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Effects of Remifentanyl, a New Short-acting Opioid, on Cerebral Blood Flow, Brain Electrical Activity, and Intracranial Pressure in Dogs Anesthetized with Isoflurane and Nitrous Oxide

William E. Hoffman, Ph.D.,* Francesca Cunningham, Pharm.D.,† Michael K. James, Ph.D.,‡
Verna L. Baughman, M.D.,* Ronald F. Albrecht, M.D.§

Background: A new short-acting opioid, remifentanyl, is metabolized by esterase activity in blood and tissue. It is important to know whether remifentanyl may decrease the time to recovery of opioid-induced cardiovascular and cerebral effects compared to that of other short-acting agents such as alfentanil.

Methods: Baseline measures were made during 1% end-tidal isoflurane and 50% N₂O in oxygen in dogs. Approximately equipotent low- and high-dose remifentanyl (0.5 and 1.0 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) or alfentanil (1.6 and 3.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) were infused for 30 min each (total infusion time 60 min) followed by a 30-min recovery period. Blood pressure, heart rate, and intracranial pressure were recorded continuously. Electroencephalogram measurements were made using aperiodic analysis, and regional cerebral blood flow using radioactive microspheres.

Results: Both remifentanyl and alfentanil decreased blood pressure and heart rate 25–30%. Cortex, hippocampus, and caudate blood flow decreased 40–50% during opioid infusion, but flow changes in lower brain regions were modest or absent. The electroencephalogram showed a shift from low-amplitude, high-frequency activity during baseline to high-amplitude, low-frequency activity during opioid infusion. During a 30-min recovery period, heart rate, electroencephalogram, and regional cerebral blood flow recovered to baseline levels in remifentanyl- but not in alfentanil-treated dogs. Blood pressure and intracranial pressure decreased during opioid infusion and increased above baseline levels during the recovery period in remifentanyl-treated dogs.

Conclusions: These results show that the cardiovascular and cerebral effects of remifentanyl and alfentanil are similar but that recovery of these parameters occurs sooner following remifentanyl. (Key words: Anesthetics, intravenous: alfentanil; remifentanyl. Brain: blood flow; electroencephalogram.)

CURRENTLY available short-acting opioids, such as alfentanil, depend on redistribution of the drug from the brain to other body tissues and secondary elimination due to either metabolism or excretion. The secondary elimination for alfentanil has a half-life ranging from 70 to 90 min.¹ A new short-acting opioid, remifentanyl (3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-amino]1-piperidine]propanoic acid, methyl ester, hydrochloride) (Glaxo Inc. Research Institute, Research Triangle Park, NC), contains an ester in the pendant chain of the piperidine nitrogen that is susceptible to inactivation by blood and tissue esterases.² According to studies in dogs and rats, the plasma half-life of remifentanyl is 10 min or shorter.³ Previous studies have shown that remifentanyl has analgesic and cardiovascular effects similar to those of alfentanil but with a shorter duration of action.³ The purpose of these experiments was to evaluate the time to onset of response and recovery and the magnitude of response of electroencephalogram (EEG) and regional cerebral blood flow (rCBF) observed with equipotent doses of remifentanyl and alfentanil.

Materials and Methods

These experiments were performed after approval from the Institutional Animal Care Committee. In 25 male hounds (22–31 kg), anesthesia was induced with intravenous injection of thiamylal sodium (35 mg/kg) and was maintained with 2% end-tidal isoflurane and 50% N₂O in oxygen after tracheal intubation. Paralysis was produced by intravenous infusion of vecuronium

* Associate Professor, Anesthesiology Department.

† Assistant Professor, Anesthesiology Department.

‡ Group Leader, Department of Pharmacology.

§ Professor and Chairman, Anesthesiology Department.

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Address reprint requests to Dr. Hoffman: Anesthesiology Department, University of Illinois Hospital, 1740 West Taylor, Chicago, Illinois 60612.

($1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). Body temperature was measured using a rectal thermistor probe and maintained at 39°C using a heating pad as indicated by the Merck Veterinary Manual. Heart rate was recorded with standard electrocardiography. Both femoral arteries and veins were catheterized for continuous measurement of mean arterial blood pressure, drug administration, and arterial blood samples. A thoracotomy was performed, and a left atrial catheter was placed for microsphere injections to measure rCBF.

The left zygomatic arch was resected and the skull exposed for measurement of left middle cerebral artery blood flow velocity. A 2-MHz ultrasonic probe was placed on the left temporal bone and fixed in a frame. Middle cerebral artery blood flow velocity was measured continuously using a Medasonics Transcranial Doppler (Mountain View, CA). A Yellow Springs thermistor probe (Yellow Springs, OH) was inserted between the skull and a muscle layer as a reference for brain temperature and was maintained at 39°C throughout the study. A burr hole was drilled over the sagittal sinus and a catheter inserted for blood samples. A second burr hole was drilled and a 21-G spinal needle inserted in the lateral ventricle for measurement of intracranial pressure (ICP). These holes were sealed with dental cement. At the completion of surgery, isoflurane was adjusted to 1.0% with 50% N_2O ventilation. The dogs were placed in a prone position with the head above the chest and allowed 90 min to stabilize. Saline was infused intravenously at a rate of $4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ throughout the study for fluid maintenance.

Protocol

The dogs were assigned randomly to one of four groups. Each dog in group 1 received an intravenous saline infusion at a rate of 0.5 ml/min for 30 min and at a rate of 1 ml/min for another 30 min. The infusion was added to the maintenance saline infusion. This was followed by a 30-min recovery period. All dogs in groups 2, 3, and 4 received the same volume infusion rate as dogs in group 1. Group 2 received alfentanil at a rate of $1.6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 30 min followed immediately by a 30-min infusion of $3.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and a 30-min recovery period. The concentration of alfentanil was 70–99 $\mu\text{g}/\text{ml}$, depending on the weight of the dog. In a previous report, $1.6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ has been reported to decrease the minimum alveolar

concentration (MAC) for inhalational anesthesia by 50%.⁴ Group 3 received a 30-min infusion of $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ remifentanil followed by $1.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ of the drug for 30 min and a 30-min recovery period. The concentration of remifentanil was 22–31 $\mu\text{g}/\text{ml}$, depending on the weight of the dog. In previous studies, it was found that $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ remifentanil decreased MAC by 50%, indicating that this was a dose equivalent to $1.6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ alfentanil.⁵ Group 4 received the same infusion of remifentanil as group 3, but blood pressure was maintained at baseline levels by a simultaneous intravenous infusion of phenylephrine at a concentration of 40 $\mu\text{g}/\text{ml}$ and a rate of 0.2–0.5 ml/min.

Arterial blood samples were taken at baseline and at 15 and 30 min during low- and high-dose opioid drug infusion and at 15 and 30 min during the recovery period. Blood concentrations of remifentanil and alfentanil were measured by Glaxo Inc. using high-resolution mass spectrometry selected ion monitoring (HRGC/MS/MIS). The alfentanil blood assay is a validated HRGC/MS/MIS analysis with a calibration range of 1–3,000 ng/ml. It involves a single-step liquid-liquid extraction of whole blood followed by chromatographic cleanup using basic silica gel. Fentanyl is used as a recovery standard in the method. The alfentanil assays were completed at Triangle Laboratories of Atlanta, Inc. (Atlanta, GA). The remifentanil assay uses a capillary HRGC/MS/MIS method for the determination of remifentanil in blood and has been revalidated progressively in response to pharmacokinetic needs. || The method relies on immediate precipitation of blood proteins with acetonitrile to stabilize the drug, followed by liquid-liquid extraction with methylene chloride. Collection tubes were prespiked with tetradeuterated remifentanil as an internal standard to correct for variations in recovery between samples. The quantitation range of the assay was 0.1–250 ng/ml.

In group 3, cerebral autoregulation was tested during $1\text{-}\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ remifentanil infusion with an intravenous injection of 4 $\mu\text{g}/\text{kg}$ phenylephrine. This injection was made at 20 min after the start of the high dose of remifentanil and produced a hypertensive response for approximately 4 min with a peak response at 2–3 min. Changes in cerebral blood flow (CBF) velocity were measured before the phenylephrine injection and at the peak of the hypertensive response, which lasted 4–5 min.

The EEG activity was evaluated bilaterally by aperiodic analysis using a Life Scan (Neurometrics, San

|| Unpublished results. 1992.

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Diego, CA). A squared function of the electrical amplitude determined within the following frequency bands: $\sigma = 0.5\text{--}3.0$ Hz, $\theta = 3.1\text{--}8.0$ Hz, $\alpha = 8.1\text{--}12.0$ Hz, and $\beta = 12.1\text{--}30$ Hz. The fraction of activity of each band in relation to total electrical activity was determined. Data were averaged over 1-min epochs.

Regional Cerebral Blood Flow

Regional cerebral blood flow was measured four times in each dog using ^{57}Co -, ^{113}Sn -, ^{85}Sr -, and ^{46}Sc -labelled 15- μm microspheres (New England Nuclear, Boston, MA). Stock solutions containing 500,000 microspheres/ml were suspended in isotonic saline with 0.05% Tween-80 (New England Nuclear). Microspheres were vortexed for 1 min, and 5 ml was withdrawn (2.5×10^6 microspheres), injected into the left atrium, and flushed in with 5 ml of saline. Starting 10 s before each microsphere injection and continuing for 90 s after the injection, blood was withdrawn from the femoral artery at a rate of 10 ml/min. The injection of microspheres was performed at the end of the equilibration period, at the end of each of the two infusion periods, and at the end of the 30-min recovery period. At the end of the experiment, the dog was killed with Beuthanasia D Special solution (Schering Plough Animal Health Corp, Kenilworth, NJ, 10 ml/dog). The brain was removed, and 1–2 g of tissue was dissected bilaterally from the following regions: cortex, hippocampus, cerebellum, caudate, hypothalamus, brain stem, and medulla. The activity of each microsphere in brain and blood samples was measured using a Nuclear Data 635 multichannel analyzer (Chicago, IL). Cerebral blood flow was calculated according to the formula: $\text{CBF} = (\text{tissue activity/blood activity}) \times (\text{withdrawal rate/tissue weight}) \times 100$.

Arterial and sagittal sinus blood samples were taken after each CBF measurement for determination of blood gas tensions, pH, and oxygen content. Blood gas tensions and pH were measured with an IL 1303 blood gas analyzer (Lexington, ME).

Statistics

Data are reported as mean \pm SD. Results were compared using a general linear model repeated measures analysis of variance (Systat, Evanston, IL). After main effects were tested, differences between dependent variables were analyzed using a matrix design as developed by Systat. Differences in treatments between groups were determined using Tukey's *post hoc* tests. A Pearson product moment correlation was used to de-

termine the relationship between the change in mean blood flow velocity from baseline compared to the change in cortex CBF.

Results

During the study, arterial carbon dioxide tension was maintained at 34–37 mmHg, arterial oxygen tension at approximately 150 mmHg, and pH at 7.4 with no significant difference between groups or treatments ($P > 0.10$). Mean arterial pressure decreased to approximately 90 mmHg during remifentanyl and alfentanil infusion (table 1). At the end of the alfentanil infusion, mean arterial pressure recovered moderately but not completely over the next 30 min. An increase in mean arterial pressure occurred within 10 min of turning off the remifentanyl infusion, which increased above baseline levels. A similar overshoot was observed in remifentanyl-treated dogs in which blood pressure was controlled during the infusion. Heart rate decreased 30% during remifentanyl or alfentanil infusion. This decrease was not affected by blood pressure control. Heart rate recovered completely after the remifentanyl but not alfentanil infusion. Intracranial pressure increased above baseline levels in remifentanyl-treated dogs during the recovery period.

Middle cerebral artery velocity decreased 25–30% during alfentanil and remifentanyl treatment and was not affected by control of blood pressure during remifentanyl infusion. Recovery of mean blood flow velocity was significant following remifentanyl ($P < 0.01$) but not alfentanil treatment. Cerebral autoregulation was tested by phenylephrine-induced hypertension during high-dose remifentanyl infusion in group 3. Phenylephrine (4 $\mu\text{g}/\text{kg}$) increased blood pressure from 96 ± 16 mmHg to 120 ± 21 mmHg ($P < 0.01$). Mean blood flow velocity did not change (27 ± 4 cm/s before, 26 ± 4 cm/s with phenylephrine; $P > 0.10$), indicating that autoregulation was intact.

In sham-treated dogs, rCBF did not change from baseline during the four control measures (table 2). Cerebral blood flow decreased in forebrain but not hindbrain regions during alfentanil infusion. No significant recovery of CBF was observed after alfentanil treatment. Remifentanyl decreased forebrain blood flow, and modest decreases also were noted in hindbrain blood flow. Decreases in CBF were not different between dogs with and without blood pressure control during remifentanyl infusion. Cerebral blood flow returned to baseline levels at the end of the recovery period following remifentanyl treatment. There was a significant

Table 1. Mean Arterial Pressure (MAP), Intracranial Pressure (ICP), Heart Rate (HR), and Mean Middle Cerebral Artery Blood Flow Velocity (V_m) during Drug Treatment

Group	Treatment	n	MAP (mmHg)	ICP (mmHg)	HR (min/L)	V_m (cm/s)
Sham	Baseline	5	123 ± 8	21 ± 6	179 ± 35	38 ± 8
	Sham (30 min)		124 ± 10	19 ± 4	179 ± 35	36 ± 8
	Sham (60 min)		121 ± 12	19 ± 7	178 ± 35	36 ± 8
	Sham (90 min)		120 ± 13	19 ± 8	179 ± 37	35 ± 11
Alfentanil	Baseline	7	125 ± 13	16 ± 7	170 ± 30	47 ± 7
	Low dose		94 ± 20*†	11 ± 4*†	120 ± 27*†	31 ± 9†
	High dose		93 ± 24*†	12 ± 4†	110 ± 24*†	26 ± 7†
	Recovery		107 ± 19†	16 ± 7	134 ± 27*†	35 ± 10
Remifentanil	Baseline	7	135 ± 18	23 ± 11	159 ± 12	44 ± 8
	Low dose		97 ± 13†	14 ± 6†	108 ± 12*†	26 ± 4†
	High dose		101 ± 15†	21 ± 9	102 ± 21*†	26 ± 5†
	Recovery		145 ± 19*	28 ± 10†	174 ± 19	40 ± 4
Remifentanil with phenylephrine	Baseline	5	125 ± 9	17 ± 4	159 ± 11	42 ± 12
	Low dose		126 ± 15	12 ± 2	123 ± 10*†	26 ± 3†
	High dose		124 ± 10	15 ± 4	118 ± 10*†	26 ± 2†
	Recovery		140 ± 2*†	24 ± 6†	163 ± 12	41 ± 10

Values are mean ± SD.

* $P < 0.05$ versus sham at same treatment time.

† $P < 0.05$ versus baseline.

correlation between the change in mean blood flow velocity from baseline and the change in cortex CBF, analyzed over all treatments and all dogs ($r = 0.52$, $P < 0.05$).

During baseline measurements, the fraction of EEG activity that was β activity was high and the fraction that was σ activity was low. This did not change in sham-treated dogs (group 1; fig. 1). Remifentanil and

alfentanil infusion increased the σ fraction and decreased the β fraction. These changes were reversed in remifentanil-treated dogs 15–20 min after the end of the infusion. These effects were not altered by blood pressure control in remifentanil-treated dogs. No reversal of alfentanil-induced EEG changes was observed during the 30-min recovery period.

Blood concentrations of remifentanil and alfentanil

Table 2. Regional Cerebral Blood Flow during Drug Treatment

Group	Treatment	n	Blood Flow ($\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$)						
			Cortex	Hippocampus	Cerebellum	Caudate	Hypothalamus	Brainstem	Medulla
Sham	Baseline	5	156 ± 82	107 ± 65	109 ± 70	128 ± 61	81 ± 57	48 ± 26	56 ± 23
	Sham (30 min)		150 ± 90	124 ± 42	105 ± 40	136 ± 39	86 ± 30	49 ± 19	61 ± 16
	Sham (60 min)		148 ± 100	141 ± 94	120 ± 64	138 ± 47	101 ± 58	58 ± 29	70 ± 30
	Sham (90 min)		144 ± 114	119 ± 76	113 ± 50	132 ± 57	89 ± 48	58 ± 25	72 ± 29
Alfentanil	Baseline	7	141 ± 51	146 ± 65	89 ± 18	131 ± 57	71 ± 31	34 ± 13	61 ± 24
	Low dose		86 ± 20*	79 ± 21*	85 ± 22	73 ± 19*	62 ± 17	32 ± 10	54 ± 12
	High dose		79 ± 14*	79 ± 21*	80 ± 11	71 ± 15*	62 ± 10	31 ± 10	54 ± 14
	Recovery		83 ± 27*	73 ± 31*	85 ± 27	76 ± 40*	62 ± 19	35 ± 16	54 ± 15
Remifentanil	Baseline	7	154 ± 62	125 ± 45	98 ± 31	159 ± 80	78 ± 19	52 ± 15	67 ± 11
	Low dose		74 ± 17*	72 ± 26*	74 ± 21	73 ± 22*	55 ± 11*	34 ± 6*	47 ± 9*
	High dose		78 ± 16*	78 ± 24*	77 ± 15	75 ± 11*	61 ± 13	39 ± 8	51 ± 8
	Recovery		140 ± 46	102 ± 14	80 ± 16	142 ± 36	73 ± 19	44 ± 9	57 ± 14
Remifentanil with phenylephrine	Baseline	5	167 ± 62	153 ± 100	93 ± 51	179 ± 132	90 ± 42	42 ± 23	78 ± 47
	Low dose		68 ± 21*	60 ± 20*	59 ± 14	71 ± 59*	47 ± 13*	30 ± 13	42 ± 9
	High dose		79 ± 21*	77 ± 34*	67 ± 17	75 ± 12*	54 ± 13	39 ± 10	49 ± 12
	Recovery		152 ± 55	112 ± 48	118 ± 64	185 ± 70	93 ± 44	54 ± 14	70 ± 23

* $P < 0.05$ versus baseline within each group.

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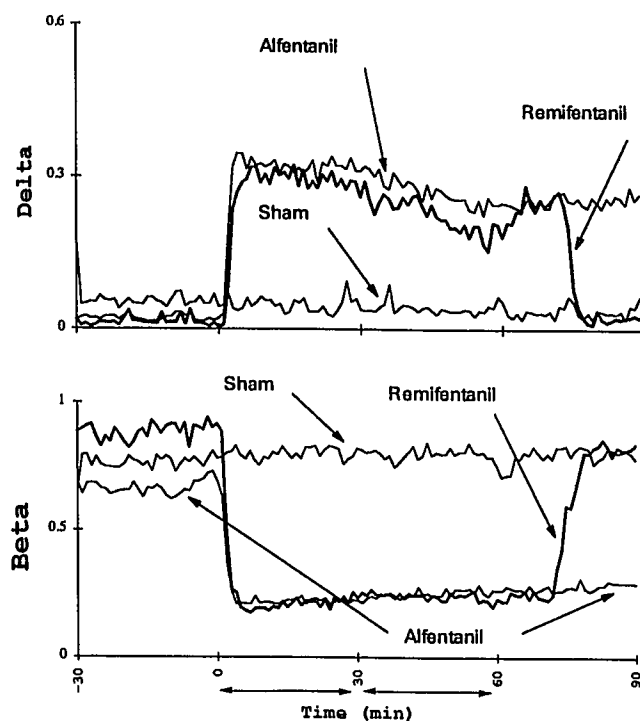


Fig. 1. σ and β fraction of brain electrical activity during opioid administration. The time line indicates the periods of low- and high-dose drug infusion. Time 0–30 min represents the start of low-dose opioid administration, time 30–60 represents the start of high-dose opioid, and time 60–90 represents the recovery period. Each data line represents an average of all animals within each treatment group. Group 4 (not shown) was similar to remifentanil (group 3). σ fraction was increased and β fraction was decreased by opioid infusion ($P < 0.01$) and recovered in remifentanil- but not alfentanil-treated dogs. Under baseline conditions, the standard deviation of the σ fraction was 0.01–0.06. During opioid treatment, the standard deviation increased to 0.09–0.14. The standard deviation of the β fraction ranged between 0.20 and 0.28 under baseline conditions in all groups. During opioid treatment, the standard deviation of the fraction decreased to 0.05–0.10.

(fig. 2) increased in a stepwise manner during low- and high-dose drug infusion. Measures made at 15 and 30 min of low- and high-dose drug infusion suggested that steady-state plasma concentrations were produced more quickly with remifentanil compared to alfentanil. Remifentanil plasma concentrations were 5% above baseline levels at 15 min of recovery and were not different from baseline at 30 min. Alfentanil blood concentrations were 30% above baseline levels at 15 min and 20% above baseline at 30 min of recovery.

James MK, Vuong A, Grizzle MK, Schuster SV, Shaffer JE: Hemodynamic effects of G187084B, an ultra-short-acting μ -opioid analgesic, in anesthetized dogs. *J Pharmacol Exp Ther* 263: 84–91, 1992.

Discussion

In these studies, remifentanil and alfentanil decreased blood pressure, heart rate, EEG activity, ICP, and CBF to a similar degree. The two drug doses of each, remifentanil and alfentanil, produced changes that were not dose-related, suggesting that they represented a near-maximum response.[#] During a 30-min recovery period, cardiovascular and EEG changes were reversed in remifentanil- but not alfentanil-treated dogs. This supports previous reports that the cardiovascular and analgesic effects of remifentanil are shorter than those associated with alfentanil.^{3,#} The time course of the recovery of blood pressure and heart rate following remifentanil was shorter (5–10 min) compared to the recovery of EEG activity and CBF velocity (15–20 min). This suggests that recovery of CBF is more closely related to neuronal activity than blood pressure during opioid anesthesia. Recovery of cardiovascular parameters and brain function are likely due to decreases in blood and brain-tissue remifentanil concentration, respectively. The different time course of recovery may reflect the metabolism of remifentanil by blood and brain tissue esterases. However, the relationship between brain tissue metabolism of remifentanil, EEG activity, and CBF needs to be examined more specifically.

Two problems with this study may be related. Under baseline conditions, CBF and ICP appear to be elevated. Previous studies have shown that 1.4% isoflurane produces lower CBF than was noted here.^{6,7} However, the addition of nitrous oxide to isoflurane can increase CBF 100%.^{8,9} In a previous study using 1% isoflurane and 50% N_2O , we found similar baseline measures of CBF.¹⁰ We chose a background anesthesia with isoflurane and nitrous oxide because it produced EEG activity similar to that of nitrous oxide alone while providing adequate anesthesia. However, it is likely that isoflurane/nitrous oxide potentiated the cardiovascular and EEG effects of the opioids, producing greater effects than may have occurred in unanesthetized dogs. Cerebral autoregulation was intact in our study, which is consistent with this level of isoflurane administration.⁷ Cerebral blood flow decreased during opioid infusion both with and without blood pressure control using phenylephrine infusion. Phenylephrine has little direct effect on cerebral vasculature,¹¹ indicating that the decrease in rCBF was due to opioid-induced vasoconstriction. The changes in rCBF noted with remifentanil and alfentanil are consistent with a previous study evaluating sufentanil in isoflurane/nitrous oxide-anesthetized dogs.¹⁰

Under baseline conditions, ICP was greater than ex-

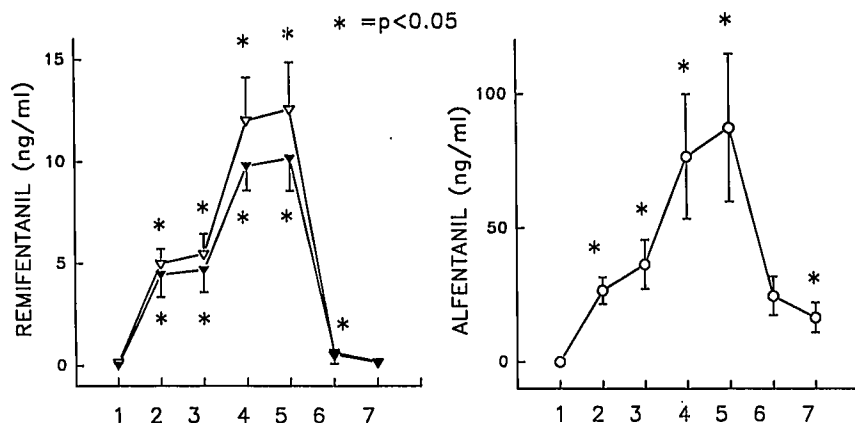


Fig. 2. Blood concentrations of remifentanyl and alfentanil during drug infusion and recovery. The closed and open circles indicate remifentanyl infusion with and without blood pressure control, respectively. Significance indicates difference from baseline. The timed measures are as follows: 1 = baseline; 2 = 15 min low-dose opioid infusion; 3 = 30 min low-dose opioid infusion; 4 = 15 min high-dose opioid infusion; 5 = 30 min high-dose opioid infusion; 6 = 15 min recovery; and 7 = 30 min recovery.

pected. This also may be the result of using nitrous oxide for baseline anesthesia. Nitrous oxide can increase ICP due to increases in CBF^{8,9} and cerebral blood volume.¹² We observed that remifentanyl and alfentanil decreased ICP. This likely is associated with cerebral vasoconstriction and a decrease in cerebral blood volume. In remifentanyl-treated dogs, ICP gradually returned toward baseline levels during drug infusion. The return to baseline is not due to a change in CBF, because these measures were unchanged during remifentanyl infusion. The short time course of the increase in ICP during remifentanyl infusion suggests that it is not due to changes in CSF production.¹³ However, it is possible that increased resistance to CSF reabsorption combined with an increase in CSF production could explain the increase in ICP.¹⁴ Opioid-induced venodilation may be produced by stimulation of presynaptic opioid receptors and inhibition of sympathetic vasoconstriction.¹⁵ This occurs with a slower time course than the arterial vasoconstrictor effects. Cerebral venous dilation or increased CSF volume may decrease intracranial compliance and increase ICP above baseline levels when the cerebral vasoconstrictor effects of the opioid are reversed. The recovery of blood pressure and ICP above baseline levels is likely due to hyperdynamic cardiovascular activity with baseline anesthesia, because these changes have not been observed in barbiturate-anesthetized dogs.[#]

Blood concentrations of remifentanyl and alfentanil indicate a shorter half-life of remifentanyl compared to alfentanil. Infusion rates of alfentanil were 3 times greater than remifentanyl, consistent with the difference in potency between the drugs. However, blood concentrations of alfentanil were 8 times greater than that of remifentanyl after 30 min of the low- and high-dose opioid infusions. Measures of blood opioid concentra-

tion at 15 and 30 min of low- and high-dose drug infusion showed that remifentanyl approached a steady state sooner than did alfentanil. These differences are consistent with a rapid metabolism of remifentanyl and a faster clearance of the opioid compared to alfentanil during the recovery period.

It is possible that the different time course of recovery of responses with alfentanil compared to remifentanyl is due to inappropriate dose comparisons. In guinea pig ileum, remifentanyl is approximately 8 times more potent than alfentanil as an opioid agonist.¹⁶ However, the ED₅₀ for analgesic activity was similar for remifentanyl and alfentanil (3.2 nm/kg and 2.0 nm/kg, respectively).³ We based our doses on a previous report that 1.6 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ alfentanil decreased the MAC for enflurane by 50%⁶ and our preliminary studies that a similar reduction in MAC was observed with a 0.5- $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ remifentanyl infusion.⁶ Our results and a previous report⁴ indicate that we have approached near-maximum responses on blood pressure, heart rate, EEG activity, and CBF with these doses. This suggests that the difference in the recovery of hemodynamics and brain function following remifentanyl and alfentanil are a function of drug metabolism and not of inconsistent dose comparisons.

In conclusion, we observed that the hemodynamic, EEG, and cerebral vascular effects of alfentanil and remifentanyl were similar in isoflurane/nitrous oxide-anesthetized dogs. Recovery of these parameters occurred within 30 min after remifentanyl but not alfentanil treatment. Recovery of blood pressure and heart rate was observed sooner (5–10 min) than recovery of EEG activity and CBF velocity (15–20 min) after cessation of remifentanyl infusion. This suggests that metabolism of the opioid occurs sooner in blood than in brain tissue. Further studies are required to evaluate

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the increase of mean arterial pressure and ICP above baseline during recovery.

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References

1. Bower S, Hull CJ: The comparative pharmacokinetics of fentanyl and alfentanil. *Br J Anaesth* 54:871-877, 1982
2. Feldman PL, James MK, Brackeen MF, Bilotta JM, Schuster SV, Lakey AP, Lutz MW, Johnson MR, Leighton HJ: Design synthesis and pharmacological evaluation of ultrashort- to long-acting opioid analgetics. *J Med Chem* 34:2202-2208, 1991
3. Schuster SV, Bilotta JM, Lutz MK: Analgesic activity of the ultrashort acting opioid, remifentanyl (abstract). *FASEB J* 5:A860, 1991
4. Hall RI, Szlam F, Hug CC Jr: The enflurane sparing effect of alfentanil in dogs. *Anesth Analg* 66:1287-1291, 1987
5. Salmenpera M, Wilson D, Szlam F, Hug CC Jr: Anesthetic potency of the opioid, G187084B, in dogs (abstract). *ANESTHESIOLOGY* 77:A368, 1992
6. Cucchiara RF, Theye RA, Michenfelder JD: The effects of isoflurane on canine cerebral metabolism and blood flow. *ANESTHESIOLOGY* 40:571-574, 1974
7. McPherson RW, Traystman RJ: Effects of isoflurane on cerebral autoregulation in dogs. *ANESTHESIOLOGY* 69:493-499, 1988
8. Hansen TD, Warner DS, Todd MM, Vust LJ: Effects of nitrous oxide and volatile anaesthetics on cerebral blood flow. *Br J Anaesth* 63:290-295, 1989
9. Drummond JC, Scheller MS, Todd MM: The effect of nitrous oxide on cortical cerebral blood flow during anesthesia with halothane and isoflurane, with and without morphine, in the rabbit. *Anesth Analg* 66:1083-1089, 1987
10. Werner C, Hoffman WE, Baughman VL, Albrecht RF, Schulte am Esch J: Effects of sufentanil on cerebral blood flow, cerebral blood flow velocity, and metabolism in dogs. *Anesth Analg* 72:177-181, 1991
11. Sokrab T-EO, Johansson BB: Regional cerebral blood flow in acute hypertension induced by adrenaline, noradrenaline and phenylephrine in the conscious rat. *Acta Physiol Scand* 137:101-105, 1989
12. Archer DP, Labrecque P, Tyler JL, Meyer E, Trop D: Cerebral blood volume is increased in dogs during administration of nitrous oxide or isoflurane. *ANESTHESIOLOGY* 67:642-648, 1987
13. Artru AA: Isoflurane does not increase the rate of CSF production in the dog. *ANESTHESIOLOGY* 60:193-197, 1984
14. Artru AA: Cerebrospinal fluid dynamics, *Clinical Neuroanesthesia*. Edited by Cucchiara RF, Michenfelder JD. New York, Churchill Livingstone, 1990, pp 41-76
15. Kobari M, Gotoh F, Fukuuchi Y, Amano T, Suzuki N, Uematsu D, Obara K, Gogolak I, Saando P: Effects of (D-Met2,Pro5)) enkephalinamide and naloxone on pial vessels in cats. *J Cereb Blood Flow Metab* 5:34-39, 1985
16. James MK, Feldman PL, Schuster SV, Bilotta JM, Brackeen MF, Leighton HJ: Opioid receptor activity of G187084B, a novel ultrashort acting analgesic, in isolated tissues. *J Pharmacol Exp Ther* 259:712-718, 1991