Drug Update

Remifentanil hydrochloride : an Opioid for the 21st Century

Lt Col DK Sreevastava*, Col AK Bhargava+

MJAFI 2004; 60 : 177-178

Introduction

Remifentanil hydrochloride is a recent addition to the group of narcotic analgesics [1]. It is structurally unique as it has an ester linkage that renders it susceptible to hydrolysis by nonspecific plasma and tissue esterases to inactive metabolites. This pathway of metabolism is responsible for its uniquely evanescent effect. Thus, the side effects for which opioids are much maligned are extremely transient when remifentanil is used.

Pharmacokinetics

Remifentanil has certain remarkable pharmacokinetic features [2] such as an extraordinary clearance of nearly 3 litres/minute, very short half-life of 3-10 minutes, exceptionally short time to peak effect of about 1.6 minutes (as effect-site concentration of remifentanil reaches a peak within 1.1 minutes only). Clinically, these properties translate into prompt achievement of steady-state concentration in the plasma and its effect site leading to rapid onset of effect and less accumulation than other opioids irrespective of the duration of the infusion. It also implies predictable termination of effects, hence allowing precise titration of its dose and action. The pharmacokinetics are unchanged in renal or hepatic failure. In addition, esterase metabolism appears to be a very well preserved system with little variability between individuals, which contributes further to the predictability of drug effect and enhances its safety profile.

Clinical effects

The effects are similar to all other opioids in equipotent doses. However, because of rapidity of onset, the effects may seem to be exaggerated. It causes dose-dependent hypotension, bradycardia and depression of respiration. Peak effects occur within 3-5 minutes of a single dose of remifentanil, however recovery is equally rapid. Remifentanil may cause chest wall rigidity after single doses of >1µg/kg administered over 30-60 seconds. Excessive muscle rigidity can be treated by decreasing the rate or discontinuing the infusion of remifentanil or by administering a neuromuscular blocking agent. Unlike morphine, it does not cause elevation in plasma histamine levels after administration of higher doses.

Clinical uses, dosages and administration

During general anaesthesia, as the analgesic component, remifentanil is initially administered as a bolus of 1 µg/kg intravenous (IV) over 60 to 90 seconds, followed by an infusion rate of 0.25-1 µg/kg/min along with a hypnotic or volatile agent for the induction of anaesthesia [3]. Maintenance infusion doses are in the range of 0.05-2µg/kg/min. Additional boluses of 1µg/kg can be given on as required basis. The rate of administration during anaesthesia can be titrated upward in 25-100% increments or downward in 25-50% decrements every 2-5 minutes to attain the desired level of effect.

In similar dosages, it is useful in selected, at-risk patients for suppression of the transient sympathetic nervous system response to direct laryngoscopy and tracheal intubation.

During general anaesthesia with a laryngeal mask, remifentanil infusion @ 0.05 µg/kg/min or less, provides supplemental analgesia while allowing spontaneous ventilation with propofol or isoflurane. In these situations, bolus doses of remifentanil are not recommended because of high incidence of side effects.

Remifentanil has been evaluated in a clinical trial in children 2-12 years of age undergoing strabismus surgery with satisfactory results [4, 5]. While in paediatric patients, the doses remain unchanged, in elderly patients (> 65 years) the pharmacodynamic activity of remifentanil increases with advancing age and therefore the starting doses should be decreased by 50%.

It has been used safely in coronary artery bypass graft (CABG) and neurosurgery with good results. Particularly, it is useful for long operations, when a quick recovery is desired (neurological assessment, wake-up test).

*Associate Professor, +Professor and Head, Department of Anaesthesia and Critical Care, Armed Forces Medical College, Pune.

For postoperative analgesia, remifentanil should be initially administered by continuous infusion at a rate of 0.1 µg/kg/min. The infusion rate may be adjusted every 5 minutes in 0.025 µg/kg/min increments to balance the patient's level of analgesia and respiratory rate. Rates greater than 0.2 µg/kg/min are generally associated with respiratory depression (respiratory rates less than 8 breaths/min). In addition, bolus doses also should be avoided because of a high incidence of apnea, muscle rigidity and tachycardia.

As a part of sedation technique, remifentanil, in the dosages of 0.05 to 0.10 µg/kg/min in combination with midazolam, 2 mg IV, provides effective sedation and analgesia during monitored anaesthesia care or when a profound analgesic effect is desired transiently (eg. performance of a block).

Its use in obstetric practice cannot be recommended at present since it is associated with high incidence of maternal desaturation and other side effects and is not shown to be superior to any of the existing methods.

Precautions

Remifentanil produces adverse events that are characteristic of opioids, such as respiratory depression, bradycardia, hypotension and skeletal muscle rigidity. These events fortunately dissipate within minutes of discontinuing or decreasing the infusion rate of remifentanil. Notwithstanding this, precautions as mentioned below should be taken to avoid accidents.

Remifentanil should be administered only by persons specifically trained in the use of potent opioids. Such training must include the establishment and maintenance of a patent airway and assisted ventilation.

Incremental infusion rate should not exceed 0.025µg/kg/min at 5 minute intervals. Because of rapid offset of effect, discontinuation of an infusion of remifentanil should be preceded by the establishment of adequate postoperative analgesia.

Continuous infusions of remifentanil should be administered only by an infusion device. IV bolus administration of remifentanil should be used only during the maintenance of general anaesthesia.

Injections of remifentanil should be made into IV tubing at or close to the venous cannula and should immediately be cleared to prevent the inadvertent administration of remifentanil at a later point in time. Failure to do so has been associated with the appearance of respiratory depression, apnea and muscle rigidity upon the administration of additional fluids or medications through the same IV tubing.

Remifentanil should not be administered into the same IV tubing with blood due to potential inactivation by nonspecific esterases in blood products.

Due to the presence of glycine in the formulation, remifentanil is contraindicated for epidural or intrathecal administration. Remifentanil is also contraindicated in patients with known hypersensitivity to fentanyl analogs.

Conclusion

The utility of remifentanil stems from rapidity of onset of its effect, ability to titrate its desired effect and to maintain a sufficient plasma opioid concentration to suppress the stress response and finally rapidity of recovery from its effects. It has proven to be of immense value in anaesthetic practice. It is because of these features, remifentanil has been called a "designer drug" and rightly so, since it allows the user to practically "dial" its effect making it truly the opioid for the 21st century.

References

1. Burkle H, Dunbar S, Van Aken H. Remifentanil : A novel short acting µ-opioid. Anesth Analg 1996;83:646-51.
2. Egan TD, Lemmens JHM, Fiset P et al. The pharmacokinetics of the new short acting opioid remifentanil (G187084B) in healthy adult male volunteers. Anesthesiology 1993;79:881-92.
3. Hogue CW, Bowdle TA, O'Leary C et al. A multicenter evaluation of total intravenous anaesthesia with remifentanil and propofol for elective inpatient surgery. Anesth Analg 1996;83:279-85.
4. Grundmann J, Uth M, Eichner A, Wilhelm W, Larsen R. Total intravenous anaesthesia with propofol and remifentanil in paediatric patients : a comparison with a desflurane-nitrous oxide inhalation anaesthesia. Acta Anaes Scand 1998;42:845-50.
5. Sreevastava DK, Madan R, Mahendru A, Rewari V, Kaul HL. Total intravenous anaesthesia with propofol and remifentanil versus inhalational anaesthesia using halothane, nitrous oxide and pethidine in children undergoing strabismus surgery. (In press).