Remifentanil Pharmacokinetics and Pharmacodynamics
A Preliminary Appraisal

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Summary

Remifentanil is a novel, short-acting μ-receptor opioid agonist currently in the late stages of development. A member of the 4-anilidopiperidine class, it is unique among the currently marketed agents because of its ester structure. Remifentanil undergoes widespread extrahepatic metabolism by blood and tissue nonspecific esterases, resulting in an extremely rapid clearance of approximately 3 L/min (180 L/h). Like the other members of this class of drugs, remifentanil is lipophilic and is widely distributed in body tissues with a steady-state volume of distribution of approximately 30 L.

Because of its unique metabolic pathway (among this group of drugs) and rapid clearance, remifentanil represents a new pharmacokinetic class of opioid. Unlike the other fentanyl congeners, termination of the therapeutic effect of remifentanil mostly depends on metabolic clearance rather than on redistribution. The context-sensitive half-time [defined as the time necessary to achieve a 50% decrease in blood (or plasma) concentration after termination of a variable-length, continuous infusion targeted to maintain a steady-state concentration, where the 'context' is the duration of the infusion] is strikingly short for remifentanil, and this is perhaps the most compelling evidence of the pharmacokinetic singularity of the drug. Determined by computer simulation, the context-sensitive half-time of remifentanil is approximately 3 minutes, and is independent of infusion duration.
Pharmacodynamically, remifentanil is similar to the other fentanyl congeners. The drug produces physiological changes consistent with potent μ-receptor agonist activity, including analgesia and sedation. Its adverse effect profile (like that of the other drugs of this class) includes ventilatory depression, nausea, vomiting, muscular rigidity, bradycardia and pruritus. Because it does not release histamine upon injection, remifentanil has fewer haemodynamic adverse effects than morphine. The therapeutic potency of remifentanil is somewhat less than that of fentanyl, with an effective concentration (producing 50% of maximal effect, as measured by electroencephalography) of approximately 15 to 20 μg/L. Speed of onset of effect is very rapid and is similar to that of alfentanil, which is reflected in a $t_{1/2}ke0$ (a parameter used to characterise the delay between peak blood drug concentration and peak pharmacodynamic effect utilising a theoretical effect compartment) of approximately 1 to 2 minutes.

Remifentanil is likely to be a welcome addition to the anaesthesia drug formulary. Anaesthetists have long recognised the need for a short-acting opioid with a predictable pharmacokinetic profile. Because the length of surgical procedures is often unpredictable, and because the level of surgical stimulation against which the depth of anaesthesia must be balanced is highly variable and dynamic, the advantages of predictably short-acting agents are obvious.

1. Chemical and Physical Properties

Remifentanil is a novel, short-acting μ-receptor opioid agonist currently undergoing phase III development in the US. While chemically related to the fentanyl family of short-acting phenylpiperidine derivatives commonly used as supplements to general anaesthesia, remifentanil is structurally unique among currently available opioids because of its ester linkage.

The ester structure of remifentanil renders it susceptible to hydrolysis by blood and tissue nonspecific esterases, resulting in very rapid metabolism. Remifentanil may thus constitute the first true ultra–short-acting opioid for use as a supplement to general anaesthesia, or any time that a short-lasting opioid effect is desired.

The aim of this review is to summarise the current knowledge of the clinical pharmacology of remifentanil, and to provide a preliminary appraisal of its clinical potential.