sedation: hypnotic agent (propofol days 1–3; midazolam days 4 and 5) and fentanyl ($n = 37$) or morphine ($n = 40$) according to routine clinical practice. For each regimen, agents were titrated to achieve optimal sedation (Sedation–Agitation Scale score 1–3) and analgesia (Pain Intensity score 1–2).

Results Overall, between-patient variability around the time of neurological assessment was statistically significantly smaller when using remifentanil (remifentanil 0.44 versus fentanyl 0.86 [$P = 0.024$] versus morphine 0.98 [$P = 0.006$]. Overall, mean neurological assessment times were significantly shorter when using remifentanil (remifentanil 0.41 hour versus fentanyl 0.71 hour [$P = 0.001$] versus morphine 0.82 hour [$P < 0.001$]). Patients receiving the remifentanil-based regimen were extubated significantly faster than those treated with morphine (1.0 hour versus 1.93 hour, $P = 0.001$) but there was no difference between remifentanil and fentanyl. Remifentanil was effective, well tolerated and provided comparable haemodynamic stability to that of the hypnotic-based regimen. Over three times as many users rated analgesia-based sedation with remifentanil as very good or excellent in facilitating assessment of neurological function compared with the hypnotic-based regimen.

Conclusions Analgesia-based sedation with remifentanil permitted significantly faster and more predictable awakening for neurological assessment. Analgesia-based sedation with remifentanil was very effective, well tolerated and had a similar adverse event and haemodynamic profile to those of hypnotic-based regimens when used in critically ill neuro-intensive care unit patients for up to 5 days.

Keywords: analgesia-based sedation, fentanyl, intensive care, morphine, remifentanil

bpm = beats per minute; CPP = cerebral perfusion pressure; GCS = Glasgow Coma Score; HR = heart rate; ICP = intra-cranial pressure; ICU = intensive care unit; MAP = mean arterial pressure; PI = Pain Intensity; SAS = Sedation–Agitation Scale; SD = standard deviation.

Introduction

Fentanyl and morphine are commonly used in the neuro-intensive care unit (neuro-ICU) setting. However, when administered over several days, the elimination of these traditional opioids can become prolonged as a result of redistribution and accumulation. This can result in unpredictable and/or delayed emergence from sedation when the regimen is discontinued to allow neurological assessments. Propofol and midazolam are the most commonly used hypnotic agents because of their effectiveness and short elimination half-lives [1,2]. Propofol is usually preferred during the first 2–3 days after admission to ICU because its use allows for frequent assessments of progression of neurological damage or recovery. If sedation is to be extended beyond 3 days, propofol is often replaced with midazolam on the basis of its lower cost. With these hypnotic agents, the risk for accumulation and unpredictable or delayed emergence is potentially smaller than with traditional opioids. In view of this, the opioid dose is usually minimised, with the hypnotic agent adjusted to maintain patient comfort. Thus, currently used sedative regimens could be considered to be predominantly hypnotic-based treatment regimens.

Remifentanil hydrochloride is a potent, selective μ-opioid receptor agonist, for the provision of analgesia in mechanically ventilated critically ill patients. Remifentanil has an onset of action of about 1 min and quickly achieves steady state. Unlike existing opioids, however, it is rapidly metabolised by non-specific blood and tissue esterases [3] to a clinically inactive metabolite. This results in an elimination half-life of less than 10 min, which is independent of the duration of infusion [4]. These characteristics make remifentanil very easy to titrate to effect and allow administration at higher doses than are normally used with traditional opioids without concerns about accumulation and unpredictable and/or delayed recovery. Synergistic interaction between remifentanil and sedatives results in sedative-sparing effects of volatile [5] and intravenous [6] agents.

When ventilation is controlled, remifentanil does not cause an increase in intracranial pressure when administered to patients undergoing craniotomy [7]. The cerebral haemodynamic effects of remifentanil compared with those of alfentanil [8] and fentanyl [9] are similar; remifentanil also has a safety profile similar to that of other opioids [8-10]. The predictable offset of action allows a rapid emergence from anaesthesia without the need for naloxone [9]. Other studies have confirmed that remifentanil can provide good haemodynamic control during particularly stimulating stages of craniotomy procedures yet still provide rapid and predictable emergence from anaesthesia [11,12]. The usefulness of remifentanil in patients undergoing awake craniotomy has also been demonstrated [13,14].

This study was designed to compare the safety and efficacy of analgesia-based sedation with conventional hypnotic-based sedation in patients with brain injuries requiring sedation during mechanical ventilation. Remifentanil was to be initiated and titrated to provide optimal sedation and analgesia *before* the addition of propofol (days 1–3) or midazolam (days 4 and 5) according to a predefined dosing algorithm. This type of regimen has already been shown to be both achievable and effective in post-surgical ICU patients [15]. The hypnotic-based treatment regimen required the opioid (fentanyl or morphine) and propofol (days 1–3) or midazolam (days 4 and 5) to be started simultaneously and then titrated to provide optimal sedation and analgesia, according to standard clinical practice.

Methods

This randomised, open-label, observational, parallel group study was conducted at 17 hospitals in six countries in Europe (4 in Greece, 4 in Spain, 3 in Belgium, 3 in The Netherlands, 2 in Germany, 1 in Austria). The study was conducted in accordance with good clinical practice and with the guidelines set out in the Declaration of Helsinki. After local and national ethics committee approvals, a total of 161 patients with acute brain injuries or who had undergone intracranial surgery were recruited. Informed consent or assent was obtained from all patients or their legal representatives. Patients were randomised on a 2:1:1 basis to receive either an analgesia-based treatment regimen in which patients initially received only remifentanil ($n = 84$), which was then titrated to provide optimal analgesia and sedation *before* the addition of a hypnotic agent (if required), or a hypnotic-based treatment regimen in which patients received a hypnotic agent and either fentanyl ($n = 37$) or morphine ($n = 40$) for analgesia and sedation, which were administered simultaneously and then titrated to response. For all three treatment groups, on days 1–3 the hypnotic agent was propofol, and on days 4 and 5 propofol was replaced with midazolam.

Patients with an acute, severe neurological insult or injury or who had undergone elective or emergency neurosurgery were eligible for entry into the study if they were aged 18–80 years, weighed 120 kg or less, had been admitted into the ICU within the past 24 hours, were intubated and were expected to require mechanical ventilation for 1–5 days. Patients were excluded from the study if they had or were likely to require one of the following: long-acting (or continuous administration of) neuromuscular blocking drugs to facilitate mechanical ventilation during the study period, barbiturate administration before or during the study period, or an epidural block during the maintenance or extubation phases of the study (see below). Any patients who failed to demonstrate signs of recovery or responsiveness within 6 hours of stopping any analgesia/sedation regimen in use at the time of screening for study entry were excluded from the study. Patients who were likely to require a tracheostomy with spontaneous ventilation within 5 days of starting the study drug treatment were excluded. Patients were also excluded if they had suffered severe, associated traumatic injury, if they had a neurological condition that

Table 1

Definition of Sedation–Agitation Scale scores*

Score	Definition	Description
1	Patient is not rousable	Patient may move or grimace minimally to stimuli but does not communicate or follow commands
2	Patient is very sedated	Patient can be roused by physical stimuli but does not communicate or follow commands; may move spontaneously
3	Patient is sedated	Patient is difficult to rouse, awakens to verbal stimuli or gentle shaking but drifts off again; will follow simple commands

*The Sedation-Agitation Scale score is a seven point scale score [15], but only scores 1–3 were required for our study.

might affect the ability to assess their Sedation–Agitation Scale (SAS) score [16], if they were admitted for status epilepticus or if they had moderate or severe renal impairment (predicted creatinine clearance of less than 50 ml min^{-1}). Patients with a history of allergy to opioids, benzodiazepines or propofol or of alcohol or drug abuse were also excluded from the study. Pregnant or lactating women were excluded from the study.

The treatment period comprised the time interval from the start of study drug administration until their permanent discontinuation, and was composed of three phases: first, the maintenance phase, from the start of the study drugs up to 5 days of treatment with the study drugs or until withdrawal of the patient or start of the extubation phase; second, the extubation phase, from the time that the patient was eligible for extubation until the time of actual extubation; and third, the post-extubation phase, from the time that the patient was extubated until the study drugs were discontinued.

In addition, there was a post-treatment period: from the time of discontinuation of the study drugs until 24 hours later or until discharge from ICU, whichever occurred first, and a follow-up period from 24 hours after stopping infusion of the study drugs until either ICU discharge or the end of day 7 after the start of study drugs, or death, whichever event occurred first.

Treatment protocol

The goal of treatment was to maintain each patient at an optimal level of sedation, based on an SAS score in the range 1–3 (Table 1) without clinically significant pain for the 5 days of the study period or until the start of the extubation process, whichever occurred first. Pain was assessed with a six-point Pain Intensity (PI) scale, in which 1 was no pain, 2 was mild pain, 3 was moderate pain, 4 was severe pain, 5 was very severe pain, and 6 was worst possible pain. If the patient could be roused they were asked if they had any pain. If the patient was unconscious, raised heart rate (HR) and/or blood pressure were used as indicators that the patient had moderate or worse pain. Clinically significant pain was defined as a score of 3 or more. SAS and PI scores were assessed by the investigator or study nurse throughout the treatment period.

On completion of the treatment period (that is, from the extubation phase onwards), sedation and pain relief were administered at the discretion of the investigator and in accordance with local practice.

Remifentanil-based treatment

To assess the remifentanil-based regimen to provide optimal patient comfort, patients were treated in accordance with a modified version of a previously reported dosing algorithm [15,17] in which they received an initial infusion of remifentanil, which was titrated to response, *before* the propofol infusion was started. The remifentanil infusion was started at an initial rate of 9 μg kg^{-1} h^{-1} and was increased in increments of at least 1.5 μg kg^{-1} h^{-1} at intervals of 5–10 min depending on clinical need or severity of illness up to 18 μg kg^{-1} h^{-1}. If the target scores for patient comfort (SAS = 1–3; PI = 1–2) were not achieved with remifentanil alone (infusion rate at 18 μg kg^{-1} h^{-1}), additional sedation was provided by administering a bolus dose of propofol (up to 0.5 mg kg^{-1}) and/or a propofol infusion starting at a rate of 0.5 mg kg^{-1} h^{-1}, at the investigator's discretion. If the target SAS range of 1–3 was still not achieved, the patient received incremental increases in the remifentanil infusion to a maximum rate of 60 μg kg^{-1} h^{-1} and/or additional boluses and/or increases in the infusion rate of propofol up to a maximum dose of 4 mg kg^{-1} h^{-1} to attain and then maintain optimum analgesia and sedation. The remifentanil infusion rate was increased in preference to propofol when more intense analgesia was required.

The remifentanil/propofol treatment regimen was maintained for the first 3 days of the study. Patients who required analgesia and sedation beyond study day 3 had their propofol treatment discontinued and replaced with midazolam (recommended doses: bolus doses 0.01–0.05 mg kg^{-1}, infusions 0.03–0.3 mg kg^{-1} h^{-1}).

Hypnotic-based treatment

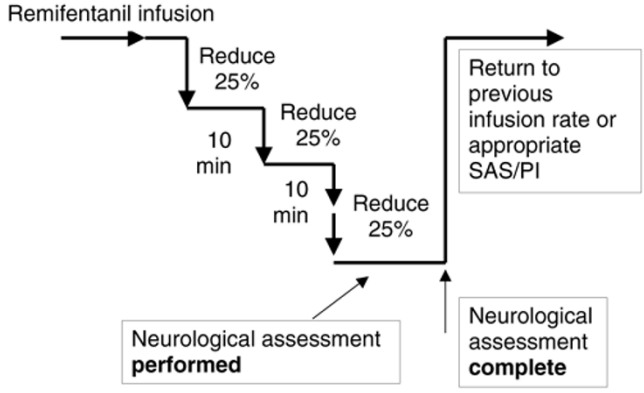
For the patients randomised to receive fentanyl or morphine, optimal analgesia and sedation as described above were achieved in accordance with routine local practice for a hypnotic-based treatment regimen. As with the remifentanil treatment group, in the patients who continued to require analgesia

and sedation beyond day 3, propofol was discontinued and replaced with midazolam in accordance with local transitioning protocols. The infusion rates of fentanyl and morphine and bolus doses and infusion rates of propofol and midazolam were not specified in the protocol but were those that were used as part of routine clinical practice at each investigating site.

Bolus doses of remifentanil, morphine or fentanyl were not administered during the maintenance period of the study, to avoid and minimise any systemic or intracranial haemodynamic side effects.

If a patient in any of the three treatment groups showed signs of hypotension (more than 25% fall in mean arterial pressure [MAP] from baseline) or bradycardia (HR less than 40 beats per minute (bpm) for less than 1 min, less than 60 bpm for more than 1 min), the opioid and/or hypnotic drug infusion rates were to be reduced as considered appropriate by the individual investigator, and the patient was reassessed 10 min later.

Figure 1



Downward titration of remifentanil for neurological assessment.

Patient monitoring

All patients were monitored intensively throughout the study. Baseline Glasgow Coma Score (GCS), SAS, PI, MAP and HR were recorded before the administration of study drugs. When available, intra-cranial pressure (ICP) and cerebral perfusion pressure (CPP) were also recorded. SAS, PI, MAP, HR, ICP and CPP were then recorded at the time of any changes in study drug infusion rates or bolus dosing and at 10 min intervals afterwards until adequate SAS and PI scores were attained. Once target SAS and PI scores were attained, haemodynamic monitoring was performed at 1–4 hour intervals. In addition, haemodynamic parameters were recorded at the start of down-titrations of study drugs for neurological assessment of patients and when the assessments were completed. SAS, PI, MAP, HR, ICP and CPP were also recorded at the start of and at the time of adequate transitioning from propofol to midazolam at the end of day 3 and if a patient was extubated before day 5 of the study treatment period. These parameters were also recorded at the start of the final transition to an alternative analgesia/sedation regimen at the end of study day 5, at 20 min intervals after each down-titration of the remifentanil infusion as part of this process, at 30 and 60 min after the termination of the infusion and at final transition to an alternative opioid. Patients were continuously assessed for the occurrence of adverse events until 24 hours after permanent discontinuation of the study drugs, or until ICU discharge if this occurred earlier. Serious adverse events were defined as adverse events that resulted in any of the following outcomes: death, life-threatening event, prolongation of hospitalisation, or a disability or incapacity. Important medical events that did not result in death or were not life-threatening were considered serious adverse events when, on the basis of appropriate medical judgement, they jeopardised the patient and required medical or surgical intervention to prevent one of the outcomes listed above.

Neurological assessments

The level of sedation was reduced to allow neurological assessment according to individual clinical need; however, there was at least one neurological assessment in any 24-hour study period. The first assessment did not take place until at least 6 hours after starting the study drugs. The efficacy of the study treatment regimens was assessed by comparing the respective neurological assessment time intervals, defined as the time from the start of the first down-titration or withholding of the administration of either the opioid or the hypnotic component of the treatment regimen to the time at which the neurological assessment was completed.

In the remifentanil treatment group, the remifentanil infusion was reduced in decrements of not more than 25% of the current rate at 10 min intervals to a level that permitted neurological assessment of the patient to be performed (Fig. 1). This was to provide a smooth offset of analgesia. Any down-titration of the co-administered hypnotic agent was performed secondary to the initial reduction in the remifentanil infusion in decrements at the investigator's discretion. Once neurological assessment was completed, the remifentanil infusion was increased in increments of at least 1.5 $\mu g\ kg^{-1}\ h^{-1}$ until the pre-assessment infusion rate and/or target SAS and PI scores were attained. Where appropriate, the concomitant hypnotic agent was simultaneously increased to the pre-assessment infusion rate and/or until the target SAS and PI scores were attained, at the investigator's discretion. For patients in the fentanyl or morphine groups, down-titration or discontinuation of the opioid and/or hypnotic agents for neurological assessments (and subsequent up-titration afterwards) were made at the investigator's discretion and in accordance with routine practice at the investigational site.

Extubation within the 5-day study period

All patients continued on study treatment until they were judged by the investigator to be eligible to begin the extubation process. To allow for smooth emergence from the effects of remifentanil and adequate time for transitioning to alternative analgesia, the remifentanil infusion rate was decreased every 10–20 min over a period of up to 1 hour to an infusion rate of 6 $\mu g\ kg^{-1}\ h^{-1}$. The number of stages and the size of each reduction in the infusion rate were at the individual investigator's discretion. After extubation, the remifentanil infusion was immediately reduced by not more than 25% and thereafter at 10–20 min intervals until it was discontinued (that is, after three further decrements over about 1 hour). If any of the down-titrations of the initial infusion rate resulted in an alteration in MAP or HR of ± 25%, the decrements were reduced and the down-titration was performed more slowly at the investigator's discretion. Open-label bolus doses of propofol or midazolam for sedation and fentanyl or morphine for analgesia could be given at the investigator's discretion to make the patient comfortable. Patients in the fentanyl and morphine treatment groups had their study regimens tapered for extubation at the investigator's discretion and in accordance with routine clinical practice at each study site.

Transition to routine sedation and analgesia after study day 5

Patients in the remifentanil treatment group who remained intubated and required sedation or analgesia after day 5 were transitioned to an alternative opioid/hypnotic regimen used routinely at the study site. Beginning within ± 6 hours of completion of day 5, the remifentanil infusion rate was reduced in decrements of not more than 25% of the current rate at 20 min intervals in accordance with the clinical needs of the patient and the investigator's judgement. The down-titration of the remifentanil infusion was accompanied by the start of administration of an alternative opioid at a dose or rate considered appropriate for the clinical needs of the patient. Any infusion and/or bolus dosing with midazolam was maintained, although dose adjustments could be made at the investigator's discretion. If any down-titration produced a change in MAP or HR of ± 25%, the size of subsequent decrements and the intervening time intervals were adjusted accordingly.

Patients in the fentanyl or morphine treatment groups who required sedation or analgesia beyond day 5 could either continue to receive their existing treatment or could be transitioned to an alternative regimen as considered appropriate by the investigator. If a patient was transferred to an alternative regimen, SAS, PI, MAP and HR values were recorded after all dose changes during the transitioning phase and at 30 and 60 min after discontinuation of the study drug(s).

Study endpoints

The primary efficacy endpoint was the overall between-patient variability around the mean time to neurological assessment. The overall mean time to neurological assessment was assessed as a secondary end point. Other secondary end points included the mean time to neurological assessment and the between-patient variability around that time during first to the fifth 24-hour assessment period, the mean percentage of hours of optimal sedation (SAS score 1–3), descriptive pain scores, weighted mean infusion rates of remifentanil, fentanyl, morphine, propofol and midazolam, the time from starting the extubation process until extubation, the time from extubation until ICU discharge, haemodynamics, and adverse events. At the end of the study, the physician or nurse involved were asked the following question: 'How would you rate the study drug regimen in terms of its overall quality of performance in facilitating wake-up (lightening the level of sedation) to allow neurological assessment of the patient?' Assessments were ranked as excellent, very good, good, fair or poor.

Statistical methods

For each set of neurological assessments made during the treatment period, the time from altering the infusion until completion of the assessment was evaluated. From these times, the mean log-transformed time to neurological assessment was calculated for each patient. The ratio of the variance of the mean log-transformed neurological assessment times was assessed by using two-sided *F*-tests overall and on each day of the study. In the original study design it was intended that between-patient variability and mean neurological assessment times would be compared for all patients. In the protocol if a 'successful' neurological assessment was not made within 6 hours of the first downward titration, it was planned that an imputed neurological assessment time of 6 hours would be used, the rationale *a priori* being that patients did not wake up due to drug accumulation. However, neurological assessments might not have been possible owing to treatment-independent deterioration in a patient's neurological condition. It was concluded therefore that an imputation strategy was inappropriate and an observed case analysis was considered to be the most useful way of analysing the data. The log mean times to neurological assessment were analysed by unpaired *t*-tests and back-transformed to geometric means and mean ratios. As well as an overall analysis of time to neurological assessment, assessments within each 24-hour period were made. The analysis of pain and sedation control was undertaken with the Wilcoxon Rank Sum test. Median differences and their 95% confidence intervals are also quoted. The recovery endpoints were analysed with Cox proportional hazards. Hazard ratios and their 95% confidence intervals are quoted. Cerebral dynamics were collected on only a subset of the patients. These data were analysed by using an analysis of variance with baseline entered as a covariate. The proportion of patients with the most common adverse events (defined as 5% or more of patients experiencing the adverse event from any treatment group) were tabulated by treatment group and analysed with Fisher's Exact Test.

Table 2

Patient characteristics and baseline clinical assessments

Characteristic	Remifentanil	Fentanyl	Morphine
Number of patients treated	84	37	40
Mean age, years (SD)	46.8 (16.3)	49.6 (16.9)	47.3 (20.0)
Sex			
Male	44 (52%)	24 (65%)	25 (63%)
Female	40 (48%)	13 (35%)	15 (38%)
Mean height, cm (SD)	171.1 (9.1)	170.9 (7.4)	170.9 (8.5)
Mean weight, kg (SD)	76.5 (12.2)	76.5 (12.6)	75.2 (12.2)
Median duration of mechanical ventilation, days (range)	1.95 (0.16–5.00)	1.47 (0.08–5.00)	1.70 (0.19–5.00)
Reason for admission to ICU			
Subarachnoid haemorrhage	19 (23%)	7 (19%)	12 (30%)
Isolated neurotrauma	13 (15%)	4 (11%)	9 (23%)
Post-intracranial surgery	31 (37%)	18 (49%)	10 (25%)
Epidural, subdural or intracranial haematoma	16 (19%)	6 (16%)	6 (15%)
Cerebrovascular accidents[a]	3 (4%)	1 (3%)	2 (5%)
Other	2 (2%)	1 (3%)	1 (3%)
Mean SAS score (SD)	3.7 (1.5)	3.6 (1.2)	3.7 (1.5)
Mean GCS (SD)	8.4 (2.7)	8.8 (2.9)	8.6 (2.5)
Mean Pain Intensity score (SD)	2.1 (1.1)	2.1 (1.0)	2.1 (1.0)
Mean MAP, mmHg (SD)	97.2 (17.6)	100.6 (13.8)	97.4 (14.1)
Mean heart rate, bpm (SD)	89.3 (20.3)	90.9 (20.5)	88.9 (21.5)

bpm, beats per minute, GCS, Glasgow Coma Score; ICU, intensive care unit; MAP, mean arterial pressure; SAS, Sedation–Agitation Scale; SD, standard deviation. [a]Resuscitation owing to cardiac disease; treatment with interventional radiology for cerebral disorders; meningitis; encephalitis.

A total of 160 randomised patients were required for the detection of a 54% reduction in the variance of the mean log-transformed wake-up times for the patients receiving remifentanil compared with the fentanyl or morphine treatment groups by using two-sided *F*-tests with 80% power and a 0.05 level of significance.

Results

A total of 161 patients were treated in this study (84 with remifentanil, 37 with fentanyl and 40 with morphine); patient characteristics and baseline clinical assessments are summarised in Table 2. The three groups were well matched for age, physical characteristics and baseline assessments of SAS, GCS, PI, MAP and HR. Most patients were receiving intensive care after intracranial surgery. As the study progressed the number of patients in each of the treatment groups reduced in a similar fashion, predominantly because patients were recovering during the first couple of days and were being extubated. Twenty-three patients received remifentanil for 5 days.

Efficacy

Overall, between-patient variability in the time to neurological assessments was significantly smaller when using analgesia-based sedation with remifentanil compared with hypnotic-based sedation with fentanyl or morphine; mean neurological assessment times were also significantly shorter with remifentanil-based sedation (Table 3). On average, neurological assessments could be completed 0.3 hours and 0.41 hours earlier, respectively (see Table 3 for differences between remifentanil and fentanyl/morphine on each of the five days of assessment). Mean neurological assessment times overall and for each of the five days are shown in Fig. 2.

Fentanyl and morphine treatment groups were optimally sedated (SAS scores 1–3) for a significantly longer duration during the treatment period (Table 4). Although statistical differences were observed against remifentanil, optimal sedation was, on average, achieved for all treatment groups in excess of 95% of the treatment period. There was no significant dif-

Table 3

Time to and variability around individual neurological assessment

Parameter	Overall	Day 1	Day 2	Day 3	Day 4	Day 5
Remifentanil	$n = 64$	$n = 58$	$n = 33$	$n = 26$	$n = 21$	$n = 20$
Mean time to neurological assessment,[a] h	0.41	0.35	0.45	0.46	0.78	0.81
Between-patient variability	0.44	0.35	0.47	1.35	0.30	0.42
Fentanyl	$n = 32$	$n = 32$	$n = 13$	$n = 11$	$n = 7$	$n = 8$
Mean time to neurological assessment,[a] h	0.71	0.69	0.67	0.92	1.63	1.83
Mean ratio (95% CI)	1.74 (1.26, 2.41)	1.98 (1.44, 2.72)	1.48 (0.73, 3.01)	2.01 (0.93, 4.33)	2.09 (1.33, 3.30)	2.27 (1.39, 3.73)
Remifentanil versus fentanyl	$P = 0.001$	$P < 0.001$	$P = 0.274$	$P = 0.074$	$P = 0.003$	$P = 0.002$
Between-patient variability	0.86	0.86	3.01	0.51	0.13	0.10
Ratio of variability (95% CI)	1.96 (1.01, 3.45)	2.45 (1.37, 4.79)	6.41 (2.83, 19.9)	0.38 (0.15, 1.34)	0.45 (0.16, 2.61)	0.24 (0.08, 1.16)
Remifentanil versus fentanyl	$P = 0.024$	$P = 0.003$	$P < 0.001$	$P = 0.109$	$P = 0.333$	$P = 0.059$
Morphine	$n = 34$	$n = 31$	$n = 20$	$n = 10$	$n = 3$	$n = 2$
Mean time to neurological assessment[a], h	0.82	0.79	0.70	1.01	1.28	1.86
Mean ratio (95% CI)	2.01 (1.44, 2.81)	2.25 (1.60, 3.15)	1.53 (0.93, 2.52)	2.19 (0.98, 4.86)	1.65 (0.84, 3.25)	2.31 (0.87, 6.13)
Remifentanil versus morphine	$P < 0.001$	$P < 0.001$	$P = 0.091$	$P = 0.055$	$P = 0.139$	$P = 0.088$
Between-patient variability	0.98	1.03	1.27	0.48	0.12	0.02
Ratio of variability (95% CI)	2.24 (1.28, 4.28)	2.93 (1.63, 5.80)	2.71 (1.27, 6.58)	0.35 (0.14, 1.37)	0.41 (0.13, 23.0)	0.06 (0.02, 112.6)
Remifentanil versus morphine	$P = 0.006$	$P = 0.001$	$P = 0.012$	$P = 0.108$	$P = 0.659$	$P = 0.381$

Between-patient variability is a measure of predictability of wake-up for neurological assessment. CI, confidence interval. [a]Geometric mean.

ference between any of the treatment groups with regard to the incidence of pain; on average, patients had no pain or mild pain for more than 99% of the treatment period.

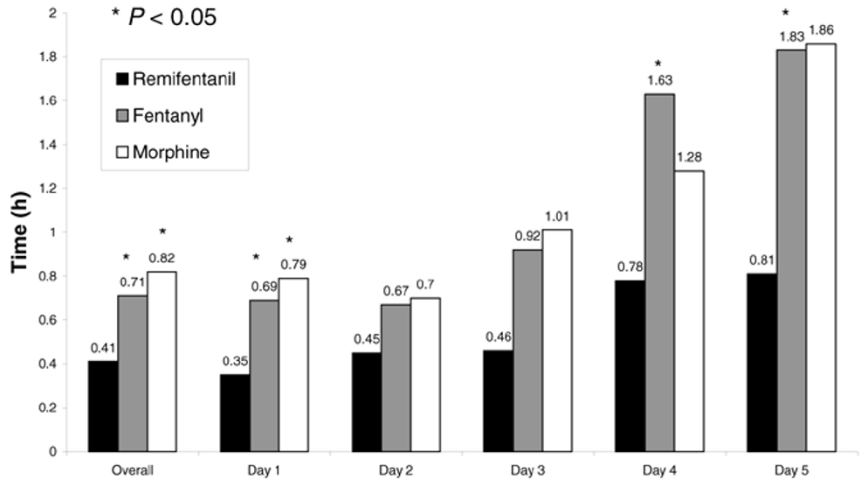
Exposure to opioids and sedative agents is shown in Table 5. Remifentanil was administered for slightly longer than in the fentanyl and morphine treatment groups. Nearly all the patients required propofol and some patients received it for longer than the recommended 72 hours. There was a trend towards reduced propofol use in the remifentanil treatment group.

Remifentanil patients were extubated significantly earlier (about 1 h) than patients who were administered a hypnotic-based regimen that included morphine ($P = 0.001$, Table 6). This difference was not observed when comparing remifentanil with fentanyl. There were no observed differences between remifentanil and fentanyl or morphine in the time from starting the extubation process until ICU discharge.

Seventy-eight per cent of physicians or ICU nurses thought that the performance of remifentanil in facilitating 'waking' the patient up to allow assessment of neurological function was either very good or excellent. This compares with 25% for fentanyl and 8% for morphine (Fig. 3).

ICP and CPP were measured in only a relatively small number of patients and are summarised in Table 7. Mean baseline values were within normal physiological ranges and there were no significant differences between remifentanil and fentanyl or morphine during the treatment period. The weighted mean

Figure 2



Geometric mean time from altering the infusion until completion of daily neurological assessments.

MAP was very similar across the three treatment groups. Mean (range) values were 73.0 (30.2–103.6), 71.0 (28.8–109.8) and 74.4 (26.2–123.7) mmHg for remifentanil, fentanyl and morphine, respectively. A similar situation was seen for HR, with respective values of 64.4 (20.0–109.6), 65.5 (22.1–105.3) and 66.6 (20.7–130.8) bpm.

Safety

There were six deaths in this study, four in the remifentanil group, none in the fentanyl group and two in the morphine group. None of the deaths were considered to be related to the study drugs. Most adverse events reported in this study occurred during the maintenance phase of the treatment period (Table 8). No adverse events were reported during the follow-up period of the study. Adverse events leading to premature discontinuation from the study involved bradycardia, cerebral infarction, oedema, hypotension and intracranial haemorrhage in the remifentanil group, raised ICP in the fentanyl group, and bradycardia and raised ICP in the morphine group. Although the overall incidence of patients with adverse events seemed to be slightly higher in the remifentanil group, most of this involved isolated events and there was no significant difference between remifentanil and either of the comparator opioids in adverse events occurring in 5% or more of patients: these involved hypotension, bradycardia and polyuria. Serious adverse events occurred in 5% of patients in each treatment group (four remifentanil patients involving bradycardia, cerebral infarction, oedema or intra-cranial haemorrhage; two fentanyl patients involving cardiac arrest, hypotension or raised ICP; two morphine patients involving cerebral infarction, post-operative complication or raised ICP). There was only one drug-related serious adverse event involving bradycardia in a patient treated with remifentanil. This occurred in a 63-year-old male with a history of atrial fibrillation receiving remifentanil in combination with propofol for analgesia and sedation after spontaneous intracerebral (right temporo-occipital) haemorrhage. About 51 hours after starting the remifentanil infusion, the patient developed severe bradycardia (less than 50 bpm), considered to be life threatening. The remifentanil infusion was discontinued and the bradycardia resolved 20 min after the remifentanil infusion was stopped. The investigator considered there was a reasonable possibility that the bradycardia was caused by remifentanil, although the patient's concurrent atrial fibrillation was also cited as a possible cause of the event.

Discussion

The present study was a comparison of sedation techniques, designed to compare an analgesia-based treatment regimen using remifentanil with conventional hypnotic-based sedative practice in patients with neurotrauma. In the analgesia-based treatment group the remifentanil infusion was started and titrated to response to provide optimal sedation and patient comfort *before* the administration of any sedative agent. In the hypnotic-based treatment group sedation and analgesia were started at the same time, with the sedative agent being predominantly titrated to provide patient comfort.

The study was complex in design and the reduction in sedation or wake-up process for neurological assessment was not specifically defined but was left up to the discretion of the investigator and local practice in each hospital. The study used two different sedative agents because it was considered normal clinical practice to change from propofol to midazolam for patients who are in the ICU for more than 3 days. This treatment regimen was based on the opinions of clinicians who were consulted during the development of the study design. Overall, remifentanil afforded significant reductions in mean neurological assessment times and between-patient variability around these times using a well-balanced group of patients.

Table 4

Sedation and pain control during the treatment period

Parameter	Remifentanil ($n = 84$)	Fentanyl ($n = 37$)	Morphine ($n = 40$)
Optimal sedation (SAS = 1–3)			
Percentage hours, median (range)	95.6 (15–100)	98.1 (87–100)	99.0 (0–100)
Median difference (95% CI)		-2.36 (-4.4, -1.0)	-2.30 (-4.2, -0.9)
P[a]		<0.001	<0.001
No pain or mild pain			
Percentage hours, median (range)	99.3 (72–100)	99.7 (79–100)	99.2 (15–100)
Median difference (95% CI)		0.0 (-0.5, 0.0)	0.0 (-0.4, 0.3)
P[a]		0.495	0.928
Moderate pain			
Percentage hours, median (range)	0.4 (0–28)	0.0 (0–5)	0.1 (0–9)
Median difference (95% CI)		0.0 (0.0, 0.4)	0.0 (0.0, 0.2)
P[a]		0.154	0.647
Severe, very severe or worst possible pain			
Percentage hours, median (range)	0.0 (0–3)	0.0 (0–1)	0.0 (0–4)
Median difference (95% CI)		0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
P[a]		0.111	0.963

CI, confidence interval; SAS, Sedation–Agitation Scale. [a]Value for treatment difference (remifentanil versus comparator).

Table 5

Exposure to opioids and sedatives

Parameter	Remifentanil ($n = 84$)	Fentanyl ($n = 37$)	Morphine ($n = 40$)
Opioid			
Median duration of opioid infusion, h (range)	47.3 (3.8–120)	35.2 (0.2–120)	40.9 (4.5–120)
Median weighted mean opioid infusion rate: remifentanil and fentanyl, μg kg^{-1} h^{-1}; morphine, mg kg^{-1} h^{-1} (range)	15.4 (3.0–38.2)	3.6 (0.1–7.9)	0.1 (0.0–6.8)
Propofol			
Number of patients who received a propofol infusion	76 (90%)	37 (100%)	37 (93%)
Median duration of propofol infusion, h (range)	24.3 (0.0–118)	24.5 (0.0–119.4)	41.7 (0.7–115.3)
Median weighted mean propofol infusion rate, mg kg^{-1} h^{-1} (range)	1.93 (0.2–68.8)	2.49 (0.5–11.5)	2.30 (0.3–18.1)
Midazolam			
Number of patients who received a midazolam infusion	30 (36%)	11 (30%)	12 (30%)
Median duration of midazolam infusion, h (range)	47.3 (0–117.1)	48.1 (2.3–112.1)	22.4 (1.8–101.4)
Median weighted mean midazolam infusion rate, mg kg^{-1} h^{-1} (range)	0.18 (0–17)	0.11 (0–2.3)	0.13 (0.1–0.5)

The reduced variability is indicative of better control of the patient's level of sedation and greater predictability in the offset of sedative effects when awakening the patient for neurological assessment. Reduced variability in the duration of optimal sedation has recently been reported by Muellejans and colleagues [15]. In a group of predominantly post-cardiac surgical ICU patients, it was suggested that the superior titratability of remifentanil results in a better quality of sedation for critically ill patients. The superior control of analgesia and sedation afforded by remifentanil is supported by the ICU phy-

Table 6

Recovery results for patients who became eligible to start the extubation process within 5 days of the start of the study drug infusion

Parameter	Remifentanil ($n = 47$)	Fentanyl ($n = 22$)	Morphine ($n = 28$)
Median time on mechanical ventilation during the treatment period, h (range)	24.83 (12.5–110.2)	24.08 (16.4–70.0)	37.04 (17.8–98.2)
Hazard ratio relative to comparator		1.21	0.71
95% CI		0.70, 2.10	0.43, 1.18
P		0.500	0.188
Median time from the start of the extubation process until actual extubation, h (range)	1.00 (0.0–97.2)	0.68 (0.0–5.6)	1.93 (0.0–96.2)
Hazard ratio relative to comparator		1.23	0.42
95% CI		0.70, 2.13	0.25, 0.71
P		0.474	0.001
Median time from the start of extubation process until ICU discharge, h (range)	43.50 (2.4–150.0)	42.90 (2.2–120.6)	49.63 (3.7–144.2)
Hazard ratio relative to comparator		1.34	0.98
95% CI		0.76, 2.37	0.56, 1.70
P		0.316	0.928

CI, confidence interval; ICU, intensive care unit.

sician or nurse satisfaction scores, in which remifentanil was considered to be either excellent or very good by 78% of the users; this was clearly differentiated from fentanyl and especially morphine, with scores of 25% and 8%, respectively.

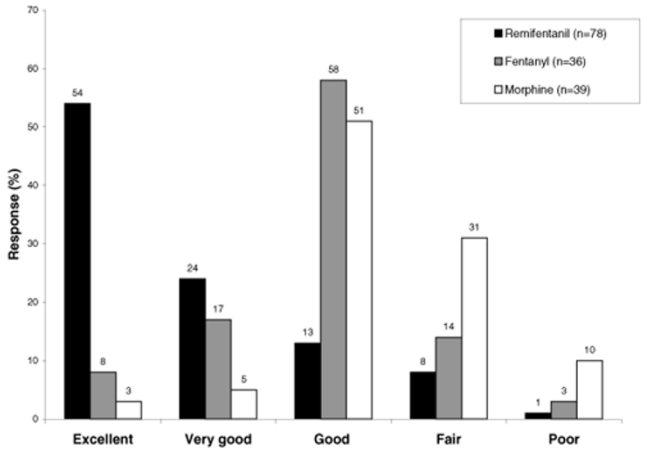
Given that statistical differences were shown overall and at day 1, does this mean that remifentanil is only suitable for the first day of the patient's stay in the ICU? Even though 161 patients took part in this study, the lack of consistent differences between the treatment groups from day 2 onwards is probably a result of the diminishing number of patients. Hence the latter part of the study could only show trends (see Fig. 2) and did not have the power to demonstrate statistical differences.

It is clear that analgesia-based sedation was as effective as hypnotic-based sedation, with patients being optimally sedated (SAS score 1–3) for more than 95% of the treatment period. The largest median difference between remifentanil and the comparator opioids was -2.36% (Table 4), with a maximum of -4.4%. Although the median percentage of hours of optimal sedation was highly significantly different ($P < 0.001$), such a small difference is not likely to be clinically significant.

Rapid and predictable emergence from sedation is very important in patients with neurotrauma. Clinicians need to be able to assess their patient's neurological function rapidly; however, this is not always possible when using conventional hypnotic-based sedation because of the unpredictable elimination of conventional sedative and analgesic agents. The predictable, organ-independent metabolism of remifentanil, which is unaffected by impaired kidney and liver function, results in a rapid and predictable offset of action of remifentanil and eliminates 'hangover' sedation often experienced with conventional sedative and analgesic agents. Analgesia-based sedation with remifentanil therefore has the potential to reduce the need for additional procedures such as CT (computed tomography) scanning, to permit earlier detection of neurological deterioration and to allow neurosurgeons to make earlier decisions concerning the need for further operative procedures.

When remifentanil was first used in anaesthesia, post-operative pain occurred more frequently because of the rapid offset of effects. A change in the early treatment of post-operative pain relief was needed and as a result this problem should no longer occur [18]. In a double-blind study using remifentanil in

Figure 3



Intensive care unit physician or nurse satisfaction score.

Table 7

Cerebral haemodynamics

Parameter	Remifentanil ($n = 20$)	Fentanyl ($n = 10$)	Morphine ($n = 12$)
ICP			
Mean baseline, mmHg (SD)	11.7 (6.3) ($n = 16$)	10.8 (8.1) ($n = 8$)	16.7 (9.0) ($n = 10$)
LS mean, mmHg	11.97	13.93	10.31
LS mean differences		1.95	-1.66
95% CI		-1.70, 5.60	-5.22, 1.90
P[a]		0.285	0.351
CPP			
Mean baseline, mmHg (SD)	80.5 (9.1) ($n = 12$)	85.5 (15.8) ($n = 5$)	73.6 (17.6) ($n = 8$)
LS mean, mmHg	68.77	75.58	76.99
LS mean differences		6.81	8.22
95% CI		-8.13, 21.74	-5.29, 21.72
P[a]		0.359	0.223

CI, confidence interval; CPP, cerebral perfusion pressure; ICP, intra-cranial pressure; LS, least square; SD, standard deviation. [a]Remifentanil versus fentanyl/morphine, adjusting for baseline.

Table 8

Premature discontinuation due to an adverse event, and adverse events recorded during the study

Parameter	Remifentanil ($n = 84$)	Fentanyl ($n = 37$)	Morphine ($n = 40$)
Premature discontinuation from the study due to an adverse event	6 (7%)	1 (3%)	2 (5%)
Patients with any adverse event	32 (38%)	9 (24%)	12 (30%)
Patients with a drug-related adverse event	21 (25%)	3 (8%)	4 (10%)
Number (%) of patients with any adverse event			
Treatment period			
Maintenance phase	29 (35%)	8 (22%)	10 (25%)
Extubation phase	2 (2%)	0	0
Post-extubation phase	2 (2%)	0	0
Post-treatment period	5 (6%)	4 (11%)	2 (5%)
Number (%) of patients with a serious adverse event	4 (5%)	2 (5%)	2 (5%)
Number (%) of patients with a drug-related serious adverse event	1 (1%)	0	0

Summary of adverse events occurring in 5% or more of patients

Event	Remifentanil	Fentanyl	Morphine	P[a]	P[b]
Hypotension	12 (14%)	4 (11%)	2 (5%)	0.774	0.223
Bradycardia	5 (6%)	2 (5%)	2 (5%)	1.000	1.000
Polyuria	3 (4%)	2 (5%)	0	0.641	0.550

[a]Remifentanil versus fentanyl. [b]Remifentanil versus morphine.

the critically ill [15], pain after discontinuation of remifentanil has been reported. It is likely that the double-blind design of that study meant that pain transition could not be optimised. In the present open-label study doctors could proactively pre-

empt pain by the administration of longer-acting analgesics well before stopping the remifentanil infusion, with the result of there being no difference in pain scores between remifentanil and the comparator opioids.

The median weighted mean dose of remifentanil observed in this study was slightly higher than that reported in previous studies [15,19,20]. In addition, in previous studies 43–78% of patients did not require administration of a sedative agent [15,19,20]. In the present study almost all the patients required propofol, and the median weighted mean dose of propofol was much higher than the mean value of about 0.5 mg kg^{-1} h^{-1} reported previously [15]. This observation might be due to the deeper level of sedation targeted in this study. Remifentanil interacts with all sedative agents in a synergistic manner. When using remifentanil-based sedation, the recommended starting dose of propofol is 0.5 mg kg^{-1} h^{-1} which is much lower than that used for hypnotic-based sedation. This is an important point to remember: if a 'normal' sedative dose of propofol (3 mg kg^{-1} h^{-1}) is administered with the recommended starting dose of remifentanil, adverse sequelae such as hypotension might occur. The reduced number of patients from day 4 onwards makes it difficult to draw any conclusions about midazolam-sparing effects when using remifentanil.

The median weighted mean infusion rate of remifentanil was lower than 18 μg kg^{-1} h^{-1} and almost all the patients received propofol. This could have resulted in the sedative agent's being the rate-limiting agent during the periods of neurological assessment. Despite this, significant differences between treatment regimens were observed. To take full advantage of its unique properties, remifentanil must be started on its own and titrated to response *before* the addition of a sedative agent at a reduced dosage.

It has been reported that fentanyl, sufentanil and alfentanil can increase ICP [21,22], probably because of a vasodilatory response, secondary to systemic hypotension or changes in arterial P_{CO_2}, particularly in patients with hypovolaemia [23,24]. However, analgesia and sedation are often used to decrease ICP [25]. Although only measured in a small number of patients, baseline ICP and CPP values were within normal ranges and the physiological effect of remifentanil was not different from that observed with fentanyl or morphine.

The numerically higher incidence of adverse events in the remifentanil group might have been because of the open-label design of the study. Most of the adverse events were non-specific and it is important to note that there were no differences between the remifentanil and the comparator opioids in the frequency of adverse events occurring in 5% or more of patients. The most frequently reported adverse events were generally typical for opioids, with hypotension accounting for up to 45% of the number of patients reporting any adverse event. When hypotension occurred it was easily treated by routine clinical measures. In general, the systematic monitoring of the basic haemodynamic profile (MAP, HR, ICP, CPP) permitted remifentanil and propofol to be co-administered without sudden decreases in arterial blood pressure. Remifentanil has a potency similar to that of fentanyl [26]. Although not significantly different, the slightly higher incidence of hypotension in the remifentanil group is perhaps expected, given the higher dose of remifentanil administered.

Conclusions

The present study has demonstrated that the important clinical properties of remifentanil (such as rapid onset and offset of action, organ-independent metabolism and lack of accumulation) make it well suited for use in critically ill patients with neurotrauma. Analgesia-based sedation with remifentanil, titrated to response *before* the addition of any sedative agent, offered significantly faster and more predictable time to assessment of neurological function than a hypnotic-based technique. These data support the lack of accumulation and predictable offset of action of remifentanil. Both techniques were very effective in providing patient comfort and there was a trend towards less use of propofol in the remifentanil group. Although not seen when comparing remifentanil with fentanyl, there was a significantly shorter time to extubation compared with hypnotic-based sedation with morphine. Both techniques provided similar haemodynamic stability. There was a strong physician or nurse preference for use of remifentanil. Although data were limited, there was no evidence of any difference in ICP or CPP between remifentanil and the hypnotic-based treatment groups. Remifentanil was well tolerated in neurotrauma patients requiring intensive care for up to 5 days.

Competing interests

AK, KM, SS, AK, JS and BS received payment from GlaxoSmithKline (either personally or to their respective department) according to the number of patients recruited. AJTK is an employee of GlaxoSmithKline.

Acknowledgements

We acknowledge the contribution of the following to the conduct of the study: in Austria, Professor Illievich (Universitätsklinik f. Anästhesie und Allg. Intensivmedizin, Neurochirurgische Intensivmedizin, Vienna); in Belgium, Dr De Deyne (ZOL Campus St Jan, Genk), Dr Hantson (Clin. Univ. St. Luc, Brussels) and Dr Damas (CHR de la Citadelle, Liège); in Germany, Professor Wissing (J.-W. Goethe Universität, Frankfurt) and Professor Radke (Martin-Luther-Universität, Halle); in The Netherlands, Dr Maas (Academisch Ziekenhuis Rotterdam/Dijkzigt, Rotterdam) and Dr Punt (Atrium Heerlen Afdeling Anaesthesie, Heerlen); in Spain, Dr López (Hospital Infanta Cristina, Badajoz), Dr Bonome (Hospital Juan Canalejo, La Coruña), Dr Quero (Hospital Gregorio Marañón, Madrid) and Dr Sanchez-Isquierdo (Hospital 12 de Octubre, Madrid).

References

1. Carrasco G, Cabre L, Sobrepere G, Costa J, Molina R, Cruspinera A, Lacasa C: **Synergistic sedation with propofol and midazolam in intensive care patients after coronary artery bypass grafting.** *Crit Care Med* 1998, **2:**844-851.

Key messages

In neurotrauma patients requiring intensive care for up to 5 days, analgesia-based sedation using remifentanil compared with a standard hypnotic-based technique provided the following:

- a significant reduction in the mean time taken to wake the patient for assessment of neurological function;
- a significantly reduced mean between-patient variability in the time to wake-up, making the performance of this assessment more predictable;
- a significantly shorter time to extubation than with a hypnotic-based regimen using morphine as the analgesic;
- no clinical differences in pain and sedation scores;
- a trend towards reduced dosing with propofol;
- comparable haemodynamic and cerebral haemodynamic stability;
- higher user satisfaction rating by physicians and nurses;
- a similar safety profile.

2. Carrasco G, Molina R, Costa J, Soler J-M, Cabre L: **Propofol vs midazolam in short-, medium- and long-term sedation of critically ill patients.** *Chest* 1993, **103:**557-564.
3. Westmoreland CL, Hoke JF, Sebel PS, Hug CC Jr, Muir KT: **Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GR90291) in patients undergoing elective surgery.** *Anesthesiology* 1993, **79:**893-903.
4. Kapila A, Glass PS, Jacobs JR, Muir KT, Hermann DJ, Shiraishi M, Howell S, Smith RL: **Measured context-sensitive half-times of remifentanil and alfentanil.** *Anesthesiology* 1995, **83:**968-975.
5. Lang E, Kapila A, Shlugman D, Hoke JF, Sebel PS, Glass PSA: **Reduction of isoflurane minimal alveolar concentration by remifentanil.** *Anesthesiology* 1996, **85:**721-728.
6. Fragen RJ, Randel GI, Librojo ES, Clarke MY, Jamerson BD: **The interaction of remifentanil and propofol to prevent response to tracheal intubation and the start of surgery for outpatient knee arthroscopy [abstract].** *Anesthesiology* 1994, **81:**A376.
7. Warner DS, Hindman BJ, Todd M, Sawin PD, Kirchner J, Roland CL, Jamerson B: **Intracranial pressure and hemodynamic effects of remifentanil versus alfentanil in patients undergoing supraventorial craniotomy.** *Anesth Analg* 1996, **83:**348-353.
8. Hoffman WE, Cunningham F, James MK, Baughman VL, Albrecht R: **Effects of remifentanil, a new short-acting opioid, on cerebral blood flow, electrical brain activity, and intracranial pressure in dogs anesthetized with isoflurane and nitrous oxide.** *Anesthesiology* 1993, **79:**107-113.
9. Guy J, Hindman BJ, Baker KZ, Borel CO, Maktabi M, Ostapkovich N, Kirchner J, Todd MM, Fogarty-Mack P, Yancy V, Sokoll MD, McAllister A, Roland C, Young WL, Warner DS: **Comparison of remifentanil and fentanyl in patients undergoing craniotomy for supratentorial space-occupying lesions.** *Anesthesiology* 1997, **86:**514-524.
10. Warner DS: **Experience with remifentanil in neurosurgical patients.** *Anesth Analg* 1999, **89:**33-39.
11. Coles JP, Leary TS, Monteiro JN: **Propofol anesthesia for craniotomy: a double-blind comparison of remifentanil, alfentanil and fentanyl.** *J Neurosurg Anesthesiol* 2000, **12:**5-20.
12. Gesztesi Z, Mootz BL, White PF: **The use of a remifentanil infusion for hemodynamic control during intracranial surgery.** *Anesth Analg* 1999, **89:**1282-1287.
13. Johnson KB, Egan TD: **Remifentanil and propofol combination for awake craniotomy: case report with pharmacokinetic simulations.** *J Neurosurg Anesthesiol* 1998, **10:**25-29.
14. Hans P, Bonhomme V, Born JD: **Target-controlled infusion of propofol and remifentanil combined with bispectral index monitoring for awake craniotomy.** *Anaesthesia* 2000, **55:**255-259.
15. Muellejans B, López A, Cross MH, Bonome C, Morrison L, Kirkham AJT: **Remifentanil versus fentanyl for analgesia based sedation to provide patient comfort in the intensive care unit: a randomized, double-blind controlled trial.** *Crit Care* 2004, **8:**R1-R11.
16. Riker RR, Picard JT, Fraser GL: **Prospective evaluation of the Sedation–Agitation Scale for adult critically ill patients.** *Crit Care Med* 1999, **27:**1325-1329.
17. Kirkham A, Fisher G, Kessler P: **A dosing algorithm for the use of remifentanil in providing optimal sedation and analgesia in ICU patients [abstract].** *Intensive Care Med* 2001, **Suppl 2:**s238.
18. Servin FS: **Remifentanil: an update.** *Curr Opin Anaesthesiol* 2003, **16:**367-372.
19. Breen D, Wilmer A, Bodenham A, Bach V, Bonde J, Kessler P, Albrecht S, Shaikh S: **Offset of pharmacodynamic effects and safety of remifentanil in intensive care unit patients with various degrees of renal impairment.** *Crit Care* 2004, **8:**R21-R30.
20. Kessler P, Chinachoti T, Van Der Berg P, Stanley A, Kirkham A: **Remifentanil vs. morphine for the provision of optimal sedation in ICU patients [abstract].** *Intensive Care Med* 2001, **Suppl 2:**s239.
21. Albanese J, Viviand X, Potie F: **Sufentanil, fentanyl and alfentanil in head trauma patients: a study on cerebral hemodynamics.** *Crit Care Med* 1999, **27:**407-411.
22. Sperry RJ, Bailey PL, Reinman MV: **Fentanyl and sufentanil increase intracranial pressure in head trauma patients.** *Anesthesiology* 1992, **7:**416-420.
23. Albanese J, Durbec O, Vivian X: **Sufentanil increases intracranial pressure in patients with head trauma.** *Anesthesiology* 1993, **79:**493-497.
24. Trindle MR, Dodson BA, Rampil IJ: **Effects of fentanyl versus sufentanil in equianesthetic doses on middle cerebral artery blood flow velocity.** *Anesthesiology* 1993, **78:**454-460.
25. Rhoney DH, Parker D Jr: **Use of sedative and analgesic agents in neurotrauma patients: effects on cerebral physiology.** *Neurol Res* 2001, **23:**237-259.
26. James MK, Feldman PL, Schuster SV, Bilotta JM, Brackeen MF, Leighton HJ: **Opioid receptor activity of GI87084B, a novel ultra-short acting analgesic in isolated tissues.** *J Pharmacol Exp Ther* 1991, **259:**712-718.