REVIEW ARTICLE

Remifentanil: A Novel, Short-Acting, μ-Opioid

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In recent years, concerted development has provided the anesthestist with more potent opioids possessing shorter durations of action. Although it is essential that the potency of an opioid confer titratibility for profound analgesia, this characteristic should be complimented by its ability to safely restore respiratory function when treatment is ended.

Remifentanil is a novel, μ-opioid receptor agonist with an analgesic potency similar to that of fentanyl. By virtue of predominant metabolism by nonspecific esterases, remifentanil is the first in the class of an esterase-metabolized opioid within the 4-anilidopiperidine series of drugs. Because of remifentanil's rapid systemic elimination, with a half-life of 8–10 minutes, it should have pharmacokinetic advantages in clinical situations requiring predictable termination of effect.

It is our understanding that remifentanil is currently under investigation by the regulatory authorities in different countries, which will probably result in its final approval and marketing in Germany, Great Britain, and other European countries this year and in the United States within the next year. Most studies on remifentanil to date have been published as abstracts, and thus the potential uses of remifentanil for anesthesia, analgesia, and sedation may become even better known once studies now under way are published. This review will focus on the pharmacology of remifentanil and clinical experience reported to date.

Basic Pharmacology and Metabolism

Remifentanil is the hydrochloride salt of 3-(4-methoxycarbonyl-4-[(1-oxopropyl)-phenylamino]-1 piperidine) propanoic acid, methyl ester (Figure 1). Structure-activity studies of the 4-anilidopiperidines as analgesics have led to the development of several new synthetic opioids (1). All anilidopiperidines act on the μ-opioid receptor. This receptor type, first cloned in 1992 (2,3), resembles other opioid receptor types in that it has seven transmembrane domains, intracellular and extracellular loops, and several different glycosylation sites (4,5). The analgesic effect is mediated through coupling to a guanine nucleotide-binding protein (G-protein), which concomitantly results presynaptically in an inhibition of excitatory neurotransmitter release and postsynaptically in an inhibition of cyclic adenosine monophosphatase, suppression of voltage-sensitive calcium channels, and hyperpolarization of the postsynaptic membrane through increased potassium conductance (6,7).

Although chemically related to opioids such as fentanyl, alfentanil, or sufentanil, remifentanil was synthesized by Feldman et al. (1) through a specific analysis and modification of the basic anilidopiperidine structure. The introduction of a methyl ester group onto the N-acyl side chain of the piperidine ring conferred increased susceptibility to hydrolytic metabolism by esterases and thereby rapid termination of effect (Figure 1).

Remifentanil (molecular weight = 413) is lipophilic with an octanol/water partition coefficient of 17.9 at a pH of 7.4. It will be commercially available as a water-soluble lyophilized powder containing the free base and glycine as a vehicle to buffer the solution (pH 3; pKa in water 7.07). Receptor binding studies have shown remifentanil's selectivity and affinity for the μ-opioid receptor, which is greater than for the δ- or κ-opioid receptor (8). Furthermore, it does not significantly bind to other nonopioid receptor groups. The specificity and affinity of remifentanil at the μ-opioid receptor is also demonstrable through competitive antagonism by naloxone (9).

The specific plasma and tissue esterases that are responsible for its rapid elimination are not entirely known. However, remifentanil does not appear to be a substrate for butyrylcholinesterases (pseudocholinesterase), and thus its clearance should not be affected by cholinesterase deficiency (10) or anticholinergics (11). Remifentanil is predominantly metabolized via esterases to an acid metabolite, GI-90291, and to a lesser

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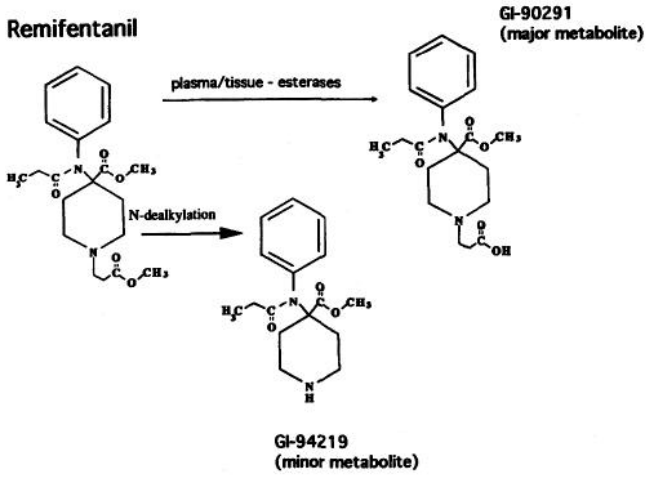

Figure 1. Metabolic pathway of remifentanil (GI-87084B), modified from Egan et al. (17). Remifentanil is metabolized by plasma and tissue esterases to its major metabolite, GI-90291, which possess only ½000–¼000 of the analgesic potency. A second metabolite, GI-94219, results from N-dealkylation of the original remifentanil.

extent by N-dealkylation to a second metabolite, GI-94219. The major metabolic product, GI-90291, is ½000–¼000 less potent compared with remifentanil and should not have any effect at clinical doses of remifentanil. Renal excretion of this metabolite has been estimated at 90% (12). The analgesic potency of remifentanil is about 20–30 times greater than that of alfentanil in humans (12,13).

Spinal Administration

The spinal administration of remifentanil in preliminary animal studies revealed that the vehicle glycine, an inhibitory neurotransmitter, in the present formulation potentially produces reversible, naloxone-insensitive motor dysfunction after continuous, but not after acute, bolus intrathecal administration (14,15). Hence, the spinal or epidural administration of remifentanil is not recommended in humans until a glycine-free preparation has been developed and further safety studies are performed.

Clinical Pharmacology

The pharmacology of remifentanil suggests that the rapid onset and recovery of its effect will be a unique tool in certain clinical circumstances, i.e., day-stay surgery, monitored anesthesia care, long inpatient surgery etc., where rapid recovery is desirable (16). The steady-state volume of distribution in humans has been estimated to be 33 L. Its clearance from the central compartment, which is independent of gender (17), is estimated to be 2.9 L/min and its systemic half-life is about 9–11 min (18).

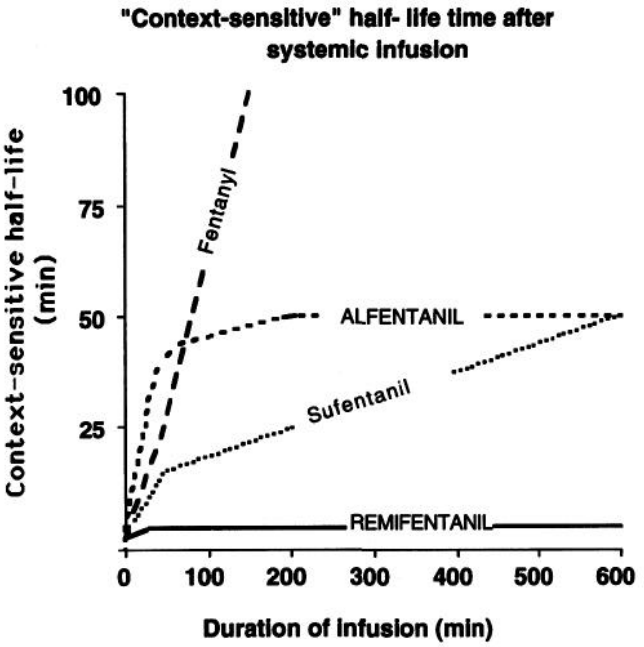

Figure 2. Computer simulation of the "context-sensitive" half-life time (CSHT) for remifentanil (3.65 min), alfentanil (58.5 min), sufentanil (240 min), and fentanyl (262.5 min). Note that remifentanil's CSHT is independent of the duration of infusion. Modified from Egan et al. (17).

"Context-sensitive" half-life time (CSHT) (19), the time to a 50% decrease of an effective site concentration after infusion is stopped, was estimated by computer simulation to be about 4 min for remifentanil, independent of the infusion duration (18). In contrast, for alfentanil, sufentanil, and fentanyl the CSHT was much longer and was dependent on the infusion duration (Figure 2). A similar result was also reported in a volunteer study by Kapila et al. (20) in which, after a 3-h infusion, the CSHT for remifentanil was 3 min compared with 44 min for alfentanil, whereas the pharmakodynamic recovery based on reestablished respiration was achieved within 15 min for remifentanil and in more than 45 min for alfentanil after cessation of infusion. Conceivably remifentanil could be used for long surgeries, when a quick recovery time is desired, e.g., for neurological assessment (wake-up test in spinal surgery).

Of course, any advantage of an opioid possessing a short recovery period may be considered a disadvantage if the delivery is suddenly discontinued, whether intentionally or inadvertently. This could result in relatively sudden onset of pain and perhaps withdrawal if administered for a long time. Hence, continuous intensive monitoring and assessment of the patient are necessary. Although some clinicians may avoid drugs that require continuous administration because of the cost of appropriate delivery systems, remifentanil's independence of the concentrations infused, their duration, and liver or kidney function

Table 1. Anticipated Dosing Recommendations for Systemic Administration of Remifentanil (Ultiva®, Dosing Sheet) for Bolus Injection and Continuous Infusion in Different Indications

Indication	Remifentanil—bolus dose (μg/kg)	Remifentanil—continuous infusion dose	
		Starting rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Range ($\mu g \cdot kg^{-1} \cdot min^{-1}$)
Induction of anesthesia in ventilated patients	1	0.5–1	
Maintenance of anesthesia in ventilated patients			
N_2O (66%)	0.5–1	0.4	0.1–2
Isoflurane (starting dose 0.5 MAC)	0.5–1	0.25	0.05–2
Propofol (starting dose 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.5–1	0.25	0.05–2
Parenteral analgesia in immediate postoperative period	Not recommended	0.1	0.025–0.2

MAC = minimum alveolar anesthetic concentration.

makes it a drug that should potentially find a unique place in clinical practice.

Anticipated dosage recommendations based on the package recommendation of the commercially available remifentanil (Ultiva®; Glaxo Wellcome) in Germany are presented in Table 1. In a recently published clinical study, Dershwitz et al. (21) showed that the 50% effective dose to all surgical stimuli was 0.52 $\mu g \cdot kg^{-1} \cdot min^{-1}$, whereas Joshi et al. (22) found a 50% effective dose of 4.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for loss of consciousness. Larger doses did not delay their patients' recovery with times for spontaneous ventilation (2.5–4.6 min), tracheal extubation (4.2–7.0 min), or responding to verbal commands (3.0–4.6 min) after infusion was stopped. Those short recovery and tracheal extubation times are in accordance with other studies (23,24).

Preliminary findings in children suggest that remifentanil has a pharmacokinetic profile in pediatric patients similar to that in adults. However, because of some equivocal results in a small study group, further studies will be required to confirm these findings (25).

Organ-Specific Pharmacology

Central Nervous System

Hoffman et al. (26) investigated the cerebral effects of remifentanil in isoflurane-anesthetized dogs by infusing alfentanil and remifentanil to equivalent titrated electroencephalogram (EEG) end points. The effects regarding cerebral blood flow (CBF) (reduction) and cerebral metabolic oxygen requirements (no effect) were similar for both opioids. However, the remifentanil group showed a more rapid recovery in CBF and EEG patterns after infusion was terminated. Human studies with remifentanil and nitrous oxide (N_2O) revealed an intact cerebral vascular reactivity to carbon oxide and a CBF similar to that with anesthesia with isoflurane/N_2O or fentanyl/N_2O (27). A study in humans undergoing surgery for space-occupying lesions found no change in the intracranial pressure for patients treated either with alfentanil or remifentanil. Reduction of the cerebral perfusion pressure was observed with higher doses of alfentanil and remifentanil and linked to the depression of the systemic hemodynamics (28). Estimates of potency by EEG revealed a 16-fold higher potency for remifentanil compared with alfentanil (29). Patients under remifentanil/N_2O anesthesia show EEG patterns similar to those of awake patients under midazolam sedation (30). There have been no reports of recall events or seizure activity (31). In an open study, remifentanil (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) as an intravenous analgesic adjunct was recently reported to be an alternative to propofol for supplemental sedation in patients undergoing surgery under local anesthesia (32).

Cardiovascular System

The hemodynamic response to remifentanil appears to be similar to that of other anilidopiperidines, i.e., mild bradycardia and a decrease of 15%–20% in arterial blood pressure may be observed (21). Pitts et al. (33) showed that the maximum cardiovascular depression was seen after the first dose of remifentanil and could be mostly be prevented through premedication with glycopyrrolate. However, these effects are not mediated through histamine release by remifentanil (34). Recently, there has been a resurgence of interest in the early tracheal extubation of patients undergoing heart surgery. Open heart surgery using a total intravenous anesthesia technique with remifentanil instead of fentanyl allows a faster extubation (35). However, the positive effects of remifentanil on recovery rate, length of stay in intensive care, cost reduction, etc. are not certain because the two controversial studies (35,36) represent too small a number ($n = 18$) to be conclusive.

In a study in which patients over the age of 70 yr received 3 times (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) the recommended induction dose, the hemodynamic effects were accompanied with profound hypotension (37), suggesting a more careful monitoring of those patients and an appropriate dosing regimen.

Metabolism of remifentanil during hypothermia was investigated in patients undergoing cardiopulmonary bypass surgery (38). As predicted, a prolongation of the half-life from 6 to 12 min after a reduction from 37°C body core temperature to about 28°C was seen (39), and the whole blood concentrations during cardiopulmonary bypass first decreased due to reduced enzymatic hydrolysis before reaching prebypass levels after rewarming (38). As an adjunct to sedation, remifentanil displays a more favorable hemodynamic profile in comparison with propofol in patients receiving regional anesthesia (40).

Respiratory System

In nonintubated patients, remifentanil produces respiratory depression in a dose-dependent fashion (9,41). However, because of remifentanil's lack of accumulation during continuous systemic administration, this effect is not expected to last for more than 10–15 min after discontinuation of the infusion. Infusion rates of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in awake patients and <0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in isoflurane anesthesia (1.2%) permit spontaneous breathing (41). Comparisons between patients receiving remifentanil and propofol infusions have shown remifentanil to be associated with lower arterial oxygen saturation and higher end-tidal carbon dioxide values in spontaneously breathing patients (32). Termination of remifentanil infusion is associated with a prompt spontaneous recovery of the responses to hypoxia and hypercarbia (9). A small pilot study by Peacock et al. (42) suggested a dosage regimen of a remifentanil starting infusion of less than 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in combination with propofol 133 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for total intravenous anaesthesia with spontaneous ventilation. However, it is the authors' opinion that this technique should not be used until further safety studies for remifentanil in spontaneously ventilated patients are published.

Hepatic and Renal Systems

Two groups (43,44) have investigated the effects of remifentanil in patients with liver disease. Both investigations revealed no significant difference in the clearance between the patients with liver disease and those with normal liver function. Interestingly, the same rate of clearance during the anhepatic phase of liver transplantation has been observed (44). Thus, as yet, the metabolism of remifentanil has not been found to be affected by hepatic function. However, it is reported that patients with severe liver impairment might be more vulnerable to the respiratory depression induced by remifentanil (43).

The effects of remifentanil on respiratory depression in severe renal disease has been investigated. No clinically significant difference was demonstrated between renally impaired patients and controls, suggesting that remifentanil-based anesthesia would be suitable for patients with renal disease (45).

Miscellaneous

As mentioned above, systemically administered remifentanil does not release histamine (34). It blocks the stress hormone response in a dose-dependent fashion (46). Intraocular pressure seems to be unaffected by remifentanil during eye surgery under local anaesthesia as shown by Sung et al. (47). Remifentanil causes adverse effects typical of μ-opioids, i.e., nausea, vomiting, pruritus, muscle rigidity, and cardiopulmonary suppression (18,19,22). However, there has been no higher incidence for nausea or vomiting reported for remifentanil compared with alfentanil (12). Comparison with fentanyl in patients undergoing eye surgery revealed a lower frequency of postoperative nausea for remifentanil (8%) compared with fentanyl (54%) (47). The incidence of muscle rigidity after intravenous delivery of remifentanil is similar to that with alfentanil (12). Although this appears to be mainly moderate, it might be prevented by slow injection of bolus doses of remifentanil over 60–90 s.

General Anesthesia

Remifentanil as a sole drug would not generally be considered suitable for the induction of anesthesia. However, its use in combination with N_2O, thiopental, or propofol for the induction of anesthesia was investigated in several studies (23,48). An infusion bolus of remifentanil (2 μg/kg), followed by a continuous infusion of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ plus thiopental (2.5 mg/min) induced loss of consciousness within minutes in patients undergoing major elective surgery (23). Induction of anesthesia with propofol (1 mg/kg) combined with bolus administration of remifentanil (1 μg/kg) and continuous infusion rates of 1 or 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ provide loss of consciousness within a median time of 4 min (48). Furthermore, significantly fewer patients receiving remifentanil at 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ responded to endotracheal intubation compared with those receiving it at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [6% vs 25%; $P < 0.05$ (48)]. A comparative study has shown that an infusion bolus of remifentanil at 1.0 μg/kg followed by a continuous infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was more effective than alfentanil (20 μg/kg bolus; 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$)

in obtunding the response to endotracheal intubation (18%–27%) (24).

The ability of remifentanil to exert synergy with hypnotic drugs has also been shown in an investigation of minimum alveolar anesthetic concentration (MAC) requirements of isoflurane (49). Remifentanil plasma concentrations of 1.2 ng/mL decreased the MAC of isoflurane by 50% with no further decreases at concentrations of up to 32 ng/mL, suggesting a ceiling effect. Comparable studies have reported a 50% reduction in MAC of isoflurane at fentanyl plasma concentrations ranging from 0.5 to 1.7 ng/mL and alfentanil concentrations of approximately 29 ng/mL with a similar ceiling effect (50,51). Thus, based on the ability of MAC reduction within comparable plasma concentrations, remifentanil appears also to be as potent as fentanyl (16).

Anesthesia with remifentanil, based on the dosing recommendation in Table 1, can be induced either with a slowly delivered loading bolus (1 μg/kg over 60–90 s) or with a gradual starting of the initial infusion (0.5–1 $\mu g \cdot kg^{-1} \cdot min^{-1}$; 10 min prior to endotracheal intubation) and a standard dose of a hypnotic agent (propofol, thiopental, or isoflurane). Preadministration of glycopyrrolate will reduce the incidence of bradycardia. For maintenance of analgesia after endotracheal intubation, the infusion rate of remifentanil can be titrated according to the patient's requirement and the anesthetic technique (Table 1). Because of the rapid onset and short duration of remifentanil, the rate of delivery can be increased in 25%–100% increments or decreased in 25%–50% increments. Due to its synergism with hypnotic drugs, isoflurane or propofol should be reduced concomitantly to prevent excessive depth of anesthesia.

Prior to emergence from anesthesia provided with remifentanil, postoperative pain management should be considered. Thus, before cessation of the remifentanil infusion, a potent antipyretic analgesic or a small amount of a long-acting opioid could be administered.

Summary

Because of remifentanil's unique pharmacokinetics, its systemic administration may be suitable for clinical settings where a potent, fast-acting, systemic μ-opioid with a rapid recovery is required, e.g., short painful intervention in the emergency room or the intensive care unit, or procedures in the day surgery or endoscopy suite. Total intravenous anesthesia for longer lasting procedures may become more promising because of the predictability of the offset of remifentanil even after long infusions. Its closest competitor, alfentanil, depends on its small volume of distribution for rapid termination of its effect, but still possesses the potential to accumulate because of its relatively long terminal elimination half-life. Remifentanil might be the first potent μ-opioid that does not accumulate in this fashion, and therefore it opens promising new clinical perspectives (52). However, as mentioned above, the relative short-lasting analgesic effect after cessation of the remifentanil infusion might require new, sophisticated techniques from the anesthetist to prevent immediate onset of postoperative pain.

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