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Continuous Intrathecal Administration of Short-lasting μ Opioids Remifentanil and Alfentanil in the Rat

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Background: **Lipid soluble μ opioids given intrathecally produce a potent, dose-dependent analgesic response, which because of rapid clearance, is of short duration. Such agents delivered by continuous infusion can result in systemic accumulation and significant extraspinally mediated side effects. The effects of intrathecal infusions of two lipid-soluble μ opioids were investigated: remifentanil, an esterase metabolized agent with an inactive metabolite, and alfentanil.**

Methods: **Rats with chronic lumbar intrathecal catheters received intrathecal infusions (in flow rates of 1.0 μl/min and 0.1 μl/min) of remifentanil or alfentanil and were tested for hind paw thermal withdrawal latency, supraspinal side effects (sedation, block of pinna, and corneal responses) and motor impairment. Remifentanil was delivered either in a glycine formulation (R_g) or in a saline vehicle (R_s). Separate studies with the glycine vehicle also were undertaken.**

Results: **At an infusion rate of 0.1 μl/min, remifentanil and alfentanil produced naloxone-reversible, dose-dependent analgesia and supraspinal side effects with the intrathecal ED_{50} (μg/min; 95% confidence interval) for analgesia: R_s = 1.5 (1.2–1.8), R_g = 1.2 (0.7–2.3); alfentanil = 1.5 (1.4–1.6) and for supraspinal side effects: R_s = 1.7 (1.4–1.9); R_g = 1.9 (1.6–2.4); alfentanil = 1.5 (1.4–1.7). There was no difference in potency or time until onset for analgesia at either delivery rate (12–20 min), whereas for supraspinal side effects, 1.0 μl/min resulted in a faster onset for R_g. Recovery of normal thresholds after equianalgesic doses was faster in R_s than alfentanil and for the supraspinal index faster in R_s and R_g groups. R_g, but not R_s or alfentanil, produced a dose-dependent motor impairment after 90 min of intrathecal infusion at a flow rate of 0.1 μl/min. Both glycine in R_g and glycine (matching glycine dose) alone showed parallel time courses for motor impairment and similar intrathecal ED_{50} (6.6 *vs.* 6.4 μg/min over 90 min) for this nonnaloxone reversible effect. Intrathecal bolus administration of the same total dose of glycine showed no significant motor effects.**

Conclusions: **Remifentanil has a rapid onset like alfentanil but shows a faster recovery of action after intrathecal infusion. Despite its rapid clearance, remifentanil induces supraspinal side effects at analgesic effective doses. Moreover, in the current formulation, with glycine, a reversible motor impairment can occur after intrathecal delivery. (Key words: Analgesics: μ opioid: alfentanil; remifentanil. Complications: motor function. Side effects: spinal; supraspinal. Vehicles: glycine.)**

REMIFENTANIL (3-[4-methoxycarbonyl-4[(1-oxopropyl)phenyl-amino] 1-piperidine]] propanic acid, methylester, hydrochloride) a μ-pioid agonist with a similar potency to fentanyl,[1] is rapidly metabolized[2,3] by plasma and tissue esterases to an inactive (<1% the potency) metabolite (GR90291A).[4,‡] Systemic remifentanil in humans displays classic μ-receptor effects, notably analgesia, sedation, muscle rigidity, nausea, and respiratory depression,[5,6] all of which are readily reversed by naloxone.§ In humans, remifentanil is approximately 60-fold more potent than alfentanil‖ based on steady-state blood concentrations.

μ Opioids are commonly used to produce analgesia by either epidural or intrathecal administration. The spinal action of several anilinopiperidines, notably lofentanil, fentanyl, alfentanil, and sufentanil has been previously studied in animal models and in humans.[7,8] Of interest is the relationship between the pharmaco-

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‡ Schuster SV, Bilotta JM, Lutz MK: Analgesic activity of the ultrashort acting remifentanil (abstract). FASEB 1991; 5:A860.

§ Amin HM, Sopchak AM, Esposito BF, Graham CL, Batenhorst RL, Camporesi, EM: Naloxone reversal of depressed ventilatory response to hypoxia during continuous infusion of remifentanil (abstract). ANESTHESIOLOGY 1993; 79:A1203.

‖ Glass PSA, Kapila A, Muir KT, Hermann DJ, Shiraishi M: A model to determine the relative potency of mu opioids: Alfentanil versus remifentanil (abstract). ANESTHESIOLOGY 1993; 79:A378.

kinetics of the opioid and the side effect profile observed with a continuous delivery mode. Agents with high octanol-water coefficients (log P) will show a rapid onset of action because of rapid movement into the tissue, a shorter duration of action because of rapid clearance into the parenchymal vasculature[7,8] and may be less likely to be subject to a supraspinal redistribution because of rapid clearance from the intrathecal space.[9] However, lipid-soluble agents, through higher plasma concentrations, may lead to supraspinal redistribution with concomitant supraspinal side effects.[7,8,10] Remifentanil with a log octanol-water partition coefficient (log P) = 1.25 at *p*H 7.3, will likely show a rapid onset and clearance after spinal delivery, with a time course similar to that of alfentanil, but may be less likely to show a systemic accumulation because of its rapid metabolism in blood, as suggested by previous bolus spinal delivery.[11] Therefore, we sought to examine the action of continuously delivered intrathecal remifentanil and alfentanil with regard to antinociception and supraspinal side effects in a well-defined rodent model.

Materials and Methods

Animal surgery and testing was approved by the institutional animal care committee of the University of California, San Diego. All procedures were performed according to this protocol. Rats (male Sprague Dawley, Harlan Industries, Indianapolis IN) weighing 300–325 g were implanted and thereafter kept in separate cages on a 12 h light/dark cycle with water and food supply provided *ad libitum*. Each rat was implanted with an intrathecal catheter as described later. Animals were randomly assigned to the several treatment groups.

Animal Preparation

The surgical insertion of the intrathecal catheters was performed using a modified version of the techniques as previously described.[12] For insertion, the animals were anesthetized with halothane (2% or 3% in 50% O_2/air). After shaving and preliminary cleaning of the surgical area on the back of the head and neck with alcohol and betadine, the rat was placed in a stereotaxic head holder for insertion of the intrathecal catheter. Intrathecal catheters were made out of polyethylene tubing (PE-10, ID 0.28 mm, OD 0.61 mm) with a small knot for fixation under the skin. Implantation of the intrathecal catheters was performed after incision of the atlantooccipital membrane. The catheter was inserted into the intrathecal space and passed to the rostral edge of the lumbar enlargement, 8.5 cm from the cisterna magna. The catheter external arm was then subcutaneously tunneled and fixed under a skin suture.

After the surgical procedures, a recovery period of at least 5 days was allowed before initiating the injection series. Neurologic status of the animal was assessed after surgery and before testing after flushing the intrathecal catheter with 10 μl normal saline. Animals with impaired motor function or an elevated sensory threshold were killed.

Intrathecal Injection

Animals were connected to a microinjection syringe pump (Harvard pump 22, Harvard Apparatus, South Natick, MA) *via* a length of calibrated PE-50 tubing. Drugs were injected at either a rate of 1.0 μl/min (remifentanil in glycine [R_g], alfentanil) or in a rate of 0.1 μl/min (R_g, alfentanil) or as a control remifentanil without vehicle (R_s) all over 90 min. Before testing for the 0.1 μl/min flow rate, the intrathecal catheter was preloaded with 6.5 μl of the different compounds (calibration verified a volume of 6.5 μl from one end of the PE-10 tubing to the other).

Drugs

Drugs given intrathecally in this study were remifentanil hydrochloride with its vehicle glycine (R_g; MW = 413) remifentanil hydrochloride (R_s; MW = 369), and glycine (MW = 75). These drugs were provided by Glaxo. (Research Triangle Park, NC). Alfentanil hydrochloride (MW = 453) by Janssen (Janssen Pharmaceutica, Titusville, NY). Naloxone hydrochloride (Dupont Pharmaceutical, Wilmington, DE) was given intraperitoneally. All drugs were dissolved in sterile normal saline (0.9% USP). The R_g studies were carried out with solutions prepared from ampules containing 5 mg remifentanil and 15 mg glycine/ampule, the glycine was prepared from ampules containing glycine, 17 mg/ampule (both drugs provided by Glaxo). The remifentanil alone was prepared from the powder. Infusion rates were expressed in micrograms per minute. Doses were prepared in two different concentrations such that the dose per minute was delivered in an infusion rate of 1.0 μl/min and 0.1 μl/min. Control experiments were carried out with the vehicle (normal saline or glycine) delivered intrathecally.

Experimental Design

Typically, rats were used in three to five separate experiments, separated by an interval of 4 or 5 days. Animals were randomized to receive R_g, R_s, alfentanil, glycine, or normal saline (5–8 animals per dose/group). Agonist dose-response curves were obtained for intrathecal infusions of the different drugs. Antagonist response studies were carried out during the plateau with infusion doses that yielded a just maximal effective analgesic dose of the agonist. Naloxone was injected intraperitoneally in a dose of 1 mg/kg body weight (0.2 ml/kg body weight).

Test Measures

For each drug, the following test measures were obtained periodically before and after injection.

Antinociception. The antinociceptive effect was quantified by measuring the latency of withdrawal evoked by exposing the hind paw to a thermal stimulus. To accomplish these studies, unanesthetized rats were placed in methyl methacrylate polymer cages (9 × 22 × 25 cm) on top of a glass plate. The thermal stimulus was maneuvered under the glass to focus the projection bulb on the plantar surface[13,14] (UARDG, Department of Anesthesiology 0818, University of California, San Diego, La Jolla, CA). Initiation of the current to the bulb started a timer. Bulb current and time were automatically terminated when paw elevation was sensed by photodiodes or when an interval of 20 s (cutoff time) had passed. To avoid variations in paw starting temperature, the underglass surface was maintained at 30°C by a feedback-controlled heater fan. The aiming of the focused stimulus was reliably accomplished by a mirror attached to the stimulus, which permitted visualization of the undersurface of the paw. Light beam intensity was monitored by a measurement of bulb current and the stimulus intensity was calibrated daily by assessing the temperature change after 10 s sensed by an underglass thermocouple ($T_{1/2}$ = 0.2 s). After placing the rat in the plastic cages, a 20-min adaptation period was allowed. The first measurement was done on both hind paws, the response latencies averaged and counted as baseline score (time 0). Tests were then made at 5, 10, 15, 20, 30, 40, 60, and 90 min during drug delivery and at 3, 5, 10, 15, and 30 min after the end of the infusion.

Supraspinal Effects. To score the behavioral changes before and during treatment of the animal, a supraspinal effects index was employed consisting of four different parameters that have been shown to be dose-dependently blocked by opioids.[15] These measured responses included: pinna reflex, cornea reflex (both evoked by light touch of the surface of pinna or cornea with a small piece of PE-10 tubing), evoked movement (startle reflex evoked by tapping on the cage wall), and signs of spontaneous movement (*e.g.*, grooming, chewing, ambulation). Each parameter was scored as: 0 = normal (brisk pinna/cornea reflex response or startle reflex, spontaneous movement within 30 s of the assessed time point; 1 = attenuated (touch with tubing for pinna or cornea reflex or knocking on cage wall does result in a slow reflex behavior, touch or knocking has to be repeated at least twice); or, 2 = response completely absent (no reflex was shown after 3 times of touching cornea or pinna both sides, no startle behavior was displayed after 3 times knocking against cage wall and no spontaneous movement was observed for > than 1 min). To permit a sensitive assessment of the supraspinal effect, a supraspinal effects index was employed, which consisted of summing the individual scores for the four measurements at each time point, permitting a total score of 8. To determine the reliability of the method, 50 rats were observed by two investigators; one blinded as to treatment and the other not blinded. The overall agreement between the two observers was reflected by the significant correlation coefficient (0.91) obtained with the two sets of observations. Tests for the supraspinal side effects were concomitant with antinociceptive testing performed (at 5, 10, 15, 20, 30, 40, 60, and 90 min during drug delivery and at 3, 5, 10, 15, and 30 min after the end of the infusion).

Motor Impairment. Before, during, and after the administration of the different agents, the hind paw of the animal was displaced with a flexible probe and the rat's reaction was scored as 0 = normal (immediately repositioned); 1 = attenuated (more than 1 s for repositioning); or 2 = completely absent (no repositioning of the hind paw). This test was assessed for both hind paws and the scores were compiled (maximal score = 4/animal/time point).

Statistical Analysis

Data are expressed as mean of 5–8 animals and ± SEM. For the time course studies, latencies are indicated in seconds, each time point representing 5–8 animals. For further analysis, the thermal latencies and the sedation index scores were converted to %MPE according to the formula:

$$\% \text{ MPE} = \frac{\text{response latency with drug} - \text{baseline latency} \times 100}{\text{cutoff time (20 s)} - \text{baseline latency}},$$

or

$$\% \text{ MPE} = \frac{\text{supraspinal index with drug} - \text{baseline score} \times 100}{\text{cutoff score (8)} - \text{baseline}}$$

or

$$\% \text{ MPE} = \frac{\text{motor impairment with drug} - \text{baseline score} \times 100}{\text{cutoff score (4)} - \text{baseline}}.$$

Dose-response curves are presented as the %MPE. For all drugs, the dose-response analysis as described by Tallarida and Murray[16] was accomplished. The effective dose for 50% of subjects (ED_{50}) and the 95% confidence intervals were calculated using a least-squares linear regression model, where the log dose values were used. Changes in the thermal latency and supraspinal index with and without antagonist treatment were tested for significance using an unpaired Student's *t* test. Critical values of $P < 0.05$ were considered as statistically significant. Comparison in the time until onset of analgesia or supraspinal side effects and time until recovery until at least 50% MPE were conducted using two-way analysis of variance.

Results

Analgesia

After the initiation of the intrathecal infusion of R_g, R_s, or alfentanil, there was a rapid increase in the thermal escape latency that reached an apparent steady state, as defined by response latencies within 15 min for both remifentanil and alfentanil. These latencies remained essentially stable for the 90-min interval of infusion (fig. 1).

The magnitude of the increase in hind paw response latencies were dependent on the infusion concentration (figs. 2 and 3). The ED_{50} values for the several agents are presented in table 1. As indicated, there was no difference between R_s, R_g, and alfentanil. There was no difference between the peak plateau effects produced with the infusion rates of 0.1 or 1.0 μl/min, *e.g.*, the effects were proportional to the dose in micrograms of opioid delivered per minute.

Glycine alone, at the highest concentration examined, was without an acute effect (*e.g.*, <60 min) on the thermal withdrawal latencies at infusion doses that corresponded to those used in the presence of remifentanil, *e.g.*, 3–9 μg/min did not produce an increase in the thermal escape latency of the animals at intervals up to 60 min. However, at longer intervals there was a dose-dependent increase, up to approximately a 50% MPE of the thermal withdrawal latency (fig. 4). This increased latency was, however, accompanied by an increase in motor impairment (see later).

Supraspinal Index

After the initiation of infusion of remifentanil or alfentanil, there was a rapid onset of depression of behavioral reactivity, as indicated by an increase in the supraspinal index and this depression remained stable during the 90-min infusion interval (fig. 1). The behavioral depression was characterized by reduced spontaneous activity, as well as reduced corneal and pinnae reflexes. The degree of depression was dose-dependent (figs. 2 and 3). The ED_{50} values for the supraspinal index are presented in table 1.

Regarding glycine alone, there were no significant changes in the supraspinal index, during the 90-min infusion interval (fig. 4).

Time of Drug Effect Onset

To determine the effect of different flow rates on the time course for analgesia and supraspinal side effects, the time for each rat to reach and return to the individual 50% MPE for both assessments was determined and the group means were calculated (table 2). Peak plateau effect for analgesia and side effect index were independent of infusion rate. Comparison between R_g and alfentanil revealed an increase of about 30–50%, respectively, in the time to onset in analgesia, when matched by dose for peak analgesic effects within the two different flow rates. However, there appeared to be only a modest increase in the onset for analgesia with remifentanil (flow rate of 0.1 μl/min). Regarding the supraspinal action, the time to onset of side effects was decreased at the faster rate (table 2).

Time until recovery after the standard 90-min infusion revealed a more rapid recovery to 50% effect for analgesia and supraspinal index at the higher flow rate for both R_g and alfentanil (significant for analgesia only for alfentanil; table 2). Supraspinal side effects were decreased to 50% MPE of the index more rapidly in both flow rates for R_g than for alfentanil, whereas an-

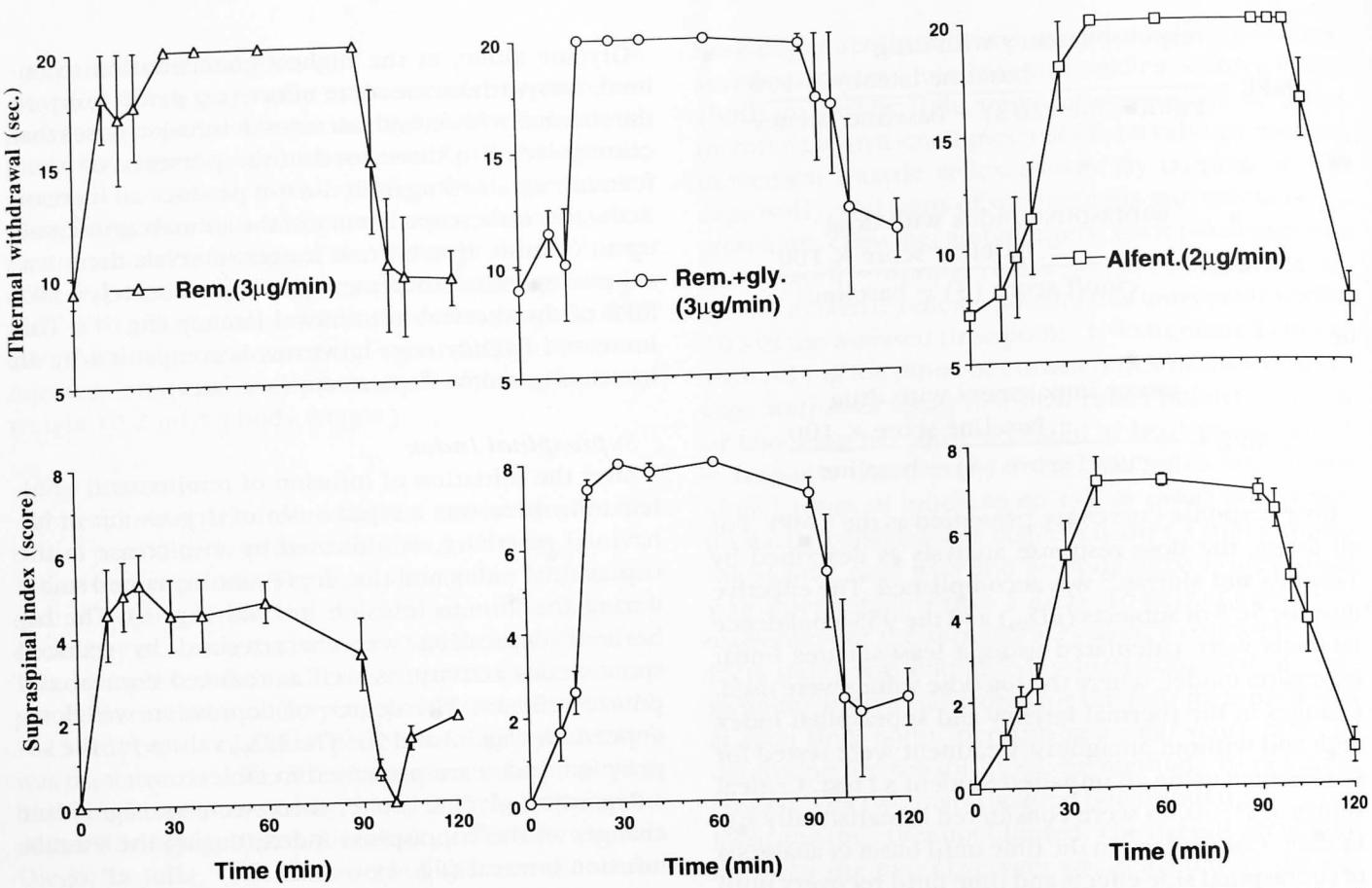

Fig. 1. Time course for the thermal withdrawal latencies (*top*: cutoff 20 s) during (0–90 min) and after (90–120 min) intrathecal infusion (0.1 μl/min) of equianalgesic doses of remifentanil, remifentanil + glycine, and alfentanil and for the supraspinal side effects (*bottom*: supraspinal index cutoff = 8). Each point represents the mean and SEM of 5–8 animals.

algesia only showed a faster decrease for R_g (R_s revealed tendency to a faster recovery, but not significant against R_g as shown in fig. 1) in comparison to alfentanil with the flow rate of 0.1 μl/min (table 2).

Analgesia Versus *Supraspinal Index*

Increasing infusion doses of alfentanil or remifentanil delivered in a rate of 0.1 μl/min or 1.0 μl/min (in both formulations, R_s and R_g) resulted in a dose-dependent increase in the supraspinal index and in the paw withdrawal latency. Plotting the supraspinal index as %MPE *versus* analgesic effect as %MPE revealed a positive correlation between the two variables for both remifentanil and alfentanil, with the slopes of both being positively inflicted (fig. 5). Comparisons of the slope of the regression line demonstrated that the ordering of the slopes for drug delivery at 1.0 μl/min showed a difference ($y = 11.4 + 0.6x$; $r = 0.9$ for remifentanil and $y = 7.6 + 0.9x$ $r = 1$ for alfentanil; $P < 0.05$ Spearman's rank test). However, there was no difference in the higher concentrations with the slower delivery rate of 0.1 μl/min. Comparison of the ED_{50} ratio (ED_{50} supraspinal index/ED_{50} analgesia in μg) revealed the following ratio at 1.0 μl/min: 1.3 (±0.1) for remifentanil (R_g) *versus* 0.9 (±0.3) for alfentanil, whereas at a flow rate of 0.1 μl/min, a tendency for moderately higher ratios for remifentanil also was seen: 1.6 (±0.7) for R_g, 1.2 (±0.2) for R_s and 1 (±0.1) for alfentanil.

Motor Impairment

Over the 90-min infusion period and the subsequent recovery period, neither R_s nor alfentanil had any effect on motor function. In contrast, R_g resulted in a dose-dependent increase in the motor impairment score. Time until onset of the impairment started around 60 min infusion time and peaked just after termination of the 90-min infusion (*e.g.*, 100 min; fig. 4). All animals recovered by 8–12 h after termination of infusion (data

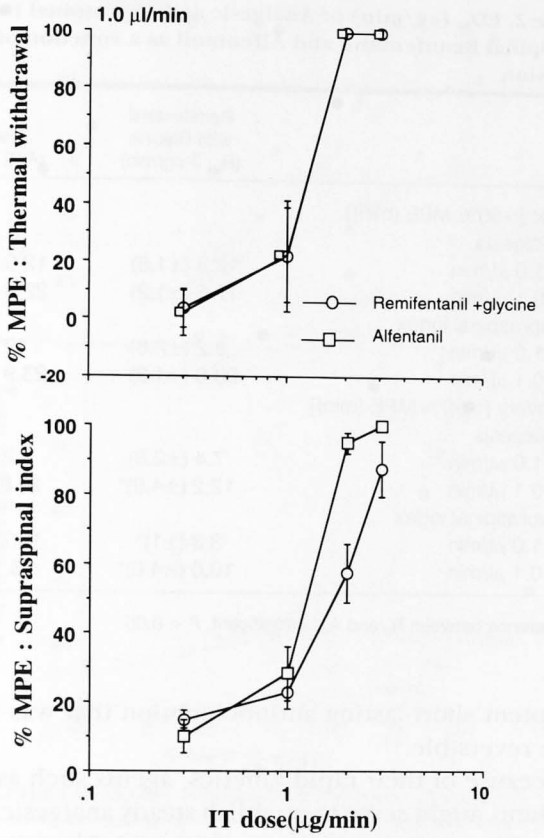

Fig. 2. Dose-response curves in μg/min for analgesia (thermal hind paw withdrawal [*top*]) and supraspinal side effects (supraspinal index) in percentage of maximal possible effect for intrathecal continuous infusions in a volume of 1.0 μl/min of Remifentanil + glycine and alfentanil. Each point represents the mean and SEM of 5–8 animals.

not shown). The ED_{50} for the motor dysfunction assessed at 100 min revealed the ED_{50} to be 6.4 ± 0.7 μg/min (calculated for the total dose over 90 min). There was no difference in the onset or the dose dependency of motor dysfunction between the delivery of glycine alone or R_g (ED_{50} in μg: 6.6 ± 0.9; fig. 6).

Antagonist and Controls

Naloxone (1 mg/kg) administered intraperitoneally resulted in a significant reduction in the spinal and supraspinal effects of the highest administered intrathecal doses of the analgesic and supraspinal index response ($P < 0.05$) of both μ opioids, R_g, R_s, and alfentanil but did not affect saline or glycine animals (fig. 7). Motor impairment in R_g and glycine was not reversed or decreased after intraperitoneal naloxone administration.

Intrathecal continuous infusion of normal saline in a volume of either 1.0 μl/min or 0.1 μl/min did not produce any significant increase in the thermal withdrawal latency or the supraspinal index (fig. 7).

Discussion

Peripheral Clearance and Side Effects

Remifentanil is an intermediate, lipid-soluble μ opioid agonist that is rapidly metabolized to an inactive isomer by plasma and tissue esterases.[2,3] In humans and animals, systemic delivery[4,6] results in a very short-lasting opioid action, consistent with its rapid clearance from the circulation. Continuous delivery has been shown to result in the rapid achievement of steady state whereas termination of delivery results in a rapid reversal of the opioid effect, consistent with a lack of

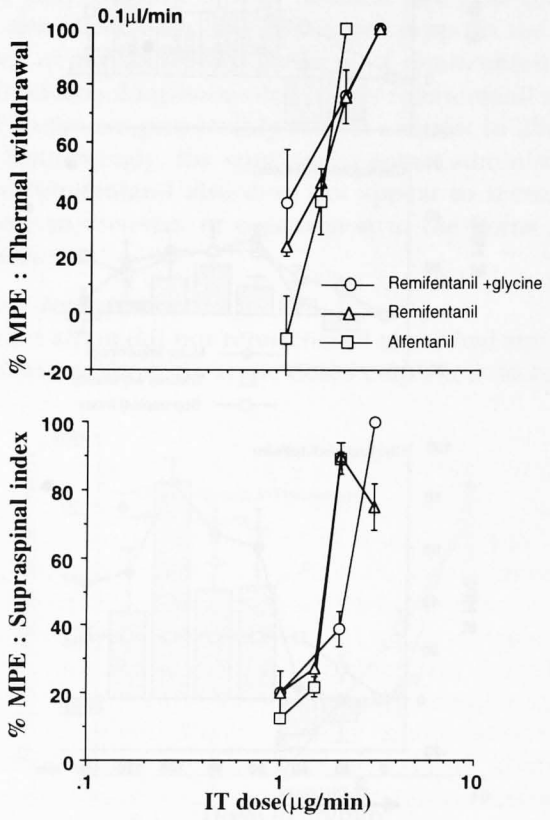

Fig. 3. Dose-response curves in μg/min for analgesia (thermal hind paw withdrawal, upper graph) and supraspinal side effects (supraspinal index) in percentage of maximal possible effect for intrathecal continuous infusions in a volume of 0.1 μl/min of remifentanil + glycine and alfentanil. Each point represents the mean and SEM of 5–8 animals.

Table 1. ED_{50} (μg/min)

	Remifentanil with Glycine (R_g)	Remifentanil (R_s)	Alfentanil (A)
1.0 μl/min			
Analgesia	1.0 (0.8–1.4)	*	1.0 (0.5–2.0)
Supraspinal index	1.3 (0.9–1.7)	*	0.9 (0.6–1.4)
0.1 μl/min			
Analgesia	1.2 (0.7–2.3)	1.4 (1.2–1.8)	1.5 (1.4–1.6)
Supraspinal index	1.9 (1.6–2.4)	1.7 (1.4–1.9)	1.5 (1.4–1.7)

* Studies in the volume rate of 1.0 μl/min were only performed for R_g and A.

accumulation. Recently, we have shown that similar to alfentanil, another intermediately lipid-soluble agent, bolus delivery of intrathecal remifentanil would yield

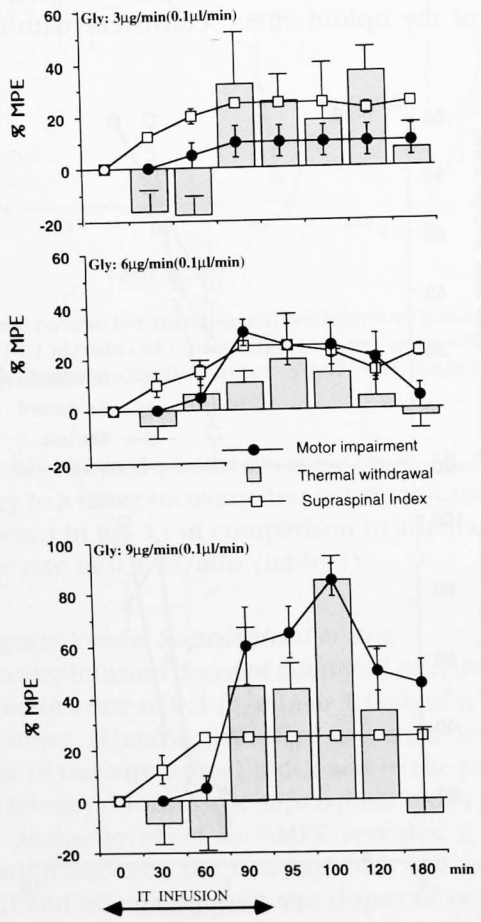

Fig. 4. Graphs show the time course for motor impairment, analgesia (thermal withdrawal latency) and change in supraspinal side effects (supraspinal index) expressed in percentage of maximal possible effect for different doses of intrathecal continuous infusion (0.1 μl/min) of glycine. Each data point represents the mean and SEM of five or six animals.

Table 2. ED_{50} (μg/min) of Analgesic and Supraspinal Index for Spinal Remifentanil and Alfentanil as a Function of Infusion

	Remifentanil with Glycine (R_g, 3 μg/min)	Alfentanil (A, 2 μg/min)
Onset [>50% MPE (min)]		
Analgesia		
1.0 μl/min	12.3 (±1.5)	12.6 (±0.9)
0.1 μl/min	17.5 (±1.2)	22.8 (±3.9)
Supraspinal index		
1.0 μl/min	8.2 (±2.6)	12 (±1.5)
0.1 μl/min	20.0 (±1.8)	23.9 (±2.3)
Recovery [>50% MPE (min)]		
Analgesia		
1.0 μl/min	7.4 (±2.8)	8.2 (±2.2)
0.1 μl/min	12.2 (±4.6)*	19.8 (±2.6)*
Supraspinal index		
1.0 μl/min	3.3 (±1)*	10.7 (±1.8)*
0.1 μl/min	10.0 (±4.0)*	18.1 (3.0)*

* Difference between R_g and A_g is significant, $P < 0.05$.

a potent short-lasting antinociception that was naloxone reversible.[11]

Because of their rapid kinetics, agents such as remifentanil might serve to establish steady analgesic levels through continuous delivery. Lipid-soluble agents that are slowly metabolized such as alfentanil and sufentanil have been employed using continuous epidural delivery but the rapid clearance of these agents from the spinal space into the vasculature has led to the appearance of a significant plasma level that results in the loss of the therapeutic advantage contemplated for spinally delivered agents, *i.e.,* significant supraspinal side effects are noted. Because of its rapid metabolism through plasma and tissue esterases, continuous spinal infusion of remifentanil might yield an analgesic action with fewer side effects because of rapid plasma inactivation.

In the current study, when the analgesic *versus* supraspinal index was plotted, a significant linear regression was noted over the range of infusion doses. This differs from our previous observation with bolus delivery, where at low doses of remifentanil, there was little supraspinal action, whereas at the highest dose, an increase in supraspinal activity was noted.[11] While the practical significance of the supraspinal index associated with the action of remifentanil is not clear, it can be used to compare the profile of spinal remifentanil actions with those of other spinally delivered agents in the same model. Thus, after bolus delivery,

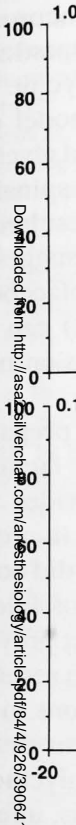

Fig. 5. Graphs sho centage of maxim and the thermal trathecal infusion Each point presen different doses.

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After bolus de at steady state re action than ren rapid plasma me to alfentanil. In lation between for the two age tabolism of the the likelihood that the suprasp infusion likely half-life, althou clude a suprasp three-compartm mifentanil also distribution thro

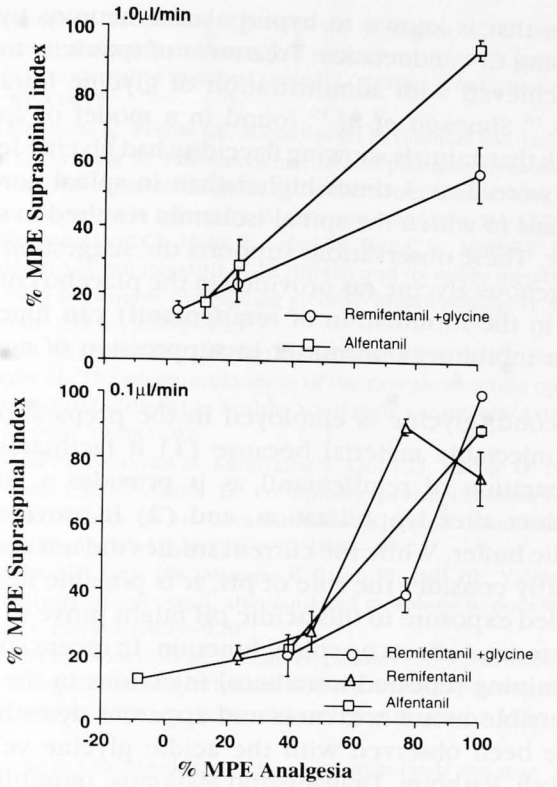

Fig. 5. Graphs show the relationship between changes in percentage of maximal possible effect in the supraspinal index and the thermal withdrawal thresholds after continuous intrathecal infusions over different doses of the respective drug. Each point presents the mean and SEM of 5–8 animals of the different doses.

alfentanil, unlike remifentanil, displayed a close covariance between the increase in the supraspinal index and the analgesic effect.

After bolus delivery, it thus appears that alfentanil at steady state results in a more prominent supraspinal action than remifentanil, presumably reflecting the rapid plasma metabolism of remifentanil as compared to alfentanil. In the current study, the close correlation between analgesia and the supraspinal effects for the two agents was unexpected. The rapid metabolism of the agent was hypothesized to diminish the likelihood of a supraspinal action. We suspect that the supraspinal effects produced by the ongoing infusion likely reflect on the finding that the plasma half-life, although short, is not sufficiently so to preclude a supraspinal redistribution in the rat. The three-compartment model for the distribution of remifentanil also includes the possibility for slow redistribution through tissue stores.

Relative Potencies for Analgesia and Supraspinal Side Effects

In previous work, we noted that the spinal bolus administration of remifentanil and alfentanil resulted in ED_{50} (μg) for analgesia of 0.7 for remifentanil and 16 for alfentanil.[11] In the recent study, the continuous administration revealed almost similar relative potencies for analgesia with both μ opioids. We suggest that this similarity is attributable to the rapid clearance and metabolism of remifentanil during continuous administration. Thus, remifentanil appears to be less potent, whereas alfentanil appears to be more active because of its moderate accumulation.

Onset and Offset of Spinal Opioid Action

Regarding the time course, the time of onset of spinal opioid action in the rodent animal has been shown to covary with lipid solubility. Remifentanil appeared to produce a faster onset of analgesic response in equianalgesic doses than alfentanil after intrathecal administration only with the slower infusion rate. The more rapid rate of recovery of remifentanil supports the efficiency of the metabolic pathway of remifentanil in the blood after continuous delivery of remifentanil and blood stores are presumably low in contrast to alfentanil. Interestingly, the continuous spinal administration of remifentanil also does not appear to increase the time to recovery in comparison to the bolus administration.[11]

Motor Impairment

Neither alfentanil nor remifentanil alone had any effect on motor function at the doses employed. In con-

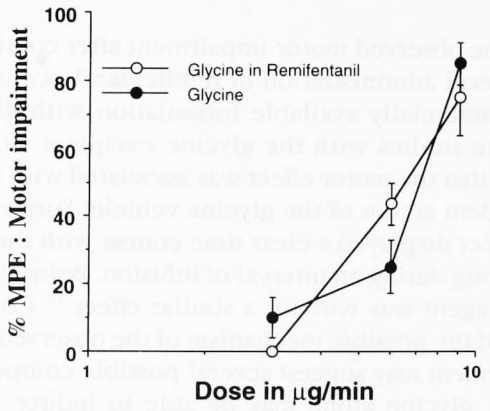

Fig. 6. Graph shows the dose response curve for motor impairment assessed at 100 min after start of experiment (peak) after intrathecal continuous infusion (0.1 μl/min) of remifentanil + glycine and glycine alone. Each point represents the mean and SEM of five or six animals.

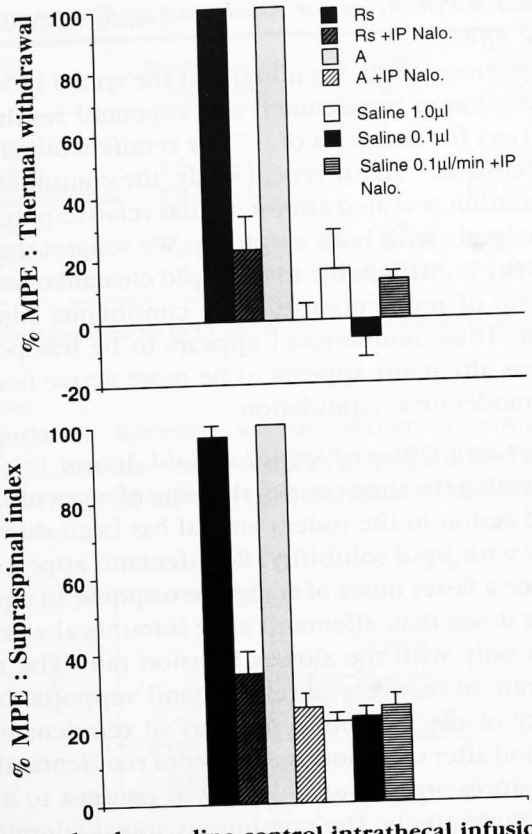

Fig. 7. Graphs show saline control intrathecal infusion over 90 min (mean of 5 + SEM animals per bar) and reversal with intraperitoneal administered Naloxone (1 mg/kg/body weight) of the antinociceptive response (*top:* percentage of maximal possible effect: Thermal withdrawal) and supraspinal side effects (*bottom:* percentage of maximal possible effect: supraspinal index) in percentage of maximal possible effect after 90 min of infusion of remifentanil (3 µg/min) and alfentanil (2 µg/min). Each bar represents the mean and SEM of four animals.

trast, the observed motor impairment after continuous intrathecal administration of remifentanil occurred in its commercially available formulation with glycine. Separate studies with the glycine excipient alone revealed that the motor effect was associated with a dose-dependent action of the glycine vehicle. Surprisingly, the effect displayed a clear time course with the effect appearing during an interval of infusion. Bolus delivery of the agent was without a similar effect.[11] Consideration of the possible mechanism of the observed motor impairment may suggest several possible components.

First, glycine alone may be able to induce a local effect on receptors in the spinal cord or promote a neurotoxic effect. Glycine is a potent inhibitory transmitter that is found in the central nervous system within the brain[17] and in interneurons in the dorsal and ventral horns that is known to hyperpolarize neurons by increasing Cl-conductance. Treatment of spasticity might be achieved with administration of glycine intrathecally.[18] Simpson *et al.*[19] found in a model of spinal shock that animals showing flaccidity had glycine levels that were 2 or 3 times higher than in spinal cord of animals in which the spinal ischemia resulted in spasticity. These observations supports the suggestion that exogenous glycine (as provided in the placebo control and in the formulation of remifentanil) can function as an inhibitory transmitter in suppression of muscle tone.

Second, glycine is employed in the preparation of the injectable material because (1) it facilitates the preparation of remifentanil as it provides a visible product after lyophilization, and (2) it provides an acidic buffer. While the current studies did not systematically consider the role of *p*H, it is possible that extended exposure to this acidic *p*H might prove to have deleterious effects on spinal function. In recent studies examining repeated intrathecal injections in the dog, reversible motor weakness and apparent dysesthesias have been observed with the acidic glycine vehicle (Yaksh, Rathbun, Dragani, and Malkmus, unpublished observations).

In conclusion, in rats, it appears that the spinal action of remifentanil is consistent with its pharmacology as a potent µ-opioid agonist. Its rapid onset after the initiation of a continuous infusion and the rapid development of a dose-dependent elevation in the nociceptive threshold is consistent with this lack of any accumulation of active drug stores, even after continuous spinal infusion. Unexpectedly, in this model, the covariance of supraspinal effect with the analgesic action suggests that despite its rapid inactivation, with constant infusion there remains the likelihood that plasma levels at analgesic doses are sufficient to produce a supraspinal redistribution that leads to measurable side effects. Aside from the time course profile of this agent, the current studies provide an initial report that the glycine vehicle may be associated with a dose-dependent reversible motor weakness after spinal administration. Further studies are required to define the mechanisms of this action.

References

1. James MK, Feldman PL, Schuster SV, Bilotta JM, Brackeen MF, Leighton HJ: Opioid receptor activity of GI 87084B, a novel ultrashort acting analgesic, in isolated tissues. J Pharmacol Exp Ther 1991; 259:712–8

2. Shlugman D, Dufore S, Dershwitz M, Rosow C, Glass PSA: Respiratory effects of remifentanil in subjects with severe renal impairment compared to matched controls (abstract). ANESTHESIOLOGY 1994; 81:A1417

3. Dershwitz M, Rosow CE, Michalowski P, Connors PM, Hoke JF, Muir KT, Dienstag JL: Pharmacokinetics and pharmacodynamics of remifentanil in volunteer subjects with severe liver disease compared with normal subjects (abstract). ANESTHESIOLOGY 1994; 81:A377

4. Westmoreland CL, Hoke JF, Sebel PS, Hug C Jr., Muir KT: Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. ANESTHESIOLOGY 1993; 79:893–903

5. Egan TD, Lemmens HJ, Fiset P, Hermann DJ, Muir KT, Stanski DR, Shafer SL: The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. ANESTHESIOLOGY 1993; 79:881–92

6. Glass PS, Hardman D, Kamiyama Y, Quill TJ, Marton G, Donn KH, Grosse CM, Hermann D: Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: Remifentanil (GI87084B). Anesth Analg 1993; 77:1031–40

7. Sabbe MB, Graf MR, Mjanger E, Tiseo PJ, Hill HF, Yaksh TL: Spinal delivery of sufentanil, alfentanil and morphine in dogs. ANESTHESIOLOGY 1994; 81:899–920

8. Yaksh TL, Noueihed RY, Durant PA: Studies of the pharmacology and pathology of intrathecally administered 4-anilinopiperidine analogues and morphine in the rat and cat. ANESTHESIOLOGY 1986; 64: 54–66

9. Payne R: CSF distribution of opioids in animals and man. Acta Anaesthesiol Scand Suppl 1987; 85:38–46

10. Caldwell LE, Rosen MA, Shnider SM: Subarachnoid morphine and fentanyl for labor analgesia. Efficacy and adverse effects. Reg Anesth 1994; 19:2–8

11. Buerkle H, Yaksh TL: Comparison of the spinal actions of the μ opioid remifentanil with alfentanil and morphine in the rat. ANESTHESIOLOGY 1996; 84:94–102

12. Yaksh TL, Rudy TA: Analgesia mediated by a direct spinal action of narcotics. Science 1976; 192:1357–8

13. Dirig DM, Yaksh TL: Differential right shifts in the dose response curve for intrathecal morphine and sufentanil as a function of stimulus intensity. Pain 1995; 62:321–8

14. Hargreaves K, Dubner R, Brown F, Flores C, Joris J: A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. Pain 1988; 32:77–8

15. Boersma FP, Meert TF, Vercauteren M: Spinal sufentanil in rats: Part I: Epidural versus intrathecal sufentanil and morphine. Acta Anaesthesiol Scand 1992; 36:187–92

16. Tallarida RJ, Murray RB: Manual of Pharmacologic Calculations with Computer Programs, 2. New York, Springer, 1986

17. Araki T, Yamano M, Murakami T, Wanaka A, Betz H, Tohyama M: Localization of glycine receptors in the rat central nervous system: An immunocytochemical analysis using monoclonal antibody. Neuroscience 1992; 25:613–24

18. Hall PV, Smith JE, Lane J, Mote T, Campbell R: Glycine and experimental spinal spasticity. Neurology 1979; 29:262–7

19. Simpson RK, Robertson CS, Goodman JC: Glycine: An important component of spinal shock. Neurochem Res 1993; 18:887–92