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Remifentanil by bolus injection: a safety, pharmacokinetic, pharmacodynamic, and age effect investigation in human volunteers†

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Background. Although remifentanil's short-acting pharmacokinetic profile makes it well suited for procedures during which a brief period of intense analgesia is required, setting up an infusion pump for brief procedures is inconvenient. The clinical pharmacology of remifentanil administered by bolus injection, a more convenient alternative, has not been explored in detail. The primary aim of this study was to examine the safety of single bolus doses of remifentanil in conscious, healthy, adult volunteers breathing room air. Secondary aims included the evaluation of remifentanil pharmacokinetics and analgesic effects after bolus injection and a comparison of these issues in younger *vs* older adults.

Methods. Using a randomized, double-blind, placebo-controlled, dose-escalation, crossover study design, 64 subjects (16 over 60 years old) received remifentanil or placebo by bolus injection in a fixed unit dose separated by a 1 h washout period. Respiratory effects were assessed using a respiratory intervention scale. Analgesic effects were assessed using pressure algometry. A population pharmacokinetic model was constructed using non-linear, mixed-effects modelling techniques based on arterial blood samples. Computer simulations were performed to illustrate the clinical application of the pharmacokinetic model.

Results. Dose-related increases in both respiratory and analgesic effects were observed. In general, the respiratory depression observed was mild and easily treated with requests to breathe or the administration of oxygen, although the older cohort (and some younger subjects) experienced more substantial respiratory depression at lower doses. The pharmacokinetics of bolus-dose remifentanil were adequately described by a two-compartment model. The pharmacokinetic simulations illustrated the potential utility of bolus-dose remifentanil.

Conclusions. Bolus injection could potentially be a safe and effective means of administering remifentanil in clinical situations requiring a brief period of intense analgesia. Because some subjects, both old and young, experienced significant respiratory depression even at low doses, careful monitoring of respiratory function is essential.

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Remifentanil is a short-acting, esterase-metabolized opioid in widespread clinical use in numerous countries.[1 2] Used as an adjunct to general anaesthesia and monitored anaesthesia care and also as an analgesic in the post-anaesthesia care unit and intensive care unit, remifentanil is typically administered by continuous infusion via a programmable infusion pump.

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Table 1 Respiratory intervention scale

Score	Definition
0	Pulse oximeter reading (Sp_{O_2}) above 90%. No intervention required.
1	Sp_{O_2} ⩾86% but ⩽90% for >5 s. No intervention required but may consider rapid intervention if necessary.
2	Sp_{O_2} ⩽85% for >5 s. Verbal prompts (up to three prompts) to take a breath restored the Sp_{O_2} to >85%.
3	After three verbal prompts to take a breath failed to restore Sp_{O_2} to >85% for >5 s, oxygen 2 litres min^{-1} are applied via a nasal cannula, and restored the Sp_{O_2} to >85%.
4	Intervention 3 failed to restore Sp_{O_2} to >85% for >5 s. A verbal prompt to take a deep breath (with nasal oxygen in place) was made, and restored Sp_{O_2} to >85%.
5	Intervention 4 failed to restore Sp_{O_2} to >85% for 5 s. A tactile and verbal stimulus to breathe was made and restored Sp_{O_2} to >85%.
6	Intervention 5 failed to restore Sp_{O_2} to >85%. Naloxone 0.4 mg was given to reverse hypoxaemia. Positive-pressure ventilation with oxygen 100% by bag and mask was delivered if needed.

Because of its short-acting pharmacokinetic profile, remifentanil may be well suited for clinical situations in which a brief period of intense analgesia is desirable such as during painful diagnostic and therapeutic procedures performed outside the operating room. In such settings, practitioners may find the gathering of the necessary equipment and the setting up of an infusion pump apparatus excessively inconvenient and therefore unappealing. If remifentanil could be safely and efficaciously administered by bolus injection in such situations, practitioners may find the ease and simplicity of the technique more appropriate for the out-of-operating-room setting.

To date, there is very little information describing the clinical pharmacology of remifentanil by bolus injection in awake subjects breathing room air. In fact, the current product labelling in the USA recommends bolus dosing of remifentanil only in patients who are undergoing general anaesthesia.

The primary aim of this observational study was to examine the safety of single bolus doses of remifentanil in conscious, healthy, adult volunteers breathing room air, particularly in terms of respiratory effects. Secondary aims included the evaluation of remifentanil pharmacokinetics and analgesic effects after bolus injection and a comparison of these aspects of remifentanil's clinical pharmacology in younger and older adults (over 60 yr). We hypothesized that remifentanil would be well tolerated in younger adults in bolus doses up to 200 μg and that older subjects would exhibit more substantial respiratory effects at all doses.

Methods and materials

After obtaining institutional approval and informed consent, potential volunteers were screened for study eligibility within 2 weeks of participation, with a target enrolment of approximately 60 subjects. The study was conducted as a randomized, double blind, two-period crossover, placebo-controlled, dose-escalation clinical trial.

Only English-speaking volunteers 18–59 yr (younger group) and 60 yr and over (older group) who were generally healthy (ASA I–II) were eligible for enrolment. All volunteers were required to be within 50% of their ideal body weight based on criteria described by Abernethy and Greenblatt.[3] Female volunteers were required to be non-lactating and to be either sterile (i.e. post-menopausal or surgically sterilized) or using an effective method of contraception. Potential subjects were excluded if they had a history of alcohol abuse or illegal drug use, a history of hypersensitivity to opioids, or a record of significant psychiatric illness that might impair their capacity to give informed consent. Volunteers with renal or hepatic disease were also excluded, as were volunteers whose concurrent medications included drugs that are known to interact significantly with opioids (including oral opioid analgesics).

Volunteers reported to the study site having abstained from tobacco products for 12 h, from solid food intake for 8 h and from clear fluid intake for 4 h. Instrumentation included an 18 G i.v. catheter in an arm (with normal saline infusing at 100 ml h^{-1}) in all subjects and a 20 G radial artery catheter in subjects in whom blood samples for remifentanil concentration measurement were to be obtained (see below). Also, a nasal cannula was applied to each subject at the beginning of the experiment in preparation for the possible administration of oxygen after drug administration.

Safety monitoring included a finger pulse oximeter (Sp_{O_2}), a three-lead continuous ECG and an automated arterial pressure cuff attached to the arm opposite the i.v. catheter. As a means of measuring ventilatory frequency, expired carbon dioxide was continuously measured (sampled through the nose).

In a randomized, double-blind, crossover manner, subjects received either remifentanil or placebo as the first treatment in a fixed unit dose (i.e. not weight adjusted) by bolus injection as rapidly as clinically feasible (i.e. 2–3 s). After a 1 h washout period, the second treatment was injected in a similar fashion, completing the crossover. Each dose was diluted in 8 ml of normal saline; each injection was immediately followed by a flush of normal saline (10 ml). Beginning with a unit dose of 25 μg, six subjects were studied at each dose level. The dose was increased in increments of 25 μg until a total of four out of six subjects in

one dosage group experienced significant respiratory depression (see below) or until a maximum dose of 200 μg was reached.

Respiratory depression effects were measured using the respiratory intervention scale (RIS) as shown in Table 1. In brief, the RIS is an observer assessment that quantifies the degree of respiratory depression by incorporating the Sp_{O_2} and the subject's responsiveness into a graded score reflecting the degree of intervention necessary to normalize the subject's oxygenation status as assessed by pulse oximetry. The maximum RIS score was the primary endpoint for the measurement of respiratory depression (i.e. the RIS is a 'one-time' measurement). Significant respiratory depression was arbitrarily defined as a RIS score of 3 or more; once four of six subjects in a single dosage group reached a RIS score of 3 or more, the dosage escalation was stopped. The RIS methodology has been described in more detail elsewhere.[4] As the primary respiratory effect measure, the maximum RIS score during the first 15 min after each injection was recorded. Episodes of apnoea and respiratory depression were also recorded as they occurred. Apnoea was defined as no breath for 15 s or longer and respiratory depression was defined as an Sp_{O_2} less than or equal to 85% for longer than 5 s or a ventilatory frequency of less than or equal to 8 bpm for 1 min or longer.

Pressure algometry was used to assess analgesic effect. In brief, the pressure algometer is a hydraulic device that is attached to the subject's middle to upper leg in a stable and comfortable position (the algometer is housed in two sheets of clear, thick plastic which are used to immobilize the leg). A painful stimulus is produced by applying the algometer's pressurized metal plunger (a flat circular surface, 1 cm in diameter) to the skin at the anteromedial flat surface of the tibia. Under the control of the investigator, the plunger pressure is incrementally increased (approximately 2 psi per s) up to a maximum pressure of 60 psi, which was arbitrarily defined as the maximal noxious stimulus. For each measurement, the subject was instructed to 'say stop when you cannot tolerate the pain any longer'. Subjects were educated on the use of pressure algometry and were allowed to practice several algometry measurements before beginning the experiment. The pressure algometry methodology employed has been described in more detail elsewhere.[5] Pressure algometry measurements were made at 1, 3, 5 and 7 min after each treatment (injection) and then every 2 min until two consecutive measurements were within 15% of baseline. The onset of analgesia was defined as the time to achieve a pressure algometry measurement greater than 15% above baseline. The duration of analgesia was defined as the interval during which the pressure algometry measurement was greater than 15% above baseline.

Safety and drug effect measurements were made at preset intervals, with initial baseline measurements being made 15 min before the first treatment. The Sp_{O_2}, ventilatory frequency, heart rate and systolic, diastolic and mean arterial pressures were recorded every minute during the first 15 min after drug administration and then every 15 min during the 45 min washout phase.

Other adverse events such as episodes of nausea, vomiting and muscle rigidity were recorded as they occurred. In order to capture these events, volunteers were instructed to report spontaneously any concerns or disturbing symptoms to the investigator; volunteers were asked 'How do you feel?' by the investigators 15 min after each injection.

The analgesic response (i.e. the maximal algometry pressure tolerated) and the respiratory depression responses (i.e. the maximal RIS score and the minimum Sp_{O_2}), were compared between different doses within each subject group (i.e. older *vs* younger) using the Kruskal–Wallis test corrected for multiple comparisons. These effects were also compared between subject groups using the Mann–Whitney rank sum test. $P<0.05$ was considered significant.

In subjects who received 75 μg or more, arterial blood samples of 3 ml were obtained at preset intervals with the most rapid sampling immediately after treatment injection (samples were obtained during both the placebo and remifentanil limbs to maintain blinding). Samples were collected into heparinized tubes at baseline and at 1, 2, 4, 6, 8, 10, 15, 20, 30, 45 and 60 min after injection of the study drug (both remifentanil and placebo). To prevent continued metabolism of remifentanil after sample collection, the drawn blood was immediately transferred into previously prepared glass tubes containing citric acid, and frozen at –70°C until the time of assay.

Remifentanil blood concentrations were measured by a high-pressure liquid chromatography method employing ultraviolet detection. The assay was validated between 0.1 and 100 ng ml^{-1} with an interassay coefficient of variation of less than 15% for concentrations greater than 0.1 ng ml^{-1}. The sample preparation and assay methodology are described in detail elsewhere.[6]

The raw concentration *vs* time data were analysed using several techniques. First, as an exploratory manoeuvre, each individual subject's pharmacokinetic parameters were estimated using standard compartmental modelling techniques. Guided by the results of this preliminary analysis, a mixed-effects population model was constructed. Finally, to help bring clinical meaning to the pharmacokinetic analysis, computer simulations were performed using the mixed-effects population pharmacokinetic model. Because it had been previously demonstrated for the remifentanil dose range employed in this study, linear pharmacokinetics were assumed for the purposes of this analysis.[7]

Using the 'two-stage' approach implemented on WinNonlin (version 3.0, Pharsight Corporation, Mountain View, CA, USA), both two- and three-compartment mamillary models were fitted to the raw concentration *vs* time data to estimate each individual's pharmacokinetic parameters. These biexponential and triexponential disposition equations were parameterized in terms of clearances and apparent distribution volumes. Initial parameter esti-

Table 2 Subject characteristics. Data are mean (range) for age, or mean (SD)

	Younger group (*n*=48)	Older group (*n*=16)
Age (yr)	28.2 (20–48)	67.4 (60–75)
Sex (male/female)	29/19	10/6
Height (cm)	174.0 (8.5)	171.7 (9.8)
Weight (kg)	72.5 (12.5)	74.9 (12.2)

Table 3 Number of subjects at each dose. *No further dosage escalation because all four subjects (of six potential subjects in the dosage group) experienced an RIS score of 4. **No further dosage escalation because the maximum protocol dosage had been achieved

Dose (μg)	Younger group	Older group
Placebo	48	16
25	6	6
50	6	6
75	6	4*
100	6	0
125	6	0
150	6	0
175	6	0
200	6**	0

mates were obtained from our previous work.[8] Because the magnitude of the errors between the measured concentrations (C_m) and the concentrations predicted (C_p) by the model were presumed to be proportional to the predicted concentration, a proportional ($1/C_p^2$) variance model was used for each fit.

Guided by the results of the individual compartmental analysis in terms of the number of compartments and the initial parameter estimates, a mixed-effects model was built using WinNonmix (version 2.0, Pharsight Corporation, Mountain View, CA, USA), a mixed-effects modelling program. Mixed-effects modelling simultaneously analyses an entire population's data and provides estimates of typical values for the parameters, along with an estimate of the parameter's interindividual variability within the population studied.

Interindividual error on each parameter was modelled using a log-normal error model:

$$\theta_{individual} = \theta_{typical}\, e^{\eta_{individual}}$$

where $\theta_{individual}$ is the true value in the individual, $\theta_{typical}$ is the population mean estimate and $\eta_{individual}$ is a random variable whose distribution is estimated by WinNonmix with a mean of 0 and a variance of ω^2. The estimates of ω obtained with WinNonmix are similar to the coefficient of variation (CV) often used in standard descriptive statistics. Residual intra-individual error was modelled assuming a constant coefficient of variation. The two-compartment model was parameterized in terms of distribution volumes and clearances.

Table 4 Summary of respiratory intervention scale scores by dose

Group	Dose (μg)	*n*	Median	Minimum	Maximum
Younger	Placebo	48	0	0	2
	25	6	0	0	1
	50	6	1	0	1
	75	6	1	0	2
	100	6	1	0	4
	125	6	2	0	4
	150	6	2	1	4
	175	6	2	0	3
	200	6	3	0	4
Older	Placebo	16	0	0	1
	25	6	1	0	2
	50	6	2	0	3
	75	4	4	4	4

The performance of the population model constructed using WinNonmix was assessed in terms of the ability to predict the measured blood concentrations. This was accomplished by plotting the observed concentrations against the predicted concentrations and by plotting the weighted residuals (WRs) as computed by WinNonmix against the predicted concentrations. These plots were then examined for accuracy and bias.

Computer simulations using the mixed-effects model were performed to illustrate the clinical implications of the pharmacokinetic analysis. The simulations predict the effect-site concentrations that would result from two alternative remifentanil dosing regimens that might be applied in clinical situations requiring a brief period (15 min) of intense analgesia (i.e. a 100 μg bolus followed by a 50 μg bolus every 2.5 min, and a 100 μg bolus followed by a 25 μg bolus every 1.5 min). The simulations were designed to target effect-site concentrations that are associated with analgesia and spontaneous ventilation (3–6 ng ml^{-1}).[9] The rate constant characterizing the equilibration between the plasma and the effect site concentrations (k_{e0}) used for these simulations was obtained from our previous work.[10]

Results

Sixty-four subjects were enrolled and completed the study, including 48 in the younger group and 16 in the older group. Subject characteristics are summarized in Table 2. The number of subjects enrolled for each dosage level (including placebo) is summarized in Table 3.

There was a clear pattern of gradually increasing respiratory depression as the dosage was increased, although younger subjects receiving 75 μg or less experienced minimal respiratory depression, as reflected in RIS scores typically of 1 or less. In general, the respiratory depression, manifested by decreased respiratory rate and Sp_{O_2}, was rapid in onset (minimum Sp_{O_2} observed within the first 2–4 min after injection) and short lived, rapidly responding to prompting and/or oxygen administration as

Table 5 Summary of onset, duration, maximum and time to maximum (T-max) analgesic response as measured by pressure algometry for selected dosage groups

Group	Parameter	Dose (μg)	*n*	Mean	SD	Minimum	Maximum
Younger	Onset (min)	Placebo	48	0.7	1.7	0	9
		50	6	0.8	0.4	0	1
		100	6	2	1.7	1	5
		200	6	1.7	1	1	3
	Duration (min)	Placebo	48	1.5	4.4	0	22
		50	6	6.3	4.3	0	10
		100	6	7	5.8	2	18
		200	6	8	6.8	0	16
	Maximum (% increase)	Placebo	48	10.3	14.5	0	55.6
		50	6	62.5	34.3	13	110.5
		100	6	73.2	32.5	26.3	119
		200	6	105.4	59.4	15.8	192.3
	T-max (min)	Placebo	48	2.1	2.7	0	9
		50	6	2.7	2.3	1	7
		100	6	3.3	1.5	1	5
		200	6	3	1.8	1	5
Elderly	Onset (min)	Placebo	16	1.1	2.7	0	11
		25	6	1.3	1.9	0	5
		50	6	0.8	0.4	0	1
		75	4	1	0	1	1
	Duration (min)	Placebo	16	4.3	6.6	0	18
		25	6	5	5.5	0	10
		50	6	9.7	6.6	0	18
		75	4	9.5	5.7	2	14
	Maximum (% increase)	Placebo	16	25.3	42.6	0	172.7
		25	6	31.9	26.2	0	60.7
		50	6	66.3	34.7	9.5	118.8
		75	4	92.7	45.8	50	140
	T-max (min)	Placebo	16	3	4.5	0	15
		25	6	3	2.4	0	5
		50	6	3.7	2.7	1	9
		75	4	2	2	1	5

specified by the RIS. Even at the highest doses (100–200 μg) administered to younger subjects, the respiratory depression observed was mild and easily managed, with RIS scores typically between 0 and 3.

Older subjects experienced more significant respiratory depression at lower doses than did the younger groups, with an average RIS score of 4 in the 75 μg dose group of the older cohort (further dosage escalation was therefore not undertaken). In fact, all four of the older subjects who received 75 μg exhibited a RIS score of 4. However, as with the younger cohort, the respiratory depression observed in the older subjects was short lived and easily managed as specified by the RIS.

A summary of RIS scores for both the younger and older cohorts is displayed in Table 4. No subject in either group at any dose required more than administration of nasal canula oxygen (2 litre min^{-1}) and verbal prompting to breathe to restore oxygenation to satisfactory levels (i.e. no subject achieved a RIS score greater than 4).

For the older group, the analgesic response (compared with placebo) reached significance at doses above 50 μg ($P<0.05$). The increase in RIS and decrease in Sp_{O_2} levels were also significant at doses above 50 μg compared with placebo ($P<0.05$). For the younger group, the analgesic and respiratory depression responses (both RIS and Sp_{O_2}) reached significance at doses of 75 μg and above compared with placebo ($P<0.05$). Between groups, the older group showed significant decreases in Sp_{O_2} and increasing RIS score at the 75 μg level compared with younger adults given the same dose ($P=0.02$ and $P=0.01$, respectively).

The most serious respiratory events were episodes of apnoea, occurring in four subjects (a 68-yr-old male receiving 75 μg, a 36-yr-old male receiving 150 μg, a 27-yr-old female receiving 75 μg and a 21-yr-old male receiving 200 μg). All of these apnoeic episodes occurred within the first 5 min after injection and lasted for 1 min or less. An additional subject (a 26-yr-old male receiving 175 μg) experienced an episode of respiratory depression that lasted for 1 min. Although these events were obviously regarded as serious, they were easily managed.

There was a clear pattern of gradually increasing analgesia as the dose was increased, although subjects receiving 25 μg or less had algometry responses not significantly different from placebo ($P<0.05$), particularly for the older group. As with the respiratory effects, the algometry effects were rapid in onset and short-lived, with the maximal effects typically occurring within 1–2 min and lasting on average about 8 min. A summary of the analgesic response (i.e. onset, duration, maximal and time to maximal) as measured by pressure algometry for selected

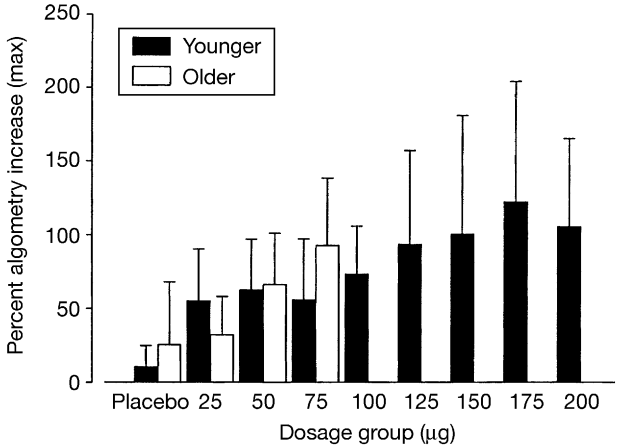

Fig 1 The maximum percent algometry increase for each dosage group. The younger cohort is represented by the solid bars; the older cohort by the open bars. Error bars represent SD. Note that the older cohort dose escalation ended at 75 μg.

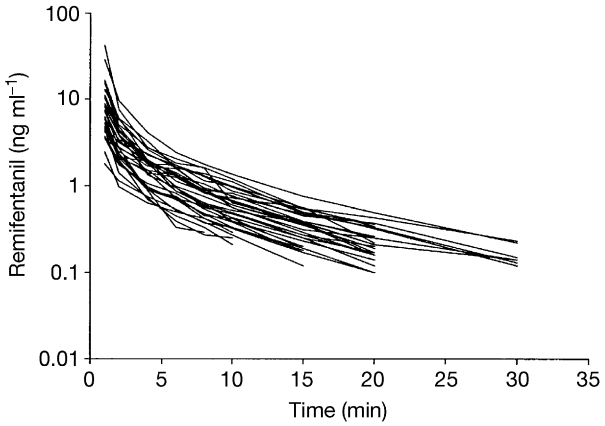

Fig 2 The raw concentration *vs* time curves for subjects in whom arterial blood samples were collected (subjects who received 75 μg or more). Note that no data from the older cohort are included (i.e. older cohort dose escalation ended at 75 μg).

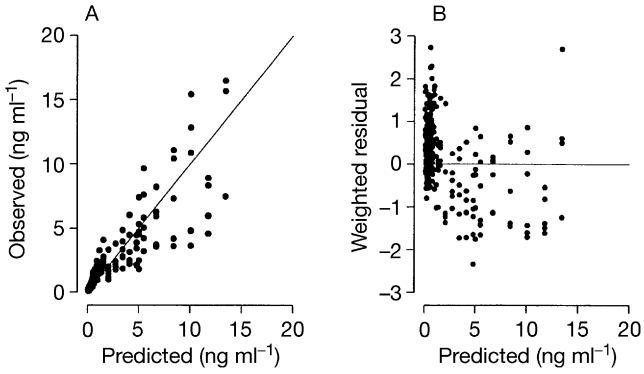

Fig 3 A graphical assessment of mixed-effects model performance. (A) The observed *vs* predicted concentrations (note that two data points are off the scale of this graph). (B) The weighted residuals *vs* the predicted concentrations.

doses is displayed in Table 5. The maximum percent algometry increase for each dosage level is displayed in Figure 1.

With regard to non-respiratory adverse events, in general the subjects tolerated the study very well. Although some subjects exhibited minor changes in heart rate and arterial pressure, there were no episodes of bradycardia or hypotension that were judged to be clinically significant. Similarly, no episodes of muscle rigidity, or nausea or vomiting were detected by the investigators or reported by the subjects.

The drug administration scheme applied in this protocol resulted in concentration *vs* time curves characteristic of bolus injections. The raw concentration *vs* time data are displayed in Figure 2. The raw concentration *vs* time data were adequately described by a two-compartment model. The average 'two-stage' parameter estimates were a central clearance of 4.3 (SD 1.4) litre min^{-1}, an intercompartmental clearance of 3.5 (2.5) litre min^{-1}, a central distribution volume of 9.1 (7.1) litre and a peripheral distribution volume of 13.4 (7.1) litre. These parameter values were used as initial estimates for the mixed-effects population analysis. The final data set for mixed-effects population analysis consisted of 273 measured blood concentrations and 48 dosing records. The mixed-effects, two-compartment model parameter estimates were a central clearance of 4.1 litre min^{-1} (CV 16.4%), an intercompartmental clearance of 1.5 litre min^{-1} (CV 21.9%), a central distribution volume of 5.6 litre (CV 26.5%) and a peripheral distribution volume of 10.9 litre (CV 21.2%).

The mixed-effects model performance was typical of compartmental models based on bolus drug administration where the measured drug concentrations decrease below the assay sensitivity quickly (i.e. the model does not perform as well as those based on more 'data rich' studies). The model tended to slightly 'overpredict' in the first 1–2 min after injection, with a tendency to slightly 'underpredict' thereafter. This shortcoming could probably be addressed by the addition of a third compartment, but the 'two-stage' analysis of individual subjects suggested that only two compartments were necessary. The plots of observed concentrations against predicted concentrations and WRs against predicted concentrations are displayed in Figure 3.

Computer simulations

The results of the pharmacokinetic simulations are displayed in Figure 4. The upper panel, a simulation of a 100 μg bolus followed by 50 μg every 2.5 min, results in effect-site concentrations ranging from approximately 3 to 5.5 ng ml^{-1} within the dosage interval. The lower panel, a simulation of a 100 μg bolus followed by 25 μg every 1.5 min, results in effect-site concentrations ranging from just over 3 to just over 4 ng ml^{-1} within the dosage interval. The more frequent dosing interval of course results in less fluctuation and more closely approximates a steady-state infusion.

Discussion

This study has investigated the pharmacokinetics and pharmacodynamics of bolus-dose remifentanil in a healthy adult volunteer population, with a special focus on respiratory safety. The primary finding of the study is that remifentanil by bolus injection in doses of up to 200 μg is typically well tolerated in young, healthy adult subjects breathing room air, producing manifestations of repiratory depression that can be managed with verbal prompting to breathe and the administration of supplemental oxygen by nasal canula. Other essential findings of the study are that remifentanil by bolus injection produces substantially more significant respiratory depression in older adults (age over 60 yr) and that bolus-dose remifentanil can produce substantial analgesic effects that are characteristically short-lived.

The use of bolus-dose remifentanil is not new. Several investigators have examined the pharmacodynamics of bolus-dose remifentanil in various clinical settings. For example, remifentanil by bolus injection has been shown to be effective in preventing an untoward haemodynamic response to laryngoscopy and tracheal intubation.[11–13] Bolus-dose remifentanil has been used successfully in combination with propofol for orotracheal intubation without muscle relaxants.[14 15] Remifentanil by intermittent bolus injection has also been used successfully as a means of controlling undesirable increases in heart rate and arterial pressure during craniotomy procedures.[16]

We studied remifentanil's effects when given by fixed dose bolus injection to adults breathing room air. The study was primarily aimed at assessing the potential safety of remifentanil injection for procedures that might take place in various locations outside the operating room where patients will be breathing spontaneously without an artificial airway. Overall, the study confirmed that bolus doses of up to 200 μg are well tolerated by younger adults breathing room air, in terms of both respiratory and haemodynamic effects. Significant respiratory depression is to be expected, but it can typically be managed with supplemental oxygen administered by nasal canula and prompting to breathe.

Examining the pharmacokinetic simulations is perhaps the best way to understand the study's clinical implications. As demonstrated by the simulations in Figure 4, frequent small bolus doses of remifentanil can be expected to produce a concentration *vs* time curve in the site of action (i.e. 'effect site') that is a reasonable approximation of a steady-state infusion. Additional clinical study and computer simulation investigation will be necessary to identify the optimal dosage regimen for various clinical applications. It is important to recognize that the current study did not examine the safety of repeated bolus doses of remifentanil, although the fact that remifentanil's pharmacokinetics are linear suggests that pharmacokinetic simulation is a valid and useful way of exploring the clinical implications of new dosage regimens.[7] Although not

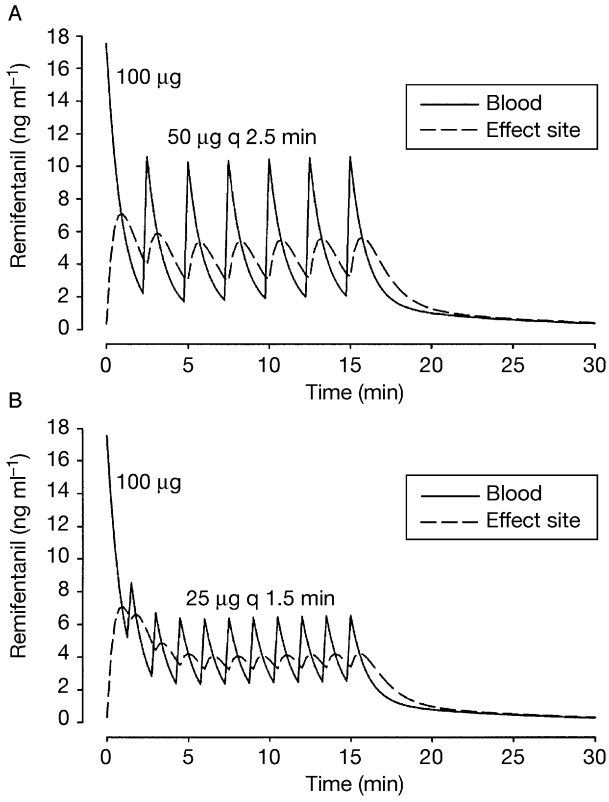

Fig 4 Two pharmacokinetic simulations of potential remifentanil bolus injection dosage regimens. (A) Simulation of a 100 μg bolus followed by a 50 μg bolus repeated every 2.5 min for 15 min. (B) Simulation of a 100 μg bolus followed by a 25 μg bolus every 1.5 min for 15 min. Blood concentrations are represented by the solid line; apparent effect-site concentrations are represented by the dotted line.

presented here, comparison of the pharmacokinetic simulations shown in Figure 4 with simulations using the remifentanil pharmacokinetic parameters published by Minto and colleagues[17] were substantially similar, suggesting that kinetic parameters for remifentanil estimated from bolus injection administration are not markedly different from those estimated from continuous infusion administration. This issue has been a concern for some i.v. anaesthetics such as propofol.[18]

In order to safely use remifentanil by bolus injection in patients breathing room air, it is important to understand not only the magnitude of the expected respiratory effects but also the time course of these effects. Babenco and colleagues[19] studied the time course of respiratory depression induced by remifentanil (by bolus injection) using a carbon dioxide rebreathing technique in healthy volunteers. They observed peak respiratory depression at 2.5 min after injection with substantial recovery at 6 min and essentially complete recovery by 15 min after injection. Although we did not study the time course of remifentanil's respiratory effects in the same way because our respiratory depression end-point was a one-time maximal score (i.e. the RIS), in general our findings are consistent with the more detailed

observations of Babenco and colleagues; that is, the respiratory depression we observed was maximal in the first few minutes after injection, substantially recovered within 6 min and essentially resolved within 15 min after injection.

Several nuances relating to the respiratory depression observed in this study deserve highlighting. For example, it is important to note that some of the subjects who experienced the most severe respiratory events in this study had received doses that were substantially less than the maximum dose studied. It is also very important to emphasize that the older subjects in this study clearly exhibited more pronounced respiratory depression than younger subjects. In older patients with certain co-morbidities (e.g. coronary artery disease), the degree of respiratory depression we observed after bolus remifentanil injection would certainly be viewed as serious and clinically very significant.

The limited literature addressing the hazards of bolus-dose remifentanil in terms of respiratory depression is certainly a cause for concern. In studying the safety and efficacy of bolus-dose remifentanil (with an ongoing continuous infusion) for pain management in the immediate postoperative period, several investigators have observed a high incidence of potentially life-threatening respiratory events (e.g. apnoea).[20–22] Although perhaps not entirely relevant to most clinical settings because of the intermittent nature of the pain, similarly serious adverse respiratory events have been observed when bolus-dose remifentanil has been employed as an analgesic for the relief of labour pain.[23 24]

Because the degree of respiratory depression subjects experienced was highly variable and was occasionally significant even at relatively low remifentanil doses, careful monitoring of respiratory function would be critical in the clinical setting when using remifentanil by bolus injection. Although all episodes of respiratory depression observed in the 64 subjects enrolled in this study were successfully treated with verbal prompting to breathe and the supplementation of inspired oxygen by nasal cannula, skills in the recognition and treatment of inadequate respiration would be obligatory when using bolus-dose remifentanil. Appreciation of the substantial respiratory depression synergy between opioids and sedatives would also be essential. Because of these dangers, it would be prudent for clinicians to gain experience with the clinical pharmacology of remifentanil by infusion before considering the use of remifentanil by bolus injection.

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