

Pharmacokinetics of remifentanyl and its major metabolite, remifentanyl acid, in ICU patients with renal impairment[†]

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Background. The pharmacokinetics of remifentanyl, an opioid analgesic metabolized by non-specific esterases, and its principal metabolite, remifentanyl acid (RA), which is excreted via the kidneys, were assessed as part of an open-label safety study in intensive care unit (ICU) patients with varying degrees of renal impairment.

Methods. Forty adult ICU patients with normal/mildly impaired renal function (creatinine clearance [CL_{cr}] 62.9 (SD) 14.5 ml min⁻¹; n=10) or moderate/severe renal impairment (CL_{cr} 14.7 (15.7) ml min⁻¹; n=30) were included. Remifentanyl was infused for up to 72 h, at a starting rate of 6–9 µg kg⁻¹ h⁻¹ titrated to achieve a target sedation level, with additional propofol (0.5 mg kg⁻¹ h⁻¹) if required. Intensive arterial sampling was performed for up to 72 h after infusion. Pharmacokinetic parameters obtained by simultaneous modelling of remifentanyl and RA data were statistically compared between the two groups.

Results. Remifentanyl pharmacokinetics were not significantly affected by renal status. RA clearance in the moderate/severe group was reduced to about 25% that of the normal/mild group (41 (29) vs 176 (49) ml kg⁻¹ h⁻¹, *P*<0.0001). Metabolic ratio, a predictor of the ratio of RA to remifentanyl concentrations at steady state, was approximately eight-fold higher in the moderate/severe group relative to the normal/mild group (116 (110) vs 15 (4), *P*<0.0001). Maximum RA levels approached 700 ng ml⁻¹ in the moderate/severe group.

Conclusions. Although RA accumulates in patients with moderate/severe renal impairment, pharmacokinetic modelling predicts that RA concentrations during a 9 µg kg⁻¹ h⁻¹ remifentanyl infusion for up to 15 days would not exceed those reported in the present study, for which no associated prolongation of µ-opioid effects was observed.

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Critically ill patients in the intensive care unit (ICU) often experience pain, anxiety, agitation and confusion, while being exposed to numerous potentially noxious stimuli attributable to diagnostic, therapeutic and nursing interventions. Most critically ill patients require a combination of analgesia (provided by an opioid) and sedation (provided by benzodiazepines or other hypnotics) during at least part of

their stay in the ICU. Opioids such as fentanyl, sufentanyl and morphine are traditionally used for the provision of analgesia. Elimination of opioids may be prolonged in critically ill patients, due to organ-dependent elimination

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and, in some cases, formation of active metabolites (e.g. morphine-6-glucuronide¹²). There is therefore a potential for accumulation of drug, metabolite or both and hence unpredictable or delayed recovery from analgesia and sedation, particularly during weaning from mechanical ventilation.

Remifentanyl (remifentanyl hydrochloride) is an opioid with a rapid onset of action of about 1 min which quickly achieves steady state. It has a context-sensitive half-life of 2–3 min, which is independent of the duration of infusion.³ Remifentanyl is not a substrate for plasma cholinesterase and therefore its metabolism is not subject to genetic variance. Unlike existing opioids, remifentanyl exhibits a predictable, rapid metabolism by non-specific esterases in the blood and tissues, principally to a carboxylic acid derivative, remifentanyl acid (RA).⁴ This organ-independent elimination of remifentanyl makes it a useful agent in the ICU setting, where patients commonly have some degree of organ dysfunction.⁵ These features of remifentanyl combine to make it easy to titrate to the desired analgesic effect and allow it to be administered for long periods and at higher doses than are normally used with traditional opioids, without the risk of significant accumulation. A number of studies have looked at the potential role and use of remifentanyl in the critically ill.^{6–13}

Whilst remifentanyl elimination is essentially independent of renal and liver function, RA is eliminated via the kidneys, and its elimination is prolonged in patients with severe renal impairment (predicted creatinine clearance (CL_{cr}) <10 ml min⁻¹).¹⁴ RA therefore accumulates in these patients. Since RA has never been administered to man, the concentration at which μ -agonist effects are likely to be seen has not been ascertained. A remifentanyl infusion of 0.2 μ g kg⁻¹ min⁻¹ results in respiratory depression and, according to simulations by Minto and colleagues,¹⁵ that equates to a remifentanyl blood concentration of approximately 5 ng ml⁻¹ in volunteers. RA has been demonstrated to be much less potent (1/4600) a μ -opioid agonist than the parent molecule in dogs,¹⁶ and assuming the same potency ratio applies to man, it is therefore thought not to result in any clinically relevant effects at concentrations below 900 ng ml⁻¹. A clinical trial was designed primarily to determine any potential safety issues that might arise as a result of the accumulation of RA in renally impaired ICU patients given a continuous remifentanyl infusion for up to 72 h. This length of infusion was chosen as a cautious approach, which would on average allow steady-state concentrations of RA to be approached and also complied with the 72 h restriction in the propofol data sheet in some countries. In addition to the pharmacodynamic effect, adverse events and haemodynamic profiles, the pharmacokinetic profiles of remifentanyl and RA were assessed. The specific objectives of the analysis were to characterize the pharmacokinetics of remifentanyl and RA using both model-independent and compartmental modelling methods, and to correlate the

pharmacokinetic parameters obtained to the degree of renal impairment.

Methods

Study design

This was an open-label, non-comparator study assessing the safety and pharmacokinetic profiles of remifentanyl and RA after administration of remifentanyl by continuous i.v. infusion for up to 72 h 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. Written informed consent/assent was obtained from all patients or their representatives. Following local and national ethics committee approvals, 40 patients were recruited altogether, from three centres in the UK, two in Denmark, two in Germany and one in Belgium.

Male or female (of non-child bearing potential or using contraception) post-surgical and medical patients were eligible for entry into the study if they were aged 18 yr or more, weighed 120 kg or less, and if they were expected to require mechanical ventilation for a further 24–72 h. Patients should have had a sedation–agitation scale (SAS) score in the range 2–4 at admission to the ICU (score of 2: patient is very sedated, can be roused by physical stimuli but does not communicate or follow commands, may move spontaneously; score of 3: patient is sedated, difficult to rouse, awakens to verbal stimuli or gentle shaking but drifts off again, will follow simple commands; score of 4: patient is calm and cooperative, easily rousable and follows commands).¹⁷

During an initial screening period, the patient's renal function was measured by estimating CL_{cr} from plasma and urinary creatinine concentrations and urine volumes over a minimum period of 4 h with extrapolation to 24 h.¹⁸ Patients with an estimated CL_{cr} of 50 ml min⁻¹ or higher were classified as having normal renal function or mild renal impairment; patients with values below 50 ml min⁻¹ were classified as having moderate/severe renal impairment.

Remifentanyl (lyophilized powder in sterile vials each containing 5 mg of the compound, provided by GlaxoSmithKline UK, reconstituted and diluted to 50 ml using standard diluents) was administered as a continuous i.v. infusion for a maximum of 72 h. The remifentanyl infusion started at a dose of 6 or 9 μ g kg⁻¹ h⁻¹, and was then titrated according to a dosing algorithm.¹⁹ Propofol (starting dose 0.5 mg kg⁻¹ h⁻¹) was administered as an additional infusion if required when the remifentanyl infusion rate requirements reached 12 μ g kg⁻¹ h⁻¹. During the treatment period, patients were continuously assessed and the remifentanyl (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 only mild pain. In addition, scheduled down-titrations of the remifentanyl

regimen by 25% of the initial rate at 10 min intervals were performed at 8, 24 and 48 h. The infusion rate was reduced until an offset of remifentanyl's pharmacodynamic effects was observed. If propofol was being infused at the time of a scheduled down-titration, it was maintained at a constant infusion rate. Study treatment was permanently discontinued after a maximum of 72 h, by reducing the remifentanyl infusion rate by 25% at 10 min intervals. Any propofol which was infused at this time was maintained at a constant rate until 30 min after the remifentanyl had been stopped and then decreased in decrements. After the remifentanyl was finally discontinued, the patient was switched to standard therapy of the investigator's choice. Although the intention was for patients to complete the 72 h of remifentanyl infusion, there was no minimum infusion period for entry into the trial and all patients who received remifentanyl and had measurable remifentanyl concentrations were included.

Sample acquisition, handling and processing

Arterial blood samples (5 ml) were collected from all patients into tubes containing citric acid and were frozen for subsequent assay at the following time points: before the start of the remifentanyl infusion and at 15 and 30 min, and 1, 2 and 4 h after starting the infusion; at 08:00 h and 20:00 h each day (unless these times were within 4 h of a scheduled down-titration); and at the 8, 24 and 48 h scheduled down-titrations (immediately before the first down-titration step and before the infusion rate was turned up again). If the remifentanyl infusion was temporarily discontinued during a scheduled down-titration, a blood sample was obtained immediately before discontinuation and at 5, 10 and 30 min or just before the infusion was restarted, whichever occurred first. At final treatment discontinuation (72 h maximum), blood samples were obtained immediately before the first down-titration, before the infusion was decreased by 25% of the initial rate at 10 min intervals (three samples) and immediately before the infusion was finally discontinued. During the post-treatment period, blood samples were obtained at approximately 5, 10 and 30 min, and at 1, 2, 4, 8, 24, 40, 56 and 72 h after final discontinuation of remifentanyl infusion.

On the occasions that renal replacement therapy (RRT) was performed, at the time of starting dialysis and after the system had been stabilized, two blood samples were obtained simultaneously from the line entering the dialysis machine and from the line exiting the dialysis machine.

Assay method

The concentrations of remifentanyl and RA in whole blood were determined using validated assay procedures. The method, a specific liquid chromatography tandem mass spectrometry method, was a modification of a previously published method,²⁰ which involved solid-phase extraction

with methanol instead of dichloromethane and enables simultaneous quantification of free remifentanyl and RA. The lower limit of quantification (LLQ) for both analytes was 0.1 ng ml⁻¹. Intra-assay precision values at LLQ were less than 20% and accuracy values were within 100 (20)%, with reference to the nominal value. Overall intra- and inter-assay precision values were less than 15% and accuracy values within 100 (15)% of the nominal value.

Pharmacokinetic analysis

The following parameters were determined for remifentanyl and RA using standard model-independent methods in WinNonlinTM professional version 3.1²¹ maximum plasma concentration (C_{max}), the first time to reach C_{max} (t_{max}), and area under the plasma concentration–time curve (AUC) to the last sample time (AUC_{last}). The metabolic ratio was calculated as the ratio of AUC_{last} of RA to that of remifentanyl.²² The extraction of remifentanyl and RA during RRT was determined as the ratio (%) of the concentration in the samples taken from the lines entering and exiting the dialysis equipment.

Simultaneous pharmacokinetic modelling of the individual remifentanyl (parent) and RA data was performed using NONMEM.²³ Visual inspection of the data indicated that remifentanyl concentrations during the post-infusion period were adequately characterized by a monoexponential decline. However, RA concentrations during the post-infusion period were characterized by either a mono- or a biexponential pattern. Consequently, simultaneous compartmental analysis of parent drug and metabolite involved fitting either a two- or a three-compartment model to the blood concentration–time data, with one compartment associated with the parent drug and one or two compartments with the metabolite, with a variable zero-order input rate to the parent compartment. The pharmacokinetic model is depicted in Figure 1.

The full structural pharmacokinetic model used in NONMEM is given below in differential equation form:

$$dR_1/dt = k_0/V - (R_1 k_{12})$$

$$dM_2/dt = (R_1 k_{12}) - (M_2 k_{23}) + (M_3 k_{32}) - (M_2 k_{20})$$

$$dM_3/dt = (M_2 k_{23}) - (M_3 k_{32})$$

where R_1 is the concentration of remifentanyl in compartment 1; M_2 and M_3 are the concentrations of RA in compartments 2 and 3, respectively; k_0 is the remifentanyl infusion rate, V is the volume of distribution of remifentanyl (compartment 1), and k_{12} is the total elimination rate constant of remifentanyl, assuming that all the parent drug is converted into the metabolite.

To facilitate the fitting process, the model was re-parameterized in terms of remifentanyl clearance (CL) and volume of distribution (V), and RA clearance (CL_m), central

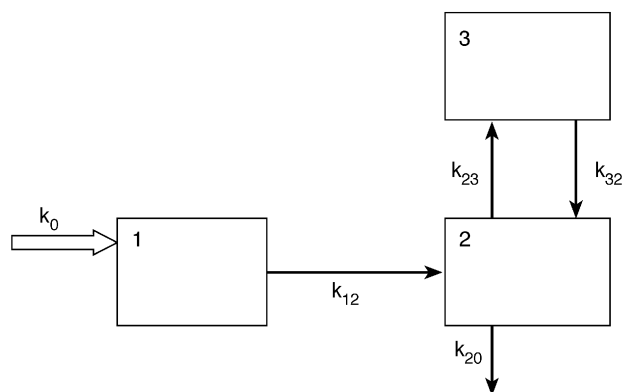


Fig 1 Graphical representation of the combined pharmacokinetic model for remifentanyl and its metabolite (remifentanyl acid; RA). Compartment 1 is associated with remifentanyl and compartments 2 and 3 with RA. k_0 is the remifentanyl zero-order infusion rate, k_{12} and k_{20} the first-order elimination rate constants of remifentanyl and RA, respectively, and k_{23} and k_{32} the intercompartmental rate constants for RA between compartments 2 and 3.

compartment volume (V_{m1}), intercompartmental clearance (Q_m) and peripheral compartment volume (V_{m2}), which were estimated as primary parameters. From these the compartmental rate constants were estimated as follows:

$$k_{12} = CL/V$$

$$k_{20} = CL_m/V_{m1}$$

$$k_{23} = Q_m/V_{m1}$$

$$k_{32} = Q_m/V_{m2}$$

The elimination half-life of remifentanyl ($t_{1/2}$) was estimated as $t_{1/2} = \ln(2)/k_{12}$. The half-lives associated with the alpha (α) and beta (β) of the exponential form of the model for RA [$M(t) = Ae^{-\alpha t} + Be^{-\beta t}$] were derived from the appropriate rate constants.²⁴ The phase that on average contributed most to the total AUC was termed the elimination phase and the corresponding half-life as the RA elimination half-life.

Since this analysis involved individual data, the variance model in NONMEM represented intra-individual variability (ϵ), with different ϵ values estimated for remifentanyl (ϵ_R) and RA (ϵ_M), both assumed to arise from a log-normal distribution.

The reduced structural pharmacokinetic model (one compartment for remifentanyl and one compartment for RA, i.e. excluding compartment 3 in Figure 1) and variants of the variance model were also tested. The same parameterization in terms of CL and V for remifentanyl and CL_m and V_{m1} for RA was applied and the compartmental rate constants were estimated as follows:

$$k_{12} = CL/V$$

$$k_{20} = CL_m/V_{m1}$$

Table 1 Physical characteristics of patients. Renal function was assigned by the clinician, based on the patient's estimated creatinine clearance (CL_{cr}). Normal/mildly impaired renal function corresponded to an estimated CL_{cr} of 50 ml min⁻¹ or higher; moderate/severe renal impairment corresponded to an estimated CL_{cr} below 50 ml min⁻¹. SAPS II, simplified acute physiology score II.²⁵ Ranges are given in parentheses

	Normal/mild renal impairment	Moderate/severe renal impairment
Number of patients treated	10	30
Creatinine clearance (ml min ⁻¹)	62.9 (44–84)	14.7 (0–49)
Mean SAPS II	41.0 (31–57)	53.2 (16–91)
Mean age (yr)	68.6 (54–78)	65.7 (31–81)
Male	9 (90%)	22 (73%)
Female	1 (10%)	8 (27%)
Mean weight (kg)	79.6 (68–96)	75.6 (38–110)

For this model, the elimination half-life of RA was estimated as $t_{1/2,m,k_{20}} = \ln(2)/k_{20}$.

In both models, it was assumed that all remifentanyl was converted to RA. Since 95–98% of a remifentanyl dose is recovered in urine as RA,¹⁴ this assumption was not expected to have led to any significant bias in the parameter estimates.

Model discrimination was based on the NONMEM objective function, taking into account the estimation error and the degree of correlation between the parameters. Residual plots were inspected for goodness of fit and lack of bias. The likelihood ratio was used to assess whether the difference in the NONMEM objective function between the model with a biexponential decline for the RA data (more complex) and that with a monoexponential decline (base model) indicated an improved fit of the model to the data, as follows. A change in the NONMEM objective function of more than 3.84 (based on the likelihood ratio, which is approximately χ^2 distributed for one degree of freedom) when compared with the base model was considered significant ($P < 0.05$). A superior model was also expected to reduce residual error terms.

Finally, any association between covariates likely to affect the pharmacokinetic parameters of remifentanyl and RA (e.g. CL_{cr} , body weight, age) was explored graphically.

Statistical analysis

Descriptive statistics were used to summarize the pharmacokinetic parameters of remifentanyl and RA in the two groups and for the following three subgroups in the moderate/severe group: patients who had no RRT (subgroup A); patients having intermittent RRT (i.e. RRT starting or ending within the period of the pharmacokinetic sampling) (subgroup B); patients who had continuous RRT for the duration of pharmacokinetic sampling (subgroup C). As patients in this study received individualized remifentanyl regimens for different lengths of time, only the ranges of maximum concentrations and AUC values are reported.

Appropriate statistical methods (ANOVA by group) were employed to test for differences in the pharmacokinetic parameters of remifentanyl and RA between the renal function groups. $P < 0.05$ was considered statistically significant. To elucidate any differences, an exploratory ANOVA and contrast analyses between the normal/mild group and the three moderate/severe subgroups were also performed. All statistical analyses were performed in SAS® System version 8.

Results

Study design

Forty patients were recruited into the study, 10 in the normal/mild group and 30 in the moderate/severe group; all were evaluable for the pharmacokinetic analyses. In a previous pilot study,²⁶ 12 patients with normal renal function or mild renal impairment were included, and their pharmacokinetic profiles were characterized. There was therefore thought to be no need to include more mild/normal patients in the present study. The ratio 3:1 still permits statistical comparisons. The baseline physical and clinical characteristics of these patients are summarized in Table 1. The mean age and weight values were similar between the two groups, although the proportion of male patients in the normal/mild group was higher than in the moderate/severe renal impairment group.

There were differences in CL_{cr} between the two groups, as expected from the study stratification, although these were not tested for statistical significance. Mean CL_{cr} at screening was 62.9 (SD) 14.5 ml min⁻¹ in the normal/mild group and 14.7 (15.7) ml min⁻¹ in the moderate/severe group. Only two patients in the normal/mild group had a CL_{cr} value greater than 80 ml min⁻¹, indicating normal renal function.

More patients with moderate/severe renal impairment had higher simplified acute physiology score II values²⁵ (associated with higher hospital mortality rate) than those in the normal/mild group.

Of the 30 patients in the moderate/severe group, five patients underwent continuous RRT, nine underwent intermittent RRT, and 16 patients required no RRT. Four different methods of RRT were used: haemodialysis ($n=3$), continuous venovenous haemodialysis ($n=2$), continuous venovenous haemofiltration ($n=4$) and continuous venovenous haemodiafiltration ($n=5$). There was no evidence for remifentanyl being extracted during RRT; RA appeared to be extracted by approximately 60% in the three cases of haemodialysis. None of the patients in the normal/mild group needed RRT.

The duration of the remifentanyl infusion ranged from 45.4 to 72.8 h in the normal/mild group and from 4.8 to 72.5 h in the moderate/severe group; on average it was shorter for the moderate/severe group (mean 43.1 h) than for the normal/mild group (mean 70.4 h). The weighted mean

remifentanyl infusion rate requirement was slightly lower in the moderate/severe group (10.1 µg kg⁻¹ h⁻¹) than in the normal/mild group (13.1 µg kg⁻¹ h⁻¹). Requirement for supplementary propofol infusions was also lower in the moderate/severe group (53%) than in the normal/mild group (70%), with mean propofol infusion rates in the two groups being 0.7 and 1.3 mg kg⁻¹ h⁻¹, respectively. These differences in remifentanyl and propofol requirements between the moderate/severe and the normal/mild group were not statistically significant, and within each group, remifentanyl and propofol requirements did not change with time.

Pharmacokinetics

Remifentanyl concentrations in both renal function groups rose immediately after starting the i.v. infusion and declined rapidly during the down-titration phase and after discontinuation of the remifentanyl infusion. For more than half of the patients, there were fewer than three quantifiable concentrations in the post-infusion samples. Maximum levels of remifentanyl were observed at various times during the infusion period, reflecting fluctuations in the remifentanyl dosing rate (Fig. 2).

RA concentrations showed a gradual increase after starting the remifentanyl infusion. Maximum levels of RA in the blood were generally observed just before the final remifentanyl infusion down-titration, indicating a slow accumulation towards steady state. RA profiles were not very sensitive to changes in the remifentanyl dosing rate. After discontinuation of the remifentanyl infusion, when comparing the profiles in patients for whom a similar number of post-infusion samples were available, RA levels appear to decline in a biexponential fashion for patients in the normal/mild group, and in a monoexponential fashion for patients in the moderate/severe group (Fig. 3), with RA concentrations in the blood samples from patients in the moderate/severe group generally much higher than those from the patients in the normal/mild group. The two profiles that show no decline of remifentanyl or RA concentrations in Figures 2 and 3 correspond to subjects who continued to receive remifentanyl, at the investigator's decision, beyond the 72 h study regimen. This was taken into account in the pharmacokinetic analysis.

A three-compartment model (parent drug one compartment; metabolite two compartments) was found to be statistically superior in providing the best fit for the combined parent and metabolite data for patients in the normal/mild group, while a two-compartment model (parent drug one compartment; metabolite one compartment) was found to be adequate for the majority of the patients in the moderate/severe group. Observed and predicted RA semi-logarithmic concentration–time plots from representative patients demonstrating two- and one-compartment behaviour are shown in Figures 4 and 5.

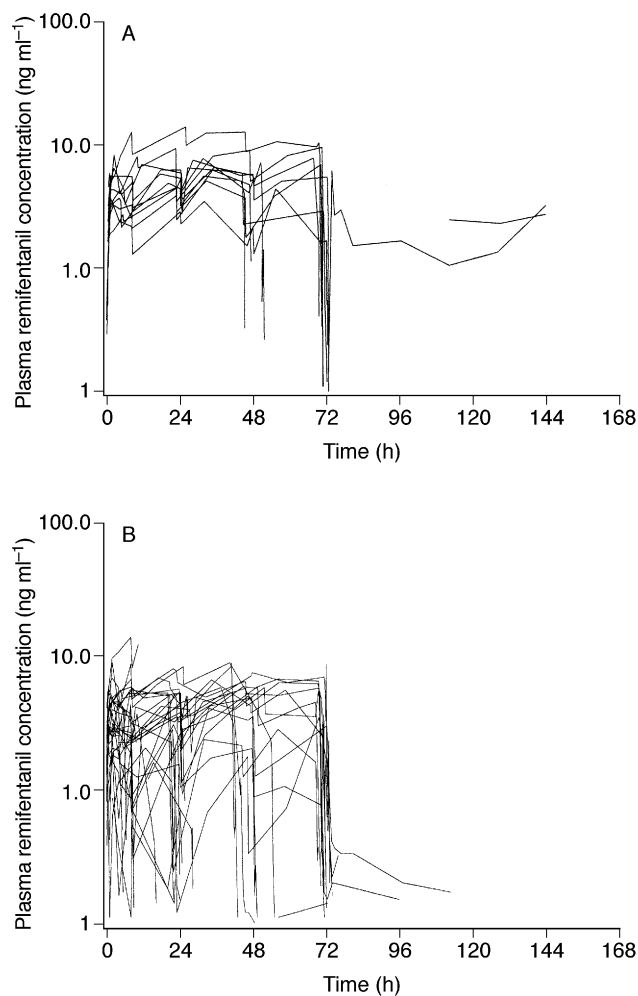


Fig 2 Semilogarithmic plots of individual remifentanyl concentrations in the two groups: (A) normal/mild; (B) moderate/severe renal impairment.

The principal pharmacokinetic parameters for remifentanyl and RA are summarized in Tables 2 and 3. Remifentanyl CL and V appeared to be higher in the moderate/severe group overall compared with the normal/mild group, but the interindividual variability in the parameters was high. The mean $t_{1/2}$ of remifentanyl was longer in the moderate/severe group than in the normal/mild group.

Mean metabolic ratio was about 8-fold higher in the patients in the moderate/severe group compared with the normal/mild group (Table 2). CL_m in the moderate/severe group was approximately 25% of that in the normal/mild group (Table 3), and was linearly related to CL_{cr} (Fig. 6, $r=0.845$, $P=0.0962$ and $P<0.0001$ for the intercept and slope, respectively). Two half-lives were estimable in the normal/mild group, the terminal-phase one being similar to the single half-life estimated for the moderate/severe group.

Statistical analysis of remifentanyl and RA pharmacokinetic parameters indicated that the differences in metabolic ratio, CL_m and RA half-life ($t_{1/2m,k_{20}}$ vs $t_{1/2m,\alpha}$) between the

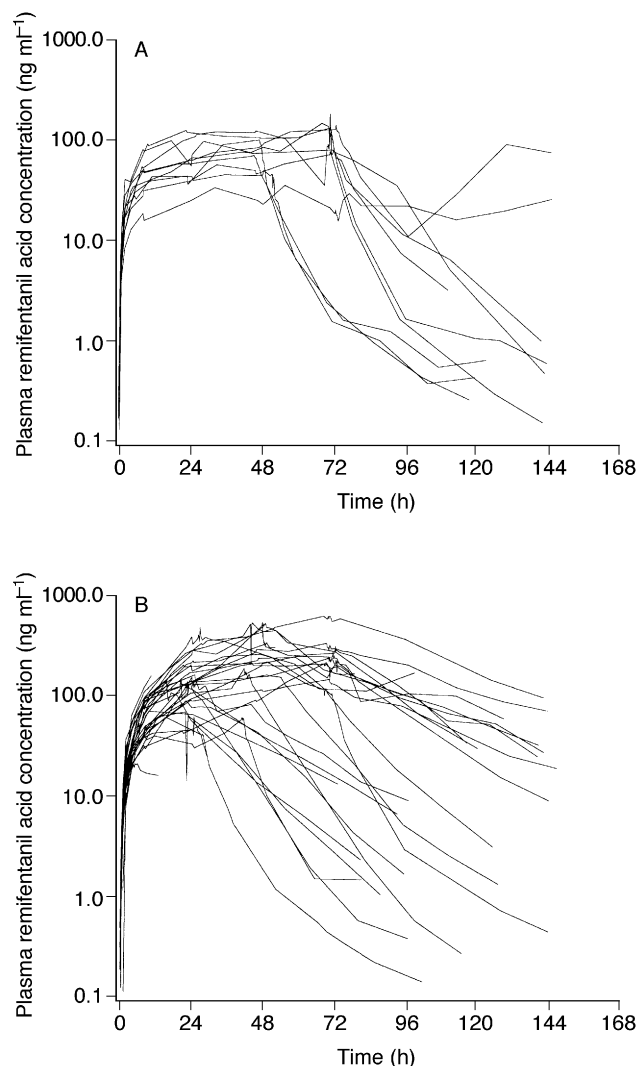


Fig 3 Semilogarithmic plots of individual remifentanyl acid concentrations in the two groups: (A) normal/mild; (B) moderate/severe renal impairment.

moderate/severe and normal/mild groups were statistically significant, all at $P<0.0001$ (Table 4).

Discussion

The wide variation in remifentanyl and RA C_{max} and AUC_{last} values primarily reflected differences in remifentanyl infusion rate and duration, with confounded interpatient variability in pharmacokinetic parameters.

The metabolic ratio is indicative of the ratio of the RA to remifentanyl concentrations at steady state.²² The mean metabolic ratio for the normal/mild renal function group in this study (15.1) is consistent with the estimate obtained in a previous study in patients with mild renal impairment (17.0).²⁶ The metabolic ratio increased to 116 in patients with moderate/severe renal impairment and the difference would have been even larger if the complete AUC of the

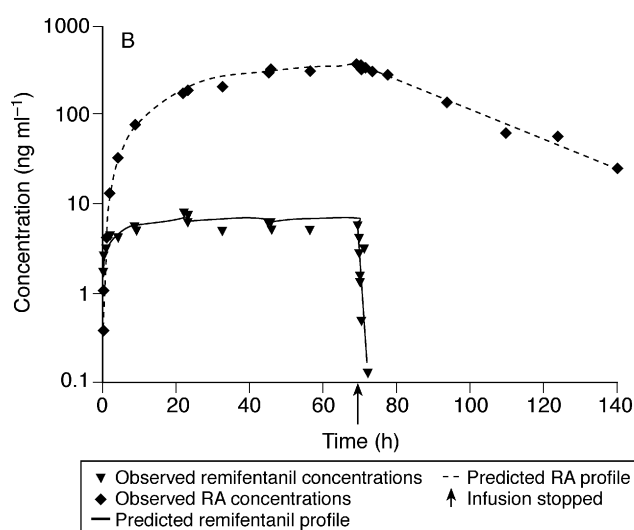
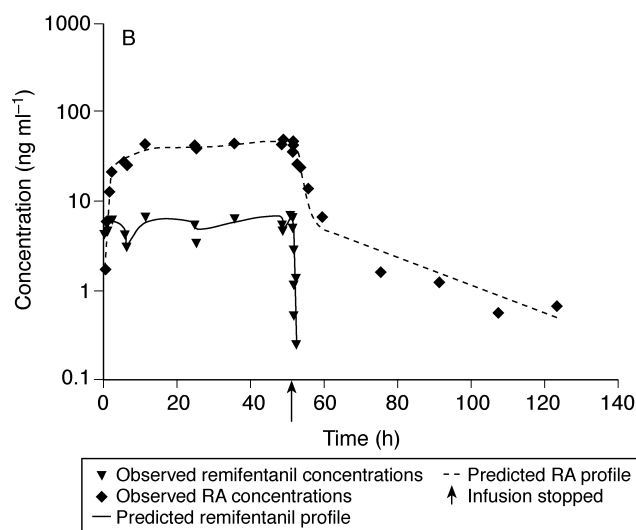
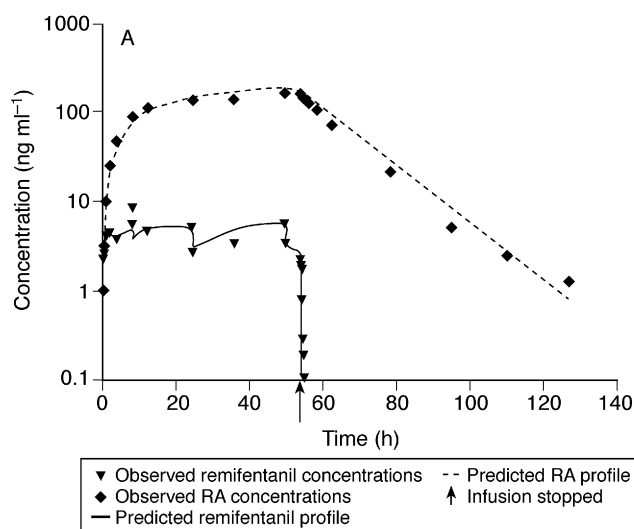
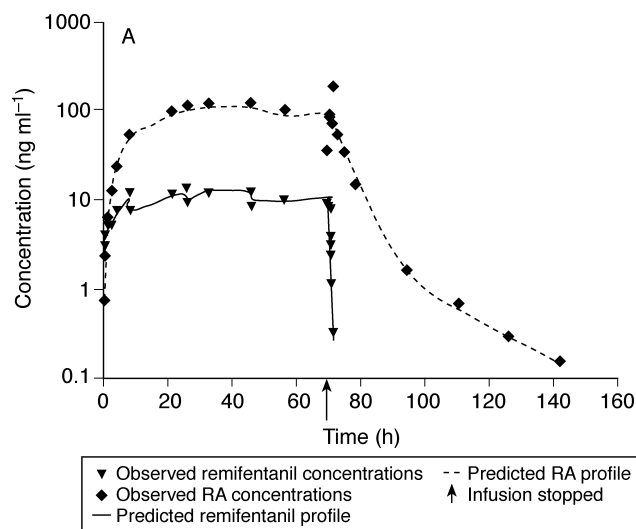


Fig 4 Two examples of patients' remifentanyl and remifentanyl acid (RA) concentration-time profiles demonstrating biexponential decline (normal/mild renal impairment group).

Fig 5 Two examples of patients' remifentanyl and remifentanyl acid (RA) concentration-time profiles demonstrating monoexponential decline (moderate/severe renal impairment group).

metabolite was estimable. This increase is consistent with previous findings in patients with severe renal failure.¹⁴ The differences observed in the metabolic ratio between the moderate/severe subgroups (mean metabolic ratio 70, 132 and 192 for subgroups A, B and C, respectively) inversely correlated with the differences in CL_{cr} in these subgroups (mean CL_{cr} 24.0, 5.3 and 1.8 $ml\ min^{-1}$ respectively).

One-, two- and three-compartment models have previously been used to describe the pharmacokinetics of remifentanyl in humans,^{4,14,15} while the pharmacokinetics of RA have been previously described by a one-compartment model, reporting a half-life of 1.5 h in healthy patients.¹⁴ The present data only supported a one-compartment model for remifentanyl. The concentrations of RA in the normal/mild group declined in a biexponential manner,

suggesting a two-compartment model, with a much longer terminal half-life, as was also the case in a recent study of similar design using the same assay for analyte determination.²⁶ The ability to observe a slow terminal phase, previously undetected,¹⁴ in patients with normal renal function was probably due to the high concentrations of RA, the increased assay sensitivity and the extended sampling period employed in that previous study²⁶ and the present one. This terminal phase, apparently unaffected by renal function, accounted for about 25% of the total AUC and probably represents a slowly equilibrating distribution compartment, which becomes rate limiting at later times. A one-compartment model adequately described RA concentrations in patients in the moderate/severe group. Either a combined three-compartment model (normal/mild group) or

Table 2 Model-independent pharmacokinetic parameters for remifentanyl and remifentanyl acid following remifentanyl infusion in intensive care unit patients with various degrees of renal impairment. Subgroups A, B and C were undergoing no, intermittent or continuous renal replacement therapy, respectively. Data are mean (SD) or range. Pharmacokinetic terms are explained in the text

	Normal/mild renal impairment	Moderate/severe renal impairment			
	(n=10)	Subgroup A (n=16)	Subgroup B (n=9)	Subgroup C (n=5)	A, B and C (n=30)
Creatinine clearance	62.9 (14.5)	24.0 (16.0)	5.34 (5.33)	1.80 (2.47)	14.7 (15.7)
Remifentanyl					
C_{max} (ng ml ⁻¹)	4.44–14.0	1.57–13.7	2.06–6.75	1.83–8.61	1.57–13.7
AUC _{last} (ng h ml ⁻¹)	175–745	7.83–384	34.3–338	12.0–388	7.83–388
Remifentanyl acid					
C_{max} (ng ml ⁻¹)	37.1–194	22.1–533	73.9–602	155–697	22.1–697
AUC _{last} (ng h ml ⁻¹)	1860–8080	160–21000	2100–28900	5810–50200	160–50200
Metabolic ratio	15.1 (4.40)	70.1 (75.3) (n=11)	132 (79.2) (n=8)	192 (177)	116 (110) (n=24)

Table 3 Compartmental pharmacokinetic parameters for remifentanyl and remifentanyl acid following remifentanyl infusion in intensive care unit patients with various degrees of renal impairment. Data are mean (SD). na, not applicable; [†]for the three-compartment model only; [‡]t_{1/2,m,α} for normal/mild (best model three-compartment), t_{1/2,m,k₂₀} for moderate/severe (best model two-compartment); [§]excluding patients 16142 (parameters not estimable) and 16141, 16160, 16166 (best model three-compartment). Pharmacokinetic terms are explained in the text

Group	Normal/mild	Moderate/severe			
		Subgroup A	Subgroup B	Subgroup C	A, B and C
Creatinine clearance	62.9 (14.5)	24.0 (16.0)	5.34 (5.33)	1.80 (2.47)	14.7 (15.7)
Remifentanyl	(n=10)	(n=16)	(n=9)	(n=5)	(n=30)
CL (ml min ⁻¹ kg ⁻¹)	44.3 (14.4)	49.3 (32.7)	50.5 (35.6)	105 (103)	59.0 (52.9)
V (litre kg ⁻¹)	0.737 (0.645)	1.17 (1.27)	1.29 (1.08)	4.47 (4.48)	1.76 (2.34)
t _{1/2} (min)	11.4 (7.24)	15.9 (12.8)	21.6 (24.8)	32.9 (13.5)	20.5 (17.8)
Remifentanyl acid	(n=10)	(n=12) [§]	(n=9)	(n=5)	(n=30) [§]
CL _m (ml h ⁻¹ kg ⁻¹)	176 (49.3)	56.5 (35.1)	25.3 (13.1)	33.7 (11.8)	41.4 (28.9)
V _{m1} (litre kg ⁻¹)	0.719 (0.224)	0.835 (0.159)	0.701 (0.205)	0.820 (0.302)	0.786 (0.208)
Q _m (ml h ⁻¹ kg ⁻¹) [†]	125 (189)	na	na	na	na
V _{m2} (litre kg ⁻¹) [†]	0.685 (0.509)	na	na	na	na
t _{1/2,m} (h) [‡]	2.48 (1.03)	14.2 (10.5)	25.0 (18.7)	17.2 (3.20)	18.5 (13.6)
t _{1/2,m,β} (h) [‡]	16.6 (6.99)	na	na	na	na

a two-compartment model (moderate/severe group) was therefore used for simultaneous modelling of parent and metabolite data.

Mean remifentanyl CL was 59.0 (SD 52.9) ml min⁻¹ kg⁻¹ in the moderate/severe group and 44.3 (14.4) ml min⁻¹ kg⁻¹ in the normal/mild group; the difference was not statistically significant. V and t_{1/2} were estimated to be 1.76 (2.34) litre kg⁻¹ and 20.5 (17.8) min in the moderate/severe group and 0.737 (0.645) litre kg⁻¹ and 11.4 (7.24) min in normal/mild group, respectively. Large variability was observed in both these variables and any apparent differences in the mean estimates were not statistically significant ($P=0.0735$ and $P=0.0824$, respectively), and are not expected to have a clinically significant effect on recovery. These observations are also consistent with a previous study in volunteers with renal failure where no significant differences in the pharmacokinetics of remifentanyl were observed compared with healthy volunteers,¹⁴ although the dosage and duration of remifentanyl treatment in that study were much lower. Exploratory contrast analysis between subgroups (results available on request) indicated that the trend in remifentanyl volume mainly reflected extremely large differences in the

volume estimates of two patients in the moderate/severe group undergoing continuous RRT (subgroup C) compared with all other subgroups. Such differences in volume of distribution might be due to an effect of any concomitant fluid replacement therapy these patients might have undergone and in addition, continuous RRT is known to cause large fluid shifts and hence transient hypervolaemia in such patients. The overall trend in the half-life of remifentanyl was again found to mainly reflect differences between subgroup C and the other subgroups, and is attributable to differences in volume of distribution. In a recent study in 13 end-stage renal failure patients undergoing RRT,²⁷ it was reported that remifentanyl clearance was significantly reduced and terminal half-life increased relative to matched control patients with normal renal function. As a result, remifentanyl blood concentrations were significantly higher in the renal failure group. However, the changes were clinically modest and it was suggested that they may be explained by a reduced volume of distribution in the period following haemodialysis. In the present study, although a (not significant) prolongation of remifentanyl half-life was observed, volume of distribution was, if anything, increased

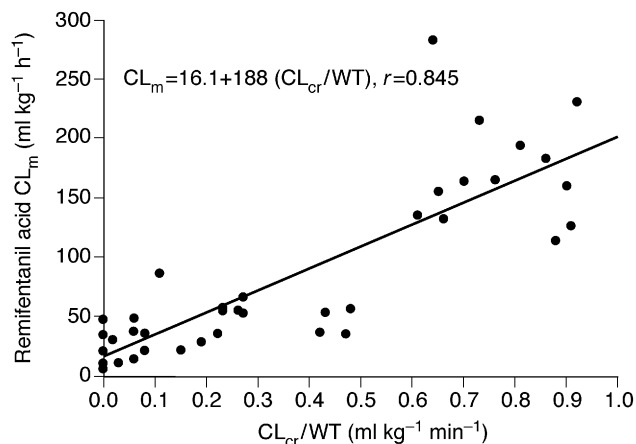


Fig 6 Scatter plot of remifentanyl acid clearance (CL_m) vs creatinine clearance (CL_{cr}), including regression line.

in patients undergoing RRT and no consistent effect on remifentanyl clearance, or remifentanyl concentrations was observed.

Mean CL_m was significantly decreased in the moderate/severe group compared with the normal/mild group: 41.4 (28.9) vs 176 (49.3) $ml\ h^{-1}\ kg^{-1}$. The differences between the normal/mild group and all three subgroups of the moderate/severe group were statistically significant and it appears that CL_m is linearly related to CL_{cr} (Fig. 6). The mean elimination half-life of RA, as estimated by $t_{1/2,m,\alpha}$ for the three-compartment combined model in the normal/mild group, was 2.48 (1.03) h, which is similar to that previously reported for patients with mild renal impairment (2 h).²⁶ It was also significantly shorter than the single RA half-life estimated by the two-compartment combined model for the moderate/severe group, 18.5 (13.6) h. In contrast, the half-life of RA associated with the terminal phase in the normal/mild group ($t_{1/2,m,\beta}$, three-compartment model) was 16.6 h, and this was not significantly different from the single half-life estimated for the moderate/severe group. Due to the different compartmental models used, a comparison of these half-lives is not strictly statistically permissible, but the results of the statistical analyses can be used to elucidate underlying mechanisms. In renal impairment, it is the elimination of RA that is affected, as demonstrated by the decrease in CL_m in the present study. The shift in the metabolite kinetics from two compartments to one is consistent with a prolongation of RA elimination half-life (which can be assumed to be given by $t_{1/2,m,\alpha}$ in the normal/mild group) with increasing severity of renal impairment. In the study in patients with mild renal impairment,²⁶ a 2-fold increase in $t_{1/2,m,\alpha}$ has been observed relative to normal patients, while the terminal half-life $t_{1/2,m,\beta}$ remained unaltered. It can be expected that, if $t_{1/2,m,\alpha}$ is further prolonged in moderate/severe renal impairment, the two phases may no longer be distinguishable, and that would be consistent with the previously reported 20-fold increase of

Table 4 Statistical comparisons between the normal/mild and moderate/severe groups. Pharmacokinetic terms are explained in the text. *Statistically significant

Parameter	Least squares mean ratio	95% confidence intervals	P value
Metabolic ratio	5.56	3.08, 10.0	<0.0001*
Remifentanyl			
CL	1.13	0.746, 1.70	0.5634
V	1.80	0.92, 3.52	0.0824
$t_{1/2}$	1.60	0.95, 2.69	0.0735
Remifentanyl acid			
CL_m	0.20	0.13, 0.31	<0.0001*
V_{m1}	1.10	0.88, 1.38	0.3824
$t_{1/2,m,\alpha}$ vs $t_{1/2,m,k_{20}}$	6.84	4.50, 10.4	<0.0001*
$t_{1/2,m,\beta}$ vs $t_{1/2,m,k_{20}}$	1.01	0.668, 1.51	0.9787

RA half-life in severe renal impairment.¹⁴ It can then be safely assumed that the single half-life estimated in the moderate/severe group in the present study reflects this prolongation in RA elimination half-life, as a result of the increased severity of renal impairment. Although this situation called for mixed-effects modelling in order to statistically evaluate covariate effects such as that of renal function and patient characteristics on RA pharmacokinetics, all attempts to estimate population pharmacokinetic parameters and their variability in NONMEM failed to converge.

In exploratory plots of pharmacokinetic parameters vs the covariates age and weight, no obvious trends were observed. It was not possible to illustrate the previously found effect of age¹⁵ on remifentanyl pharmacokinetics since patients were unevenly distributed (three aged 31–40 yr, 37 aged 54–81 yr). In addition, the small number of female patients included in the study and their uneven distribution (9/40, one in the normal/mild group and eight in the moderate/severe group) did not permit any gender comparisons.

Pharmacodynamic results of the same clinical trial, presented by Breen and colleagues,²⁸ showed no evidence of any clinically relevant prolongation of μ -opioid effects, as assessed by the time to the offset of the pharmacodynamic effects. The main finding relevant to the discussion of RA pharmacokinetics was that the difference in the mean time to offset between the normal/mild and moderate/severe groups after 72 h of remifentanyl administration was only 17 min, even when RA concentrations reach up to 500 times those of remifentanyl in individual patients with a significant degree of renal impairment.

In order to assist future study designs in ICU patients who might require remifentanyl administration for longer than 72 h, remifentanyl and metabolite simulations were performed using mean parameter estimates obtained here, with CL_m expressed as a function of CL_{cr} , using the equation given in Figure 6. Simulations for average patients with

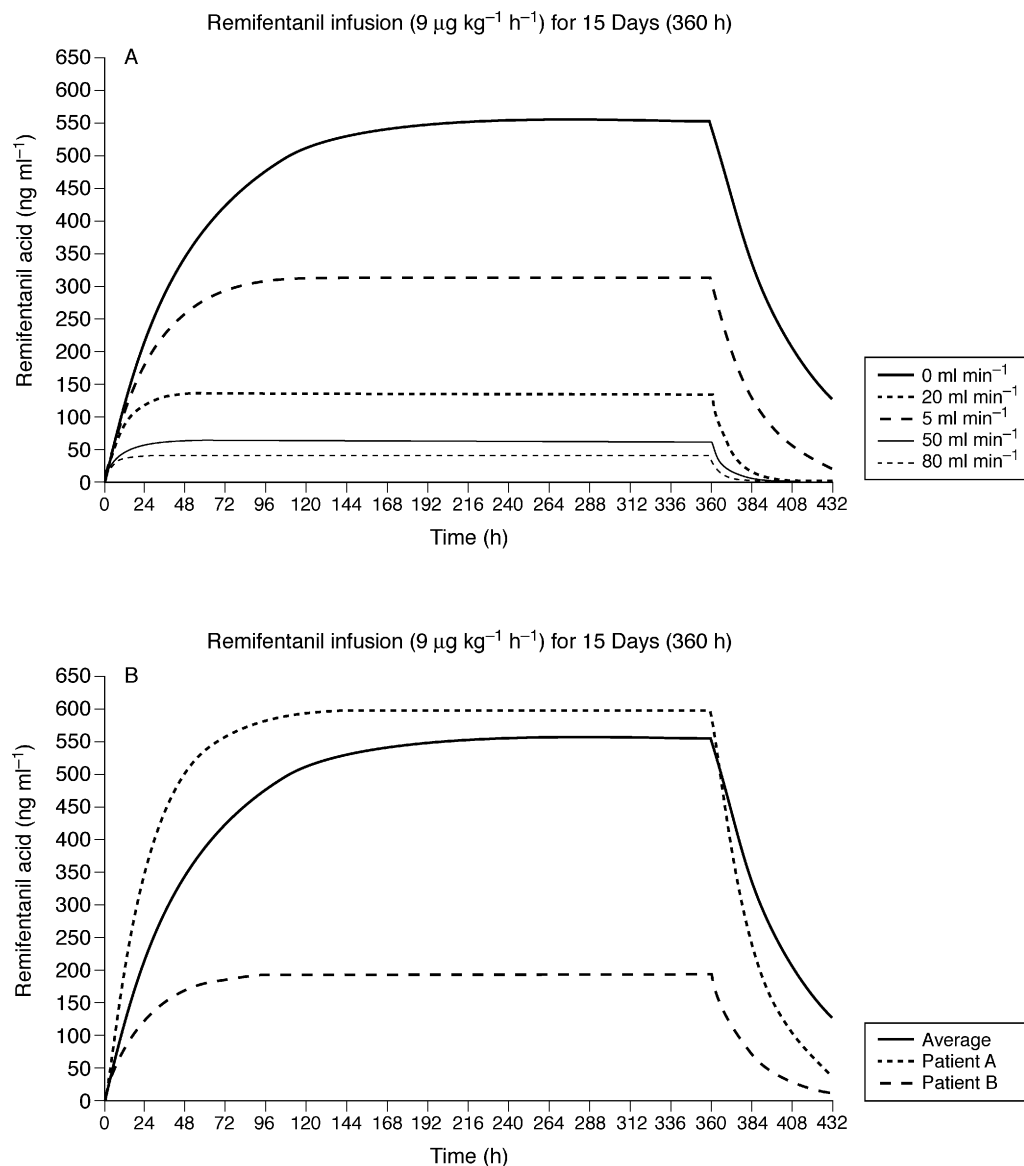


Fig 7 Simulated remifentanyl acid concentrations for an average individual (weight 75 kg) with (A) various degrees of renal impairment (CL_{cr} 0, 5, 20, 50 and 80 ml min⁻¹) and (B) for average individual with 0 CL_{cr} together with the patients with the highest observed remifentanyl acid C_{max} (Patient A, CL_{cr} =5 ml min⁻¹) and the highest metabolic ratio (Patient B, CL_{cr} =0 ml min⁻¹).

various degrees of renal impairment receiving a 9 µg kg⁻¹ h⁻¹ continuous remifentanyl infusion for 15 days are presented in Figure 7A.

Had we obtained a population pharmacostatistical model, it would have been possible to report confidence intervals on the RA concentrations predicted by the model. Instead, together with the average estimate for CL_{cr} =0 ml min⁻¹, we present in Figure 7B predictions based on two extreme individuals, one with the highest observed RA C_{max} (Patient A, CL_{cr} =5 ml min⁻¹) and one with the highest metabolic ratio (Patient B, CL_{cr} =0 ml min⁻¹). These simulations predict that in the worst-case scenario, RA concentrations would reach steady state by 144 h (6 days) and would not be expected to exceed 600 ng ml⁻¹. Such concentrations of RA

were observed in the present study, when higher infusion rates were used, and according to the results cited above from Breen and colleagues,²⁸ were not associated with any prolongation of µ-opioid effects, as assessed by the time to the offset of the pharmacodynamic effects.

In conclusion, the pharmacokinetics of remifentanyl were not significantly altered in ICU patients with moderate/severe renal impairment compared with those with normal/mild impaired renal function, even after continuous i.v. administration for up to 3 days. CL_m decreased in a linear fashion with decreasing CL_{cr} , and in patients with moderate/severe renal impairment was reduced to 25% that of the normal/mild group. The metabolic ratio increased by 8-fold in the moderate/severe group relative to the normal/mild

group, predicting average RA concentrations at steady state more than 100-fold those of remifentanyl in patients with moderate/severe renal impairment. Simulations using the pharmacokinetic parameters obtained from the study predict that in patients with renal failure, RA concentrations would reach steady state after 6 days of continuous infusion and, for a remifentanyl regimen of $9 \mu\text{g kg}^{-1} \text{h}^{-1}$, these concentrations would not exceed those reported in the present study, for which no associated prolongation of μ -opioid effects was observed.

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