Remifentanil, an Esterase-Metabolised Opioid
What Advantages Does It Offer in Analgesia and Anaesthesia?

Marylin Lauwers, Frederic Camu and Caroline Vanlersberghe

Department of Anaesthesiology, Flemish Free University of Brussels Medical Center, Brussels, Belgium

Summary

Esterase hydrolysis is a metabolic pathway that can be exploited to increase the rate of metabolism and elimination and so reduce the duration of the pharmacodynamic effects of drugs. Previously applied to β-adrenergic blocking agents and muscle relaxants, this concept was recently used to develop an esterase-metabolised opioid, remifentanil.

Remifentanil has a predictable rapid onset, short duration and rapid offset of analgesic effect. This is likely to allow easy titration of analgesia to changing anaesthesia requirements during surgery. The metabolism of remifentanil by non-specific esterases in the blood and tissues prevents accumulation, even when given at high dosages over prolonged periods. Clinical recovery from anaesthesia is very rapid, irrespective of the age or physical status of the patient or the type or duration of surgery. In addition, the non-organ dependent elimination of remifentanil obviates the usual requirement for opioid dose adjustments in patients with hepatic impairment.

Adverse events of remifentanil are those typical of μ-opioid receptor agonists, including respiratory depression, muscle rigidity, hypotension and bradycardia.

Thus, the major benefits of remifentanil, the prototype esterase-metabolised opioid, are the achievement of intense, titratable intraoperative analgesia allowing for rapid clinical recovery without the risk of inducing recurrent postoperative respiratory depression. In addition, residual opioid activity disappears rapidly following discontinuation of the drug.

Opioids are an important component of balanced or total intravenous anaesthesia techniques through their ability to block autonomic nervous system and somatic physiological responses to noxious surgical stimuli. Thus, they reduce the surgical stress and its endocrine, immune and metabolic responses, effects that have been linked with an increased incidence of postoperative morbidity and ischaemic events. The most widely used opioids are morphine and the synthetic phenylpiperidine μ-opioid receptor agonists alfentanil, fentanyl and sufentanil.

All these opioids are capable of producing profound analgesia, but this action is often accompanied by typical adverse effects, both during and after anaesthesia. Recent developments in the perioperative use of opioid analgesics aimed to improve both their pharmacodynamic and pharmacokinetic properties. The pharmacokinetics of opioid analgesics suggest slow elimination when administered
for prolonged periods at dosages optimal for haemodynamic stability. Indeed, recovery from clinical effects is delayed and respiratory depression may persist after anaesthesia. Opioid drugs with a more predictable pharmacokinetic profile would offer better control of the state of anaesthesia, thereby improving patient care and the safety of anaesthesia.

Esterase hydrolysis is a metabolic pathway that can be exploited to increase the rate of metabolism and elimination and so shorten the pharmacodynamic effects of drugs. Previously applied to β-adrenergic blocking agents (esmolol) and muscle relaxants (mivacurium chloride), this concept was recently used to develop an esterase-metabolised opioid, remifentanil. This article reviews the clinical pharmacology of remifentanil, an opioid that is structurally related to fentanyl, but which has pharmacological characteristics that provide flexibility in treatment. It is a potent selective μ-opioid receptor agonist with little activity at κ- or δ-opioid receptors, and is distinguished from other analogues by its unique metabolic fate and ultra-short duration of action.12

1. Pharmacodynamics

Studies of remifentanil in healthy volunteers evaluated analgesia, sedation and respiratory depression, the major components of opioid action.

1.1 Analgesia

Remifentanil did not produce analgesia at doses below 0.5 μg/kg. In contrast, at doses of 1.5 and 2 μg/kg, analgesia with remifentanil was comparable with that seen with alfentanil 16 and 32 μg/kg. Analgesia was rapid in onset with both opioids, with a maximal effect at 1 to 3 minutes, and of short duration (less than 20 minutes).13

Measurement of analgesia is difficult in paralysed, anaesthetised patients. The EEG is therefore used as a surrogate measure of opioid drug effect on the CNS to estimate plasma concentration–effect relationships. Studies indicate that equilibration between blood concentration and effect site concentration occurs more rapidly with remifentanil [equilibration half-time (t1/2ke0) = 0.75 minutes] than with alfentanil, fentanyl or sufentanil (t1/2ke0 = 1.1 to 7 minutes).

1.2 Sedation

High dosages of remifentanil (2 to 8 μg/kg/min) induced sedation and increased delta wave activity on the EEG in human volunteers.14 The spectral edge frequency (the frequency beneath which 95% of the EEG power resides) is related to the concentration of drug in the blood. The arterial concentration of remifentanil associated with 50% of the maximal drug effect on spectral edge frequency was 19.9 μg/L, indicating that remifentanil is approximately half as potent as fentanyl and 30 times more potent than alfentanil.15 Concentration-dependent effects of remifentanil were demonstrated on the early cortical waves of the auditory evoked response, which are related to the degree of hypnosis, and of somatosensory response after tracheal intubation.16

1.3 Respiratory Depression

High doses of remifentanil significantly increased the peak elevation of arterial carbon dioxide (pCO2) and peak reduction of arterial oxygen levels (pO2).13 The relative potency of remifentanil compared with alfentanil for inducing respiratory depression was 23:1. The peak effects of both drugs occurred at 5 minutes post-dose, but the duration of effect was longer for alfentanil (30 minutes) than for remifentanil (20 minutes). These studies indicated that remifentanil infusions of 0.1 μg/kg/min and higher are likely to induce respiratory depression in unstimulated patients.

Respiratory depression disappeared faster with remifentanil than with alfentanil, due to the much more rapid offset kinetics of remifentanil.17 The time to 50% recovery of minute ventilation after ending drug administration was 5.4 minutes for remifentanil and 54 minutes for alfentanil. However, the reversal of the respiratory depressant effect with naloxone was less pronounced than for alfentanil (given at a dose ratio of 20:1), suggesting that high dosages of remifentanil (> 0.025 μg/kg/min) can overcome competitive receptor blockade.18