

EDITORIAL I

Remifentanyl—an opioid for the 21st century

Remifentanyl is a fentanyl derivative with an ester linkage (3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine] propanoic acid, methyl ester). It is a pure μ agonist [1] and the rapid breakdown of the ester linkage by non-specific tissue and plasma esterases is responsible for its unique characteristics. Considerable work is underway investigating this new opioid but, as yet, few data are available in the literature. However, these data enable an initial assessment of the properties of remifentanyl and its potential use in anaesthesia.

The speed of onset of action of remifentanyl is similar to that of alfentanil [2]. In patients undergoing elective inpatient surgery, the volume of distribution at steady state was 25–40 litre, total clearance 4.2–5 litre min^{-1} and terminal $T_{1/2}$ 10–21 min. Clearance was not affected significantly by body weight, sex or age [3], and it is likely to be independent of renal or hepatic function [4–6]. Furthermore, remifentanyl is a poor substrate for butyrylcholinesterases (pseudocholinesterases) *in vitro* and clearance should be unaffected by cholinesterase deficiency or administration of anticholinesterases [data on file, Glaxo].

The main metabolic product of ester hydrolysis is a carboxylic acid derivative (GI90291) which is excreted by the kidneys (elimination half-life 88–137 min [3]). Although elimination of GI90291 is delayed in renal failure [6], significant pharmacological effects are unlikely as its potency relative to remifentanyl is only 0.1–0.3 %.

At present, remifentanyl is formulated in glycine, an inhibitory neurotransmitter. Consequently, spinal or extradural administration is not recommended and there are no data on administration of remifentanyl by these routes.

Rapid biotransformation to minimally active metabolites should be associated with a short, predictable duration of action with no accumulation of effect on repeated dosing or with continuous infusion. The available data suggest that remifentanyl behaves in this way. Because of its pharmacokinetics, similar properties were expected of alfentanil [7]. However, clinical experience has shown that prolonged infusion of alfentanil may be associated with prolonged recovery time. It is now appreciated that the offset of clinical effect is not simply a function of the half-life, particularly in multicompartmental systems. It may be affected by rate of equilibration between plasma and effector site, method of administration (e.g. continuous infusion, intermittent boluses) and duration of infusion [8, 9]. Hughes,

Glass and Jacobs [10] proposed the use of context-sensitive half-time ($T_{1/2\text{context}}$) and defined this as the time for the plasma concentration to decrease by 50 % after terminating an i.v. infusion designed to maintain a constant plasma concentration. Context refers to duration of infusion. They demonstrated that context-sensitive half-times of commonly used i.v. anaesthetic agents and opioids could differ markedly from elimination half-lives and were dependent on duration of infusion.

In contrast, because of the unique metabolism of remifentanyl, its $T_{1/2\text{context}}$ should be rapid and relatively independent of the duration of infusion. This has been confirmed by *in vivo* studies. Remifentanyl $T_{1/2\text{context}}$ was 3.1 min after a 3-h infusion (at a rate sufficient to depress minute ventilation by 40–70 %) with a time to pharmacodynamic recovery, as determined by minute ventilation, of 5.8 min. In comparison, the times for alfentanil were 44 and 34.2 min, respectively [11]. In another study, remifentanyl and alfentanil were infused i.v. at rates of 0.05 $\mu\text{g kg}^{-1} \text{min}^{-1}$ and 0.5 $\mu\text{g kg}^{-1} \text{min}^{-1}$, respectively, for 4 h. These infusion rates resulted in a similar degree of respiratory depression. On termination of the infusions, ventilation recovered in 8 min after remifentanyl and 61 min after alfentanil [12].

It has been confirmed that the effects of remifentanyl are antagonized by naloxone [13]. Its potency is similar to that of fentanyl, and 15–30 times that of alfentanil [14, 15]. The effects of remifentanyl on arterial pressure and heart rate after bolus administration of various doses of remifentanyl (2–30 $\mu\text{g kg}^{-1}$) have been investigated 10 min after induction of anaesthesia with etomidate and midazolam and maintenance with nitrous oxide–isoflurane–vecuronium [16]. Mean reductions in arterial pressure and heart rate in excess of 20 % were found, the effects being unrelated to dose. I.v. administration of remifentanyl resulting in hypotension was not associated with histamine release. More detailed haemodynamic investigations are awaited, as are comparisons with other opioids.

The EEG effects of remifentanyl are similar to those of other opioids in humans [17] and dogs [18]. Remifentanyl infusion is associated with an age-related reduction in the MAC of isoflurane in humans [19]. For example, at age 40 yr, MAC was reduced by 50 % at a target remifentanyl plasma concentration of 1.2 ng ml^{-1} . The effect was more marked in older patients. A ceiling effect was observed at 32 ng ml^{-1} and MAC was not reduced to zero.

Inevitably, nausea and vomiting may be consequences of remifentanyl administration. However, because of its rapid clearance, the incidence of these side effects may prove to be less compared with other opioids in some situations. For example, in patients undergoing unilateral eye surgery under local anaesthesia and i.v. fentanyl or remifentanyl, the incidence of nausea after surgery in the recovery room was 54 % and 8 %, respectively [20]. However, it is necessary for these provisional data to be confirmed in larger studies.

The characteristics of a remifentanyl–nitrous oxide anaesthetic technique have been reported in the US literature [21–23]. Haemodynamic stability and rapid recovery were described. However, such techniques, without the use of an i.v. or volatile anaesthetic drug, are unlikely to gain widespread acceptance in the UK because of concerns regarding awareness. Studies are underway investigating the use of remifentanyl infusions with propofol or volatile anaesthesia but few data are available at present.

Rapid i.v. infusion of large doses of potent opioids are associated with an incidence of muscle rigidity and remifentanyl is no exception. In a comparative study of remifentanyl $1\text{-}\mu\text{g kg}^{-1}$ bolus followed by $0.5\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$ and alfentanil $25\text{-}\mu\text{g kg}^{-1}$ bolus followed by $1\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$, the incidence of muscle rigidity was 8 % and 5 %, respectively [data on file, Glaxo]. The majority of cases were described as mild or moderate (i.e. manual ventilation was still possible). As with other opioids, the incidence and severity are dependent on dose and rate of administration.

Based on the evidence so far presented, it may be that remifentanyl will be used widely because of its predictability and easily reversible effects. However, its use also presents the anaesthetist with a significant challenge. If remifentanyl is the only opioid administered during anaesthesia, it must be remembered that shortly after the end of the procedure, the patient will not benefit from opioid-based analgesia. This problem must be addressed if remifentanyl is to be used for procedures associated with significant postoperative pain. Such techniques may include reducing the infusion rate of remifentanyl to analgesic doses (which should be relatively simple), immediate administration of longer acting opioids as the effects of remifentanyl begin to fade and increased awareness of the possibilities of local anaesthesia.

Such a short-acting and predictable opioid has not been available before to anaesthetists and it is difficult to predict precisely where its niche will lie. However, it has numerous potential applications ranging from short stimulating procedures to prolonged infusions where rapid recovery is required. Possibilities abound, not only in anaesthesia but in intensive care medicine. Overall, it represents a unique alternative to the currently available opioids and the results of further studies are awaited with interest.

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