The Pharmacokinetics and Electroencephalogram Response of Remifentanil Alone and in Combination with Esmolol in the Rat[1]

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Purpose. The goal of this study was to determine if the co-administration of esmolol (ES), a short acting cardioselective β-blocker, significantly alters the pharmacokinetics and/or pharmacodynamics of remifentanil (REMI), an ultra short-acting opioid, in the rat.

Methods. Sprague-Dawley rats (N = 8, Wt. = 325 ± 15g) were surgically implanted with stainless steel cerebrocortical EEG electrodes three days before the study. Each rat was dosed with REMI (15 μg/kg/min), and REMI & ES (15 μg/kg/min and 600 μg/kg/min) for 21 minutes in a random crossover design. Six serial blood samples were collected over 25 minutes into test-tubes containing 0.5ml acetonitrile. Blood samples were extracted with methylene chloride and analyzed by a validated GC-MS assay. EEG was captured and subjected to power spectral analysis (0.1–50 Hz) for spectral edge (97%).

Results. No significant differences ($p < 0.05$) were found in clearance (REMI = 287 + 73 ml/min/leg vs. REMI & ES = 289 ± 148 ml/min kg) or Vd (REMI = 286 ± 49 ml/kg vs REMI & ES = 248 + 40 ml/kg). A linked sigmoid E_{max} PK-PD model was used and the pharmacodynamic parameters were not statistically different. Mean E_{max} and EC_{50} after REMI were 18.0 ± 6.0 Hz and 32 ± 12 ng/ml; and after REMI + ES were 19 + 4.8 Hz and 26 + 8.6 ng/ml.

Conclusions. At the doses tested, there is no pharmacokinetic or pharmacodynamic interaction between remifentanil and esmolol in the rat.

KEY WORDS: remifentanil; esmolol; pharmacokinetics; pharmacodynamics; electroencephalogram.

INTRODUCTION

Remifentanil (ULTIVA®) is a novel, synthetic ultra short-acting opioid which binds μ receptors (1,2). It belongs to the family of phenylpiperidine derivatives which include fentanyl, alfentanil and sufentanil. Remifentanil is unique among this group by undergoing extrahepatic metabolism. An ester linkage within its structure is highly susceptible to hydrolysis by non-specific esterases in the blood and other tissues. This results in rapid clearance and a short terminal half-life which appear to be independent of renal or hepatic function (3,4). Remifentanil exhibits a total body clearance of 168 l/hr to 300 l/hr in man (2,5) which is approximately 3 to 4 times higher than hepatic blood flow (80 l/hr). It has a volume of distribution of 390 ml/kg (6). The terminal half-life for remifentanil is between 10 and 48 minutes (2,5,7) in man and about 6 minutes in dogs (Glaxo Report UPC/94/016). In comparison, alfentanil has a terminal half-life of 1–2 hours; sufentanil has a half-life of 2–4 hours and fentanyl between 3–4 hours in man (8). The chemical structure of remifentanil and its major metabolic pathway are shown in Figure 1.

Pharmacologically, remifentanil produces analgesia and at high doses, anesthesia (defined as loss of consciousness). It slows electroencephalogram (EEG) activity similar to other potent μ-agonists. Fentanyl, alfentanil and subentanil produce a decrease in frequency and an increase in amplitude of the EEG (9–12). At high doses or maximum effect, there is a predominance of delta wave activity (0–4 Hz). The EEG effects of remifentanil have been studied in dogs (13,14), and in human volunteers (7). Glass *et al.* (6) examined the analgesic effects of remifentanil in a dose-escalation study which also compared the potency of remifentanil to that of alfentanil.

Esmolol is an ultra short-acting cardioselective β-blocker administered intravenously to decrease heart rate and blood pressure during surgical procedures. Esmolol undergoes extensive extra-hepatic metabolism and has similarly a short half-life (15) as remifentanil. Non-specific esterases in the blood and other tissues metabolize esmolol into the inactive acid metabolite ASL-8123 and methanol (16). Esmolol structure and its metabolite are shown in Figure 2. Following a two hour infusion in humans, esmolol had an apparent volume of central compartment of 867 ml/kg and a total body clearance of 285 ml/min/kg (15).

Remifentanil and esmolol are metabolized by non-specific esterases in the blood and other tissues. It is possible that both drugs may be administered together during surgical procedures. The objective of this study was to determine if the co-administration of esmolol would significantly alter the pharmacokinet-

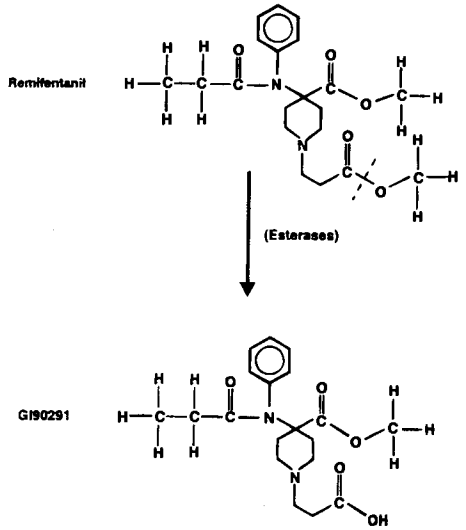

Fig. 1. Chemical structure of remifentanil and major metabolite.

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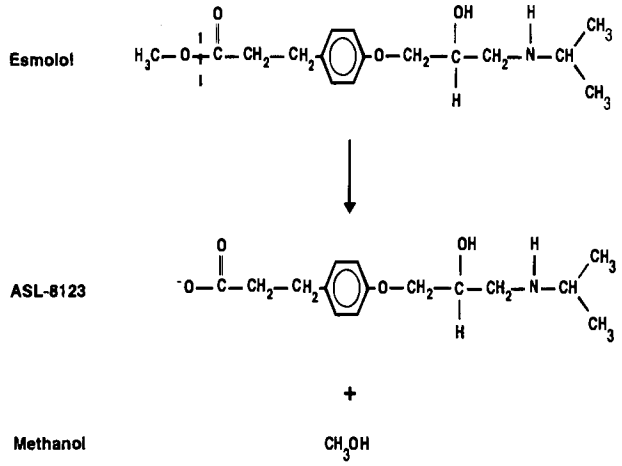

Fig. 2. Chemical structure of esmolol and metabolite.

ics and the pharmacodynamics of remifentanil using the EEG spectral edge (97%) as a surrogate marker.

MATERIALS AND METHODS

Drugs and Reagents

Remifentanil hydrochloride and the internal standard D-4GI87084 were donated by Glaxo Wellcome. Esmolol hydrochloride (Brevibloc®, 10mg/ml) was purchased from Ohmeda Inc. (Liberty Corner, NJ). Drug solutions at the desired concentrations were prepared using 0.9% Sodium Chloride injectable solution, U.S.P (Abbott Laboratories, North Chicago, IL). Two drugs in combination were used for anesthesia during electrode implantation, ketamine hydrochloride 100mg/ml (Park-Davis, Morris Plains, NJ) and xylazine 20mg/ml (Phoenix Pharmaceuticals, St. Joseph, MO). HPLC-grade acetonitrile and GC-grade methylene chloride (Fisher Scientific, Fair Lawn, NJ) were used in this study.

Animals

This study was carried out in male Sprague-Dawley rats weighing 310–340 g which were purchased from Hilltop Laboratories Inc. (Scottsdale, PA). Each animal had two indwelling cannulae: a jugular vein cannula for drug infusion and a femoral artery cannula for blood sampling. The animals were singly housed and maintained in a AAALAC-accredited animal facility operated on a 12-hr light/dark cycle at a room temperature of 72 ± 2°F. They received Purina 5001 chow and water *ad libitum*. The animals were handled and cared for according to the *Guide for the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources* (National Research Council; NIH Publication No. 86-23).

Pharmacokinetic Study

Eight rats were administered two infusions, remifentanil [treatment I, 15 μg/kg/min] and remifentanil plus esmolol [treatment II, 15 μg/kg/min and 600μg/kg/min] for 21 minutes in a randomized crossover design. Treatments I and II were administered 48 hours apart. The drugs were infused into the jugular vein cannula by a Medfusion Syringe pump, model 2010 (Medex Inc., Duluth, GA). Each animal received a total of 2 (±0.2) ml of drug solution in normal saline per treatment. Six serial blood samples of 0.25ml each were collected over 25 minutes from the femoral artery cannula into test-tubes containing 0.5ml acetonitrile. An additional 1.5 ml of acetonitrile was added to each test tube upon sample collection to ensure complete inactivation of esterases in the blood. An internal standard of deuterated remifentanil (D-4GI87084) in acetonitrile was added to correct for differences in recovery and stability among samples. Remifentanil blood concentrations were determined by a validated GC-MS assay. The extraction procedure was developed and validated using human and dog blood (17) and then cross validated for monkey and rat blood. Blood samples were extracted (liquid-liquid) with 4 ml of methylene chloride and the organic phase was transferred to clean test tubes and stored at −85°C until analyzed. Assay validation in rat blood covered a concentration range of 1 ng/ml to 1000 ng/ml/ The correlation coefficient was >0.99 and intra and inter-assay variability was less than 15% for all concentrations evaluated. The lower limit of quantitation was 0.4 ng/ml.

Pharmacodynamic Studies

Three days prior to the drug study, the rats were anesthetized with 70% ketamine hydrochloride (100mg/ml) − 30% xylazine (20mg/ml) using a dosage of 1 ml/kg and were surgically implanted bilaterally with cerebrocortical stainless steel electrodes which rested on the surface of the dura mater (18,19). Using short pieces (about 3 cm long) of Nichrome wire, all electrodes were soldered to miniature Dale connectors which were secured to the animal's skull with dental acrylic.

About 30 min prior to drug infusion, the rats were placed in individual chambers and connected to multiconductor EEG cables which were connected to mercury commutators (Dragonfly, Silver Spring, MD). EEG signals passed from the commutators to universal amplifiers (Gould, East Rutherford, NJ) through an electronic relay box (Dragonfly, Silver Spring, MD), and were captured by a MacIntosh-based software (QND 2.9, Neurodata, Pasadena, CA).

Data Analysis

Bayesian analysis (20–22) was performed using the Adapt II pharmacokinetic package (23). The pharmacokinetic parameters (Vd, Cl, $t_{1/2}$) were estimated by non-linear regression. Goodness of fit was based on visual inspection, final residual sum of squares and random distribution of residuals. Bayesian analysis requires the use of population priors and it is especially useful in studies where limited sampling is necessary. Mean pharmacokinetic parameters estimated in a previous study (24) were used as the population priors in this study. Mean values of volume of distribution and elimination rate constant of the remifentanil alone group in the previous study served as population priors for rats receiving treatment I and mean values of the remifentanil plus esmolol group were used as population priors for treatment II.

Raw signals were filtered at 0.1–50 Hz and analyzed off-line by Fast-Fourier transformation (FFT), separating the EEG into frequency bins between 0.1 and 50 Hz. Edge frequency (or spectral edge) of 97%, mean frequency, total power and relative power (0.1–4.0 Hz) were determined for each animal

starting with 15 min pre-dose and until the EEG returned to baseline following end of infusion. Power is defined as the square of the amplitude of the waves in μV divided over frequency (Hz). A spectral edge of 97% represents the frequency below which 97% of the area of the power vs. frequency histogram is found (25). Relative power is the percent contribution of the 0.1–4 Hz band to total power. Spectral edge data were analyzed using a one-compartment, linked sigmoid E_{max} PK-PD model (26) (PCNONLIN® ver.4.2). PK-PD parameters were estimated using non-linear regression with ordinary least squares. The pharmacodynamic component of the model consisted of the Hill equation:

$$SE = E_0 - \frac{E_{max} \cdot C^{\gamma}}{IC_{50}^{\gamma} + C^{\gamma}}$$

where SE is spectral edge (Hz); E_0 (Hz) is baseline spectral edge; E_{max} (Hz) is maximum effect caused by remifentanil concentrations; IC_{50} (ng/ml) is remifentanil concentration yielding 50% of maximum decrease in spectral edge; C is remifentanil concentration (ng/ml) in the theoretical effect compartment; and γ is the sigmoidicity factor (unitless) which describes the steepness of the concentration-effect curve. Estimated PK-PD parameters included E_0, IC_{50}, E_{max}, γ and $t_{1/2}$ k_{e0}.

Statistical Analysis

Pharmacokinetic parameters of treatments I and II were compared using paired *t*-test. Differences between the two treatments were considered significant when $p < 0.05$. Similarly, a paired *t*-test was used to compare the pharmacodynamic parameters estimated for the two treatments. A *p*-value of less than 0.05 was considered significant.

RESULTS

Pharmacokinetics

A one-compartment model was used to fit remifentanil arterial blood concentrations. Previous studies (24) with more frequent blood sampling had shown that a one-compartment model best described the disposition of remifentanil in rats. The pharmacokinetic parameters (Cl, Vd and terminal $t_{1/2}$) for the two treatments are listed in Table 1. The estimated clearance for remifentanil was about 300 ml/min/kg and the terminal half-life was less than 1 min regardless of whether remifentanil was infused alone or in combination with esmolol. Similarly, no significant difference ($p < 0.05$) in Vd between treatments was observed. The estimated Vd was between 240 and 290 ml/kg.

Pharmacodynamics

The effect of remifentanil on rat EEG was similar to the action of other opioids at high doses. Within seconds of the start of infusion, a sharp decrease in frequency and a high increase in amplitude were observed, culminating in delta waves at maximum effect. Mean frequency decreased from a baseline of 9–10 Hz to less than 4 Hz within 5 min. Conversely, there was a concomitant increase in total power from about 10 μV^2/Hz to over 50 μV^2/Hz. Representative graphs of EEG parameters (power, relative power, mean frequency and spectral edge) for remifentanil alone and in combination with esmolol are shown in Figures 3 and 4, respectively. A counter clock-wise hysteresis resulted from the plot of the effect of remifentanil on spectral edge as a function of arterial blood concentrations (Figure 5). The pharmacodynamics of remifentanil were well characterized by a sigmoid E_{max} model. A one-compartment linked PK-PD model with fixed individual PK parameters provided a good estimate of k_{e0} which resulted in the collapse of the hysteresis loop. Figure 6 illustrates the collapsed loop as well as the sigmoid nature of remifentanil effect on spectral edge in the rat. Table 2 lists the PK-PD parameters estimated in this study. No significant differences between the two treatments were observed ($p < 0.05$) for any of the PD parameters.

Spectral edge declined from a baseline of 38 (±3.8) Hz to 18 (±6) Hz in treatment I and from 40 (±2.4) Hz at baseline to 19 (±4.8) Hz in treatment II (remifentanil plus esmolol). IC_{50} values which give an indication of the potency of remifentanil were 32 (±12) ng/ml for treatment I and 26 (±8.6) ng/ml for treatment II. Equilibration half-lives ($t_{1/2}k_{e0}$) into the effect compartment were 1.77 (±0.64) min and 2.19 (±0.43) min for treatments I and II, respectively. Gamma (γ), which is a measure of the steepness of the concentration-effect curve, was not well estimated in some of the rats. This is reflected by the relatively large standard deviations associated with the mean values for each treatment. The difference between the

Table I. The Pharmacokinetics of Remifentanil (REMI) After Administration of REMI Alone and in Combination with Esmolol (ES)

	Treatment I			Treatment II		
	REMI (15 μg/min/kg)			REMI & ES (15 μg/min/kg + 600 μg/min/kg)		
Rat	Vd (ml/kg)	Cl (ml/min/kg)	$t_{1/2}$ (min)	Vd (ml/kg)	Cl (ml/min/kg)	$t_{1/2}$ (min)
42	323	217	1.03	224	180	0.86
44	356	331	0.74	259	284	0.63
48	235	235	0.69	297	550	0.37
51	272	311	0.61	230	223	0.72
52	255	260	0.68	209	167	0.87
53	226	201	0.78	223	194	0.80
54	281	320	0.61	224	222	0.70
56	342	421	0.56	320	493	0.45
Mean	**286**	**287**	**0.71**	**248**	**289**	**0.67**
S.D.	**49**	**73**	**0.15**	**40**	**148**	**0.18**
CV%	**17**	**25**	**21**	**16**	**51**	**27**

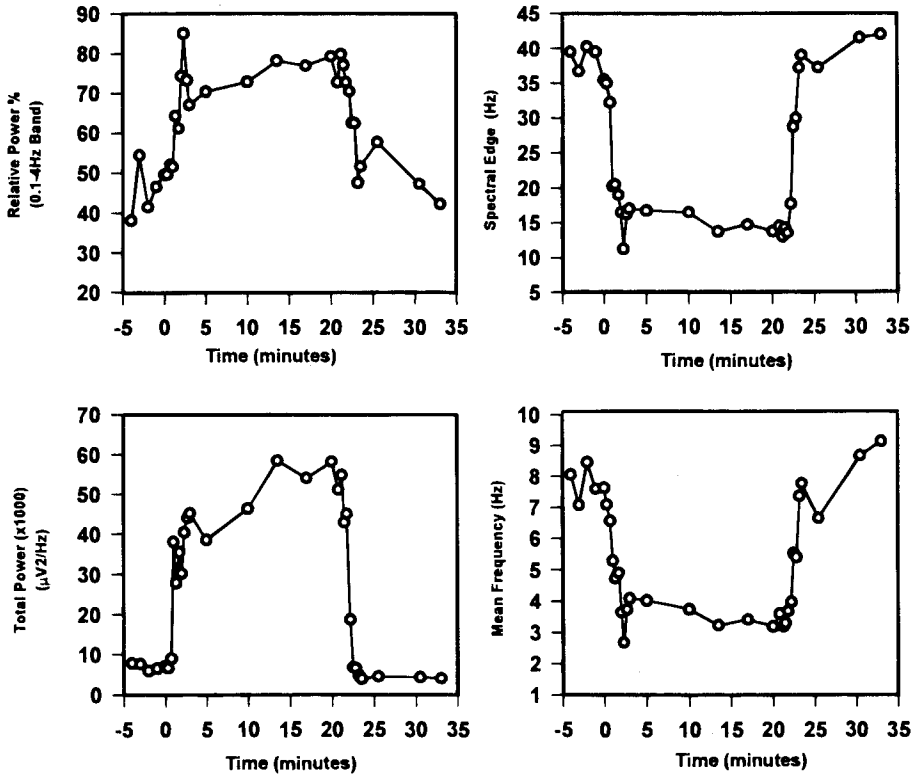

Fig. 3. Fast Fourier transformed EEG profiles following single i.v. infusion of remifentanil to a representative animal.

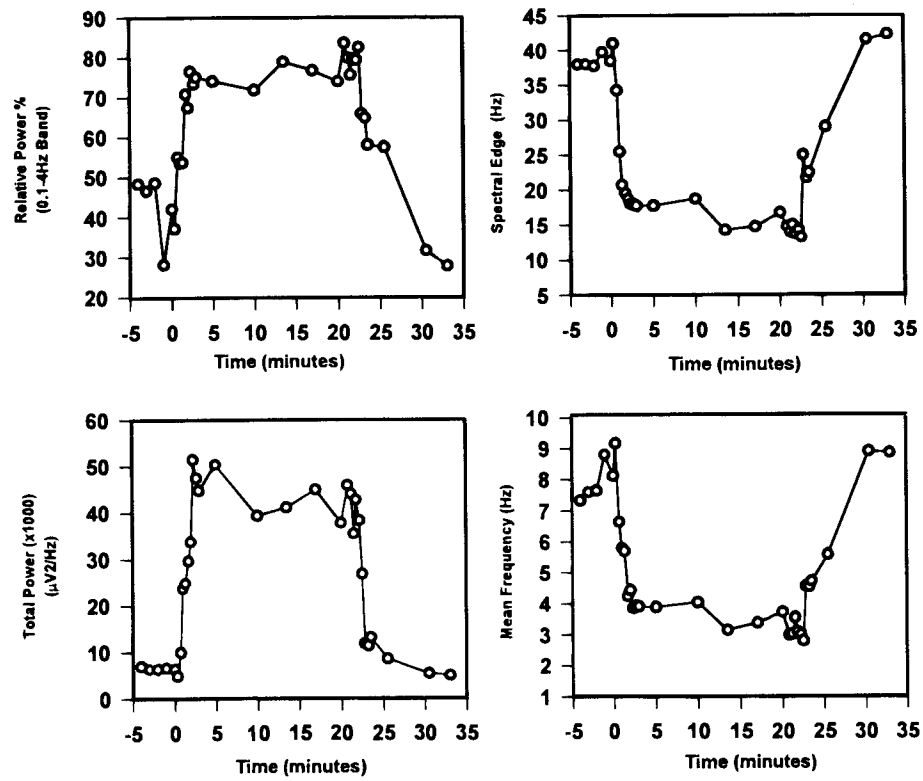

Fig. 4. Fast Fourier transformed EEG profiles following single i.v. infusion of remifentanil and esmolol to a representative animal.

Table II. The Pharmacodynamics of REMI After Administration of REMI Alone and in Combination With ES

	Treatment I				Treatment II			
	REMI (15 μg/min/kg)				REMI & ES (15 μg/min/kg+600μg/min/kg)			
Rat	E_0 (Hz)	EC_{50} (ng/ml)	E_{max} (Hz)	$t_{1/2}k_{e0}$ (min)	E_0 (Hz)	EC_{50} (ng/ml)	E_{amx} (Hz)	$t_{1/2}k_{e0}$ (min)
42	30	25	12	3.24	39	33	21	2.66
44	40	28	20	2.07	42	20	18	2.42
48	40	56	24	1.43	36	13	25	1.54
51	38	31	24	1.57	41	25	25	2.58
52	36	25	27	1.38	40	36	16	2.45
53	40	28	11	1.39	39	26	15	2.17
54	40	41	13	1.41	43	37	17	2.07
56	41	20	17	1.69	38	19	11	1.60
Mean	**38**	**32**	**18**	**1.77**	**40**	**26**	**19**	**2.19**
S.D.	**3.8**	**12**	**6.0**	**0.64**	**2.4**	**8.6**	**4.8**	**0.43**
CV%	**10**	**36**	**33**	**36**	**6**	**33**	**26**	**20**

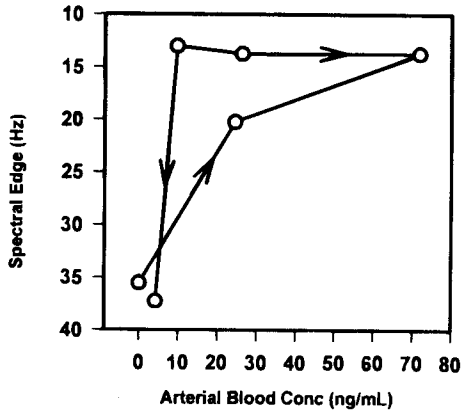

Fig. 5. Remifentanil blood concentration vs. spectral edge hysteresis loop in a representative animal.

two treatments, however, was negligible. Gamma averaged 13 (±10) in treatment I and 12 (±11) in treatment II.

DISCUSSION

This study evaluated the possible drug-drug interaction between remifentanil and esmolol in the rat. Remifentanil was administered alone and in combination with esmolol to male Sprague-Dawley rats in a randomized two-way cross-over design. The remifentanil infusion rate (15 μg/kg/min) was selected after a pilot study with EEG monitoring showed that maximum effect, manifested by significant delta-wave activity, was achieved with this infusion rate. Higher doses resulted in significant seizure activity and cardiovascular instability which confounded the accurate determination of EEG parameters.

The selection of the esmolol dose was guided by previous animal studies (16,27). Esmolol is metabolized very rapidly by blood and tissue non-specific esterases with widely differing activities among various species. Quon and Stampfli (28) and Quon *et al.* (29) evaluated the rate of esmolol hydrolysis in the blood of humans, dogs, guinea pigs and rats. Esterase activity was greatest in guinea pig and rat blood, followed to a much lesser extent by dog and human blood. The *in-vitro* half-lives of esmolol in guinea pig and rat whole blood were less than one minute and 2.27 minutes, respectively. In contrast, the half-lives in dog and human whole blood were 12.5 and 27.2 minutes, respectively. Additionally, the location of the esterase activity was also species dependent. For example, in guinea pig and rat blood it was localized mainly in the plasma while in dog and human blood the esterase activity was localized in the cytosol of red blood cells (15,28).

Sodium fluoride (NaF) appears to inhibit at least some of the blood esterases involved in the metabolism of esmolol. The *in-vitro* addition of 0.7 M NaF to human, dog and rat whole blood increased the half-life of esmolol by 20 fold or greater. The same concentration of NaF added to guinea pig whole blood resulted in a 10–20 fold increase in half-life (28). NaF, on the other hand, had little effect on the half-life of remifentanil in human blood. This suggests that remifentanil and esmolol maybe metabolized by different enzyme systems.

The effect of remifentanil on esmolol pharmacokinetics was not evaluated in this study. To determine esmolol levels from treatment II (remifentanil/esmolol combination), it would have been necessary to split blood samples upon collection since the assay (GC-MS) could only detect one drug at a time. Our experience has been that any sample handling prior to

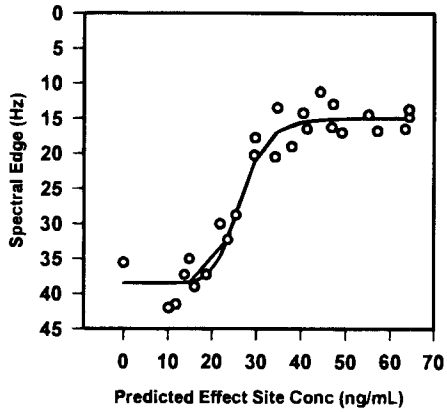

Fig. 6. Remifentanil predicted effect site concentration vs. spectral edge (collapsed hysteresis) loop in a representative animal.

protein precipitation with acetonitrile causes a measurable loss of remifentanil due to rapid metabolism by esterases in rat blood. A similar loss would have been expected for esmolol. Under such circumstances, overestimation of clearance for one or both drugs could be possible. Therefore, a decision was made to limit the study to the evaluation of remifentanil pharmacokinetics and pharmacodynamics after administration of remifentanil alone and in combination with esmolol.

The disposition of remifentanil in this study was best described by a one compartment model. Goodness of fit was based on visual inspection, final residual sum of squares and random distribution of residuals. Total blood volume obtained from each rat was 1.5 ml per treatment while 2 (±0.2) ml of drug solution in normal saline were infused per treatment. Samples were collected from the femoral artery cannula. Remifentanil concentrations are significantly higher in arterial blood when compared to venous blood (unpublished data). This is consistent with the fact that remifentanil is metabolized by tissue as well as blood esterases.

Previous studies in dog and man have described the disposition of remifentanil using two-or three-compartment models (5–7). Given the extremely fast elimination of remifentanil in the rat, it is likely the initial disposition phase is too rapid to measure accurately. The terminal half-life was estimated to be between 30 and 45 seconds in both treatments. In comparison, the half-life is about 6 min in dogs (Glaxo Report UPC/94/016, unpublished) and 10 to 48 min in man (2,5,7). In our study, clearance in rats was estimated to be about 7 times greater when compared to clearance in man (290 vs. 41.2 ml/min/kg, respectively) (6).

No significant differences were observed ($p < 0.05$) for pharmacokinetic parameters between the two treatments. Mean clearance was estimated to be 287 (±73) ml/min/kg in treatment I (remifentanil alone), which is the same clearance of 289 (±148) ml/min/kg found in treatment II (remifentanil plus esmolol). The terminal half-life was 0.71 (±0.15) min in treatment I and 0.67 (±0.18) min in treatment II. A significant PK drug interaction between remifentanil and esmolol would have altered the clearance of remifentanil and/or its volume of distribution. No significant changes in Vd were observed: 286 (±49) ml/kg for treatment I vs. 248 (±40) ml/kg for treatment II. Therefore, we conclude at the doses tested, the co-administration of esmolol does not significantly alter the pharmacokinetics of remifentanil in the rat model.

Pharmacologically, remifentanil had a very rapid onset and a short duration of action. Within about 30 seconds of start of infusion, the rats began to exhibit behavioral stupor. This was followed by significant muscle rigidity and respiratory depression. The intensity of the latter two effects began to decline within a few minutes of start of infusion, and the rats maintained spontaneous respiration. Significant changes in the EEG were observed within the first minute of infusion. As the rats went from an alert to a stuporous state (< 1 min) EEG changed from high frequency/low amplitude to low frequency/high amplitude, culminating in significant delta wave activity at maximum effect. Corneal reflex and tail pinch withdrawal were absent within 1–2 minutes of the start of infusion. Most rats, however, responded to sudden noises throughout the infusion period (20 min) and it was necessary to keep the experiment setting as quiet as possible. Once the infusion ended, changes in EEG patterns (decrease in amplitude and increase in frequency) were observed within 2–3 min. Recovery to baseline occurred within 4 to 8 min after end of infusion.

Raw EEG data were analyzed off-line using Fast-Fourier transformation. Total power, relative power, mean frequency and spectral edge (97%) were determined for each rat. PK-PD modeling, however, was limited to the spectral edge parameter. Studies with remifentanil and other opioids have demonstrated the usefulness of EEG spectral edge as a pharmacodynamic endpoint (7,25). The spectral edge is a univariate parameter which identifies the frequency below which 97% (95% or other) of EEG power is found (7). It serves as a method of EEG data reduction.

In this study of the pharmacodynamic parameters of remifentanil after administration alone (treatment I), baseline (E_0) was estimated to be 38 (±3.8) Hz; E_{max} was 18 (±6) Hz; IC_{50} was 32 (±12) ng/ml; and $t_{1/2}k_{e0}$ was 1.77 (±0.64) min. The relatively short $t_{1/2}k_{e0}$ indicates that remifentanil equilibrates rapidly into the effect compartment (rapid onset), which is consistent with observations made during this study. There are no published studies of the effect of remifentanil on rat EEG using spectral edge as a pharmacodynamic endpoint. The effects of remifentanil (3μg/kg/min) and alfentanil on the EEG were contrasted in healthy male volunteers (7). Using a spectral edge of 95%, their estimates of remifentanil pharmacodynamic parameters were as follows: baseline (E_0) was 19 (±2.9) Hz; E_{max} was 13.8 (±3.8) Hz; IC_{50} was 19.9 (±5.2) ng/ml; and $t_{1/2}k_{e0}$ was 1.6 min. In light of the different spectral edge frequencies used (97% vs. 95%) the pharmacodynamic values obtained in our study in rats are not very different from the values previously reported (7) in this clinical study. This suggests that rats can serve as a useful model for the EEG effects of opioids in man.

When remifentanil blood concentration was related to EEG spectral edge, counter clockwise hysteresis was observed. This indicates that changes in spectral edge lag behind changes in the concentration of remifentanil in the blood. In other words, spectral edge is not directly related to blood levels. The use of a hypothetical effect compartment in the pharmacodynamic model eliminates the temporal dissociation between drug concentration and effect, resulting in direct correlation between the two.

Comparison of the pharmacodynamic parameters between treatments I and II showed no significant differences ($p < 0.05$). Relative potency (IC_{50}), maximum effect (E_{max}) and equilibration half-time ($t_{1/2}k_{e0}$) were the same regardless whether remifentanil was administered alone or in combination with esmolol. This leads us to conclude that at the doses tested, co-administration of esmolol does not influence the pharmacodynamics of remifentanil in the rat.

In summary, we conclude that remifentanil has an extremely short (less than 1 min) half-life in the rat. The disposition of the drug is best described by a one-compartment model. The equilibration half-life ($t_{1/2}k_{e0}$) into the effect compartment was also very short, indicating a rapid onset. Co-administration of esmolol at the doses tested does not significantly alter the pharmacokinetics or the pharmacodynamics of remifentanil in the rat.

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REFERENCES

1. A. H. Amin, A. M. Sopchak, B. F. Esposito, L. G. Henson, R. L. Batenhorst, A. W. Fox, and E. M. Camporesi. *J. Pharmacol. Exp. Therap.* **274**:34–39 (1995).
2. T. D. Egan, H. J. Lemmens, P. Fiset, D. J. Hermann, K. T. Muir, D. R. Stansky, and S. L. Shafer. L. *Anesthesiology* **79**:881–892 (1993).
3. J. F. Hoke, K. T. Muir, P. S. A. Glass, D. Shlugman, C. E. Rosow, C. E. , M. Dershwitz, and P. Michalowski. *Clin. Pharm. Ther.* **57**:148 (1995).
4. M. Dershwitz, J. F. Hoke, C. E. Rosow, P. Michalowski, P. M. Connors, K. T. Muir, and J. L. Dienstag. *Anesthesiology* **84**:812–820 (1996).
5. C. L. Westmoreland, J. F. Hoke, P. S. Sebel, C. C. Hug, and K. T. Muir. *Anesthesiology* **79**:893–903 (1993).
6. P. S. A. Glass, D. Hardman, Y. Kamiyama, T. J. Quill, G. Marton, K. H. Donn, C. M. Grosse, and D. Hermann. *Anesth. Analg.* **77**:1031–1040 (1993).
7. T. D. Egan, C. F. Minto, D. J. Hermann, J. Barr, K. T. Muir, and S. L. Shafer, S. L. *Anesthesiology* **84**:821–833 (1996).
8. S. K. Pandit and C. R. Green.*International Anesth. Clinics* **32**:55–79 (1994).
9. S. L. Shafer and J. R. Varvel. *Anesthesiology.* **74**:53–63 (1991).
10. J. C. Scott, K. V. Ponganis, and D. R. Stanski. *Anesthesiology.* **62**:234–241 (1985).
11. J. C. Scott, J. E. Cooke, and D. R. Stanski. *Anesthesiology.* **74**:34–42 (1991).
12. P. S. Sebel, J. G. Bovill, A. Wauquier, and P. Rog. *Anesthesiology.* **55**:203–211 (1981).
13. W. E. Hoffman, F. Cunningham, M. K. James, V. L. Baughman, and R. F. Albrecht. *Anesthesiology* **79**:107–113 (1993).
14. F. E. Cunningham, W. E. Hoffman, and V. L. Baughman. *Anesthesiology* **79**:A712 (1993).
15. R. D. Reynolds, R. J. Gorczynski, and C. Y. Quon. *J. Clin. Pharmacol.* **26**(suppl A):A3–A14, (1986).
16. C. Y. Quon and R. J. Gorczynski. *J. Pharmacol. Exp. Ther.* **237**:912–918 (1986).
17. C. M. Grosse; I. M. Davis, R. F. Arrendale, J. Jersey, and J. Amin. *J. Pharm. Biomed. Anal.* **12**:195–203 (1993).
18. N. Khazan. *Methods in Narcotics Research,* ed. by S. Ehrenpreis and A. Neidle, pp. 173–215, Marcel Dekker Inc., New York, 1975.
19. R. J. Lozito, S. La Marca, R. W. Dunn, and T. P. Jerussi. *Life Sci.* **55**:1337–1342 (1994).
20. G. E. Schumacher and J. T. Barr. *Clin. Pharm.* **3**:525–530 (1984).
21. L. B. Sheiner, S. Beal, B. Rosenberg, and V. Marathe. *Clin. Pharmacol. Ther.* **26**:294–305 (1979).
22. L. B. Sheiner and S. L. Beal. *J. Pharm. Sci.* **71**:1344–1348 (1982).
23. D. Z. D'Argenio and A. Schumitsky. *Biomedical Simulations Resource,* University of Southern California, Los Angeles, CA (1992).
24. S. H. Haidar, J. E. Moreton, Z. Liang, J. F. Hoke, K. T. Muir, and N. D. Eddington. *J. Pharm. Sci.* (in press)
25. J. C. Scott, K. V. Ponganis, and D. R. Stanski. *Anesthesiology.* **62**:234–241 (1985).
26. N. H. G. Holford and L. B. Sheiner. *Clin. Pharmacokinet.* **6**:429–453 (1981).
27. R. J. Gorczynski, J. Shaffer, and R. J. Lee.*J. Cardiovasc. Pharmacol.* **5**:668–677 (1983).
28. C. Y. Quon and H. F. Stampfli. *Drug Metab. Dispos.* **13**:420–424 (1985).
29. C. Y. Quon, K. Mai, G. Patil, and H. f. Stampfli. *Drug Metab. Dispos.* **16**:425–428 (1988).