GSC Advanced Research and Reviews
eISSN: 2582-4597 CODEN (USA): GARRC2
Cross Ref DOI: 10.30574/gscarr
Journal homepage: https://gsconlinepress.com/journals/gscarr/

(Review Article)

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Remifentanil as an anesthetic agent in children

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GSC Advanced Research and Reviews, 2024, 20(01), 001–004

Publication history: Received on 19 May 2024; revised on 29 June 2024; accepted on 02 July 2024

Article DOI: https://doi.org/10.30574/gscarr.2024.20.1.0238

Abstract

Remifentanil hydrochloride is an ultra-short-acting opioid that undergoes rapid metabolism by tissue and plasma esterases. Remifentanil is increasingly used as an adjuvant to general anaesthesia in neonates undergoing surgery because of its favourable haemodynamic and respiratory effects compared with other agents. The pharmacokinetic profile of remifentanil appears well suited for use in the sedation of children for short, day case procedures and remifentanil has been demonstrated to be an attractive drug for this purpose. Owing to higher clearances, younger children will require higher infusion rates of remifentanil than older children and adults to achieve equivalent plasma concentrations. Propofol and remifentanil appear to be gaining popularity for short procedures in children. Together they provide sedation, anxiolysis and analgesia, possibly best provided by separate continuous infusions. They also promote haemodynamic stability, minimal respiratory depression, with a rapid recovery profile. The use of remifentanil in neonates and young infants is increasing despite the difficulties in obtaining high standard objective evidence in this age group. Remifentanil's pharmacokinetic and pharmacodynamic profile in this age group is similar to that of older children, which may have several theoretical advantages. Reports of a rapid development of μ-receptor tolerance with remifentanil are in conflict; activity at δ-opioid receptors may contribute. Remifentanil produce a fall in blood pressure and cardiac index, mainly as a result of a fall in heart rate. Although atropine is able to reduce the fall in heart rate, is not able to prevent completely the reduction in cardiac index. Remifentanil has been described as a titratable opioid. It has been reported to be ideally suited to the sedation of selected neurosurgical patients who require frequent neurological examinations. It may also provide suitable analgesia based sedation in mechanically ventilated children postoperatively.

Keywords: Remifentanyl; Anaesthesia; Sedation; Children; Surgery

1. Introduction

Remifentanil has a strong affinity for μ opioid receptors although less for κ and δ. The former is antagonised by naloxone. Remifentanil is a potent mu-agonist that retains all the pharmacodynamic characteristics of its class regarding analgesia, respiratory depression, muscle rigidity, nausea and vomiting, pruritus. Remifentanil is a potent respiratory depressant and this effect has been widely studied in children. It offers a unique titratability when its effects need to be quickly achieved or suppressed. Remifentanil is an ultra-short acting synthetic opioid; it shares some similarities with other piperidine derivatives such as alfentanil and fentanyl, but with a potency 26–65 times that of alfentanil. Remifentanil is a synthetic opioid, first introduced into clinical practice in 1996. Its unique pharmacokinetic profile has resulted in a gradual increase in its popularity in paediatric anaesthesia. It is an opioid of high potency and rapid clearance, consequently lacking problems of accumulation. These characteristics give it a high degree of predictability and it has become an attractive choice for a wide variety of anaesthetic challenges, from premature neonates to the elderly. Neonates and infants have a higher clearance than older children and as a result, remifentanil has additional benefits in this group. Remifentanil showed an extremely rapid elimination similar to that in adults. The fast clearance rates observed in neonates and infants, as well as the lack of age related changes in half life, are in sharp contrast to the

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pharmacokinetic profile of other opioids. Remifentanil in a bolus dose of 5 microg/kg may cause hypotension in anesthetized children [1-12].

2. Total intravenus anesthesia

Propofol administered in conjunction with an opioid such as remifentanil is used to provide total intravenous anesthesia for children. Recommended target concentrations for both propofol and remifentanil depend on the type of surgery, the degree of surgical stimulation, the use of local anesthetic blocks, and the ventilatory status of the patient. Total intravenous anesthesia has been widely practiced in adult anesthesia since the introduction of propofol into routine clinical practice in 1982. Although there were reports of the use of total intravenous anesthesia in children as early as 1989, it is only in recent years that the practice in children has become more common. The main benefits of using a total intravenous anesthesia technique include reduced postoperative nausea and vomiting with propofol use, quicker recovery, improved quality of recovery. Results for both propofol and remifentanil in children, required a larger loading dose, expressed as per kilogram, than healthy adults. Total intravenous anesthesia techniques use propofol as the principal drug for induction and maintenance of anesthesia. The commonly used medications include the opioids remifentanil, alfentanil, and sufentanil. Ketamine is occasionally used, but it has a long context-sensitive half-time with consequent delayed awakening after prolonged exposure. Coadministration of midazolam reduces the propofol dose for induction and the amnesic effect. The high potency, fast onset, and short context-sensitive half-time of 2 to 3 min means that remifentanil can be effectively used by infusion for prolonged periods of time. There is additivity of anesthetic effect when used with propofol described in adults and in children 1 to 11 year, although effects such as apnea appear synergistic. A pharmacodynamics model describing the propofol and remifentanil additive interaction for anesthesia in children 1 to 12 year using Bispectral Index as an effect measure is similar to that reported in adults. Maintenance infusion requirements for propofol in neonates differ substantively from those in older infants and children. These may be attributed mostly to differences in pharmacokinetics. Delayed awakening, hypotension, and an increased incidence of bradycardia have been reported in neonates and infants. The initial loading dose of remifentanil may cause hypotension and bradycardia in children, prompting some to target the plasma rather than effect-site concentration when initiating an infusion. Remifentanil clearance is increased and volume of distribution also increased, care should be taken using bolus doses larger than 0.25 mcg/kg in infants less than 6 months in whom blood pressure decreases can cause a lowering of cerebral perfusion. An increase in remifentanil infusion rate is a better option. The anesthetic requirement in children with cognitive impairment may be reduced. Processed electroencephalogram use may better dictate dose. Propofol metabolism is reduced in neonates and matures over the first six months of life. Remifentanil volume of distribution and clearance are increased in neonates compared to children and adults. Sensitivity to the both sedative effects and analgesic effects is increased. Adverse effects such as hypotension are increased in neonates given propofol. These effects can lead to delayed recovery after anesthesia [13-25].

3. Emergence agitation

Emergence agitation (EA) is one of the main concerns in the field of pediatric anesthesia using short acting volatile anesthetics, such as sevoflurane. This postanesthetic behavioral disturbance is frequently developed in ophthalmological surgery, and EA may cause harm to the child and distress to caregivers, leading to dissatisfaction with the anesthetic. Fentanyl and remifentanil are short-acting opioids that are widely used in pediatric patients. Both drugs have been used as sedatives and analgesics, which can affect the hemodynamic response of blunt surgical stimulation as well as tracheal intubation. The clinical usefulness of these drugs has been suggested to reduce EA occurring post sevoflurane anesthesia. However, opioids still have some adverse effects on respiratory depression, postoperative vomiting, and opioid-induced hyperalgesia during the postoperative period. EA is commonly seen in children during the early post anesthesia period following general anesthesia. Several factors can affect the incidence of EA, including age, type of anesthetics, type of surgery, preoperative anxiety, and postoperative pain. Among these factors, EA is more common at a young age, and when sevoflurane is used during general anesthesia.

4. Outcomes

Remifentanil is an attractive drug for use in younger children and may be feasible for use in situations where spontaneous ventilation is advantageous. Remifentanil provides titratable analgesia with haemodynamic stability and prompt recovery allowing early neurological assessment which are the fundamental goals of neuroanaesthetic management. With regard to the neurocognitive effect of remifentanil, evaluated as an index of potential neuroprotection, recent studies have demonstrated that morphine and fentanyl, but not remifentanil, disrupt cholinergic neurotransmission. This disruption is known to cause postoperative delirium and impaired memory function. The addition of remifentanil to propofol reduce mean arterial pressure and heart rate without affecting CBFV (cerebral blood flow velocity). This implies that CBF (cerebral blood flow) autoregulation is preserved during remifentanil/propofol anaesthesia. Remifentanil/propofol anaesthesia increases the autoregulatory index with the suggestion of a widened autoregulatory plateau despite the lower flow status of this anaesthetic combination. Combination of remifentanil and midazolam infusions have also proved satisfactory for sedation in children requiring ventilation after cardiac surgery.

5. Discussion

Fentanyl is a short acting opioid that possesses synthetic μ receptor stimulating properties and is widely used in children as an intraoperative sedative and analgesic. Fentanyl has a short peak time and action duration after intravenous administration. Like other opioids, it has potential negative effects through central nervous system actions. Earlier administration of fentanyl, during intubation, based on hemodynamic stability during tracheal intubation, intraoperative analgesia, and postoperative complications. Remifentanil has an ester linkage and these unique pharmacokinetics allow for more rapid onset and offset. In addition, a short context sensitive half life of remifentanil allowed for intraoperative continuous infusion. Postoperative pain might develop with the use of remifentanil owing to its faster elimination properties. Remifentanil has been shown to be a useful agent for sedation during cardiac catheterisation in children owing to its favorable pharmacokinetic properties and haemodynamic stability during stressful events. Remifentanil has also been shown to provide satisfactory peri-operative control of stress response to cardiac surgery. Use of remifentanyl has been associated with N(2)0 and volatile agents for general anesthesia and with propofol for total intravenous anesthesia (TIVA). It seems very useful for sedation inside and outside the operating room and in intensive care for both short painful procedures and synchronization with mechanical ventilation.

6. Conclusion

Remifentanil representing the most predictable opioid in paediatric anesthesia. Remifentanyl is an opioid of high potency and rapid clearance, lacking problems of accumulation. These characteristics give it a high degree of predictability and it has become an attractive choice for a wide variety of anaesthetic challenges, from premature neonates to the elderly. Neonates and infants have a higher clearance than older children and as a result, remifentanil has additional benefits in this group. It is well known that continuous opioid infusions can cause tolerance. Therefore, there is evidence that remifentanil infusions may result in increased postoperative pain and increased opioid requirements.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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