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New opioids in 1-day surgery

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Abstract

The development of 1-day surgery has determined the need to adopt anaesthetic techniques that allow a quick discharge. While this is possible with loco-regional techniques, general anaesthesia has a longer recovery period because of the pharmacological profile of currently available drugs. Over the last few years, pharmaceutical research has been developing new drugs that guarantee a rapid elimination and a predictable offset to be employed in day surgery. Among these drugs, remifentanil is a new opioid which seems promising in regard to these characteristics. In this review we present pharmacokinetic and pharmacodynamic characteristics of remifentanil and the possible clinical implications that result from its use in 1-day surgery. © 1997 Elsevier Science Ireland Ltd.

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1. Introduction

New demands regarding the management of the surgical patient arise from the need to reduce the postoperative period and recovery as much as possible and the attempt to treat 'routine' patients with 1-day surgery when possible.

As regards intravenous analgesics used intraoperatively, no drug responds adequately to these new demands. In fact, the only intravenous drugs that provide an efficacious intraoperative analgesia are synthetic opioids. Opioids employed today, however, are characterised by pharmacokinetic properties which make their use unpredictable. Their relatively long duration of action (the opioid with the shortest duration of action is alfentanil: $t_{1/2\beta} = 90$ min) potentially delays the patient's recovery time and their redistribution from the tissues to the blood could cause late adverse effects.

In the last few years, new anaesthetic agents with a shorter duration of action have been studied and commercialised. Examples include muscle relaxants (mivacurium and rocuronium), a hypnotic agent (propofol) and new halogenated agents (desflurane and sevoflurane).

As for the opioids, it is only recently that a new compound that could respond to the recent demands in anaesthesia has been developed. This compound, like its precursors fentanyl, sulfentanil and alfentanil, belongs to the anilidopeperidine class with a difference in the chemical structure: an ester linkage which has the property to undergo hydrolysis by non-specific blood and tissue esterases. Among these opioids called esterase-metabolised opioids (EMO), remifentanil is the first to be commercialised and is actually in phase III study both in Europe and in the United States.

The aim of this paper is to analyse the real advantages of this new drug intraoperatively as well as postoperatively with particular attention being paid to the pharmacokinetic and pharmacodynamic properties described in the literature to date.

2. Pharmacology

Remifentanil is a hydrochloride salt of 3-[methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine] propanoic acid methyl ester. Its chemical structure is similar to that of fentanyl, alfentanil and sulfentanil,

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since they all belong to the same 4-anilidopiperidine structural class.

Remifentanil has been synthesised by the substitution of the aryl groups of the 4-anilidopiperidine structure with a lipophilic group (methyl ester). This new structure maintains the characteristics of the aryl group binding, but the enzymatic breakdown by esterases forms a polar group which has a lower affinity to the sites of action of the drug [1].

Since remifentanil is a very unstable compound, it is available as a lyophilised powder which contains free bases and glycine with the addition of hydrochloric acid or sodium hydroxide to reach a pH of 3.0. It is soluble in water ($pK_a = 7.07$) and can be prepared for injection with water or 5% dextrose solution [2].

The most important and singular pharmacokinetic characteristics of remifentanil concerns its metabolism. In fact, this drug is metabolised primarily by non-specific blood and tissue esterases. A total of 90% of the drug is de-esterified, forming a carboxylic acid, GI-90291 [2], which is eliminated with the urine without further changes [3]. A smaller part is converted to GI-94219 by an *N*-dealkylation [2]. Thus, unlike other opioids, only a minor part of remifentanil undergoes hepatic metabolism.

This is confirmed in the literature by elevated clearance values which are 3–4 times above the hepatic blood flow rate (Table 1).

The clearance of remifentanil (34.7–71.4 ml/kg per min) is higher than that of other fentanyl derivates since the clearance of fentanyl is 10–20 ml/kg per min, of sulfentanil 10–15 ml/kg per min and of alfentanil 4.2–9.0 ml/kg per min.

It seems that a fast elimination rather than the redistribution is responsible for the loss of the therapeutic effect of remifentanil [2].

As regards the distribution volumes (V_{ss}) analysed to date, they appear to be comparable to those of alfentanil. In a study in 1993, Egan et al. reported for remifentanil a V_{ss} of 31 ± 7.4 l [4] and in another randomised, crossover and comparative study between remifentanil and alfentanil, the V_{ss} for two opioids was found to be 22.4 and 38.2 l, respectively [5]. The V_{ss} of fentanyl and sulfentanil, however, are higher (280 and 173.9 l, respectively) because of their higher liposolubility.

Table 1
Remifentanil and alfentanil clearances [3–6]

References	Remifentanil	Alfentanil
Egan et al., 1993 [4]	40.0 ml/kg per min (168 l/h)	—
Westmoreland et al., 1993 [6]	58.6–71.4 ml/kg per min (246–300 l/h)	—
Glass et al., 1993 [3]	41.2 ml/kg per min (173 l/h)	9.0 ml/kg per min (37.8 l/h)
Egan et al., 1994 [5]	34.7 ml/kg per min (146 l/h)	4.2 ml/kg per min (17.6 l/h)

The half-life of distribution for remifentanil ($t_{1/2a}$) is 0.9 min, which is lower than that of fentanyl (15–20 min) and alfentanil (4–17 min). The half-life of elimination ($t_{1/2\beta}$) of remifentanil is 9.1 min [4,5], which is definitively lower that those of the other opioids: 120–240 min for fentanyl, 120–180 min for sulfentanil and 60–120 min for alfentanil.

Nothing has been published concerning the protein linkage of remifentanil, but Egan et al. [5] suppose that the drug binds to a high extent to plasma proteins, as do other opioids.

Egan et al. [4,5] and Westmoreland et al. [6] state that remifentanil has a linear pharmacokinetic which can be confirmed by the evidence that the total clearance and the V_{ss} are independent from the dose after bolus injection of 5–30 mg/kg as well as after 20 min of an infusion of 1–8 mg/kg per min of the drug.

As mentioned before, the main metabolite of remifentanil, GI-90291, is eliminated without further alterations by the kidneys. Consequently, renal impairment significantly prolongs the half-time of elimination. However, no specific clinical problems resulted in these cases, since GI-90921 is, in fact, a mu-agonist with an affinity for the mu-receptors, but this affinity is only 1/300 to 1/1000 that of remifentanil.

It seems from different published studies that remifentanil could be used without particular restrictions in patients with renal or hepatic impairment [7–10]. Moreover, no alterations in the pharmacokinetic parameters with regard to gender, age, weight and height have been documented so far [2,6].

Finally, a defect in pseudocholinesterase appears not to influence the pharmacokinetics of remifentanil. In vitro tests demonstrated that remifentanil is not a valid substrate for the butirilcholinesterase (pseudocholinesterase) [2]. In vivo, this drug does not seem to interact with succinilcholine, which is also metabolised by the pseudocholinesterase.

Many authors use a particular concept to compare the pharmacokinetics of the different opioids: the 'context-sensitive half-time' [3,4,6]. It is defined as the time needed to reduce the drug concentration by 50% after the interruption of a continuous infusion aimed at maintaining a constant plasma concentration (the context is the duration of infusion). The context-sensitive half-time is useful for drugs that, like opioids, present a complex three compartment pharmacokinetic profile and for which the half-time of elimination does not reflect the global degradation curve of the drugs.

Hughes et al. [11] stated that the context-sensitive half-time allows a more significant graphic representation of some pharmacokinetic parameters.

The context-sensitive half-time of remifentanil is very short (3–5 min) and does not increase with an increase of the infusion rate [3–6,12] Other opioids show a context-sensitive half-time which directly depends on the duration of administration and is found to be noticeably longer than that of remifentanil [2].

Kapila et al. [12] suggested that the time needed to reduce the concentration of remifentanil at their action sites of 80% is about 5 min. This corresponds approximately to the time needed to make the patient able to leave the operation theatre.

Like other 4-anilidopiperidine opioids, remifentanil interacts as a mu-receptor agonist [12]. Naloxone acts as an antagonist [13], whereas antagonists selective for other subtype receptors have no effects.

The alterations on the EEG caused by remifentanil are those of other opioids, namely, an increased amplitude and a decreased frequency of the EEG waves [14]. The potency of remifentanil is slightly inferior to that of fentanyl [15] and, as different authors suggest, 16–50 times greater than that of alfentanil [3,16,17].

The main metabolite, GI-90291, has a markedly weaker action. Cunningham et al. [18] estimate the potency to be 1/300 to 1/1000 that of remifentanil. Nevertheless, other studies are needed to establish whether or not this metabolite prolongs the duration of action of remifentanil in patients with renal impairment.

The speed of onset of the therapeutic effect of remifentanil is very fast, similar to that of alfentanil. Egan et al. [16] states that the $t_{1/2ke0}$ of remifentanil is 1.41 min and that of alfentanil 1.13 min; $t_{1/2ke0}$ is defined as the delay between the achievement of a peak blood concentration and the pharmacodynamic peak effect of a drug.

Side effects of remifentanil are comparable to those of the fentanyl-family opioids. In particular, respiratory depression appears early—as with alfentanil—but has a much shorter duration [3].

Cardiovascular effects of remifentanil are similar to those of other fentanyl derivates and are caused by a increased vagal nerve activity mediated by the CNS and not due to histamine release [2].

Remifentanil also determines nausea, vomiting and muscular rigidity [3,4].

3. Therapeutic considerations

An intraoperative intravenous opioid should have the following characteristics:

1. rapid onset of action
2. rapid and foreseeable response to dosage variations
3. intraoperative haemodynamic stability
4. absence of accumulation and consequently no effects at distance even after a prolonged administration
5. no adjustment of the dosages is necessary in patients with renal or hepatic impairment, or for other variables such as gender, age, weight and height
6. reduction of hypnotic agents and other sedatives
7. rapid resolution of the effects and early recovery from anaesthesia
8. cost reduction.

Based on the pharmacokinetic and pharmacodynamic data previously described, it seems that remifentanil meets these demands. In fact, its esterase metabolism renders the action of remifentanil foreseeable and its use easy, since no accumulation phenomena have been observed and recovery from anaesthesia is rapid. The short action of the drug may allow a continuous adaption of the dosage to the intraoperative pain intensity, which varies significantly in different surgery periods. This would result in a better balance of anaesthesia with a more specific and adequate opioid use.

There seem to be no limitations of use in patients affected by renal or hepatic impairment, or in elderly patients. Moreover, it seems to improve haemodynamic stability due to a better tolerability during the different phases and to a dosage reduction of other hypnotics (propofol [19], tiopentale [16] and isoflurane [20]) and the need for anaesthesia, and not because of a reduced cardiovascular depressant effect compared with other opioids. The reduction of hypnotics may not only have clinical advantages but also economic effects. In fact, a polypharmacological treatment to maintain an adequate anaesthesia stage is not always the most economic one since expensive drugs such as propofol and last-generation halogenates must often be associated. In addition, delivery systems and sophisticated monitoring are required.

The real economic advantages of remifentanil may not depend on a more limited anaesthetic drug consumption but on a reduction of induction, recovery and discharge times in anaesthesia. In fact, the rapid recovery from anaesthesia and the absence of a drug redistribution from the tissues to the blood reduce the risks of delayed effects and allow a rapid discharge of the patients from the operating theatre. This improves the management of the operating rooms and reduces the need for recovery rooms which are, however, rare in Italian hospitals.

The characteristics of remifentanil could make it useful in 1-day surgery and in invasive and painful diagnostic procedures that require adequate analgesia and a rapid recovery of consciousness. Remifentanil may thus be a first-choice drug for these procedures and render them safer. Physicians would thus be stimulated to employ 1-day surgery and diagnostic methods with a consequent reduction of hospital recoveries and correlated costs.

Table 2
Recommended starting infusion rates and dose ranges for remifentanil

Indication	Remifentanil bolus infusion (μg/kg)	Remifentanil continuous infusion (μg/kg per min)	
		Starting rate	Range
Induction of anaesthesia in ventilated patients	1	0.5–1	—
Maintenance of anaesthesia			
Nitrous oxide (66%)	—	0.4	0.1–2
Isoflurone (starting dose 0.5 MAC)	0.5–1	0.25	0.05–2
Propofol (starting dose 100 μg/kg per min)	—	0.25	0.05–2
Parenteral analgesia in immediate postoperative period	Not recommended	0.1	0.025–0.2
Anaesthesia in spontaneous ventilation	Not recommended	0.04	0.025–0.1

Remifentanil, like other fentanyl derivates, has some negative aspects. As with other opioids, respiratory depression, nausea, vomiting, bradycardia, hypotension and muscular rigidity are common. However, the most important problem associated with remifentanil, especially for those who have little experience with this drug, is the rapid loss of the analgesic effect after the interruption of drug administration.

This effect is inconvenient if it happens during anaesthesia but it may also be annoying shortly after recovery. In this period the patient perceives pain with maximum intensity. It is therefore advisable to administer the drug in a continuous manner, preferably with a continuous infusion device (pump), throughout the whole duration of the surgery until the closure of the skin, with the dosages proposed in Table 2. Once the patient has recovered from anaesthesia, adequate analgesic therapy should be set up as soon as possible.

Today nothing can be said about the utility of remifentanil for postoperative pain since clinical experience is lacking.

Continuous intravenous infusion during the postoperative period in hospitalised patients has given positive analgesic results, so far without side effects or dangerous inconveniences for the patient.

Remifentanil has not yet been proposed for the treatment of chronic pain but it may be interesting to evaluate its use in boluses for breakthrough pain.

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