

Remifentanyl in my practice

Remifentanyl is a congener of the fentanyl family of opioids that was approved for use as a supplement to general anesthesia (and monitored anesthesia care/acute pain management) by the United States Food and Drug Administration in 1996.¹ Pharmacodynamically, remifentanyl is in most regards indistinguishable from the other fentanyl congeners, producing analgesia, ventilatory depression and other effects typical of the fentanyl derivatives. Remifentanyl's unique feature is its short-acting pharmacokinetic profile. Remifentanyl's ester structure renders it susceptible to widespread ester hydrolysis, resulting in very rapid metabolism. Remifentanyl thus constitutes the first true "*ultrashort acting*" opioid.

Clinical Pharmacology

Remifentanyl undergoes widespread extrahepatic hydrolysis by non-specific esterases in blood and tissue to form an inactive carboxylic acid metabolite, GI90291.¹ To date, specific pharmacogenetic variants influencing remifentanyl pharmacokinetics have not been described, although a patient in whom remifentanyl was unexpectedly long acting has been reported;² remifentanyl clearance is not altered by pseudocholinesterase deficiency.^{3,4}

As a pure mu-agonist, remifentanyl produces all the opioid effects characteristic of the fentanyl family of opioids.¹ Its therapeutic effects therefore include dose-related analgesia and sedation. In terms of potency, remifentanyl is substantially more potent than alfentanil and slightly less potent than fentanyl.^{5,6}

Remifentanyl's adverse effect profile is also essentially indistinguishable from the previously marketed fentanyl congeners. Most importantly, remifentanyl produces a dose-dependent increase in the partial pressure of carbon dioxide as a result of ventilatory depression. Remifentanyl can also produce nausea, vomiting, muscle rigidity, bradycardia and hypotension. All of these effects are naloxone reversible.

It is very important to note that remifentanyl, like the other fentanyl congeners, interacts synergistically with hypnotic drugs such as propofol and the volatile anesthetic agents, resulting in a substantial reduction in the dosage required to maintain anesthesia with the hypnotics alone.^{7,8}

Remifentanyl's short acting pharmacokinetic profile is its unique pharmacologic feature. In terms of the rapidity with which concentrations fall after stopping an infusion, remifentanyl is dramatically different from the other fentanyl congeners. Remifentanyl's context sensitive half-time is short (approximately 3-5 minutes) and is independent of infusion duration.⁹

Remifentanil's latency-to-peak effect after bolus injection is also short. Remifentanil's $t_{1/2ke0}$, the parameter used to characterize the delay between peak drug levels in the plasma (or blood) and peak drug effect, is similar to that of alfentanil.^{5,10,11}

Clinical Application

Although remifentanil can be applied to most clinical situations in which the previously marketed fentanyl congeners are used, remifentanil is obviously best suited for cases where its responsive pharmacokinetic profile can be exploited. Remifentanil is perhaps best applied to cases when rapid recovery is desirable, when the anesthetic requirement rapidly fluctuates, when opioid titration is unpredictable or difficult, when there is a substantial danger to opioid overdose, when a "high dose" opioid technique is advantageous but the patient is not going to be mechanically ventilated postoperatively or when total intravenous anesthesia is the preferred approach.

In this context, one very unique aspect of remifentanil is that its use mandates a change in the traditional pharmacologic ratios of "balanced anesthesia". Because it is so pharmacokinetically evanescent, remifentanil can be infused to a profound level of opioid effect and yet enable the return of spontaneous ventilation only a few minutes later. Simulations using pharmacodynamic interaction "response surfaces" reveal that the optimal concentrations for a remifentanil anesthetic (in combination with propofol or a volatile agent) are targeted at a somewhat higher opioid concentration compared to the other, longer acting opioids.¹²

In very practical terms, the clinician must answer a few simple questions in deciding whether remifentanil might be appropriate for any given case: Is rapid recovery absolutely essential (e.g., neuroanesthesia, outpatient procedures)? Is the control of autonomic or movement responses to noxious stimuli important and perhaps problematic with longer acting opioids (e.g., patient with severe coronary artery disease for a brief outpatient procedure)? Will determination of the proper opioid dosage be difficult (e.g., children, elderly, hepatic disease patient)? Is there a substantial danger to opioid overdose (e.g., during fiberoptic intubation of the difficult airway)? Is the provision of inhalation anesthesia somehow difficult or contraindicated (e.g., malignant hyperthermia cases, airway cases requiring jet ventilation)? Is a TIVA technique obviously preferable (e.g., a patient with high risk for postoperative nausea and vomiting)? When the answers to these questions are yes, remifentanil may be helpful.¹³

References

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