Review Article
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A great tool that resurfaced during the pandemic: Remifentanil

Abstract

During anesthetic management, drugs such as fentanyl are required. This is a synthetic opioid used routinely. However, there are options derived from fentanyl, such as remifentanil, which has been referred to in the literature as an ideal opioid in anesthesiology due to its pharmacokinetic characteristics. Remifentanil is used in general or local anesthesia, as analgesic premedication for induction of anesthesia, and as an adjuvant in the maintenance of general anesthesia. In addition, it is suggested as a sedative in patients admitted to intensive care in patients undergoing mechanical ventilation, for analgesia and sedation in postoperative cardiac surgery and other types of surgeries, even in minor procedures. In this review, we focus on describing the use, properties, and anesthesiologic characteristics of remifentanil, as well as its repercussions of use.

Keywords: remifentanil, anesthesia, opioids, side effects of remifentanil, intravenous anesthesia, R-4263.

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Abbreviations: FDA, Food and Drug Administration; TIVA, intravenous anesthesia; OIT, orotracheal intubation; TCI, target-controlled information; CMRO2, cerebral metabolic rate of oxygen.

Introduction

At the end of the 1950s, Paul Janssen's group prepared a series of 4-phenyl-piperidine derivatives of pethidine with analgesic activity. One of these derivatives, phenazopyridine, gave rise to the compound "R-4263", later named "fentanyl," with a pharmacological profile typical of opiates with rapid onset of action and short duration. Fentanyl has classically been used intravenously in anesthesia. Still, thanks to pharmaceutical technology, in recent years, its interest has increased with preparations that facilitate its transdermal administration, which gives it a prolonged action, and with transmucosal absorption presentations, which makes it a fast-acting opioid without the need for intravenous administration.[1]

Its clinical use is diverse: as a complementary narcotic analgesic in general or local anesthesia, for analgesic premedication for induction of anesthesia and as an adjuvant in the maintenance of general and regional anesthesia, as a sedative in patients admitted to intensive care in patients undergoing ventilation mechanical, for analgesia and sedation in postoperative cardiac surgery and other types of surgeries, sedation/analgesia for minor procedures.[2] In the last 30 years, the role of opioids in anesthesia has undergone several changes. Initially used as a premedication and adjunct to general anesthesia, they have evolved to become the main anesthetic agents. It has been shown that the response to surgical stress can be attenuated and that, administered in sufficient doses, opioids provide better results for the patient.[3]

Anesthetic management usually requires the use of drugs such as fentanyl, which is a synthetic opioid that is used successfully on a routine basis. However, there are options derived from fentanyl, such as remifentanil, which has been referred to in the literature as an ideal opioid in anesthesiology due to its pharmacokinetic characteristics.[4] Therefore, this review focuses on remifentanil's use, properties, and anesthesiologic characteristics.

Properties and characteristics of remifentanil

The pharmacokinetic profile of remifentanil is unique and makes it an ideal choice for anesthesia and conscious sedation.[5] Remifentanil is an ultra-short-acting synthetic opioid developed in the early 1990s, approved for clinical use by the FDA (Food and Drug Administration) in July 1996, and reintroduced in Mexico at the end of 2019, authorized by Cofepris. It is a derivative of piperidines, with 92% protein binding, a molecular weight of 412 kD, pKa 7.3, with a strong affinity for the μ-opioid receptor and less for the δ and κ receptors. It does not bind to other non-opioid receptors and can be antagonized by naloxone. Its metabolite is carboxylic acid, which is pharmacologically inactive, and 90% is eliminated by the kidneys.[6]

The structure of remifentanil, like alfentanil and sufentanil, is based on its parent drug, fentanil (Figure 1). The difference is the addition of an ester group that allows it to be rapidly metabolized by nonspecific plasma and tissue esterases, which appear present from birth. This gives rise to its characteristic ultra-fast displacement and allows rapid titration [7]. In addition, it will enable it to be independent of liver and kidney function so that it can be safe in patients with kidney and liver damage. Similarly, the pharmacokinetics of remifentanil does not change in patients with pseudocholinesterase activity deficiency, so that it can be administered safely in these patients.[6]

Pharmacodynamics of remifentanil

Remifentanil belongs to the family of piperidines, with a strong affinity for the μ-opioid receptor and less for the δ and κ receptors. It shows a pharmacodynamic profile like other opioids, such as fentanyl and alfentanil. It is 20-60 times more potent than alfentanil, has one-tenth the potency of sufentanil, and is similar in power to fentanyl.[7,8] In adults, the pharmacodynamics of remifentanil is affected by age concerning potency and sensitivity to adverse effects. However, the pharmacodynamic effects in preterm infants, neonates, infants, and children are presumed to be different.[8]

The use of remifentanil in general anesthesia combined with halogenated agents such as sevoflurane provides shorter extubation and recovery times but greater pain intensity, suggesting an adequate strategy for postoperative pain control. Remifentanil has been successfully used in total intravenous anesthesia (TIVA) and propofol. Among its benefits are rapid recovery, decreased nausea, vomiting, and postoperative delirium. It has even become an ideal technique for patients at risk of malignant hyperthermia.[9] The rapid recovery is due to a relatively short half-life of only 3-4 minutes regardless of infusion time, and clinically, it takes about 6-12 minutes before the patient

resumes spontaneous ventilation after remifentanil is discontinued or is reduced to low concentration.[5]

Remifentanil profoundly blocks airway reflexes and, in most circumstances, allows tracheal intubation without using muscle relaxants in adults and children.[5] With doses of 3 µg/kg of remifentanil and 3 µg/kg of propofol, it has provided excellent intubation conditions in 90% of children.[9]

Clinical applications of remifentanil

The clinical use of remifentanil is diverse since it can be used as a complementary narcotic analgesic in general or local anesthesia, for analgesic premedication for induction of anesthesia, and as an adjuvant in the maintenance of general and local anesthesia. In addition, it is a sedative in patients admitted to intensive care in patients undergoing mechanical ventilation, for analgesia and sedation in postoperative cardiac surgery and other types of surgeries, and sedation/analgesia in minor procedures (Figure 1A).[10] The dose of remifentanil for induction and intubation appears to depend on clinical experience, user preference, and patient and operational factors. Due to its ultrashort-acting properties, it is recommended primarily as a continuous infusion administered with pump sets that allow calculations in micrograms per kilogram per minute (µg/kg/min). Avoidance of bolus drug administration is recommended due to the high incidence of cardiovascular collapse, rigidity, and respiratory depression.[11]

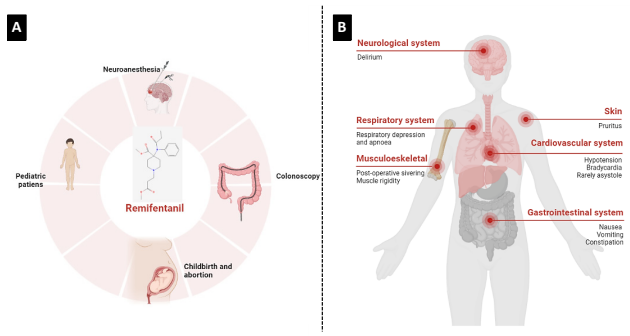

Figure 1 A) Uses in anesthesia and B) side effects of remifentanil.

Table 1 Pharmacokinetic profile of remifentanil in children and adolescents

Parameter	0-2 months	2 months-2 years	2-6 years	7-12 years	13-16 years	16-18 years
[ ] max (ng/ml)	24.2±10.2	24.5±3.7	34.8±8.2	42.5±13.7	35±10.2	42.7±12.9
Volume of distribution (ml/kg)	452.8±144.7	307.9±89.2	240.1±130.5	248.9±91.4	223.2±30.6	242.5±109.2
Clearing (ml/kg/min)	90.5±36.8	92.1±25.8	76±22.4	59.7±22.5	57.2±21.1	46.5±2.1
Half life (min)	5.4±1.8	3.4±1.19	3.6±1.19	5.3±1.4	3.7±1.1	5.7±0.7

Neuroanesthesia

Surgical resection of tumors near functional brain areas carries a significant risk of neurological disability. When tumors are close to motor areas, localization of the primary motor cortex using single electrical stimuli and electromyography helps determine the safest surgical approach. Remifentanil has a pharmacokinetic profile that suits these requirements.[21,22] Continuous intravenous administration of Remifentanil can be performed using conventional infusion pumps and rate-of-use techniques that allow the anesthesiologist to select and adjust a target plasma concentration to achieve the desired pharmacodynamic effect.[23]

The advantages of remifentanil over other opiates are great analgesic potency, short latency, rapid dosage, and elimination. For these reasons, it is the drug indicated in neurosurgical surgery since it provides hemodynamic stability, faster awakening, and better postoperative recovery than other opioids, allowing an immediate postoperative neurological evaluation.[24] On the other hand, laryngoscopy and orotracheal intubation (OIT) during induction of

Pediatric patients

In the last 30 years, the role of opioids in pediatric anesthesia has undergone several changes. Initially used as a premedication and adjunct to general anesthesia, they have evolved to become the main anesthetic agents. It has been shown that the response to surgical stress can be attenuated and that, administered in sufficient doses, opioids provide better results for the patient.[10] The limiting factor in the administration of opioids in pediatrics is the extensive pharmacokinetic and pharmacodynamic variability by age group. This variability may be a consequence of changes that occur with growth and development, which is most pronounced in the first few weeks of life. Because this inter-individual variability occurs with developmental physiological and anatomical changes, the response to the opioid is less predictable. Consequently, variability in pharmacokinetics is inevitable in periods of rapid growth.[12] With the search for a short-acting, non-accumulative, and predictable anesthetic agent, the role of fentanyl derivatives, such as remifentanil, has emerged in pediatric anesthesia.[13]

The literature on pharmacokinetics in children is scant. However, age is known to influence pharmacokinetic differences, as dose requirements in children have been higher than those reported for adults with significant weight dependency in minor patients.[14]

In general, the pharmacokinetics of remifentanil are similar in neonates, children, and adults. However, there are differences, such as volume of distribution and clearance, since these variables are more significant in neonates than in children and adults, Table 1. However, the elimination half-life does not change with age, with its average value being between 3.4 and 5.7 minutes, demonstrating rapid clearance similar to adults.[15-18] The increased volume of distribution is due to the higher percentage of total body water and higher circulating volume in the pediatric age. The increased clearance may be explained by the fact that neonates and infants have a more remarkable ability to metabolize drugs due to their relatively large liver size or increased hepatic blood flow.[19] So, the drug dose is influenced by these pharmacokinetic factors (clearance and volume of distribution) that can change with age. Therefore, higher infusion rates seem to be required in the pediatric age.[20]

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anesthesia increase the release of catecholamines through sympathetic stimulation, which can cause an increase in blood pressure, heart rate, cause arrhythmias, and cause ischemia and infarction. as well as cerebral hemorrhage, in patients with risk factors, such as hypertension and ischemic heart disease, which is undesirable, especially in patients with cardiovascular or neurosurgical diseases undergoing general anesthesia.[25]

Hypertension during OIT in neurosurgical patients may be associated with increased intracranial pressure, bleeding, adverse hemodynamic effects that may increase morbidity in such patients, and prolonged hospital stay. Therefore, the prevention and control of these hemodynamic responses are of paramount importance to preserve brain homeostasis. Opioids are used to prevent cardiovascular changes during OIT.[26] Various pharmacological strategies have been suggested to control the cardiovascular responses induced by these nociceptive stimuli. Opioids, such as remifentanil, are widely used to control cardiovascular responses induced by tracheal intubation. A dose-effect relationship exists between increasing the dose of opioids and reducing cardiovascular changes.[27]

It effectively prevents sympathetic responses induced by orotracheal intubation and other surgical stimuli. Due to its unique pharmacokinetic and pharmacodynamic profile, remifentanil is ideal for continuous intravenous infusion, whereas target-controlled information (TCI) using a computer-controlled infusion device is more effective in maintaining stability. Cardiovascular risk compared to traditional weight-adjusted inputs. Nonspecific plasma esterases hydrolyze it in blood and tissues.[28] TCI is commonly used in neurosurgery due to reduced perioperative stress response, acute systemic inflammatory response, rapid recovery, and decreased postoperative nausea and vomiting compared to halogenated anesthetics. Furthermore, remifentanil may have a neuroprotective effect that suppresses cell death by reducing the expression of TNF-α and TNFR1 proteins, which is beneficial for perioperative brain protection.[28,29]

Minto's pharmacokinetic and pharmacodynamic modeling for remifentanil is administered at a target concentration at the effect site rather than at a plasma concentration to minimize the hysteresis between blood concentration and drug effect, leading to rapidly achieving and maintaining stable drug concentrations at the effect site.[30,31] One of the most desirable features of a neuroaesthetics regimen is rapid anesthetic emergence because fast postoperative recovery is essential to assess neurologic function. These features are important in neuroanesthesia and neurointensive care management, making remifentanil a potentially ideal neuroanesthesia agent.[32]

Remifentanil is considered to have favorable effects on brain metabolism, lowering the cerebral metabolic rate of oxygen (CMRO2). However, remifentanil has been reported in large doses (up to 3 μg/kg/min), thus 6- 30 times the commonly used clinical range (0.1-0.5 μg/kg/min), it increases CMRO2 in the temporal lobe from 6.29 to 7.68 mg/100g/min.[32] Remifentanil decreases regional cerebral blood flow consumption by 40-50% in the cortex, hippocampus, and caudate. During remifentanil infusion, regional cerebral blood flow changes in a dose-dependent manner in areas involved in pain processing. At low doses (0.05 μg/kg/min), significant increases can be recorded in the lateral prefrontal cortices, inferior parietal cortices, and supplementary motor area, while decreases in the basal, medial frontal cortex, cerebellum, temporal lobe upper and midbrain gray matter.[27]

At moderate doses (0.15 μg/kg/min), regional cerebral blood flow is increased in the medial frontal and anterior cingulate cortices, the transitional occipital lobe, and the caudal periventricular gray matter. At the same time, it is decreased in the inferior parietal lobes. In these cases, regional cerebral blood flow responses were additionally detected in structures involved in the modulation of vigilance and alertness.[33] High doses of remifentanil (2-4 μg/kg/min) decrease regional cerebral blood flow in healthy volunteers. However, these doses are around 10 to 20 times higher than in the clinical setting. Large amounts of remifentanil reduce cerebral blood flow velocity despite constant perfusion pressure. This may implicate a central mechanism for the cerebral hemodynamic effects of remifentanil.[34]

Although the cerebral vascular system has admirable autoregulation and controlled hypotension is a frequently used technique in neuro anesthesiology, the damaged brain may not compensate for the reduction in mean arterial pressure, with the consequent risk of ischemia. Compared to other opioids, remifentanil anesthesia has a higher incidence of hypotensive episodes. Blood pressure decreases by approximately 30%, and this effect is more evident in elderly, hypovolemic, and obese patients.[33]

Colonoscopy

Colonoscopy allows examination and treatment of the rectum, colon, and a portion of the terminal ileum. Attention should be paid to timely scheduling, proper patient preparation, history, specific physical examination, bleeding risk assessment, adequate sedation, and pausing the team before starting sedation.[35] The complexity of endoscopic procedures has increased, and advanced endoscopic procedures are often performed as alternatives to open surgery in patients with significant comorbidities.[36] A colonoscopy is performed with the patient in the lateral position, although changing to the prone position is sometimes necessary. Colonoscope insertion is generally well tolerated, and the challenging parts of the proceedings relate to the insufflation of gases into the colon and manipulation of the colonoscope around bends. Gas insufflation and abdominal compression may increase the risk of aspiration, which is a constant risk during these procedures. Sedation and anesthesia are generally less challenging for colonoscopy than for upper endoscopy because the anesthesia clinician has access to the airway and is not shared with the endoscopist. Medications for endoscopy should be based on patient factors, physician preference and experience, and desired depth of sedation or anesthesia.[37]

Unlike other long-acting opioids, remifentanil can provide adequate analgesia for a colonoscopy without administering sedatives while allowing rapid recovery and discharge.[38] Patients referred for colonoscopy have been reported to have adequate analgesia with equivalent satisfaction, less respiratory depression, and faster recovery than patients receiving a combination of midazolam and pethidine. However, patients receiving remifentanil should understand that they are likely to be conscious during the procedure.[39]

Anesthesia during childbirth

Parenteral opioids commonly used for labor analgesia are Morphine, Pethidine, Fentanyl, Sufentanil, Alfentanil, and Remifentanil. If regional analgesia is unavailable or contraindicated, then controlled intravenous analgesia is a helpful method of labor pain management.[40] Remifentanil crosses the placental barrier but is rapidly redistributed and metabolized by the neonate, which already has plasma and tissue mats for degradation. The concentration ratio of Remifentanil in the umbilical cord/uterine artery is 0.88 ng/ml, showing a rapid exchange of maternal blood for the fetus. In comparison, the concentration ratio between the umbilical artery and the umbilical vein is 0.29 ng/ml, suggesting significant metabolism and redistribution.[41,42] Remifentanil clearance in pregnant patients appears to be twice as high as in non-

pregnant patients, showing that physiological changes in pregnancy may be responsible for this difference due to the change in volume of distribution, lower plasma protein concentration, and increased nonspecific esterase activity.[43]

The administration is intravenous via a continuous infusion pump with IV-drip support. The main adverse effects observed in pregnant patients were nausea, vomiting, pruritus, sedation, and respiratory depression.[44]

Anesthesia during abortion

Studies have been described comparing the efficacy of remifentanil-propofol with fentanyl-propofol for anesthesia in hysteroscopies. They conclude that remifentanil is safer at a dose of 0.5 µg/kg and provides more effective analgesia than fentanyl when administering deep sedation during hysteroscopies. Postoperatively, remifentanil was associated with rapid recovery. On the other hand, intraoperatively, remifentanil has been associated with clinical signs of deep anesthesia and analgesia and poor response to painful stimuli. However, it has also been associated with more frequent episodes of bradycardia and hypotension.[45,46]

Use of remifentanil in patients with COVID-19

Given the recent COVID-19 pandemic caused by the SARS-CoV2 virus, recommendations have been developed for using Remifentanil in critically ill hospitalized patients with mechanical ventilation.[47] These works recommend deep sedation with Remifentanil to achieve an excellent adaptation to the respirator. In addition, it is recommended to administer an analgesic dose of 0.5-3 µg/kg/h and a sedative dose of 3-12 µg/kg/h.[48] On the other hand, patients receiving remifentanil showed significantly less inter-patient variability in optimal sedation compared to fentanyl. In addition, remifentanil experienced significantly more prolonged pain during extubation, post-extubation, and posttreatment due to rapid compensation of remifentanil analgesia. However, in this study, remifentanil has been associated with a higher incidence of hypotension than fentanyl.[49]

In addition, precautions must be taken during orotracheal intubation since this maneuver has a high risk of viral transmission for medical personnel. Therefore, it is recommended to administer profound analgesia with remifentanil to perform rapid intubation to avoid viral transmission.[50-53]

Side effects of remifentanil use

The side effect profile of remifentanil is like that of other opioids,[5] which are listed in Figure 1B. However, these side effects are limited by the duration of the drug infusion. Histamine release is minimal, and its administration is not associated with this adverse effect.[8]

Effects on the central nervous system

Auditory and somesthetic evoked potentials are modified to a lesser extent. It has no hypnotic effect and does not cause amnesia at doses used clinically. Furthermore, it has no action on the bispectral index at usual concentrations, while it slows down the electroencephalogram tracing at higher concentrations.[54] Under conditions of normocapnia and maintenance of cerebral perfusion pressure, remifentanil does not increase cerebral blood flow or intracranial pressure.[55] In patients who received a continuous remifentanil infusion, cerebral blood flow increased from 21 to 31 ml/100 g/min.[56]

Respiratory effects

Remifentanil, used at doses of 1 mcg/kg followed by an infusion of 0.5 to 1.0 mcg/kg/min, produces respiratory depression and significant sedation and apnea in most patients.[57] Like other opiates, it causes dose-dependent respiratory depression. It is more potent than alfentanil after a bolus dose, but recovery is faster.[58] Infusion rates of 0.1 mcg/kg/min allow the patient to maintain spontaneous ventilation. The duration of respiratory depression is as short as that of analgesia. For the same surgery, doubling the dose of remifentanil does not prolong wake-up time or extubation. On the other hand, secondary apneas have not been reported regardless of the amount and duration of infusion [55]. Furthermore, the respiratory effects of remifentanil can be antagonized by naloxone.[56]

Cardiovascular effects

Like the rest of the opiates, Remifentanil can cause hypotension and moderate bradycardia. Associated with propofol or etomidate, it can reduce blood pressure by 17 to 23%. It provides good hemodynamic stability and does not produce histamine release at high doses.[56] The hemodynamic effects are identical to those of fentanyl and its derivatives: bradycardia of vagal origin, associated with a 15-20% reduction in blood pressure. Hypotension may occur, especially if the patient is hypovolemic or high doses of Remifentanil are administered together with general anesthetics, especially in patients older than 70 years and with cardiovascular pathology.[54] It lacks essential hemodynamic effects when administered at doses less than 2 µg kg-1min-1, making it a very versatile drug for hemodynamic control during surgical stress.[55]

Discussion

An ideal anesthetic should have a rapid onset of action, be safe, and be easy to administer with a relatively short duration of action. Remifentanil has been widely used as an anesthetic drug due to its rapid onset, lack of accumulation even when administered continuously, and context-sensitive short half-time. Pharmacokinetic models have been used for continuous infusion of intravenous anesthetics because remifentanil is challenging to measure in blood. Its bolus injection can cause side effects such as hypotension and bradycardia. During the registration process of new drugs, manufacturers must inform the registration authorities of the range of practical and safe doses, information that is eventually included in the summary of product characteristics or the product label sheet in the medication packaging. These recommendations can serve as a reference point to evaluate the doses administered with different pharmacokinetic models and target concentrations. The amount allocated by a TCI system depends on the patient's characteristics and the chosen target concentration. All this is to avoid or reduce the likely reported side effects of remifentanil.

Conclusion

Remifentanil is characterized by very rapid pharmacokinetics in terms of onset and disappearance of effect, with minimal difference between blood concentrations and concentrations at the site of action. On the other hand, it is a complement in general or local anesthesia, for analgesic premedication for induction of anesthesia and as an adjuvant in the maintenance of general and regional anesthesia, as a sedative in patients admitted to intensive care in patients undergoing mechanical ventilation, for postoperative analgesia and sedation for cardiac surgery and other types of surgeries, sedation/analgesia for minor procedures.

The side effect profile of remifentanil is similar to that of other opioids. However, it should be mentioned that the duration of drug infusion limits these adverse effects, so their use is safe.

Conflicts of interest

2019 – 2021 Speaker for Aspen Labs.

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