LABORATORY INVESTIGATIONS

Anesthesiology
1996; 84:94–102

Comparison of the Spinal Actions of the μ-Opioid Remifentanil with Alfentanil and Morphine in the Rat

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Background: **μ-Opioids administered spinally produce a potent, dose-dependent analgesic response in preclinical and clinical investigations. Side-effect profile of these compounds may be altered as a function of pharmacokinetics. The effects of intrathecal and intraperitoneal remifentanil, an esterase-metabolized μ opioid, alfentanil, and morphine were compared.**

Methods: **Intrathecal and intraperitoneal remifentanil, alfentanil, and morphine were examined in rats tested for hind-paw thermal withdrawal latency. The antinociceptive response was assessed and in parallel a scoring of four different parameters summarized as a supraspinal index to assess supraspinal side-effect profiles after the several drugs were delivered by the different routes.**

Results: **All opioids produced a dose-dependent analgesic response after intrathecal administration. The ordering of potency (intrathecal ED_{50} in μg) was remifentanil (0.7) > morphine (12.0) > alfentanil (16.3) > GR90291, principal remifentanil metabolite (>810 μg). Time until onset of analgesia after intrathecal or intraperitoneal delivery was morphine > remifentanil = alfentanil. When matched for analgesic effect, the relative duration of action was morphine ≫ alfentanil > remifentanil. The supraspinal index showed a dose-dependent increase for all agents. All intraperitoneal drugs showed dose-dependent increases in antinociception with potency (intraperitoneal ED_{50} in μg) of remifentanil (4.3) > alfentanil (24.4) > morphine (262). Calculation of intrathecal or intraperitoneal ratios for supraspinal side effects/analgesia (supraspinal index ED_{50}/analgesia ED_{50}) revealed remifentanil to be greatest when intrathecally administered: remifentanil (4 intrathecal: 1.4 intraperitoneal); alfentanil (0.7 intrathecal: 1.5 intraperitoneal); and morphine (1 intrathecal: 5.6 intraperitoneal).**

Conclusions: **These observations indicate that remifentanil has a powerful spinal opioid action. Consistent with its lipid-solubility, it has an early onset like alfentanil but displays a shorter duration of action after bolus delivery. Despite lipid solubility, remifentanil has a significant spinal therapeutic ratio. These observations likely reflect the rapid inactivation of systemically redistributed agent by plasma esterases. (Key words: Analgesics, opioid: alfentanil; morphine. Receptor's μ opioid; remifentanil. Sites of action: spinal cord; supraspinal.)**

REMIFENTANIL (3-[4-methoxycarbonyl-4[(1-oxopropyl) phenyl-amino] 1- piperidine]] propanoic acid, methylester, hydrochloride) is a μ-opioid agonist that is metabolized by plasma and tissue esterases. The principal metabolite is a carboxylated product (GR90291A), which is 0.003 to 0.001 times as potent as the parent.[1,‡] The elimination half-life of remifentanil is <10 min and is independent of impaired renal or hepatic function.[2,3] Systemic remifentanil in humans displays classic μ-receptor effects, notably analgesia, sedation, muscle rigidity, nausea, and respiratory depression,[4,5] all of which are readily reversed by naloxone.§ Its relative ordering of potency in guinea pig ileum is: sufentanil (EC_{50} = 0.3 nM) > remifentanil (EC_{50} = 2.4 nM) = fentanyl (EC_{50} = 1.8 nM) > alfentanil (EC_{50} = 20.1 nM).[6] In humans, based on blood levels on steady-state concentrations, remifentanil is approximately 60-fold more potent than alfentanil.‖

μ-Opioids are commonly used to produce analgesia by either epidural or intrathecal delivery. The spinal

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Received from the Department of Anesthesiology, University of California, San Diego, La Jolla, California. Submitted for publication January 23, 1995. Accepted for publication August 28, 1995. Supported in part by funds from Glaxo and DA02110.

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§ 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.

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action of several 4-anilinopiperidines, notably lofentanil, fentanyl, alfentanil, and sufentanil have been previously studied in humans and in detail in several animal models.[7,8] An important component of this interest is how the time course and side-effect profile (sedation and respiratory depression), associated with the spinal delivery of an agent, is altered as a function of drug distributional pharmacokinetics. Thus, it has been shown that agents with high octanol-water distribution 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] These properties led to the proposition that lipid-soluble agents may thus be theoretically less prone to a supraspinal redistribution because they would be more rapidly cleared from the intrathecal space.[9] The octanol-water partition coefficients are: alfentanil (logP = 2.1), sufentanil (logP = 3.24), fentanyl (logP = 3) *versus* morphine (logP = 0.15).[10,11] While the association between rate of clearance and lipid solubility is reasonable, it also has become apparent that these agents, with their rapid clearances, may achieve significant blood levels shortly after injection and that these levels may result in a supraspinal redistribution, leading to prominent supraspinal effects in animals and humans.[7,8,12] 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 alfentanil's, but may be less likely to show a systemic accumulation because of its rapid metabolism in blood. This might theoretically enhance the ratio supraspinal index/analgesia after spinal delivery (*e.g.*, less supraspinal side effects for a given analgesic level). There has been no investigation of the intrathecal pharmacodynamics of remifentanil. Therefore, we sought to examine the action of intrathecal remifentanil and, for comparison, two opioid agonists (morphine and alfentanil) with regard to antinociception and supraspinal side effects in a well-defined rodent model. As a control, we compared these results with systemically intraperitoneally delivered drugs.

Materials and Methods

Animal surgery and testing were approved by the institutional animal care committee of the University of California, San Diego. All procedures were performed according to this protocol.

Animals

Rats (male Sprague Dawley, Harlan Industries, Indianapolis IN; weighing 300–350 g) were kept in separate cages on a 12/12 h light/dark cycle. The surgical preparation of the intrathecal catheters was performed under halothane anesthesia using a modification of the previously described technique.[13] The rat was anesthetized with halothane (2–3% in 50% O_2/air mixture) and the dorsum of the skull was shaved and prepared with alcohol and povidone-iodine. The rat was then placed in a stereotaxic head holder for insertion of the intrathecal catheters and the anesthetic was lowered to 1–1.5% and delivered by a face mask. Intrathecal catheters were constructed 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 skin, exposure of the atlantooccipital membrane and incision of the dura mater. The catheter was inserted in the intrathecal space and advanced 8.5 cm to the rostral edge of the lumbar enlargement. Subsequently, catheters were subcutaneously tunneled and fixed under a skin suture. After flushing the catheter with 10 μl saline, the catheter tip outlet was plugged with a small, removable, 28-G piece of wire. 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 before testing. Animals with impaired motor function or an elevated sensory threshold were killed.

Drugs

Drugs administered intrathecally in this study were remifentanil HCl (molecular weight = 413; Glaxo, Research Triangle Park, NC), GR90291 (the principal metabolite of remifentanil (molecular weight = 362.5)); alfentanil HCl (molecular weight = 453; Janssen, Titusville, NY) and morphine sulfate (molecular weight = 337; Merck, West Point, PA). Remifentanil was obtained as a lyophilized powder (17 mg/vial) and as the lyophilized powder in ampules containing the glycine excipient (3 mg glycine/1 mg remifentanil). Naloxone HCl (Endo, DuPont/Wilmington, DE) was given intraperitoneally. All drugs (intrathecal and intraperitoneal) were dissolved in normal saline. Control experiments were carried out with either vehicle (normal saline or glycine matched for the applied remifentanil dose concentrations) delivered intrathecally or intraperitoneally.

Intrathecal Injection

For intrathecal injection, the intrathecal catheter was connected to a gear-driven microinjection syringe *via* a length of calibrated PE-90 tubing. For intrathecal delivery, drugs were injected in a volume of 10 μl followed by 10 μl normal saline to flush the catheter over a 10-s interval.

Intraperitoneal Injection

For the intraperitoneal studies, drugs were injected with a 25-G needle intraperitoneally in a volume of 1 ml. Antagonist or vehicle, as the control, was administered intraperitoneally in a similar volume.

Test measures

Antinociception. The antinociceptive effect was determined by measuring the latency to withdrawal evoked by exposing the hind paw to a thermal stimulus. To accomplish these studies, nonanesthetized rats were placed in Plexiglas 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[14,15] (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 photo diodes or when an interval of 20 s (cutoff time) had passed. To avoid variations in paw starting temperature, the surface under the glass 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 were averaged and counted as baseline score (time 0). Tests were then made at 3, 5, 10, 20, 30, 40, and 60 min after injection for alfentanil and remifentanil and at 3, 5, 10, 20, 30, 40, 60, and 120 min for morphine.

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 blocked by opioids in a dose-dependent manner.[16] These measured responses included: pinna reflex, cornea reflex (both evoked by light touch of the surface of the pinna or cornea with a small piece of PE-10 tubing), evoked movement (startle reflex evoked by tapping of 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 or knocking on cage wall does result in a slow reflex behavior, touch or knocking has to be repeated at least twice); or 2 = completely absent (no reflex was shown after 3 times of touching the cornea or pinna on 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, the 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 = 0.93, obtained with the two sets of observations.

Experimental Design

Typically, each rat was used in three separate experiments, randomly assigned to receive a single dose of remifentanil, morphine, or alfentanil, at intervals of 4–5 days. Animals showing altered threshold or motor dysfunction were not employed. Intrathecal and intraperitoneal agonist dose response curves and time effect curves were obtained for all agents. Naloxone reversibility of the effects was tested with the highest intrathecally applied dose of remifentanil (10 μg), alfentanil (100 μg), morphine (30 μg), and intraperitoneal naloxone (1 mg/kg bw) injection 10 min before intrathecal drug delivery.

Statistical Analysis

Data are expressed as means and ± SEM. For the intrathecal time course studies, latencies are shown in seconds, each time point representing five to eight animals and the SEM for the period after agonist or vehicle delivery. For the intraperitoneal dose–response curves, each point represents the mean and the SEM of four to six animals. For further analysis, the thermal latencies

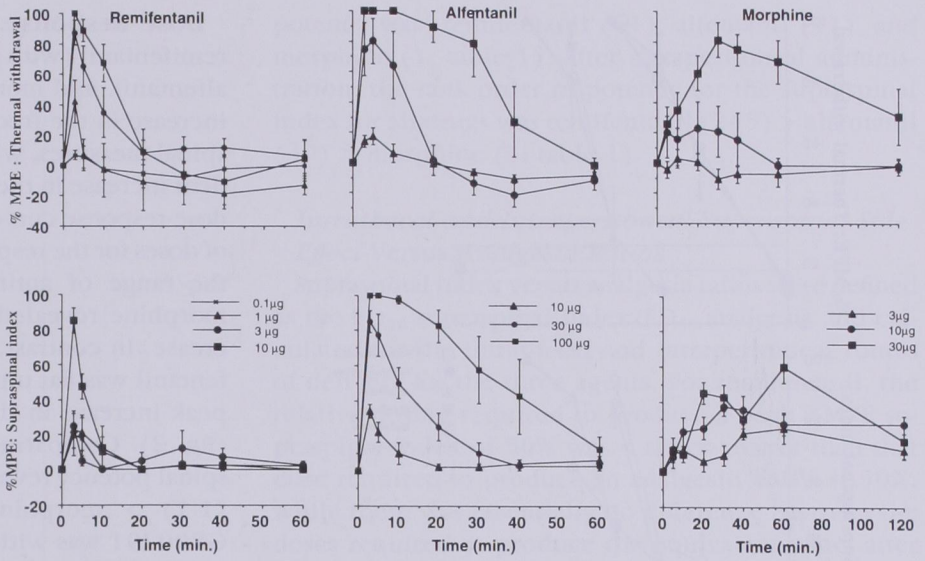

Fig. 1. The time course of intrathecal administered opioids (0–60 min for remifentanil [in its excipient glycine] and alfentanil, 0–120 min for morphine) and their percent maximum possible effect for analgesia assessed on the modified Hargreaves Box and their supraspinal side effects measured as increase in the supraspinal index. Each data point represents the mean ± SEM of five to eight animals.

and the supraspinal index scores were converted to the percent of the maximum possible effect (% MPE) according to the formula:

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

or

$$\text{supraspinal effect Index, \% MPE} = \frac{\text{supraspinal index with drug} - \text{baseline score} \times 100}{\text{cut-off score (8)} - \text{baseline}}.$$

Dose-response curves are presented as the maximum % MPE observed within the testing interval for the particular measure. For all drugs, a dose-response analysis as described by Tallarida and Murray[17] was accomplished. ED_{50} and its 95% confidence intervals were calculated with a least-squares linear regression model, where log dose values were used. Potency ratios were also calculated. Changes in the thermal latency and supraspinal index with and without antagonist pretreatment were tested for significance using an unpaired Student's t test. Critical values of $P < 0.05$ were considered as statistically significant.

Results

Intrathecal Opioids and Analgesia

Time Course. Intrathecal injection of remifentanil and alfentanil resulted in a rapid increase in the thermal withdrawal latency achieving peak effects within the first testing time of 3 min (fig. 1). In comparison, intrathecal morphine produced its maximal effect after 20–30 min. Inspection of figure 1 emphasizes that for doses having similar peak effects, the duration of action was morphine > remifentanil or alfentanil. Thus, an equally analgesic dose of remifentanil (3 μg) and alfentanil (30 μg) showed a greater than 50% effect for 12–17 min, whereas for morphine an equianalgesic dose (10–30 μg) lasted for approximately 60 min.

Dose Response. In rats, the spinally administered opioids remifentanil (with and without the excipient glycine), alfentanil, and morphine, produced a dose-dependent antinociceptive response in the thermal withdrawal test (fig. 2). GR90291 was without effect at the highest dose examined. The rank ordering of relative antinociceptive potency as compared to morphine was remifentanil (17×) > morphine (1×) > Alfentanil (0.7×). As shown in table 1, there was no statistical difference between the slopes of the dose-response curves for the several drugs. As indicated in table 1, antinociceptive dose-response curves for remifentanil in saline and remifentanil in the glycine excipient showed no differences.

Intrathecal Opioids and the Supraspinal Effect Index

Time Course. Before injection, all animals displayed normal pinnae, corneal, spontaneous movement, and evoked arousal. The spinal delivery of remifentanil, al-

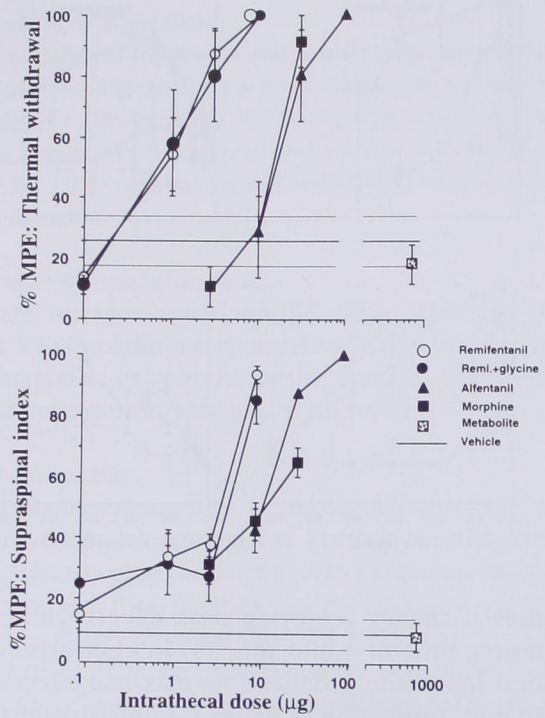

Fig. 2. Data present the dose-response curves in percent maximum possible effect of the thermal withdrawal (*top*) and percent maximum possible effect of supraspinal index (*bottom*) for the three intrathecally administered opioids (μg). Vehicle presents the data obtained with intrathecally administered glycine in a fixed dose of 30 μg. Each data point represents the mean ± SEM of five to eight animals.

fentanil, and morphine at maximal doses resulted in a significant suppression of the pinnae and corneal reflexes as well as resulted in a reduction in evoked and spontaneous movement. The peak increase in the supraspinal index for the high doses of alfentanil and remifentanil appeared within 3 min after injection. Morphine produced its peak effect (only about 60% MPE in the highest dose employed in these studies) by about 20 min after intrathecal administration (fig. 1). At scores corresponding to the ED_{50} value for the supraspinal index, rats typically showed a modest depression, but not a complete blockade of the corneal and pinnae reflexes and a noted reduction in spontaneous activity. Moreover, while they showed a distinct reduction in spontaneous activity, they were easily induced to move with a tap on the wall of the chamber. In short, the animals at this scoring level showed what would be globally described as a modest depression of arousal. Typically, at comparably effective doses, the duration of supraspinal side effects was morphine > alfentanil, remifentanil (fig. 1).

Dose Response. The intrathecal administration of remifentanil (with and without the excipient glycine), alfentanil, and morphine produced a dose-dependent increase in the frequency and magnitude of all supraspinal measures, which is reflected by the dose-dependent increase in the supraspinal index. As shown in the dose-response curves (fig. 2) carried out over the range of doses for the respective agent that corresponded with the range of antinociceptive action, alfentanil and morphine revealed a continuous dose-dependent increase. In contrast, the dose-response curve for remifentanil was flat until the highest dose at which time a peak increase in the supraspinal index was observed (fig. 2). Comparing the rank order of relative supraspinal potency revealed: remifentanil (4.2) > alfentanil (1.1) > morphine (1) >> GR90291 (table 1). GR90291 was without effect on supraspinal effect indices at the dose examined.

Comparison of Supraspinal Indices Versus *Antinociception after Intrathecal Delivery*

To address the relationship between supraspinal side effects and antinociception, we plotted the % MPE of supraspinal index versus the % MPE antinociception produced at a given dose of the respective drug (fig. 3). Thus, for example, for alfentanil at increasing doses (each point represents one concentration with the mean and SEM of 5–8 animals) an increase in the % MPE of antinociception was observed, but also concomitantly a similar rise in the supraspinal index. A similar positively inflected slope was seen for morphine. As indicated, the slope of the remifentanil regression was essentially zero when calculated for the lowest three doses, while a precipitous increase in the supraspinal index was noted at the highest dose.

Intraperitoneal Opioids

After intraperitoneal delivery, all drugs produced a potent increase in the thermal withdrawal latency with the time to peak effect being within 5 min for remifentanil and alfentanil and within 30 min for morphine. The relative duration of action (time to return to MPE ≤ 50% for thermal withdrawal latency), after approximately equipotent doses of the several drugs was morphine (30 ± 15 min) > alfentanil (10 ± 5 min) = remifentanil (10 ± 5 min; data not shown).

These supraspinal and analgesic effects of these several agents given intraperitoneally were dose-dependent. Dose response curves for these agents are presented in figure 4. The rank order of relative analgesic

Table 1. Summary of ED_{50} Values and Slopes and Confidence Intervals for Dose–Response Curves Observed after Intrathecal Delivery of Remifentanil, Alfentanil, or Morphine in the Rat

	Remifentanil (n = 21) Analgesia	Remifentanil (n = 21) Sedation	Alfentanil (n = 15) Analgesia	Alfentanil (n = 15) Sedation	Morphine (n = 15) Analgesia	Morphine (n = 15) Sedation
MPE % responses	0.7 (0.4–1.0)	2.8 (0.5–15.4)	16.3 (8.8–30.1)	10.6 (6.4–17.5)	12.0 (7.5–19.3)	11.7 (7.2–19.1)
ED_{50} (μg) (95% CI)	0.7* (0.4–1.3)	1.4* (0.9–2.2)				
Slope (95% CI)	45.1 (33.7–56.4)	24.5 (6.8–4.2)	70.4 (36.2–104.6)	57 (38.2–75.8)	82.1 (39.1–125.2)	33.9 (15.6–52.3)
r	0.88	0.54	0.77	0.87	0.74	0.74
		0.88*				
Potency ratio (morphine = 1)	17	42	0.7	1.1	1	1
		2.4*				

* With glycine.

potency was: remifentanil (61), alfentanil (11), and morphine (1; table 1). After intraperitoneal administration, the rank order of potency for the supraspinal index for all drugs was remifentanil (245) > alfentanil (39) > morphine (1; table 1).

Intrathecal and Intraperitoneal Supraspinal Side Effect Versus *Analgesia Ratios*

Supraspinal index versus analgesia ratios were defined as the ED_{50} supraspinal index/ED_{50} analgesia and calculated for the intrathecal and intraperitoneal routes of delivery for the three agents. For remifentanil, the relative dosing required to produce a peak %MPE supraspinal index of 50% was 4 times greater than that dose required to produce an analgesic %MPE = 50%, while there was essentially no difference between the doses required to produce the equivalent effect after intraperitoneal delivery. The intrathecal, but not the intraperitoneal, ratio for remifentanil exceeded that obtained for morphine or alfentanil.

Antagonist Reversibility

The effects on thermal nociception and the supraspinal side effects induced after maximally effective intrathecal or intraperitoneal doses of remifentanil, alfentanil, and morphine were reversed by pretreatment with 1 mg/kg intraperitoneal naloxone. Intraperitoneal naloxone and intrathecal saline did not produce any significant effects for antinociception or supraspinal side effects (data not shown).

Vehicles

Drug vehicles, *e.g.*, saline (10 μl) and glycine (30 μg/10 μl), did not produce significant effects after intrathecal administration either for thermal withdrawal or supraspinal index.

Discussion

Spinal Opioid Action

Spinal administration of μ-opioids produces a potent and dose-dependent analgesic response in humans and animals.[13,18,19] The mechanisms of this effect after the intrathecal injection of opioids are (1) increasing potassium conductance and thus hyperpolarization of dorsal horn neurons; and (2) presynaptic inhibition of neurotransmitter release from small primary afferent fibers.[20,21] Remifentanil has been shown to behave as a μ-opioid agonist and corresponding with this effect,

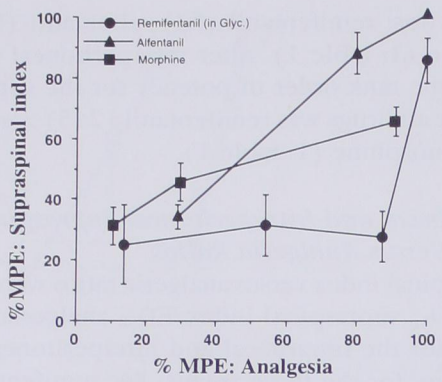

Fig. 3. Data present the comparison of intrathecally administered opioids over increasing doses and their percent maximum possible effect of the supraspinal index *versus* percent maximum possible effect of analgesia, assessed with the thermal withdrawal test. Each data point represents the mean ± SEM of five to eight animals.

the actions of the intrathecally delivered agent were readily suppressed by a dose of naloxone that has been shown to be completely effective against maximally active doses of other anilinopiperidines and μ agonists in the rat model.[7,13]

In the current study, the antinociceptive intrathecal potency ratio of the three agents after bolus delivery was remifentanil 17: alfentanil 1.1: morphine 1. These relative intrathecal potencies observed after bolus delivery are in accordance with those potencies assessed in *in vitro* assays. In humans, alfentanil and remifentanil have been delivered systemically. In these studies, the approximate potency ratio of remifentanil and alfentanil was 1:16. This corresponds favorably with the antinociceptive potency ratio observed after bolus intraperitoneal delivery in the current rat study (table 1).

Remifentanil is provided with a glycine excipient as a part of its formulation. This preparation has a buffered *p*H of around 3.5. With acute delivery in the dose ranges provided, there were no adverse effects. Importantly, the same results were obtained with the glycine excipient and the saline vehicle. Glycine alone administered in the concentrations employed had no detectable acute effects.

Onset and Offset of Spinal Drug Action

Regarding time course, the time of onset of spinal action in the rodent and dog models has been shown to covary with lipid solubility.[7,8] Thus, not unexpectedly, the rapid onset of remifentanil corresponded with that of alfentanil, rather than morphine. Because clearance rather than metabolism is believed to play a major role in the disappearance of spinal activity and because drug clearance into the vasculature is by a process depending on lipid solubility, both alfentanil and remifentanil showed corresponding rapid declines within the lower dose range.

Because the primary metabolite of remifentanil, a carboxylated product (GR90291), has been reported to have a modest degree of opioid activity,[1] we sought to determine if this agent might contribute to remifentanil's action. A dose as high as 1,100 times the ED_{50} of remifentanil, however, was without effect. We thus conclude that after spinal delivery, this agent likely plays no role in the time course of action of this agent. Whether there will be an accumulation and an attendant pharmacologic effect with this agent with chronic remifentanil infusion remains to be seen, although its very low potency after bolus delivery would argue against this action.

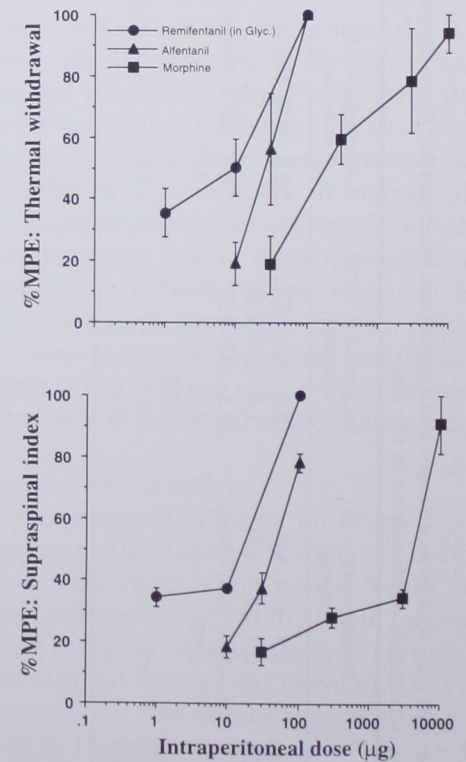

Fig. 4. Data present the dose-response curves in percent maximum possible effect of the thermal withdrawal (*top*) and percent maximum possible effect of supraspinal index (*bottom*) for the three intraperitoneally administered opioids in (μg). Each data point represents the mean ± SEM of four to six animals.

Supraspinal Side Effects Versus *Antinociception*

Opioids can yield an inhibition of brain stem function, as evidenced by the depression of the corneal and pinnae reflexes, and produce a reduction in spontaneous mobility by a supraspinal action. The spinal delivery of an opioid is promulgated on the basis of achieving a greater analgesic action and a lesser supraspinal side-effect profile. As indicated by the supraspinal index *versus* antinociception plots, remifentanil showed a flat regression at the lower dose ranges, whereas alfentanil showed a progressive enhancement across increasing doses. The failure of intrathecal remifentanil to show increased supraspinal effects at the lower doses, as compared to the progressive increase over doses by alfentanil and morphine, suggests that there was little supraspinal redistribution of remifentanil. Interestingly, with the highest dose of remifentanil, it was noted that there were prominent increments in supraspinal side effects. This may result either from an acute supraspinal redistribution with the highest dose, or the acute appearance of a substantial remifentanil blood concentration that exerts a supraspinal effect. It is possible that under normal circumstances, remifentanil is metabolized by esterases present in the tissue and/or cerebrospinal fluid, which were overcome in the presence of large concentrations of drug. The role of such central esterases on remifentanil metabolism is not known.

To characterize the relative supraspinal effects *versus* analgesic effects of the three agents after spinal and intraperitoneal delivery, a supraspinal index/analgesia ratio was calculated after bolus intrathecal and intraperitoneal delivery. This was accomplished by calculating the doses required to achieve an arbitrary end point: *e.g.*, the 50% MPE for the supraspinal index and the 50% MPE for the thermal withdrawal. Thus, based on data presented in table 1, after intrathecal or intraperitoneal delivery, these ratios for remifentanil were approximately 6 and 1, respectively; *e.g.*, by the systemic route, there was essentially no difference in the relative dosing required to produce a given degree of antinociception as compared to the intrathecal route, where it required 6 times the spinal dose to produce a given degree of supraspinal side effects for a given degree of antinociception. In contrast, for alfentanil, in this model, the supraspinal index/analgesia ratios for the intrathecal and intraperitoneal routes were essentially identical (0.7 *vs.* 1.6). Thus, after systemic delivery, the magnitude of the side effects produced by equianalgesic doses of the two agents is similar. In contrast, after spinal delivery, given equianalgesic doses of remifentanil and alfentanil, the effects of alfentanil will be accompanied by greater supraspinal side effects, in spite of the small difference in log *P* values. This difference likely reflects on the presumed rapid metabolism of remifentanil from the plasma as it moves from the spinal space. The similar ratio observed for these two lipid-soluble agents after intraperitoneal delivery likely reflects the rapid supraspinal penetration that occurs after bolus systemic delivery. The supraspinal side effects/analgesia ratio for morphine was greater after intraperitoneal than intrathecal delivery. The reason for the unexpectedly high ratio for intraperitoneal morphine is not known.

Clinical Correlation

In humans, opioids are delivered spinally to achieve a more dense analgesia with a diminished incidence for side effect, *e.g.*, it is an approach to enhance the therapeutic ratio of the opioid. Rostrocaudal redistribution is limited by the rapid clearance of the lipid-soluble agent, but such rapid clearance in humans leads to prominent supraspinally mediated side effects, including muscle rigidity, respiratory depression, nausea and vomiting, and pruritus. The current studies suggest the possibility that rapid plasma clearance, as may be achieved by plasma esterase-mediated hydrolysis of remifentanil, may enhance the ratio supraspinal side effects/analgesia. Still, the rapid pharmacokinetics displayed by agents such as alfentanil or sufentanil require that they be delivered by infusion. It is widely appreciated that such repeated or continuous delivery can result in plasma concentrations that do not differ significantly from the levels observed after parenteral delivery.[21] Accordingly, the side-effect profile of these agents are not as incrementally improved as would be anticipated because of the plasma accumulation.[19] Whether plasma clearance, although rapid, will be adequate to prominently modify the side-effect profile of intrathecal remifentanil in humans is not known. Further studies with the use of continuous remifentanil infusion models will provide more insights about the pharmacodynamics and pharmacokinetics of remifentanil. In any case, it should be emphasized that spinal delivery of this agent in humans absolutely must await appropriate preclinical safety and toxicology studies.[22]

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