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Offset of pharmacodynamic effects and safety of remifentanil in intensive care unit patients with various degrees of renal impairment

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Abstract

Introduction This open label, multicentre study was conducted to assess the times to offset of the pharmacodynamic effects and the safety of remifentanil in patients with varying degrees of renal impairment requiring intensive care.

Methods A total of 40 patients, who were aged 18 years or older and had normal/mildly impaired renal function (estimated creatinine clearance ≥50 ml/min; $n = 10$) or moderate/severe renal impairment (estimated creatinine clearance <50 ml/min; $n = 30$), were entered into the study. Remifentanil was infused for up to 72 hours (initial rate 6–9 μg/kg per hour), with propofol administered if required, to achieve a target Sedation–Agitation Scale score of 2–4, with no or mild pain.

Results There was no evidence of increased offset time with increased duration of exposure to remifentanil in either group. The time to offset of the effects of remifentanil (at 8, 24, 48 and 72 hours during scheduled down-titrations of the infusion) were more variable and were statistically significantly longer in the moderate/severe group than in the normal/mild group at 24 hours and 72 hours. These observed differences were not clinically significant (the difference in mean offset at 72 hours was only 16.5 min). Propofol consumption was lower with the remifentanil based technique than with hypnotic based sedative techniques. There were no statistically significant differences between the renal function groups in the incidence of adverse events, and no deaths were attributable to remifentanil use.

Conclusion Remifentanil was well tolerated, and the offset of pharmacodynamic effects was not prolonged either as a result of renal dysfunction or prolonged infusion up to 72 hours.

Keywords analgesia based sedation, critical care, offset times, pharmacodynamics, remifentanil, renal function, safety

CL_{cr} = creatinine clearance; HR = heart rate; ICU = intensive care unit; MAP = mean arterial pressure; PI = Pain Intensity (scale); RR = respiratory rate; SAE = serious adverse event; SAPS = Simplified Acute Physiology Score; SAS = Sedation–Agitation Scale; SDT = scheduled down-titration.

Introduction

Patients who require intensive care need effective analgesia and sedation to control pain, relieve anxiety and aid compliance with tracheal intubation, mechanical ventilation and nursing procedures. Commonly, the combination of an opioid such as fentanyl or morphine for analgesia and a hypnotic agent such as propofol or midazolam for sedation is used. All opioids have varying degrees of sedative effect at increasing doses. Elimination of traditional opioids is dependent on organ function, which is abnormal in the critically ill. The context-sensitive half-time of these drugs also increases with time. Because of this, the opioid component of a sedation regimen is usually kept to a minimum compatible with adequate analgesia, and patient comfort is provided by titrating the level of hypnosis. However, organ dysfunction and duration of drug infusion also affect the offset of effects of the hypnotic component. Prolonged use of both conventional analgesic and hypnotic agents is therefore also associated with an unpredictable and prolonged offset of effects in the critically ill.

Remifentanil hydrochloride is a potent, selective μ opioid receptor agonist that has a rapid onset of action (about 1 min) and quickly achieves a steady state. Most notably, remifentanil exhibits a predictable, rapid metabolism by nonspecific esterases in the blood and tissues [1] and has a constant context-sensitive half-time of 2–3 min, which is independent of the duration of infusion [2]. These features of remifentanil combine to make it easy to titrate to effect and allow it to be administered for long periods and at higher doses than are normally used with traditional opioids without risk for significant accumulation. The organ independent elimination of remifentanil makes it an attractive agent for use in the intensive care unit (ICU) setting, where some degree of organ dysfunction is common. A number of investigators have now studied its use in the ICU [3–13].

The principal metabolite of remifentanil, remifentanil acid, is 4600 times less potent as a μ opioid agonist than remifentanil in animal models [14]. However, this metabolite is eliminated via the kidneys, and in patients with severe renal impairment (predicted creatinine clearance [CL_{cr}] <10 ml/min) its elimination is prolonged [15]. There is therefore a potential risk that long-term administration of remifentanil in patients with severe renal impairment will result in remifentanil acid exerting clinically significant μ opioid effects because of its accumulation in the body.

The present study was conducted to assess the offset times of the pharmacodynamic effects of prolonged remifentanil infusions in ICU patients with varying degrees of renal impairment, including patients with severe renal dysfunction. A series of down-titrations of the remifentanil infusion were performed over time, so that any clinically significant μ opioid effects that might result from the accumulation of remifentanil acid in patients with significant renal impairment could be identified. The safety profile of remifentanil in these patients was assessed by recording haemodynamic parameters and adverse events throughout the study period. A remifentanil based regimen was used in the study that allowed titration of this agent in the first instance to achieve optimal patient comfort, with propofol added only if required [7].

Methods

This open label, noncomparator safety study assessed the pharmacodynamic and safety profiles of remifentanil administered by continuous intravenous infusion for up to 72 hours in ICU patients with varying degrees of renal impairment. 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. Following approval from local and national ethics committees, 40 patients were recruited from a total of eight centres (three centres in the UK, two in Denmark, two in Germany and one in Belgium).

Postsurgical and medical patients admitted to the ICU were eligible for entry into the study if they were aged 18 years or older, weighed 120 kg or less, and if they were expected to require mechanical ventilation for 24–72 hours. All patients had a Sedation–Agitation Scale (SAS) score [16] in the range 2–4 at study entry (see accompanying report by Muellejan and coworkers [17] for details of this scoring system). Female patients were included if they were of non-child-bearing potential or were using contraception. 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 treatment period (see below). Patients were also excluded if they had received any opioids or sedatives other than remifentanil, fentanyl, alfentanil, sufentanil, or propofol within the previous 24 hours. Other exclusion criteria included the presence of a neurological condition that might affect the ability to assess the patient's SAS score, a history of allergy to opioids, benzodiazepines or propofol, or a history of alcohol/drug abuse.

The study was divided into four periods. The screening period was the time from obtaining consent/assent in the ICU to the start of the administration of remifentanil. The treatment period lasted from the start of the remifentanil infusion until its permanent discontinuation after a maximum of 72 hours (with a further 30 min period for down-titration). The post-treatment period lasted from the time of permanent discontinuation until 72 hours later (or until hospital discharge or death). The follow-up period lasted from 72 hours after stopping remifentanil until the end of study day 14 (or until hospital discharge or death).

During the initial screening period, the patient's renal function was measured by estimating CL_{cr} over a minimum period of 4 hours and extrapolating this to the 24 hour CL_{cr}. Briefly,

CL_{cr} was estimated from a 4–8 hour urine collection conducted within 12 hours before the start of remifentanil administration, together with measurement of plasma and urinary creatinine concentration, using the following equation:

$$CL_{cr}\ (\text{ml/min}) = \frac{[\text{Cr}]\text{urine} \times \text{urine volume per unit time}}{[\text{Cr}]\text{plasma}}$$

The renal impairment score was derived by assigning a maximum score of 5 points based upon review of the following parameters using the Logistic Organ Dysfunction System [18]: serum urea or urea nitrogen; serum creatinine; and urine output (l/day).

Patients with an estimated CL_{cr} of 50 ml/min or greater were classified as having normal renal function or mild renal impairment, whereas those with CL_{cr} under 50 ml/min were classified as having moderate/severe renal impairment.

Baseline assessments of the patient's SAS, pain intensity (PI scale; see accompanying report by Muellejans and coworkers [17]), mean arterial pressure (MAP), heart rate (HR) and respiratory rate (RR) were recorded before starting the remifentanil infusion.

Remifentanil hydrochloride (lyophilized powder in sterile vials each containing 5 mg of the compound) was provided by GlaxoSmithKline. The contents of the lyophilized vials of remifentanil were reconstituted/diluted with standard diluent to a final concentration of 100 μg/ml.

During the treatment period all patients were continuously assessed and the remifentanil (and propofol if required) dose regimen was adjusted in order to maintain an SAS score of 2–4 (as considered clinically appropriate) with no or mild pain (PI scale score ≤ 2). The remifentanil infusion was titrated and propofol administered in a similar manner to the dosing algorithm described in the accompanying paper [17] except that a remifentanil starting dose of 6 or 9 μg/kg per hour could be administered, and more frequent up-titration of the initial remifentanil 6 μg/kg per hour infusion in 1.5 μg/kg per hour increments (at 5 min intervals) was permitted if clinically indicated.

Assessment of the offset of the effects of remifentanil

The offset of the pharmacodynamic effects of remifentanil was measured at 8, 24, 48 and 72 hours after the start of the infusion. At each of these scheduled time points, the remifentanil infusion was down-titrated. This was called a scheduled down-titration (SDT), and the offset of the pharmacodynamic effects of remifentanil was measured by monitoring changes in the patient's clinical status (including the level of sedation/analgesia) over time. At the start of each SDT the remifentanil infusion was initially reduced by 25%. Subsequent infusion rate reductions (25% of the infusion rate at the start of the SDT) were made at 10 min intervals until the infusion was discontinued if necessary (i.e. after three further decrements over a total period of 30 min). The down-titration was stopped during the 8, 24 and 48 hour SDTs if the SAS or PI scale score were inadequate or if there were clinically significant changes in MAP, HR, or RR to indicate that the drug effect was wearing off.

If the down-titration process was stopped, then the remifentanil infusion was returned to the rate in use immediately before the SDT was initiated. The patient's sedation and pain scores were then assessed and treatment adjusted according to the prescribed dosing algorithm for maintaining adequate sedation and comfort. The time elapsed between initiating the SDT and stopping the down-titration (i.e. switching back on/increasing the remifentanil infusion rate in response to clinical need) was the primary parameter used to determine the offset of the pharmacodynamic effects of remifentanil during the SDTs.

If the remifentanil infusion had been discontinued according to the SDT, and there were no clinically significant changes in the level of sedation/pain or changes in the parameters described above 30 min after discontinuation, then the patient entered the post-treatment period of the study and alternative therapy was initiated as appropriate. In this case, the time to the offset of the pharmacodynamic effects of remifentanil was recorded as the time from the start of the SDT to the time when, in the investigator's judgement, the start of the offset of the pharmacodynamic effects of remifentanil became evident. The administration of alternative treatment was to be delayed whenever possible until the offset of pharmacodynamic effects was observed.

For any patient receiving a concomitant propofol infusion during any of the SDTs, this was maintained at a constant rate while the offset of pharmacodynamic effects of remifentanil were being assessed and until the remifentanil infusion had been stopped for 30 min. The propofol infusion was then down-titrated in decrements of 25% of the initial rate at 10 min intervals and, if necessary, discontinued. The time to offset of the pharmacodynamic effects of remifentanil was recorded and the patient entered the post-treatment period as described above.

At the 72 hour SDT the remifentanil infusion rate was reduced in the same way as for the other SDTs and permanently stopped. Provided there were no changes in the patient's level of sedation/pain or changes in the parameters described above, any propofol that was being infused at this time was maintained at a constant rate until 30 min after the remifentanil had been stopped. The propofol was then decreased in decrements and the time to offset of the pharmacodynamic effects of remifentanil was recorded as previously described. The time (during or after termination of the infusion) at which, in the investigator's judgement, the start of the offset of the effects of remifentanil became evident was

recorded. The administration of alternative treatment was to be delayed wherever possible until the offset of pharmacodynamic effects was evident.

Patients could be extubated at any time during the treatment period if they were deemed eligible for this by the investigator. Any remaining SDTs of remifentanil were not conducted, and only the final down-titration following extubation was performed. After the remifentanil had finally been discontinued, the patient was switched to standard therapy at the investigator's discretion.

Sample acquisition, handling and processing

Extensive blood sampling was included in the present study in order to investigate the pharmacokinetic characteristics of remifentanil and remifentanil acid in patients with impaired renal function [19]. Only the remifentanil acid results from the blood samples taken at the time of starting the down-titration and the highest remifentanil acid concentration observed are reported here. Arterial blood samples (5 ml) were collected from all patients into tubes containing citric acid and frozen for subsequent assay.

Assay method

The concentrations of remifentanil acid in whole blood were determined using validated assay procedures. The method, a specific liquid chromatography tandem mass spectrometry (LC-MS/MS) method, was a modification of a previously published method [20] that involved solid phase extraction with methanol instead of dichloromethane and enabled simultaneous quantification of free remifentanil acid.

The lower limit of quantification for both analytes was 0.1 ng/ml, intra-assay precision values at the lower limit of quantification were under 20% and accuracy values were within 100 ± 20%, with reference to the nominal value, whereas overall intra-assay and inter-assay precision values were under 15% and accuracy values within 100 ± 15% of the nominal value.

Patient monitoring

In addition to SAS and PI scale scores, MAP, HR and RR were recorded at baseline, at the time of starting remifentanil, immediately before and 10 min after remifentanil dose adjustments, and at all scheduled times during the treatment period when blood samples were obtained for pharmacokinetic analysis. Blood samples were collected at frequent time intervals including at 15 and 30 min, and 1, 2 and 4 hours after starting the remifentanil infusion, at 08:00 hours and 20:00 hours each day, and at SDTs, but those measurements are not reported here. All patients were continuously monitored for the occurrence of adverse events throughout the study period. Serious adverse events (SAEs) were defined as adverse events that resulted in any of the following outcomes: death, life threatening event, prolongation of hospitalization, and disability/incapacity. Important medical events that did not result in death or were not life threatening were considered SAEs when, based on appropriate medical judgement, they jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes listed above.

Study end-points

The primary end-point of this study was the times to offset of the pharmacodynamic effects of remifentanil after SDTs and after permanent discontinuation. The incidences of adverse events in the two renal function groups were also recorded, and SAS and PI scale scores, and haemodynamic and respiratory parameters were regularly assessed as described above.

Statistical analyses

Because this was a safety study, no formal sample size calculation was performed. The times to offset of the pharmacodynamic effects of remifentanil during the SDTs were analyzed using the Cox proportional hazards model. The incidences of adverse events in the patients with normal renal function/mild renal impairment and in those with moderate or severe renal impairment were analyzed using Fisher's exact test. Weighted mean SAS and PI scale scores, MAP and HR values, recorded at pharmacokinetic sampling times (excluding stimulating procedures and SDTs), were summarized and analyzed using analysis of covariance. All summary statistical computations were performed using SAS version 8 software (SAS Institute Inc., Cary, NC, USA). All tests of significance were two sided and were conducted at the 5% level.

Results

The baseline demographic and clinical characteristics of the patients are summarized in Table 1. There were clear differences between the two populations. The patients with moderate/severe renal impairment tended to have greater Simplified Acute Physiology Score (SAPS) II values than did those in the normal/mild group. Twelve patients in this group had SAPS II scores greater than 52 on ICU admission, as compared with one patient in the normal/mild group.

The duration of the remifentanil infusion ranged from 45.4 to 72.8 hours in the normal/mild group and from 4.83 to 72.5 hours in the moderate/severe group.

Offset of the pharmacodynamic effects of remifentanil

The offset of the pharmacodynamic effects of remifentanil was measured at the SDTs at 8, 24, 48 and 72 hours, when the remifentanil infusion was permanently discontinued. The time to offset of the pharmacodynamic effects of remifentanil was statistically significantly longer in the moderate/severe group at the 24 hours and 72 hours SDTs, and overall there was greater variability in the times to offset of effects in this group compared with the normal/mild group (Fig. 1). These differences were not clinically significant, however. There was no real difference in the time to offset at SDTs in either group as the duration of infusion increased up to 72 hours. Also, the

Table 1

Patient demographic and clinical characteristics (safety population)

	Degree of renal impairment	
Characteristic	Normal/mild	Moderate/severe
Number of patients treated	10	30
Reason for ICU admittance		
Cardiac postsurgical	4 (40%)	7 (23%)
General postsurgical	0	10 (33%)
Medical	6 (60%)	13 (44%)
Respiratory	4 (40%)	8 (27%)
Sepsis	0	3 (10%)
Cardiovascular	1 (10%)	1 (3%)
Trauma	1 (10%)	0
Haematological	0	1 (3%)
Mean SAPS II (range)	41.0 (31–57)	53.2 (16–91)
Mean CL_{cr} (ml/min) at screening (range)	62.9 (44–84)	13.7 (0–49)
Mean renal dysfunction score at screening‡ (range)	2.3 (0–3)	4.3 (1–5)
Renal replacement therapy	0	14 (47%)
Mean baseline SAS score (range)	2.9 (2–4)	2.4 (2–4)
Mean baseline PI score (range)	1.2 (1–2)	1.1 (1–3)
Mean baseline RR (breaths/min; range)	15.6 (10–22)	14.7 (0–39)
Mean baseline MAP (mmHg; range)	79.0 (53–105)	78.3 (56–135)
Mean baseline HR (beats/min; range)	85.6 (61–126)	94.7 (62–128)
Mean age (years; range)	68.6 (54–78)	65.7 (31–81)
Sex		
Male	9 (90%)	22 (73%)
Female	1 (10%)	8 (27%)
Mean height (cm; range)	173.2 (157–180)	167.5 (120–188)
Mean weight (kg; range)	79.6 (68–96)	75.6 (38.3–110)

Renal function was assessed by estimating the patient's creatinine clearance (CL_{cr}), as described under Methods. Normal renal function/mild renal impairment was defined as an estimated CL_{cr} ≥50 ml/min. Moderate/severe renal impairment was defined as an estimated CL_{cr} <50 ml/min. ‡Logistic Organ Dysfunction Score [18]. HR, heart rate; ICU, intensive care unit; MAP, mean arterial pressure; PI, Pain Intensity (scale); RR, respiratory rate; SAPS, Simplified Acute Physiology Score [23]; SAS, Sedation–Agitation Scale.

mean time to offset between the two groups after 72 hours of administration of remifentanil was only 16.5 min. There was also no correlation between the time to offset of effects and the concentration of remifentanil acid (Fig. 2).

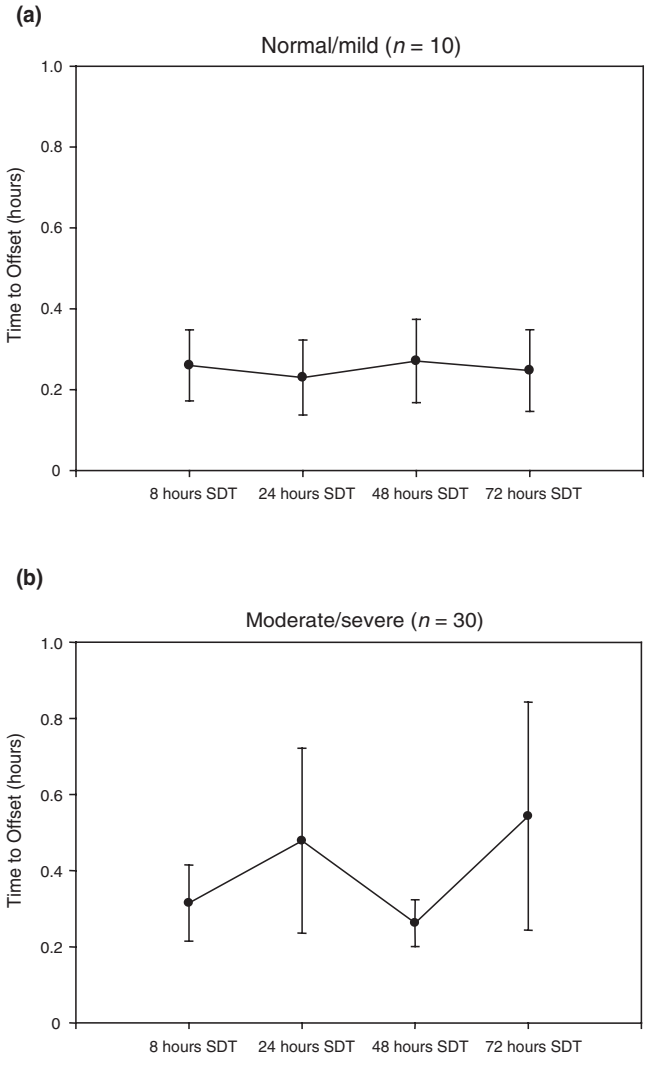
Remifentanil and propofol doses at scheduled down-titrations

The mean remifentanil infusion rate at the start of SDTs was generally greater in patients in the normal/mild group than in the moderate/severe group (Table 2), although this was not tested for statistical significance. However, the remifentanil infusion rates were comparable at each successive SDT within both groups. Using remifentanil based sedation, the addition of propofol was not required by 43% of patients. When propofol was administered there was also a trend toward a greater requirement in the normal/mild group than in the moderate/severe group at the start of each SDT. The mean propofol infusion rate was comparable at each successive SDT within both groups. Comparison of the weighted mean infusion rate for remifentanil and propofol approached statistical significance when comparing normal/mild and moderate/severe treatment groups (13.1 and 10.1 μg/kg per hour for remifentanil [$P = 0.070$], and 1.3 and 0.7 mg/kg per hour for propofol [$P = 0.071$], respectively).

Safety

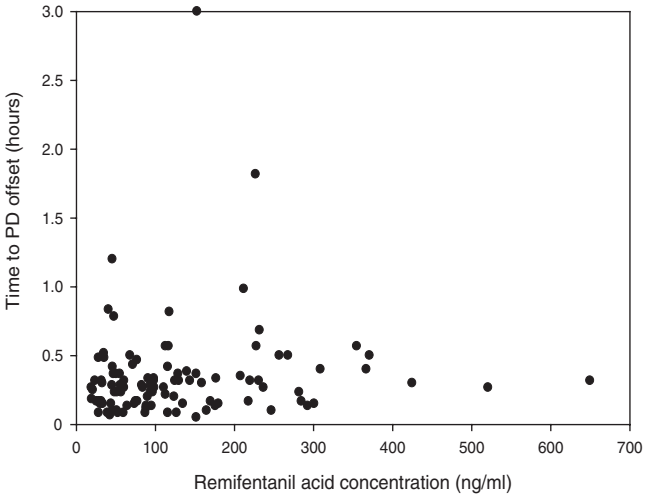
Remifentanil was well tolerated and the adverse event profile was consistent with what would be expected in ICU patients

Figure 1



Mean (± 95% confidence interval) time to offset of the pharmacodynamic effects of remifentanil at 8, 24, 48 and 72 hour scheduled down-titrations (SDTs), analyzed using the Cox proportional hazards model. **(a)** Group with normal/mild renal impairment. Numbers included at each assessment were as follows: 10 at the 8 hour SDT, 10 at the 24 hour SDT, eight at the 48 hour SDT, and six at the 72 hour SDT. **(b)** Group with moderate/severe renal impairment. Numbers included at each assessment were as follows: 28 at the 8 hour SDT, 25 at the 24 hour SDT, 15 at the 48 hour SDT, and 15 at the 72 hour SDT. *P* values are as follows (all versus group with normal/mildly impaired renal function): 0.616 at the 8 hour SDT, 0.031 at the 24 hour SDT, 0.998 at the 48 hour SDT, and 0.042 at the 72 hour SDT.

Figure 2



Scatter plot of time to the offset of pharmacodynamic (PD) effects versus remifentanil acid concentrations at the start of down-titration.

receiving a potent μ opioid agonist. A summary of all adverse events reported during the study period is presented in Table 3. There was no statistically significant difference between the renal function groups in the number of patients experiencing one or more adverse events overall (20% of patients in the normal/mild group versus 37% of patients in the moderate/severe group; $P = 0.451$) or during the treatment (10% versus 27%; $P = 0.404$) and post-treatment (10% versus 13%; $P = 1.000$) periods. There were no adverse events reported during the extubation phase.

There was also no statistically significant difference between the renal function groups in the incidence of adverse events that were considered to be possibly related to study drug by the investigator. Overall, drug related adverse events were reported in two patients (20%) in the normal/mild group and five patients (17%) in the moderate/severe group ($P = 1.000$).

None of the 17 deaths reported during the study period were considered by the investigators to be related to remifentanil. Most of the deaths occurred in patients with moderate/severe renal impairment, and included the following symptoms: multiple organ failure, cardiac arrest, sepsis, sepsis with faecal peritonitis and renal failure, emphysema, ischaemia of the small intestine, and pneumonia/apnoea.

A total of 18 SAEs were reported among 13 patients, all of whom were in the moderate/severe group. The onset of eight of these events, experienced by five patients, was before the administration of remifentanil. Seven patients experienced seven SAEs that were fatal; however, as noted above, none of the study deaths were considered to be related to remifentanil. One patient experienced two nonfatal SAEs (two reports of ventricular fibrillation), and one patient with a fatal SAE (gastrointestinal haemorrhage) that occurred during the follow-up period also experienced a nonfatal SAE (sinus arrest). One SAE was considered by the investigator to be possibly related to remifentanil. Most SAEs occurred during the treatment period of the study. The difference in incidence of SAEs in the moderate/severe and mild/moderate renal impairment groups following initiation of remifentanil treat-

Table 2

Remifentanil and propofol doses at the time of scheduled down-titrations

	Remifentanil infusion rate at start of SDT (μg/kg per hour)		Mean propofol infusion rate at start of SDT (mg/kg per hour)		Number (%) of patients receiving propofol at SDT	
Time of SDT	Normal/mild	Moderate/severe	Normal/mild	Moderate/severe	Normal/mild	Moderate/severe
8 hours	8.8 (2.8)	7.0 (3.5)	0.8 (0.1)	0.7 (0.4)	5 (50)	11 (37)
24 hours	9.7 (3.0)	7.5 (3.6)	1.3 (0.9)	1.1 (0.5)	7 (70)	8 (27)
48 hours	10.1 (3.9)	7.6 (2.7)	1.0 (0.6)	0.9 (0.6)	5 (50)	2 (7)
72 hours	9.7 (6.0)	7.7 (2.9)	1.2 (0.7)	0.8 (0.4)	4 (40)	4 (13)

Values are expressed as mean (standard deviation). SDT, scheduled down-titration.

Table 3

Adverse events reported during the study

Body system	Normal/ mild	Moderate/ severe	Total
Any event	2 (20%)	11 (37%)*	13 (33%)
Cardiovascular			
Any event	0	4 (13%)	4 (10%)
Cardiac arrest	0	2 (7%)	2 (5%)
Sinus arrest	0	1 (3%)	1 (3%)
Ventricular fibrillation	0	1 (3%)	1 (3%)
Digestive			
Any event	1 (10%)	3 (10%)	4 (10%)
Diarrhoea	1 (10%)	1 (3%)	2 (5%)
Ileus	0	2 (7%)	2 (5%)
Ischaemic bowel	0	1 (3%)	1 (3%)
Body as a whole			
Any event	0	3 (10%)	3 (8%)
Multiple organ failure	0	2 (7%)	2 (5%)
Sepsis	0	1 (3%)	1 (3%)
Musculoskeletal			
Any event	0	2 (7%)	2 (5%)
Muscle rigidity	0	2 (7%)	2 (5%)
Nervous			
Any event	1 (10%)	1 (3%)	2 (5%)
Agitation	1 (10%)	1 (3%)	2 (5%)

*$P = 0.451$ versus normal/mild group (Fisher's exact test).

ment was not statistically significant ($P = 0.165$). There were five SAEs (four different types of event) in five patients that led to premature discontinuation of remifentanil. None of these events were considered to be possibly related to remifentanil.

Haemodynamic and respiratory parameters

Haemodynamic parameters were stable throughout the treatment period. The weighted mean MAP was comparable between groups (79.6 mmHg for patients in the normal/mild group versus 77.6 mmHg for those in the moderate/severe group; not significant). The weighted mean HR was significantly higher in the moderate/severe group (92.1 beats/min) than in the normal/mild group (86.7 beats/min; $P = 0.016$); however, this is consistent with the higher baseline value in this group. The weighted mean RR was comparable between groups (15.6 breaths/min for patients in the normal/mild group versus 14.5 breaths/min for those in the moderate/severe group; not significant).

Efficacy

In terms of patient comfort, the remifentanil based treatment regimen was effective in both renal function groups. The mean percentage of hours of adequate sedation (SAS score 2–4) was comparable between groups (82.4% in the normal/mild group and 89.9% in the moderate/severe group; not significant). The mean percentage of hours of adequate pain control (PI scale score ≤ 2) was also comparable between groups (97.6% in the normal/mild group and 95.8% in the moderate/severe group; not significant).

Discussion

The aim of this study was to assess the offset of the pharmacodynamic effects and the safety profile of a remifentanil based regimen for the provision of analgesia and sedation in mechanically ventilated ICU patients with varying degrees of renal impairment. A significant proportion of the patients (25/40) had severe renal impairment ($CL_{cr} < 30$ ml/min), and 14 of these patients required renal replacement therapy in the ICU. The majority of patients (90%) in the normal function/mild renal impairment group had a SAPS II score of 52 or less. In the moderate/severe group, however, 40% of patients had a SAPS II score greater than 52. The greater mortality risk in the moderate/severe group was reflected in a higher percentage of deaths during the study (50% of patients versus 20% of the patients in the normal/mild group).

Pharmacokinetics of remifentanil and remifentanil acid in patients with impaired renal function

The pharmacokinetic data for remifentanil and the remifentanil acid metabolite in patients with impaired renal function have been investigated [19]. In summary, remifentanil kinetics were unaltered in impaired renal function, but remifentanil acid clearance decreased in a linear manner with decreasing screening CL_{cr}, and in patients with moderate/severe renal impairment remifentanil acid clearance was reduced to 20% of that in the normal/mild group. The elimination half-life was thus prolonged by sevenfold in these patients. The metabolic ratio (the ratio of the area under the curve for remifentanil acid to that for remifentanil) increased by 5.6-fold in the moderate/severe group, relative to the normal/mild group. Thus, remifentanil acid concentrations at steady state may be predicted to be more than 100-fold those of remifentanil in patients with moderate/severe renal impairment.

Offset of the pharmacodynamic effects of remifentanil

The primary objective of the study was to confirm that accumulation of remifentanil acid in patients with significant renal impairment was not associated with clinically relevant μ opioid effects. Changes in any one of a number of parameters (e.g. MAP, HR, pain, or sedation level) considered by the investigator to be the most clinically relevant for an individual patient were used to determine the offset of pharmacodynamic effects. It was not realistic or practical to standardize the measure for assessing the offset of μ opioid activity, given the necessity to ensure safety and an optimal analgesia/sedation level for each patient. The none/mild and moderate/severe groups represent diverse groups of patients who are likely to be very different in the way they metabolise drugs. For most drugs it is very difficult to extrapolate data from one population and apply it to another. Despite large differences in the patients studied and the known accumulation of remifentanil acid in patients with moderate/severe renal impairment, in practice there were no clinical differences in the time of offset of effects of remifentanil between groups, even after 72 hours of administration, because the reassessment time only changed from 14.8 min to 30.7 min. This is perhaps not surprising because the relative potency of remifentanil acid is 1/4600 that of remifentanil [14]. Thus, a concentration of remifentanil acid of 697 ng/ml (highest concentration observed) would equate to a remifentanil concentration of 0.15 ng/ml, which would in turn equate to an infusion of approximately 0.36 μg/kg per hour (0.006 μg/kg per min). This figure is over 15 times lower than the recommended starting dose of remifentanil for use in the critically ill. Therefore, the observed differences in SDTs occurred as a result of the patient population and not accumulation of remifentanil acid.

It should also be noted that the number of patients investigated decreased over time because of death or early extubation. This was more marked in the moderate/severe group. The population that was left at 72 hours in the study (particularly the moderate/severe group) was therefore probably very ill and likely to handle drugs in a different way to the population as a whole. It may be that these patients were in multiple organ failure, with altered underlying neurological states that would make them more likely to have prolonged effects of any opiate or sedative agent. Therefore, any observed differences, although minor, were as a result of the patient and not the drug or metabolite because these patients would have been slow to wake up regardless of the drugs administered. Furthermore, there were no changes in the weighted mean remifentanil infusion rates over time in either of the renal function groups that would indicate that accumulation of remifentanil acid was associated with μ opioid agonist activity necessitating a change in remifentanil infusion rate.

The present study shows remifentanil to be very effective in patients with impaired renal function, unlike many of the traditional opioids, which require intact renal function for their metabolism or elimination. The efficacy of remifentanil shown in the present study is very similar to that reported by López and coworkers [8] in a much larger group of patients requiring intensive care. Optimal SAS and PI scale scores were well maintained in the group as a whole. The provision of analgesia and sedation must be titrated according to individual patient requirements. The rapid onset and offset of action and its predictable organ independent mode of metabolism make remifentanil ideally suited to the treatment of patients with impaired renal function.

In addition to the inherent titratability of remifentanil, use of propofol in these patients using a remifentanil based technique [7] was lower than with standard hypnotic based techniques [21,22]. This was further differentiated in the moderate/severe group, who tended to need less remifentanil and propofol. This highlights a group of patients who have increased sensitivity to sedative/hypnotics. In clinical practice, because of the high degree of titratability and rapid recovery with remifentanil, there was virtually no chance of a patient being over-sedated with remifentanil, which contributed to the very short recovery times observed.

Safety

Remifentanil was generally well tolerated in both groups, which were separated by differing renal function. Although the incidence of adverse events was higher in patients with moderate/severe renal impairment than in the normal/mild group (37% versus 10%), this difference was not statistically significant ($P = 0.451$) and probably reflects the fact that these patients were more seriously ill as a group. The types of events reported were what would be expected for patients entering the ICU for medical and postsurgical reasons, and included events that are typically associated with administration of a μ opioid agonist. The cardiovascular and digestive systems were most commonly affected, with reported cases of cardiac arrest, sepsis and ileus generally reflecting events associated with the patient's underlying clinical condition rather than remifentanil.

The only serious adverse event that was considered by the investigator to be possibly related to remifentanil was an episode of sinus arrest in a 67-year-old man with a history of myocardial infarction. He had undergone laparotomy for necrotizing pancreatitis and had several episodes of atrial fibrillation requiring direct current cardioversion, digoxin and verapamil. Approximately 64 hours after starting remifentanil the patient went into sinus arrest. He recovered within 20 seconds after the administration of atropine, and continued to receive remifentanil for the 72 hour period of the study. The investigator considered that there was a reasonable possibility that the sinus arrest was caused by treatment with remifentanil, but a drug interaction between digoxin, amiodarone and remifentanil was also considered possible.

Almost half of the drug-related adverse events (3/7) were reported during the post-treatment period, and these are possibly attributable to the rapid offset of μ opioid agonist effects following discontinuation of the remifentanil infusion. Diarrhoea, which is not usually associated with administration of a μ opioid agonist, was reported during the post-treatment period as a drug-related adverse event in one patient in each group. Because opioids induce intestinal ileus and constipation by their action on peripheral μ opioid receptors, the rapid removal of this effect following remifentanil discontinuation may have resulted in an increase in gut motility. The rapid offset of its sedative and analgesic effects when remifentanil was discontinued may similarly explain the case of agitation reported as a drug related adverse event in one patient in the moderate/severe renal impairment group during the post-treatment period.

Most of the 17 deaths reported during the study occurred in the patients with moderate/severe renal impairment, and none were considered to be related to remifentanil. A higher mortality risk would be expected in these patients because they were, as a group, more critically ill than the patients in the normal/mild group.

Very similar mean HR and MAP values were observed at each scheduled assessment period in the two renal function groups. Although the weighted mean HR during the treatment period was significantly higher in the moderate/severe group than in the normal/mild group, the magnitude of the difference was not of clinical significance and could be expected given the differences between the two patient populations. This finding is also consistent with the slightly higher mean HR at baseline in patients in the moderate/severe renal group.

Conclusion

In conclusion, the safety and efficacy of remifentanil was investigated in a group of sick patients with varying degrees of renal impairment receiving intensive care. Remifentanil was shown to be a very effective agent for providing both analgesia and sedation. Accumulation of remifentanil acid in patients with renal impairment was not associated with clinically significant prolonged μ opioid effects, as demonstrated by the times to offset of the pharmacodynamic effects of remifentanil at the SDTs during the 72 hour period of infusion. There were also no clinically relevant differences in times to offset of effects between patients with normal/mild and moderate/severe renal impairment. Remifentanil was well tolerated, and the adverse event profile was consistent with what would be expected in ICU patients receiving a potent μ opioid agonist. The safety and efficacy of remifentanil is now undergoing investigation in critically ill patients for up to 10 days.

Key messages

- Remifentanil based sedation was shown to be very effective and well tolerated for providing both analgesia and sedation in a group of mechanically ventilated patients with varying degrees of renal impairment
- Overall, the μ opioid effects of remifentanil were not prolonged in patients with renal impairment. The time to offset of the pharmacodynamic effects of remifentanil were similar between the two treatment groups and were independent of the duration of infusion for up to 72 hours. This is because of the predictable, rapid, organ independent metabolism of remifentanil by nonspecific esterases in the blood and tissues
- The time to offset of pharmacodynamic effects was not correlated with the remifentanil acid concentration
- There was no evidence of increased dose requirements for remifentanil with increased duration of treatment
- The addition of propofol was not required in nearly half of the patients. When propofol was administered, consumption was lower with remifentanil based sedation

Competing interests

DB, AW, AB, VB, JB, PK and SA received payment from GlaxoSmithKline (either personally or to their respective departments) according to the number of patients recruited. SS is an employee of GlaxoSmithKline.

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