Research

Open Access

Remifentanil versus fentanyl for analgesia based sedation to provide patient comfort in the intensive care unit: a randomized, double-blind controlled trial [ISRCTN43755713]

Bernd Muellejans[1], Angel López[2], Michael H Cross[3], César Bonome[4], Lachlan Morrison[5] and Andrew JT Kirkham[6]

[1]Director of Anaesthesiology & Intensive Care Medicine, Klinikum Karlsburg, Herz-und Diabeteszentrum Mecklenburg-Vorpommern Klinik für Anaesthesiologie und Intensivmedizin, Karlsburg, Germany
[2]Consultant Anaesthesiologist, Servicio de Medicina Intensiva, Hospital Universitario Infanta Cristina, Badajoz, Spain
[3]Consultant Anaesthetist, Department of Anaesthesia, Leeds General Infirmary, Leeds, UK
[4]Attending Staff, Department of Anaesthesiology, Hospital Juan Canalejo, Servicio de Anestesiologia y Reanimación, La Coruña, Spain
[5]Consultant in Anaesthetics and Intensive Care, Department of Anaesthesia, St. John's Hospital, Livingston, UK
[6]Global Study Manager, GlaxoSmithKline Research and Development, Greenford, UK

Correspondence: Bernd Muellejans, dr.muellejans@drguth.de

Received: 2 October 2003

Accepted: 16 October 2003

Published: 20 November 2003

Critical Care 2004, **8**:R1-R11 (DOI 10.1186/cc2398)

This article is online at http://ccforum.com/content/8/1/R1

Abstract

Introduction This double-blind, randomized, multicentre study was conducted to compare the efficacy and safety of remifentanil and fentanyl for intensive care unit (ICU) sedation and analgesia.

Methods Intubated cardiac, general postsurgical or medical patients (aged ≥18 years), who were mechanically ventilated for 12–72 hours, received remifentanil (9 μg/kg per hour; $n = 77$) or fentanyl (1.5 μg/kg per hour; $n = 75$). Initial opioid titration was supplemented with propofol (0.5 mg/kg per hour), if required, to achieve optimal sedation (i.e. a Sedation–Agitation Scale score of 4).

Results The mean percentages of time in optimal sedation were 88.3% for remifentanil and 89.3% for fentanyl (not significant). Patients with a Sedation–Agitation Scale score of 4 exhibited significantly less between-patient variability in optimal sedation on remifentanil (variance ratio of fentanyl to remifentanil 1.84; $P = 0.009$). Of patients who received fentanyl 40% required propofol, as compared with 35% of those who received remifentanil (median total doses 683 mg and 378 mg, respectively; $P = 0.065$). Recovery was rapid (median time to extubation: 1.1 hours for remifentanil and 1.3 hours for fentanyl; not significant). Remifentanil patients who experienced pain did so for significantly longer during extubation (6.5% of the time versus 1.4%; $P = 0.013$), postextubation (10.2% versus 3.6%; $P = 0.001$) and post-treatment (13.5% versus 5.1%; $P = 0.001$), but they exhibited similar haemodynamic stability with no significant differences in adverse event incidence.

Conclusion Analgesia based sedation with remifentanil titrated to response provided effective sedation and rapid extubation without the need for propofol in most patients. Fentanyl was similar, probably because the dosing algorithm demanded frequent monitoring and adjustment, thereby preventing over-sedation. Rapid offset of analgesia with remifentanil resulted in a greater incidence of pain, highlighting the need for proactive pain management when transitioning to longer acting analgesics, which is difficult within a double-blind study but would be quite possible under normal circumstances.

Keywords analgesia, analgesia based sedation, critical care, fentanyl, propofol, remifentanil, renal function, sedation

HR = heart rate; ICU = intensive care unit; MAP = mean arterial pressure; PI = Pain Intensity (scale); SAPS = Simplified Acute Physiology Score; SAS = Sedation–Agitation Scale; SD = standard deviation.

Introduction

The provision of effective analgesia and sedation for patients in the intensive care unit (ICU) is important in controlling pain, relieving agitation and anxiety, and aiding compliance with mechanical ventilation, and thereby maintaining patient comfort. Agents such as propofol and midazolam are commonly used for sedation in the ICU because of their effectiveness and relatively short elimination half-lives [1,2]. The risk for accumulation and delayed recovery with these agents appears to be lower than that with traditional opioids. Consequently, opioid dose is usually minimized, with physicians choosing to manipulate the sedative dose to maintain optimal patient comfort (hypnotic based treatment regimens). However, analgesia based sedation techniques, which focus on patient comfort rather than on patient sedation by catering to the analgesic needs of the patient and adding a sedative only if necessary, are becoming more established in the ICU setting. Both approaches currently have certain limitations because metabolism and elimination of the sedative and analgesic agents may be prolonged in critically ill patients, and there is a potential for accumulation and unpredictable and/or delayed recovery, particularly during weaning from mechanical ventilation.

Remifentanil hydrochloride is a potent, selective μ opioid receptor agonist, which is indicated for use during induction and maintenance of general anaesthesia and for the provision of analgesia in mechanically ventilated critically ill patients. Remifentanil has an onset of action of about 1 min and quickly achieves a steady state. Unlike existing opioids, however, it is rapidly metabolized by nonspecific blood and tissue esterases [3] into a clinically inactive metabolite. This results in an elimination half-life of less than 10 min, which is independent of infusion duration [4]. These characteristics render 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.

A number of investigators have reported on the potential role and actual use of remifentanil in the critically ill [5–12]. The unique pharmacological profile of remifentanil has proved particularly advantageous in neurotrauma patients [13–15], patients with renal impairment [16–18], cardiac postsurgical patients [19], general postsurgical patients [20], and patients with chronic obstructive pulmonary disease and other respiratory complications [21,22]. Because of the rapid and predictable mode of metabolism, use of high doses of remifentanil has also been investigated in patients undergoing short, painful procedures [13,23,24]. Comparator studies have also been reported that confirm the rapid and predictable recovery that is achieved when using remifentanil [14,15,21,25]. There are also reports that use of remifentanil in the critically ill can reduce the need for sedative agents [17,25,26] and can offer significant cost savings [21,27].

Remifentanil may permit improvement in patient comfort in the ICU by optimizing the use of the opioid component by initiating and titrating the opioid infusion before administration and titration of a hypnotic agent. The present randomized, double-blind study was conducted to compare the efficacy and safety of remifentanil plus propofol as required with a standard regimen of fentanyl plus propofol in ICU patients requiring mechanical ventilation.

Methods

The study was conducted in accordance with good clinical practice and with the guidelines set out in the Declaration of Helsinki. Informed consent/assent was obtained from all patients or their representatives. After approval from local and national ethics committees, a total of 196 patients from 21 centres were recruited (four centres in Belgium, eight in Germany, one in The Netherlands, four in Spain, four in the UK). In total, 152 patients were randomized, in a double-blind manner, to receive either a remifentanil based regimen or a standard fentanyl–propofol regimen for analgesia and sedation in the ICU. In addition, 18 patients (12 on remifentanil/6 on fentanyl) were treated on an open-label basis as a pilot for the main study. A further 26 patients (who all received open-label remifentanil; referred to hereafter as 'practice patients') were treated at the remaining sites (up to 2 patients per site) to allow familiarization with the protocol procedures.

Patients were eligible for entry into the study if they were aged 18 years or older, weighed 120 kg or less, had been admitted into the ICU within the past 24 hours, and were intubated and expected to require mechanical ventilation for a further 12–72 hours. The maximum duration of the infusion was in accordance with propofol labelling restrictions in some countries at the time of conducting the study. To help ensure a balance in the severity of illness and patient case–mix between the two treatment groups, randomization of double-blind patients was stratified according to the patients' modified ICU admission Simplified Acute Physiology Score (SAPS) II [28] (i.e. 6–29, 30–37 and 38–52) and whether the patients were cardiac postsurgical, general postsurgical, or medical patients. The modified ICU admission SAPS II scores were calculated using data collected from the patients over at least 2 hours after their entry into the ICU. Patients were excluded from the study if they required a neuromuscular blocking agent to facilitate mechanical ventilation or if they had or were likely to require an epidural block during the maintenance phase of the study (defined as the time between starting the study drug treatment until the start of the extubation process or until 72 hours after starting the study drug infusion, whichever occurred first). Patients were also excluded if they were likely to require a tracheostomy within 4 days of ICU entry, if they had a neurological condition that might affect assessment of Sedation–Agitation Scale (SAS) score [29], if they had moderate or severe renal impairment (predicted creatinine clearance <50 ml/min), and if they had a modified ICU entry SAPS II in excess of 52. Patients with a

Table 1

The Sedation–Agitation Scale

Score	Description	Example
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bedrails, thrashing from side to side, striking at staff
6	Very agitated	Patient does not calm down in response to verbal instructions or reassurance, requires physical restraint, biting endotracheal tube
5	Agitated	Anxious or agitated but calms down in response to verbal instructions or reassurance
4	Calm, cooperative	Calm, easily rousable, follows commands
3	Sedated	Difficult to rouse, awakens to verbal stimuli or gentle shaking but drifts off again, will follow simple commands
2	Very sedated	Can be roused by physical stimuli but does not communicate or follow commands, may move spontaneously
1	Not rousable	May move or grimace minimally to stimuli but does not communicate or follow commands

history of allergy to opioids, benzodiazepines, propofol, or alcohol/drug abuse were excluded from the study.

The use of sedative and analgesic agents after ICU admission was restricted to alfentanil/fentanyl and propofol while preparations were being made to enter the patient into the study.

The treatment period was defined as the following four phases: maintenance phase (from the start of the study drug until the start of the extubation process); extubation phase (from the beginning of the extubation process until the time of actual extubation); postextubation phase (from extubation until the study drug was discontinued); and post-treatment period (from the time of discontinuation of the study drug until 24 hours later or until ICU discharge, whichever occurred first).

Treatment protocol

The aim of the study was to achieve optimal sedation and patient comfort by maintaining an optimal SAS score of 4, without clinically significant pain, until the start of the extubation process or for 72 hours, whichever occurred first. Table 1 shows the SAS scoring system. The Ramsay Sedation Scale is considered the 'gold standard' scoring system for assessing sedation in the ICU patient and was designed as a test of arousability. The SAS score was chosen for use in this study because it allows assessment of both sedation and agitation, and allows agitation to be stratified into three categories, as opposed to only one with the Ramsay Sedation Scale. Pain was assessed by the investigator/study nurse using a six point Pain Intensity (PI) scale, as follows: 1 = no pain, 2 = mild pain, 3 = moderate pain, 4 = severe pain, 5 = very severe pain, and 6 = worst possible pain. Clinically significant pain was defined as a score of 3 or more.

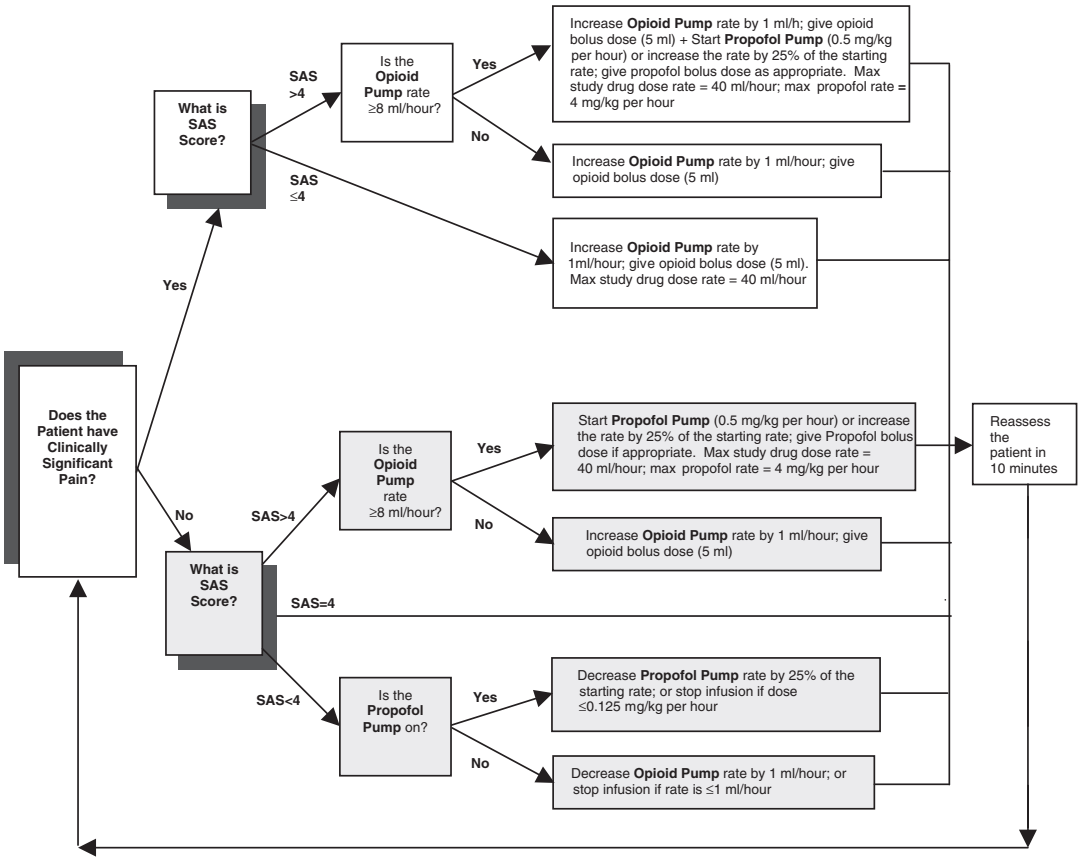
Remifentanil hydrochloride (lyophilized powder in sterile vials each containing 5 mg of the compound) was reconstituted/diluted with standard diluent. The pharmacy at each study site supplied the fentanyl from commercial stock.

Treatment was started in patients with an SAS score of 2 or greater after completion of baseline assessments. All patients received an initial infusion of blinded opioid (remifentanil: placebo bolus dose + 9 μg/kg per hour infusion at 6 ml/hour; fentanyl: 1 μg/kg bolus + 1.5 μg/kg per hour infusion at 6 ml/hour). Optimal sedation (SAS score 4) was then targeted by titrating the infusion in 1 ml/hour increments (remifentanil: placebo bolus dose + 1.5 μg/kg per hour rate increase; fentanyl: 1 μg/kg bolus dose + 0.25 μg/kg per hour rate increase). Only when the opioid infusion rate had reached the 'propofol trigger dose' (8 ml/h; remifentanil: 12 μg/kg per hour; fentanyl 2 μg/kg per hour; Fig. 1) was propofol to be administered as an initial bolus dose of up to 0.5 mg/kg and an infusion of 0.5 mg/kg per hour, and titrated in 25% increments (0.25 mg/kg bolus dose + 0.125 mg/kg per hour rate increase; Fig. 1) to treat agitation. Excessive sedation (SAS score <4) without pain was treated either by reducing or by discontinuing the propofol (if being administered) or opioid infusion. Pain was treated with an opioid bolus dose and an increase in the opioid infusion rate (as described above). If patients were both agitated and in pain, propofol and the opioid were titrated at the same time. Dose adjustments were made at 10 min intervals. The dosing algorithm described above applied only to the maintenance phase of the study.

Pain and sedation scores were assessed before each dose adjustment, according to the dosing algorithm, and reassessed 10 min after each adjustment. If, after 5 min, the investigator felt that increased analgesia/sedation was needed, then propofol or open-label fentanyl could be given.

Qualification of patients for extubation was at the discretion of individual investigators, based upon their clinical judgement. When the patient was judged to be ready to begin the extubation process, the propofol infusion (if administered) was discontinued. To allow for smooth emergence from the effects of remifentanil and time for administration of pre-

Figure 1



Dosing algorithm: maintenance phase. SAS, Sedation–Agitation Scale.

emptive analgesia, the study opioid infusion rate was decreased in four decrements to 4 ml/hour over a period of up to 1 hour. Open label bolus doses of propofol (0.5 mg/kg) for sedation and fentanyl (1 μg/kg) for analgesia could be administered if required. Epidural bupivacaine, at the recommended dose, could also be administered. Following extubation, the study opioid infusion was discontinued in four 25% decrements over a period of 1 hour. If the patient had not been extubated after 72 hours, then the study opioid infusion rate was discontinued in four decrements over a period of 1 hour, with open label bolus doses of propofol and fentanyl administered as required. Subsequently, open label infusions of sedative/analgesic agents were administered as clinically indicated and according to standard therapy following discontinuation of study opioid infusions.

Patient monitoring

In addition to SAS and PI scale scores, mean arterial pressure (MAP) and heart rate (HR) were recorded at baseline, and approximately every 20 min from the start of study drug administration for the first 6 hours, then every hour until extubation, and immediately before and 10 min after changes in study opioid or propofol dose. During extubation, these parameters were recorded every 20 min for the first 4 hours and then every hour. Following extubation, SAS and PI scale scores, MAP and HR were recorded every hour for 24 hours or until ICU discharge.

Study end-points

The primary efficacy end-point was the between-patient variability about the mean percentage of hours of optimal sedation (i.e. SAS score 4) during the maintenance phase. This end-point provided a measure of the effectiveness of the treatment regimens in achieving a constant level of optimal sedation, because a reduction in variability implies increased efficacy in maintaining stable sedation. Secondary end-points included the incidence of pain during the treatment and post-treatment periods, and comparisons of the dosages and administration of remifentanil, propofol and fentanyl. Patients' vital signs were assessed during and after treatment, and all adverse events were recorded. Serious adverse events were defined as adverse events that resulted in any of the following outcomes: death, life threatening event, prolongation of hospitalisation, and disability/incapacity. Important medical events that did not result in death or were not life threatening were considered serious adverse events when, based upon

Table 2

Patient demographic and clinical characteristics

Characteristic	Remifentanil	Fentanyl
Number of patients treated (SP)	115	81
Open label pilot patients	12	6
Open label practice patients	26	0
ITT population	77	75
Cardiac postsurgical	46 (60%)	45 (60%)
General postsurgical	25 (32%)	26 (35%)
Medical	6 (8%)	4 (5%)
Normal renal function*	68 (59%)	48 (59%)
Mild renal impairment†	47 (41%)	33 (41%)
Mean SAPS II (SD)	SP 27.9 (8.7); ITT 28.2 (8.8)	SP 27.6 (8.6); ITT 27.7 (8.8)
Mean age [years] (SD)	SP 61.3 (13.8); ITT 61.5 (13.4)	SP 59.3 (13.6); ITT 58.7 (13.9)
Sex		
Male	SP 81 (70%); ITT 55 (71%)	SP 56 (69%); ITT 52 (69%)
Female	SP 34 (30%); ITT 22 (29%)	SP 25 (31%); ITT 23 (31%)
Mean height (cm; SD)	SP 169.8 (9.5); ITT 170.4 (9.1)	SP 169.7 (9.8); ITT 169.6 (9.6)
Mean weight (kg; SD)	SP 76.9 (13.9); ITT 77.2 (12.7)	SP 74.9 (13.0); ITT 74.8 (13.9)

Renal function was assessed by predicting the patient's creatinine clearance (CL_{cr}), as described by Cockcroft and Gault [32]. *Normal renal function was defined as a predicted CL_{cr} >80 ml/min. †Mild renal impairment was defined as a predicted CL_{cr} of 50–80 ml/min. ITT, intent to treat population; SD, standard deviation; SP, safety population.

appropriate medical judgement, they jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes listed above.

Statistical methods

Analysis of safety was performed in all of the patients treated in the present study (pilot, practice, and double-blind patients; $n = 196$). Analysis of efficacy was performed on the double-blind patients (intent-to-treat population; $n = 152$). A total of 152 randomized patients were required to detect a 50% reduction in the variance of the arcsine square root transformed percentage of hours of optimal sedation for patients on the remifentanil-based treatment regimen compared with the standard treatment regimen, using a two-sided F-test with 80% power and a 0.05 level of significance. For the mean percentage of hours in which patients were optimally sedated (SAS score 4), a comparison was made between the two treatment groups using an unpaired *t*-test on the arcsine square root transformed data. The percentages of time during which patients had no or mild pain during the maintenance phase, the extubation phase, the post-extubation phase and the post-treatment period were calculated for each patient and summarized by treatment group. For each time interval, a comparison was made between the two treatment groups using Wilcoxon's rank sum test. For all patients, the times from starting the extubation process until actual extubation, from the start of the study drug infusion until ICU discharge, and from extubation until ICU discharge were analyzed using Cox's proportional hazards model.

The incidences of adverse events in the two groups were analyzed using Fisher's exact test. Weighted mean MAP and HR values, recorded from the start of the study drug infusion until 24 hours after discontinuation of study drug, were summarized by treatment group and assessed using analysis of covariance, with the prestudy drug administration value as a baseline covariate. The proportions of patients with MAP values of 50 mmHg or less, and 100 mmHg or more, and with HR below 50 beats/min and above 120 beats/min were summarized by treatment group and analyzed using logistic regression. All summary statistical computations were performed using SAS version 6.12 (SAS Institute Inc., Cary, NC, USA). All tests of significance were two-sided and carried out at the 5% level.

Results

A total of 196 patients (115 remifentanil, 81 fentanyl) were evaluable for safety. The intent to treat population (double-blind patients) included 152 patients (77 received remifentanil; 75 received fentanyl). Demographic and clinical characteristics are summarized in Table 2, which shows that the treatment groups were well matched. The majority of

Table 3

Duration of study periods

Phase/period	Remifentanil ($n = 77$)	Fentanyl ($n = 75$)
Maintenance phase	13.7 hours (2.7–73.0 hours)	14.2 hours (0.3–73.3 hours)
Extubation phase	1.0 hour (0.0–21.0 hours)	1.1 hours (0.0–4.5 hours)
Postextubation phase	1.0 hour (0.0–1.3 hours)	1.0 hour (0.0–1.3 hours)
Post-treatment period	24.0 hours (0.8–24.0 hours)	22.3 hours (0.5–24.0 hours)

Values are expressed as median (range).

Table 4

Mean percentage of hours of optimal sedation (intent to treat population)

	Remifentanil ($n = 77$)	Fentanyl ($n = 75$)	*P*
Maintenance phase			
Median duration (h; range)	13.7 (2.7–73.0)	14.2 (0.3–73.3)	NT
Mean (range) % of hours of optimal sedation	88.3 (0.0–100.0)	89.3 (32.5–100.0)	NS*
Ratio of between-patient variability (fentanyl versus remifentanil)	1.09		NS†
Maintenance phase (excluding the patient in the remifentanil group who failed to achieve an SAS score of 4)			
Mean (range) % of hours of optimal sedation	89.5 (45.2–100.0)	89.3 (32.5–100.0)	NS*
Ratio of between-patient variability (fentanyl versus remifentanil)	1.84		0.009†
Extubation phase			
Mean (range) % of hours of optimal sedation	87.7 (0.0–100.0)	95.5 (40.0–100.0)	NT
Postextubation phase			
Mean (range) % of hours of optimal sedation	92.3 (0.0–100.0)	95.7 (32.3–100.0)	NT
Post-treatment period			
Mean (range) % of hours of optimal sedation	92.6 (0.0–100.0)	91.6 (0.0–100.0)	NT

*Unpaired *t*-test on arcsine square root transformed data; †F test. NS, not significant; NT, not tested; SAS, Sedation–Agitation Scale.

patients were admitted to the ICU after cardiac surgery. In total, 84% of patients were elective admissions. Baseline SAS and PI scale scores were similar in the remifentanil (mean SAS score 3.2, mean PI scale score 1.4) and fentanyl (mean SAS score 3.5, mean PI scale score 1.5) groups. Baseline MAP and HR values were also similar between groups. The median durations of the study phases are summarized in Table 3.

Efficacy

Data for the mean percentage of hours of optimal sedation are summarized in Table 4. The two regimens had similar efficacy for the time during which patients had an optimum level of sedation, and there was no significant difference between the groups in the primary efficacy measure. The ratio of between-patient variability (fentanyl versus remifentanil) around the mean percentage of hours of optimal sedation during the maintenance phase was 1.09 (not significant). One patient in the remifentanil group failed to achieve an SAS score of 4 after the start of the study drug infusion, and their SAS score did not rise above a value of 2 despite the remifentanil infusion being stopped after 280 min. It was considered that this patient's state of unconsciousness was possibly caused by neurological injury as a result of heart valve surgery and was not related to the use of remifentanil. When the primary end-point analysis was repeated, but excluding this patient, there was significantly less variability in the transformed data for the remifentanil treatment group (variance 0.03) compared with the fentanyl treatment group (variance 0.06). The variance ratio (fentanyl/remifentanil) was 1.84 ($P = 0.009$).

Table 5 summarizes the data for patient exposure to study opioids and propofol during the maintenance phase. The median total dose of propofol administered to patients was markedly lower in the remifentanil group (378.4 mg) than in the fentanyl group (683.0 mg; $P = 0.065$). The number of propofol bolus doses administered was also lower on average in the remifentanil group, and a smaller proportion of patients (35%) in the remifentanil group than in the fentanyl

Table 5

Exposure to study opioids and propofol during the maintenance phase (intent to treat population)

Maintenance phase	Remifentanil ($n = 77$)	Fentanyl ($n = 75$)
Median duration of study opioid infusion (hours; range)	13.7 (2.7–73.0)	14.2 (0.3–73.3)
Weighted mean study opioid infusion rate (μg/kg per hour; range)	9.4 (2.3–22.8)	1.8 (0.5–6.0)
Number of patients receiving the study drug infusion for >24 hours	11 (14%)	10 (13%)
Number of patients who received a propofol infusion	27 (35%)	30 (40%)
Mean time from starting the opioid infusion to starting the propofol infusion (hours; range)	6.6 (0.2–55.6)	5.9 (0.2–38.6)
Median duration of propofol infusion (hours; range)	9.4 (0.6–53.3)	12.0 (2.5–72.3)
Mean % of time patients received a propofol infusion (range) during the maintenance phase	62.8 (3.8–98.9)	76.1 (26.9–99.0)
Median total propofol dose (mg; range)	378.4 (15.8–4690.8)	683.0 (30.0–11323.3)
Weighted mean infusion rate of propofol (mg/kg per hour; range)	0.7 (0.1–2.7)	0.8 (0.2–2.5)
Number of patients receiving the following numbers of propofol bolus doses	($n = 27$)	($n = 30$)
0	18 (67%)	14 (47%)
1–3	8 (30%)	11 (37%)
4–6	1 (4%)	4 (13%)
≥7	0	1 (3%)
Number of patients receiving the following numbers of propofol rate increases	($n = 27$)	($n = 30$)
0	17 (63%)	6 (20%)
1–3	5 (19%)	14 (47%)
4–6	3 (11%)	5 (17%)
≥7	2 (7%)	5 (17%)
Number (%) of patients receiving the following numbers of propofol rate decreases	($n = 27$)	($n = 30$)
0	16 (59%)	18 (60%)
1–3	9 (33%)	8 (27%)
4–6	2 (7%)	3 (10%)
≥7	0 (0%)	1 (3%)

treatment group received a propofol infusion (40%; significance not tested). The mean time until the propofol infusion was started (when required) was longer in the remifentanil group than in the fentanyl treatment group (6.6 hours versus 5.9 hours; significance not tested). The mean percentage of time during which patients received propofol infusion was also lower in those remifentanil treated patients who received propofol than in the fentanyl group (62.8% versus 76.1%; significance not tested). The weighted mean propofol infusion rates were similar in the remifentanil (0.7 mg/kg per hour) and fentanyl (0.8 mg/kg per hour) groups.

With regard to analgesia, the mean percentages of time in the maintenance phase during which patients had at least moderate pain were 2.6% (range 0.0–37.6%) in the remifentanil group and 3.1% (range 0.0–65.4%) in the fentanyl group (not significant). The corresponding figures for the extubation phase were 6.5% for remifentanil (range 0.0–100.0%) and 1.4% for fentanyl (range 0.0–33.3%; $P = 0.013$); for the postextubation phase they were 10.2% for remifentanil (range 0.0–75.0%) and 3.6% for fentanyl (range 0.0–66.7%; $P = 0.001$); and for the post-treatment period they were 13.5% for remifentanil (range 0.0–100.0%) and 5.1% for fentanyl (range 0.0–58.3%; $P = 0.001$). The proportions of patients experiencing pain during the maintenance phase were similar in the two groups, with 51% of patients in the remifentanil group having at least moderate pain as compared with 49% of patients in the fentanyl group. The corresponding percentages for the extubation and postextubation phases, and the post-treatment period were 23% for remifentanil and 7% for fentanyl, 33% for remifentanil and 9% for fentanyl, and 52% for remifentanil and 28% for fentanyl, respectively.

A similar proportion of patients in the remifentanil (6%) and fentanyl (8%) groups received supplementary propofol for

Table 6

Haemodynamic parameters during the study period (safety population)

	Remifentanil ($n = 115$)	Fentanyl ($n = 81$)
Mean arterial pressure		
Overall weighted mean MAP (mmHg; range)	80.9 (38–128)	79.6 (54–104)
% of time in which MAP was within 10% of mean baseline value (range)	43.1 (0–100)	48.7 (4–91)
Number of patients with MAP ≤50 mmHg	19 (17%)	8 (10%)
Number of patients with MAP ≥100 mmHg	81 (70%)	52 (64%)
Heart rate		
Overall weighted mean HR (beats/min; range)	88.3 (63–117)	88.6 (59–129)
% of time in which HR was within 10% of mean baseline value (range)	54.4 (0–100)	55.6 (5–100)
Number of patients with HR ≤50 beats/min	2 (2%)	3 (4%)
Number of patients with HR ≥120 beats/min	35 (30%)	28 (35%)

The statistical significance of the differences between groups for the mean percentages of time with heart rate (HR) and mean arterial pressure (MAP) within 10% of baseline was not tested. There were no statistically significant differences between groups for any of the other parameters.

analgesia/sedation during the extubation and postextubation phases of the study, with 60% and 67% of patients in these groups, respectively, receiving three or fewer bolus doses. The mean total dose of propofol administered during these periods was lower in the remifentanil group (77 mg, range 20–156 mg) than in the fentanyl group (89 mg, range 20–220 mg). In contrast, use of supplementary fentanyl and morphine during the extubation and postextubation phases of the study was higher in the remifentanil group, reflecting its rapid offset of action. In total, 17% of patients in the remifentanil group received additional fentanyl (≤3 bolus doses in 85%) as compared with 3% of those in the fentanyl group (≤3 bolus doses in 50%), and the mean total dose of fentanyl administered to patients in the remifentanil group (140.4 μg, range 50–250 μg) was higher than that for patients in the fentanyl group (105 μg, range 60–150 μg). Supplementary morphine was administered to 25% of patients in the remifentanil group and 13% of those in the fentanyl group, with 89% and 90% of patients in these groups, respectively, receiving three or fewer bolus doses. The mean total dose of morphine administered to patients in the remifentanil group (8.6 mg, range 1–22 mg), however, was lower than that for patients in the fentanyl group (11.4 mg, range 1–40 mg).

There were no statistically significant differences between the two treatment groups with regard to recovery parameters. The median time from starting the extubation process until extubation was 1.1 hours (standard deviation [SD] 2.8, range 0.0–21.0 hours) in the remifentanil group and 1.3 hours (SD 0.9, range 0.0–4.5 hours) in the fentanyl group. The median times from extubation until ICU discharge and from starting the study drug until ICU discharge were 25.1 hours (SD 35.6, range 1.8–137.1 hours) and 40.8 hours (SD 40.2, range 2.7–150.3 hours), respectively, in the remifentanil treated patients. The corresponding times for patients in the fentanyl group were 22.0 hours (SD 29.6, range 1.5–136.0 hours) and 39.5 hours (SD 40.5, range 0.3–151.2 hours), respectively.

Safety

Both treatment regimens were well tolerated. Of the remifentanil patients 14% received treatment for longer than 24 hours, as did 13% of the fentanyl patients. At least one adverse event was reported in 48% of patients in the remifentanil group and in 37% of those in the fentanyl group (not significant). There was also no statistically significant difference between the two groups in the incidence of drug related adverse events (23% for remifentanil and 17% for fentanyl). The most common adverse events reported during the study period were hypotension (10% for remifentanil and 9% for fentanyl; not significant), nausea (9% for remifentanil and 6% for fentanyl; not significant), fever (5% for remifentanil and 9% for fentanyl; not significant) and vomiting (5% for remifentanil and 6% for fentanyl; not significant). These events are generally typical of those associated with the use of potent μ opioid receptor agonists and with the postsurgical setting. Both groups of patients had similar, stable haemodynamics (Table 6).

Discussion

The dosing algorithm used in the present study was designed to mimic a standard fentanyl/propofol regimen in the control group, while allowing initial titration of opioid infusion before the addition of propofol to achieve and maintain optimal sedation and analgesia. This was to allow assessment of the efficacy of remifentanil as initial treatment while administering a clinically relevant treatment regimen in the control group. Thus, in essence, the study was designed to compare the use of an analgesia based technique, using remifentanil, with a hypnotic based technique using fentanyl/propofol. Because of the lower (but clinically relevant) dose of fentanyl administered, it was

expected that the majority of fentanyl patients would go on to receive propofol. In practice, both remifentanil and fentanyl were very effective in providing optimal sedation and analgesia, and fewer than 40% of the patients in either treatment group required the propofol infusion. It is notable, however, that a lower median total propofol dose was administered in the remifentanil group. Although this difference was only marginally statistically significant ($P = 0.065$), it may nonetheless be clinically important because remifentanil treated patients had less exposure to the lipid emulsion used in propofol.

Low requirements for propofol in both groups probably reflects the stringent conditions of the dosing algorithm, which demanded frequent monitoring and adjustment of the level of sedation to ensure that an SAS score of 4 was maintained. In routine clinical practice, patients are likely to be less frequently monitored and more deeply sedated, with potential for conventional opioids such as fentanyl and sedatives to accumulate. This should not happen when using remifentanil because of its rapid offset of action, which is independent of the duration of administration. It should be possible to optimize swiftly the patient's level of sedation by adjusting the remifentanil infusion rate. Starting the remifentanil infusion at 9 μg/kg per hour (0.15 μg/kg per min) and titrating to 12 μg/kg per hour (0.2 μg/kg per min) before starting the administration of propofol at 0.5 mg/kg per hour (with a bolus dose of up to 0.5 mg/kg) appeared to be clinically appropriate in the present study. Because of the synergistic interaction between remifentanil and propofol, if more conventional doses of propofol were administered (2–3 mg/kg per hour) with the doses of remifentanil used in the study, then adverse sequelae such as hypotension are likely to occur. A much reduced starting dose of propofol is therefore recommended.

The high overall percentage of time with optimal sedation observed in the study is very similar to that reported by Carrasco and coworkers [1,2], who demonstrated that the percentage of time with optimal sedation was 92% when using propofol based sedation, 88% using midazolam based sedation, and 90% using the combination. The targeted Ramsey score of 2–5 used by Carrasco and coworkers is less stringent than the SAS score of 4 used in the present study. Our study therefore demonstrates that the use of a remifentanil based sedation technique has the potential to provide at least a similar quality of sedation to that currently obtained using hypnotic based techniques. The organ independent mode of metabolism makes remifentanil the opioid of choice for use in patients with impaired renal function.

The primary end-point in the present study was the between-patient variability about the mean percentage of hours of optimal sedation during the maintenance phase. The ease of titration to effect offered by remifentanil should result in less variability in the time that patients are optimally sedated. Data from patients reaching an SAS score of 4 were significantly less variable in the remifentanil group than in the fentanyl group, indicating the potential of remifentanil use to improve patient comfort in the ICU. The ease and rapidity with which remifentanil can be titrated to effect may make it easier for ICU staff to maintain an optimal level of sedation and analgesia for individual patients, and to avoid the undesirable variations in depth of sedation.

Higgins and coworkers [30] reported that mean extubation times in postsurgical patients receiving propofol or midazolam supplemented with bolus doses of morphine were 4.3 hours and 3.5 hours, respectively. Our study data suggest that this time can be considerably reduced when using an opioid based sedative technique, because the median time from the start of the extubation process to extubation was less than 80 min in both treatment groups. In 46 postsurgical ICU patients receiving remifentanil, Wilhelm and coworkers [20] showed that two-thirds were extubated within 15 min of starting the extubation process and 87% within 45 min. Soltész and coworkers [15] also reported faster recovery when using remifentanil than with sufentanil. The similar extubation times in the remifentanil and fentanyl groups in the present study probably reflect the stringent dosing guidelines and close monitoring of patients to maintain a target sedation level, which prevented any significant accumulation of fentanyl.

The greater incidence of pain and use of supplementary analgesia in the remifentanil group during the extubation phase and beyond is consistent with its rapid offset of action and reflects constraints in optimizing the transition to alternative analgesia in the context of this double-blind study, which compared two agents with very different pharmacokinetic/dynamic characteristics. In order to avoid confounding assessment of the primary end-point, and to adhere with the confines of the study protocol, it was not possible to commence administration of longer acting analgesics until completion of the maintenance phase. It is therefore not surprising that there was a trend toward more pain and agitation in the remifentanil patients during the extubation phase and afterward. Pain was effectively treated with up to three doses of a longer acting analgesic in the majority of patients. Given the higher incidence of pain in the remifentanil group, however, larger doses and earlier administration of alternative treatment strategies than those used in the present study would appear to be warranted. This emphasizes the need to consider proactively the patient's analgesic requirements when using remifentanil so that there is a smooth transition to alternative analgesia.

The majority of adverse events reported during the present study were expected in patients requiring intensive care either for medical reasons or following surgery, and were typical for patients given μ opioid agonists. Fentanyl is frequently used in the ICU because it offers greater haemodynamic stability when compared with morphine because of its lack of histamine release. The similarity in the weighted mean MAP and HR data, and the comparable incidence of patients

with haemodynamic outliers (Table 6) in both treatment groups shows that remifentanil provided an acceptable degree of haemodynamic stability.

Conclusion

In conclusion, initiation and titration of remifentanil before administration of propofol allowed effective provision of optimal sedation and rapid extubation without the need for propofol in the majority of patients with normal renal function or mild renal impairment. Remifentanil was associated with significantly less between-patient variability in the mean percentage of time with optimal sedation than was fentanyl. The present study shows that either opioid can be effective as initial treatment for the provision of sedation and analgesia in ICU patients. To achieve this using conventional opioids such as fentanyl, however, would require almost constant patient monitoring to ensure that over-sedation caused by drug accumulation, resulting in delayed extubation, does not occur. Such intensive monitoring should be unnecessary with remifentanil. If the patient becomes over-sedated, then the rapid offset of the effects of remifentanil should allow swift optimization by altering the infusion rate. Furthermore, the risk for delayed extubation because drug accumulation should be markedly reduced with remifentanil, regardless of the duration of administration [4]. To maximize the benefits offered by remifentanil, local analgesia/sedation protocols and dosage guidelines based on the dosing algorithm used in the present study will need to be developed. One of the most significant advantages of remifentanil is its organ independent mode of metabolism. This makes it particularly valuable for use in patients with organ impairment. Studies have investigated its use in this group [16–18,31]. Remifentanil was well tolerated and provided good haemodynamic stability – similar to that observed in patients receiving fentanyl, which is the current 'gold standard' for the provision of haemodynamic stability in the ICU setting.

Key messages

- Analgesia based sedation using remifentanil allowed effective provision of optimal sedation without the need for propofol in the majority of patients
- Reduced variability in the provision of optimal sedation when using remifentanil implies improved control of patient comfort when compared with fentanyl
- Although not perceived as a clinical issue, the rapid and predictable offset of analgesic action resulted in a greater incidence of pain with remifentanil. This highlights the need for proactive pain management when transitioning to longer acting analgesia
- The remifentanil regimen was well tolerated, and the haemodynamic and adverse event profiles were similar to those of fentanyl
- The titratability, short duration of action and reduced requirement for propofol make remifentanil a very useful opioid for provision of analgesia based sedation in critically ill patients. To achieve the maximum benefit of this technique, remifentanil should be initiated and titrated to response before any sedative is administered

Competing interests

BM, AL, MHC, CB and LM 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

The authors would like to acknowledge the contribution of the following to the conduct of the study:

- Belgium: Dr J Poelaert, Dr K Vandewoude, Dr E Hoste, Dr W Temmerman and Dr J Decruyenaere, University Hospital, Gent; Dr R De Paep, Prof. L Bossaert, Dr E Hendrickx and Dr D Dohmen, University Hospital Antwerpen, Edegem; Dr M Bourgeois, Dr M Nauwynck and Dr P Laporte, AZ St. Jan, Brugge; Dr L Jacquet, Dr I Michaux and Dr P Hantson, University of St. Luc, Bruxelles
- Germany: Prof. H Van Aken, Dr C Goeters and Prof. T Möllhoff, Westfälische Wilhelms Universität, Münster; Prof. R Larsen, Dr U Grundmann, Dr C-E Ott and Dr F Bach, Universitätskliniken des Saarlandes, Homburg; Dr B Muellejans, Dr S Gründling, Dr T Friebe, Dr K Burggraf, Dr F Dehullu, Dr C Koch and Dr T Schilling, Herz-und Diabeteszentrum Mecklenburg-Vorpommern, Karlsburg; Prof. E Kochs, Dr W Reeker and Dr M Stocker, Klinikum rechts der Isar – Technische Universität Mûnchen, Mûnchen; Prof. J Scholz, Dr I Kûhnelt, Dr J Wõrdemann and T Warmbold, Universitätskrankenhaus Eppendorf, Hamburg; Dr HP Moecke, Dr A Brachmeyer and Dr S Oppermann, Allgemeines Krankenhaus Barmbek, Hamburg; Dr M Quintel, Dr E Mûnch and Dr C Stieber, Klinikum Mannheim Universitätsklinikum, Heidelberg; Dr P Kessler and Dr D Meininger, Klinikum der Johann-Wolfgang-Goethe-Universität, Frankfurt
- The Netherlands: Dr GJ Scheffer, Dr HB Smit, Dr PJM Rosseel and Dr CMP Theunissen, Ignatius Ziekenhuis, Breda
- Spain: Dr C Bonome, Dr MF Alvarez, Dr P Pose, Dr I López, Dr M González and Dr M Fraga, Hospital Juan Canalejo, La Coruña; Dr JM Campos, Dr H Litvan, Dr M Luz Maestre, Dr M Revuelta, Dr J Galán and Dr P Paniagua, Hospital Santa Cruz y San Pablo, Barcelona; Dr A López, Dr JA Juliá, Dr R Bayo, Dr L López and Dr MJ Rivera, Hospital Universitario Infanta Cristina, Badajoz; Dr LM Torres and Dr MD León, Hospital Puerta del Mar, Cádiz
- UK: Dr A Binning, Western Infirmary, Glasgow; Dr A Bodenham and Dr M Cross, Leeds General Infirmary, Leeds; Dr L Morrison, Dr D Henderson and Dr M Brockway, St. John's Hospital, Livingston, West Lothian; Dr C Snowden, Dr P Wright and Dr R Digby, Freeman Hospital, Newcastle-upon-Tyne

Statistical support for this study was provided by Julia Lees, GlaxoSmithKline, Greenford, UK.

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.
2. Carrasco G, Molina R, Costa J, Soler J-M, L Cabre: **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. Park GR, Evans TN: **Remifentanil in the critically ill - what will its place be?** *Br J Intensive Care* 1996, **6:**330-336.

6. Szalados JE, Boysen PG: **Sedation in the critically ill patient.** *Curr Opin Anaesthesiol* 1998, **11:**147-155.
7. Lenhart A: **Remifentanil in intensive care medicine.** *J Anasth Intensivbehandl* 2000, **7:**123-124.
8. Mastronardi P, Cafiero T, De Cillis P: **Remifentanil in anesthesia and intensive care.** *Minerva Anestesiol* 2000, **66:**417-423.
9. Lane M, Cadman B, Park G: **Learning to use remifentanil routinely in the critically ill.** *Care Crit Ill* 2002, **18:**140-143.
10. Lane M, Cadman B, Park G: **The use of remifentanil in the critically ill.** *Care Crit Ill* 2002, **18:**144-145.
11. Lane M, Cadman B, Park G: **Sedation and analgesia in the critically ill patient using remifentanil: frequently asked questions and their answers.** *Care Crit Ill* 2002, **18:**146-147.
12. Park G: **Improving sedation and analgesia in the critically ill.** *Minerva Anestesiol* 2002, **68:**505-512.
13. Tipps LB, Coplin WM, Murry KR, Rhoney DH, Gelmont D, Cucchiara RF, Macdonald RL, Muizelaar JP: **Safety and feasibility of continuous infusion of remifentanil in the neurosurgical intensive care unit.** *Neurosurgery* 2000, **46:**596-602.
14. Karabinis A, Hantson P, Speelberg B, Stergiopoulos S, Illievich UM, Maas A, Upadhyaya BK: **A remifentanil-based technique for analgesia and sedation in ICU patients with neurotrauma: preliminary data [abstract A549].** *Intensive Care Med* 2001, **Suppl 2:**S275.
15. Soltész S, Biedler A, Silomon M, Schopflin I, Molter GP: **Recovery after remifentanil and sufentanil for analgesia and sedation of mechanically ventilated patients after trauma or major surgery.** *Br J Anaesth* 2001, **86:**763-768.
16. Breen D, Wilmer A, Bodenham A, Bach V, Bonde J, Kessler P, Albrecht S, Shaikh S: **The offset of pharmacodynamic effects of remifentanil in ICU patients is not affected by renal impairment [abstract A284].** *Intensive Care Med* 2001, **Suppl 2:**S207.
17. Breen D, Wilmer A, Kessler P, Bach V: **Lower requirement for sedative with a remifentanil-based analgesia/sedation technique in ICU patients [abstract A701].** *Intensive Care Med* 2002, **Supp 1:**S180.
18. Hoke JF, Shlugman D, Dershwitz M, Michalowski P, Malthouse-Dufore S, Connors PM: **Pharmacokinetics and pharmacodynamics of remifentanil in persons with renal failure compared with healthy volunteers.** *Anesthesiology* 1997, **87:**533-541.
19. Main A: **Remifentanil as an analgesic in the critically ill.** *Anaesthesia* 1998, **53:**823-824.
20. Wilhelm W, Dorscheid E, Schlaich N, Niederprum P, Deller D: **The use of remifentanil in critically ill patients. An initial clinical experience report.** *Anaesthesist* 1999, **48:**625-629.
21. De Bellis P, Gerbi G, Pacigalupo P, Buscaglia G, Massobrio B, Montagnani L, Servirei L: **Experience with remifentanil in the intensive care unit.** *Minerva Anestesiol* 2002, **68:**765-773.
22. Cavaliere F, Antonelli M, Arcangeli A, Conti G, Costa R, Pennisi MA, Proietti R: **A low-dose remifentanil infusion is well tolerated for sedation in mechanically ventilated, critically ill patients.** *Can J Anesth* 2002, **49:**1088-1094.
23. Reeker W, Hanel F, Detsch O, Mollenberg O, Werner C, Kochs E: **The effects of remifentanil on systemic hemodynamic and EEG responses during endotracheal suctioning in ICU patients [abstract A203].** *Anesthesiology* 1997, **87:**A203.
24. Gupta S, Ravalia A: **Remifentanil for percutaneous tracheostomies in ITU.** *Anaesthesia* 2000, **55:**491-492.
25. Kessler P, Chinachoti T, Van Deer Berg P, Stanley A, Kirkham A: **Remifentanil vs. morphine for the provision of optimal sedation in ICU patients [abstract A406].** *Intensive Care Med* 2001, **Suppl 2:**S239.
26. Quinton P, Fletcher N, Royston D, Farrimond J, Riedel B: **Propofol sparing effect of remifentanil when added to propofol for sedation in the intensive care unit [abstract A352].** *Intensive Care Med* 2000, **Suppl 3:**S304.
27. Park GR, Evans TN, Hutchins J, Borissov B, Gunning KE, Klinck JR: **Reducing the demand for admission to intensive care after major abdominal surgery by a change in anaesthetic practice and the use of remifentanil.** *Eur J Anaesthesiol* 2000, **17:**111-119.
28. Le Gall J-R, Lemeshow S, Saulnier F: **A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study.** *JAMA* 1993, **270:**2957-2963.
29. 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.
30. Higgins TL, Vared J-P, Estafanous FG, Coyle JP, Ko HK, Goodall DB: **Propofol versus midazolam for intensive care unit sedation after coronary artery bypass grafting.** *Crit Care Med* 1994, **22:**1415–1423.
31. Dershwitz M, Hoke JF, Rosow CE, Michalowski P, Connors PM, Muir KT, Dienstag JL. **Pharmacokinetics and pharmacodynamics of remifentanil in volunteer subjects with severe liver disease.** *Anesthesiology* 1996; **84:**812-820.
32. Cockcroft DW, Gault MH: **Prediction of creatinine clearance from serum creatinine.** *Nephron* 1976, **16:**31–41.