Review article

Remifentanil in children

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Summary

Remifentanil has gained the confidence of anesthesiologists and has given a real opportunity to change the way anesthesia is given. It can be considered the ideal opioid despite many obstacles to pediatric use: the condition of ‘off-label’, the lack of wide randomized clinical trials, and the fear of adverse events because of its high potency. Experiences in the field with this opioid over the years encouraged its use. Use has been associated with N₂O 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. However, its unique pharmacokinetic characteristics causing rapid onset and offset of effect appear unchanged in small children and even in premature neonates and need to be really confirmed by further pharmacokinetic studies. Moreover, the real risks of tolerance and hyperalgesia should be evaluated in the pediatric population. In this review, we go through the newer aspects of this versatile drug that has been proposed as ‘the pediatric anesthetist’s opiate’.

Keywords: remifentanil; pharmacokinetics; pharmacodynamics; short-acting opioids; children; TCI

Remifentanil can be considered the best answer to the search for the ideal opioid because of its unique pharmacokinetic characteristics, different from any other opioid (1–4).

Pharmacokinetics

The ester-linkage makes the compound susceptible to metabolism by nonspecific plasma and tissues esterases, independent from hepatic and renal function (5,6), and it can be safely used even in anhepatic period of liver transplantation or when facing with failure or immaturity of most parenchyma (7,8).

Pharmacokinetics (PK) does not change in patients who are deficient in pseudocholinesterase activity, showing that it is not a good substrate for butyrylcholinesterase (9). Remifentanil has a rapid onset, small volume of distribution (Vd), rapid clearance (CL), and a brief half-time (1.0–1.5 min) for equilibration (t½,Ke0) between plasma and the effect compartment (10). Its extremely short context-sensitive half-life (3–5 min) and the rapid recovery from drug effect are the hallmarks of remifentanil’s unicity.
Davis et al. (11) investigated PK parameters of remifentanil in infants <2 months. Ross et al. (12) confirmed these PK parameters estimates and found that CL and Vd appeared higher compared with older age groups (2 months–18 years). However, she found that $t_{1/2b}$ does not change with age (Table 1).

Tod et al. (13) identified size, age, and organ function as the three major contributors to pediatric PK variability. Body weight is commonly used to define size, although it is recognized that there is a nonlinear relationship between weight and function. The per kg, surface area, and allometric 3/4 power models have been described as a means of predicting physiological functions from body size, such as drug clearance (14,15). Out of infancy, CL can be estimated from adult dose by an allometric 3/4 power model as follows:

$$CL_{\text{individual}} = CL_{\text{standard}} \times \left(\frac{\text{Weight}_{\text{individual}}}{\text{Weight}_{\text{standard}}}\right)^{3/4}$$

according to a universal exponential function in which the log of basal metabolic rate plotted against the log of body weight produces a straight line with a slope of 3/4 (16,17).

This law can be applied to physiological volumes (Vd, Vdss) and to time-related variables (HR, RR, drug half-time) by changing the value of the allometric exponent from 3/4 to 1 and $1/4$, respectively (15).

A wide discrepancy appears when CL estimates using the per kg size model is compared to the allometric 3/4 power model. The per kg model shows an increased CL compared to adults approximately at 1 year (Figure 1) (18). The increased clearance can be explained by the fact that infants have an enhanced capacity to metabolize drugs because of their relatively large liver size or increased hepatic blood flow. Size models alone are insufficient to predict dose in the first years of age where enzyme processes responsible for drug clearance are still developing. The drug dose is influenced by PK factors such as clearance and Vd that may change with age. Considering dose = $C_p \times Vd$, we would expect Vd to fit an allometric model with a power of unity at all weights. This does not happen with polar drugs that distribute rapidly into extracellular fluid and enter into cells more slowly.

Tissue and plasma esterase function appears mature at birth, rendering remifentanil different from other anesthetics: allometry alone without a maturation factor or organ function factor is sufficient for modeling remifentanil in all age groups (19). Rigby-Jones et al. using a two-compartment

Table 1
Pharmacokinetic parameters of remifentanil from infants <2 months up to 18 years

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Age</th>
<th>VDss (ml/kg$^{-1}$)</th>
<th>$CL$ (ml/kg$^{-1}$·min$^{-1}$)</th>
<th>$t_{1/2a}$ (min)</th>
<th>$t_{1/2b}$ (min)</th>
<th>CV (ml/kg$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davis et al. (11)</td>
<td>6</td>
<td>Neonates</td>
<td>325.33</td>
<td>80.38</td>
<td>0.42</td>
<td>4.38</td>
</tr>
<tr>
<td>Ross et al. (12)</td>
<td>8</td>
<td>0–2 months</td>
<td>452.80</td>
<td>90.50</td>
<td>#</td>
<td>5.40</td>
</tr>
<tr>
<td>10</td>
<td>2 months–2 years</td>
<td>307.90</td>
<td>92.10</td>
<td>#</td>
<td>3.40</td>
<td>#</td>
</tr>
<tr>
<td>8</td>
<td>2–6 years</td>
<td>240.10</td>
<td>76.00</td>
<td>#</td>
<td>3.60</td>
<td>#</td>
</tr>
<tr>
<td>8</td>
<td>7–12 years</td>
<td>248.90</td>
<td>59.70</td>
<td>#</td>
<td>5.30</td>
<td>#</td>
</tr>
<tr>
<td>5</td>
<td>13–16 years</td>
<td>223.20</td>
<td>57.20</td>
<td>#</td>
<td>3.70</td>
<td>#</td>
</tr>
<tr>
<td>3</td>
<td>16–18 years</td>
<td>242.50</td>
<td>46.50</td>
<td>#</td>
<td>5.70</td>
<td>#</td>
</tr>
</tbody>
</table>

Figure 1
Age-related clearance changes for a hypothetical drug. Clearance expressed using the per kg model decreases with age after 1 year to reach adult levels in adolescence. This course is not evident with the allometric 3/4 power and surface area models (reproduced from Anderson (18) with permission).
model with all structural parameters allometrically scaled to body weight modeled remifentanil in children undergoing cardiac surgery over an age range 1 months–9 years (19–21). For a child weighing 10.5 kg, she found a CL of 68 ml kg\(^{-1}\) min\(^{-1}\), an intercompartmental CL of 80 ml kg\(^{-1}\) min\(^{-1}\), a central volume (V1) of 92 ml kg\(^{-1}\), and a peripheral volume (V2) of 141 ml kg\(^{-1}\). Smaller (younger) children have increased CL when expressed as per kilogram and will require higher remifentanil infusion rates than larger (older) children and adults, to achieve equivalent blood concentrations.

When the adult PK model developed by Minto (22) is used in children, remifentanil blood concentrations are higher than expected because those parameters underpredict clearance with the per kilogram model. Allometric scaling by Rigby (19) resulted in values similar to those reported by others in children (11,12) and in adults (22) using a standardized CL of 2790 ml min\(^{-1}\) per 70 kg (Table 2).

The influence of age on the remifentanil infusion rate tolerated during spontaneous ventilation has been investigated by Barker et al. (23) in children undergoing strabismus surgery under propofol anesthesia. Using respiratory rate depression as a pharmacodynamic (PD) endpoint, the authors recorded the infusion rate able to produce a RR just greater than 10 breaths min\(^{-1}\). Children <3 years tolerated a higher infusion rate (up to 0.35 mcg kg\(^{-1}\) min\(^{-1}\)) while maintaining acceptable ventilation (23). CL estimates for age using the allometric model for a 70 kg person show a mismatch against the infusion rate in infancy (24). The higher infusion rate in those infants can be partially attributed to clearance compared to children 2–6 years in addition to a PD effect because of a greater suppression of respiratory drive in this age group (a RR of 10 breaths min\(^{-1}\) in infants cannot be compared to the same rate in the older children) (24).

Age was found by Minto (22) to be a significant covariate for both PK and PD, affecting V1 by 25%, CL by 33%, doubling t\(_{1/2}\) Keo, and halving EC\(_{50}\) in the age range 20–85 years. PK/PD studies have been proposed in children to overcome the lack of information about Keo values. This parameter is vital for the prediction of effect-site concentration using TCI systems, Keo can be approximated by a first-order rate constant using the time to peak effect methodology (25) in which different Keo are calculated and plotted to determine which value is associated with a peak effect-site concentration that matches the peak clinical effect (26).

The choice of Keo will influence the degree of plasma concentration overshoot and undershoot when the target effect-site concentration is changed (Figure 2). If a smaller Keo is used, a greater overshoot in the peak plasma concentration will be required to produce a gradient sufficient to cause the most rapid increase in effect-site concentration, but without an overshoot of the effect-site concentration above its target. Potential errors in the estimates of plasma concentration and in the degree of overshoot, resulting in excessively high plasma concentration, may produce significant adverse effects (bradycardia, hypotension, rigidity, itch, nausea, and vomiting).

### Table 2

Model comparison. Pharmacokinetic parameter values calculated using three different pharmacokinetic models. Modified by Rigby-Jones (19)

<table>
<thead>
<tr>
<th>Model</th>
<th>CL (ml kg(^{-1}) min(^{-1}))</th>
<th>V1 (ml kg(^{-1}))</th>
<th>VDss (ml kg(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigby-Jones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 kg</td>
<td>93</td>
<td>92</td>
<td>233</td>
</tr>
<tr>
<td>10.5 kg</td>
<td>68</td>
<td>92</td>
<td>233</td>
</tr>
<tr>
<td>27 kg</td>
<td>54</td>
<td>92</td>
<td>233</td>
</tr>
<tr>
<td>40 kg</td>
<td>49</td>
<td>92</td>
<td>233</td>
</tr>
<tr>
<td>Davis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean 27 kg</td>
<td>47</td>
<td>84</td>
<td>235</td>
</tr>
<tr>
<td>Minto</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight proportional (adults)</td>
<td>34</td>
<td>67</td>
<td>256</td>
</tr>
</tbody>
</table>

Figure 2

The effect of an increasing Keo on effect site concentration. A child of 10 kg was given a bolus of remifentanil 1 mcg kg\(^{-1}\) over 1 min followed by an infusion of 0.25 mcg kg\(^{-1}\) min\(^{-1}\) over 1 min. Parameter estimates were from Rigby-Jones (19). There is an overshoot with the larger Keo of 2.3 min – 1(1/2Keo 0.5 min), while the smaller keo of 0.34 min – 1(1/2keo 2 min) may undershoots and may not achieve the target concentration in the effect site.
Jeleazcov et al. (27) using a PD model of BIS response to propofol-based anesthesia supplemented by fentanyl and remifentanil found for children >1 year that the Keo of propofol decreased with increasing age, but no significant relationship was noted between age and Keo for remifentanil or fentanyl. The median $t_{1/2}$ Keo of 1 min for remifentanil was similar to the value reported by Minto in adults using BIS index (22,28).

### Pharmacodynamics

Jeleazcov et al. (27) also reported no relationship between age and half-maximum effect concentrations ($EC_{50}$) for propofol, remifentanil, and fentanyl, suggesting that the concentration–response relationships are similar in adults and children. Target effect–site remifentanil concentrations commonly used for TIVA vary. A target of 2–3 mcg$\cdot$kg$^{-1}$ is adequate for laryngoscopy, 6–8 mcg$\cdot$kg$^{-1}$ for laparotomy, and 10–12 mcg$\cdot$kg$^{-1}$ might be sought to ablate the stress response associated with cardiac surgery.

Remifentanil exhibits a strong affinity for $\mu$ receptors and less for $\kappa$ and $\delta$ opioid receptors. This makes remifentanil PD similar to those of other opioids. It has dose-dependent analgesic and sedative effects as well as adverse effects. Adverse effects are usually of limited duration. Even if it crosses the placenta, its respiratory depressant effect upon the fetus is short lived (29–31).

Akpek et al. compared remifentanil 2 mcg$\cdot$kg$^{-1}$ followed by 2 mcg$\cdot$kg$^{-1}$$\cdot$min$^{-1}$ infusion vs fentanyl 20 mcg$\cdot$kg$^{-1}$ bolus followed by 20 mcg$\cdot$kg$^{-1}$$\cdot$min$^{-1}$, both supplemented with midazolam 0.1 mg$\cdot$kg$^{-1}$$\cdot$h$^{-1}$ in 33 children (3 months–6 years) undergoing surgery for left-to-right shunting and pulmonary hypertension. The authors confirmed remifentanil safety in these patients who had no decrease in HR and blood pressure (BP) (32). Tirel et al. (33) showed that remifentanil can cause bradycardia related not only to the activation of parasympathetic activity but also to a direct chronotropic negative effect in children 6 months–15 years receiving 1 MAC sevoflurane. In this study, children with intermediary parasympathetic activity were the most sensitive to remifentanil in terms of HR decrease and the preventive effect of atropine. These results were confirmed recently by Chung et al. (34) who, dividing children in four groups (ketamine/sevoflurane, ketamine/remifentanil, midazolam/sevoflurane, and midazolam/remifentanil), found that HR and BP were significantly lower in the ketamine/remifentanil and midazolam/remifentanil groups. Furthermore, oculocardiac reflex occurred more frequently in the ketamine/remifentanil and midazolam/remifentanil groups, suggesting that remifentanil enhances the degree of bradycardia because of oculocardiac reflex (35).

Remifentanil has been shown to preserve middle cerebral artery blood flow velocity (Vmca) in adults (36), although some decrease has been noted at higher doses (37). In children, transcranial doppler showed that Vmca remained constant despite a fall in BP suggesting that cerebral blood pressure autoregulation may be preserved under remifentanil/propofof anesthesia (38).

Standing et al. (39) have described the early concentration–effect relationship between remifentanil and mean arterial blood pressure (MAP) in infants undergoing cranioplasty. Using a sigmoidal $E_{\text{max}}$ model, they predicted that a steady-state effect–site concentration of 14 ng$\cdot$ml$^{-1}$ would cause a 30% drop in MAP. This would be achieved for a typical 7.5 kg infant, with a loading dose of 36 mcg followed by an infusion of 8 mcg$\cdot$min$^{-1}$.

Histamine release is minimal with remifentanil, and Sebel et al. (40) showed that 2–30 mcg$\cdot$kg$^{-1}$ remifentanil bolus is not associated with this adverse effect.

### General anesthesia

#### Association with N2O

Adequate analgesia and rapid recovery was obtained in children 2–12 years undergoing strabismus surgery after midazolam premedication, using remifentanil 1 mcg$\cdot$kg$^{-1}$ bolus and 1–3 mcg$\cdot$kg$^{-1}$$\cdot$min$^{-1}$ infusion associated with N$_2$O70% compared with alfentanil, propofol, and isoflurane (41).

The same anesthesia technique efficacy was shown in infants aged at least 8 weeks undergoing pyloromyotomy (42).

#### Association with volatile agents

A rapid recovery was obtained in infants older than 7 days and up to 3 months undergoing mayor
abdominal surgery compared to a prolonged recovery in neonates <7 days with blended anesthesia with isoflurane, remifentanil, and epidural ropivacaine (43). The authors speculated a greater sensitivity to isoflurane in the younger group. Eck et al. (44) confirmed the safety of remifentanil associated with sevoflurane in three infants with complex medical issues (hepatic failure, cyanotic heart disease, and renal compromise) undergoing surgical ligation of a patent ductus arteriosus and surgical correction of a duodenal web.

Remifentanil used in conjunction with halothane or sevoflurane was compared to fentanyl, in a randomized double-blind study during adenotonsillectomy in ambulatory patients. Remifentanil provided faster extubation times but higher pain-discomfort score, suggesting the need of adequate pain-care strategy (45). This was not confirmed by Steinmetz et al. (46) who compared sevoflurane/fentanyl and propofol/remifentanil in infants 4–6 months undergoing cleft-lip and palate repair. They found that morphine consumption was similar; however, this study was affected by the concurrent administration of fentanyl 4 mcg · kg⁻¹ in the remifentanil group. Roulleau et al. (47) compared isoflurane associated with either remifentanil or sufentanil and found surprisingly that postoperative pain scores were even lower in the remifentanil group compared with sufentanil. Concerns about remifentanil causing a need for greater analgesic use in the recovery period require further exploration in children.

Remifentanil use with isoflurane or sevoflurane in craniosynostosis correction demonstrated no difference in hemodynamic parameters. The short recovery time in both techniques allows reliable neurological assessment immediately after surgery (48).

A recent retrospective study reports the use of remifentanil/sevoflurane for abdominal surgery in preterm neonates, full-term neonates and infants <2 years. Remifentanil doses show a progressive decrease during surgery in preterm and full-term neonates, whereas remifentanil is increased in older children (49). This is in contrast with Sammartino et al. (50) who report higher doses of remifentanil in preterm neonates undergoing analgesedation for laser therapy, using only midazolam bolus as the hypnotic drug.

Min, Crawford, and Kwak (51–53) found similar remifentanil dose requirements for oral tracheal intubation (OTI) or laryngeal mask airway (LMA) insertion using sevoflurane/propofol bolus (Table 3), while He et al. (54) showed an inverse relationship between remifentanil and end-tidal sevoflurane (Etsevo) concentration for OTI in children 3–8 years.

### Association with propofol

Remifentanil is a useful opioid when used with propofol for TIVA. Salient benefits include rapid recovery, reduced nausea, vomiting, and postoperative delirium. Furthermore, it has become the technique of choice in particular situations such as in patients with the risk of malignant hyperthermia. Remifentanil/propofol has been found safe with rapid recovery and uneventful postoperative course in three children affected by Duchenne’s muscular dystrophy undergoing spinal surgery (55).

A study by Munoz et al. (56) demonstrated that as for sevoflurane anesthesia, during propofol anesthesia (57), children 3–11 years require a remifentanil infusion rate almost twofold higher than adults (0.149 vs 0.080 mcg·kg⁻¹·min⁻¹) to block the somatic response to skin incision. These data are consistent with the increased clearance (expressed as per kilogram) described in children.

TCI using propofol with Kataria’s PK model and remifentanil with Minto’s model improves insertion

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**Table 3**

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Age</th>
<th>Hypnotic drug</th>
<th>Procedures</th>
<th>ED50</th>
<th>ED95</th>
<th>ED98</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min et al. (51)</td>
<td>25</td>
<td>3–10 years</td>
<td>Sevoflurane 5%</td>
<td>IOT</td>
<td>0.56 mcg·kg⁻¹</td>
<td>0.75 mcg·kg⁻¹</td>
</tr>
<tr>
<td>Kkwak et al. (52)</td>
<td>26</td>
<td>3–10 years</td>
<td>Propofol 2.5 mg·kg⁻¹</td>
<td>LMA</td>
<td>0.52 mcg·kg⁻¹</td>
<td>0.71 mcg·kg⁻¹</td>
</tr>
<tr>
<td>Crawford et al. (53)</td>
<td>64</td>
<td>2 months–6 years</td>
<td>Propofol 4 mg·kg⁻¹</td>
<td>IOT</td>
<td>1.7 mcg·kg⁻¹</td>
<td>2.88 mcg·kg⁻¹</td>
</tr>
</tbody>
</table>

LMA, laryngeal mask airway; OTI, oral tracheal intubation.

*Logistic regression curves of the probability of excellent or good tracheal intubating conditions did not differ significantly with age.
of supraglottic devices suppressing airway reflexes (58). In fact, Park et al. (59) found that the addition of remifentanil 7.5 ng·ml⁻¹ halved the propofol EC₅₀ (from 5 to 2.5 mcg·ml⁻¹) and improved insertion of laryngeal tube and laryngeal mask in 98 children 2–12 years.

Propofol/remifentanil achieved slower spontaneous ventilation compared to desflurane/N₂O in children 4–11 years undergoing ENT surgery, but the incidences of postoperative agitation and postoperative nausea and vomiting (PONV) were higher with desflurane/N₂O (60). Propofol/remifentanil compared to sevoflurane/fentanyl allowed a more rapid recovery of saccadic eye movements that is useful for an immediate postoperative evaluation, following strabismus surgery (61). In two randomized double-blind studies, remifentanil 2 mcg·kg⁻¹, in association with propofol, compared with fentanyl 2 mcg·kg⁻¹ and sufentanil 0.2 mcg·kg⁻¹ was found effective for blunting temporary cardiovascular intubation responses, even though inducing a more significant cardiovascular depression (62,63).

Quality differences in postoperative sleep were compared in infants between sevoflurane/fentanyl and propofol/remifentanil. Longest continuous sleep was significantly longer in the sevoflurane group than in the propofol/remifentanil group (64), supporting the evidence of a suppression of REM sleep by remifentanil and the contribution of opioids to postoperative sleep disturbances (65).

**OTI without muscle relaxants**

Remifentanil was found to be effective for OTI without muscle relaxants: remifentanil 3 mcg·kg⁻¹ with propofol 3 mcg·kg⁻¹ provided excellent conditions in 90% of children, neither increasing HR and BP nor inducing bradycardia or hypotension (66).

Crawford et al. (53) indicated a similar remifentanil dose–response relationship for OTI in infants 1–12 months and children 1–6 years. The coadministration of 4 mcg·kg⁻¹ propofol and 3 mcg·kg⁻¹ remifentanil provided good OTI conditions and stable hemodynamics. In addition, the duration of apnea (4.4 min) was comparable to that after suxamethonium 2 mcg·kg⁻¹ (4.3 min).

Recently, Verghese and coworkers have published the results on the nasal administration of remifentanil 4 mcg·kg⁻¹, reporting excellent intubating conditions after 3 min in 91.7% of children. PK blood sampling showed a peak plasma concentration at 3.47 min (67).

**Sedation for short procedures**

Several authors found remifentanil bolus and/or infusion for short painful procedures such as bone marrow aspiration and closed fracture reduction with spontaneous ventilation, although some episodes of respiratory depression were reported (68–70). Hayes et al. found that the minimum effective dose of remifentanil was 1.5 mcg·kg⁻¹ when used with propofol 2 mcg·kg⁻¹ and 0.52 mcg·kg⁻¹ when used with propofol 4 mcg·kg⁻¹. However, the two doses combinations differ with increased duration of apnea as remifentanil increases and longer recovery time with the increase in propofol (71).

Some authors also propose propofol/remifentanil (72) and methohexital/remifentanil (73) mixtures in the same syringe sometimes associated with midazolam or ketamine for short procedures. However, mixtures reduce the advantage of intravenous sedation based on the possibility of varying the hypnotic or the analgesic level according to the need of the procedure.

**Sedation in pediatric and neonatal intensive care**

Many studies report the use of remifentanil for sedation in adult intensive care. Interest concerning sedation with remifentanil in paediatric and neonatal intensive care unit is increasing, particularly because preterm neonates normally have immature clearance pathways for most drugs, delaying recovery time. Remifentanil with its esterase clearance pathway mature at birth may be a suitable drug in this cohort. Sammartino et al. used successfully midazolam/remifentanil analgosedation in 6 preterms undergoing laser therapy for retinopathy of prematurity. After a midazolam bolus 0.2 mg·kg⁻¹, remifentanil started from 0.75–1 mcg·kg⁻¹·min⁻¹ was started 1 hr before the procedure and was increased up to 3–5 mcg·kg⁻¹·min⁻¹. Only one neonate needed 20 mcg·kg⁻¹·min⁻¹ for not more than 10 min. The authors speculated that previous exposure to opioids might have led to a deregulation of receptors in number and/or function (50).
Remifentanil/midazolam was also used for sedation in 26 children 1 month–9 years receiving mechanical ventilation after cardiac surgery. Midazolam infusion 50 mcg·kg\(^{-1}\)·h\(^{-1}\) at fixed rate was given with remifentanil 0.8 mcg·kg\(^{-1}\)·min\(^{-1}\) for 60 min and decreased by 0.1 mcg·kg\(^{-1}\)·min\(^{-1}\) every 20 min until awakening (19).

Stoppa et al. (74) evaluated the analgesic effect of remifentanil on 18 mechanically ventilated newborns GA > 32 weeks. Remifentanil infusion, started at 0.25 mcg·kg\(^{-1}\)·min\(^{-1}\), was titrated to achieve three different sedation scores. The mean infusion time of remifentanil was 66.94 h, and the mean dose was 0.146 mcg·kg\(^{-1}\)·min\(^{-1}\). Mean doses of 0.09 and 0.17 mcg·kg\(^{-1}\)·min\(^{-1}\) were used to obtain the lower and the higher sedation score, respectively. Extubation mean time from the discontinuation of remifentanil was 18 min. A significant drop in HR was correlated with the dose of remifentanil as well as with an increase in SpO\(_2\) attributable to better synchronization of patients to mechanical ventilation.

Twenty neonates (28–34 weeks) needing surfactant therapy were randomized to receive an infusion of morphine 10 mcg·kg\(^{-1}\)·h\(^{-1}\) or remifentanil 1 mcg·kg\(^{-1}\)·min\(^{-1}\) following OTI with midazolam 0.2 mg·kg\(^{-1}\) and a bolus of either morphine 0.19 mg·kg\(^{-1}\) or remifentanil 1 mcg·kg\(^{-1}\), respectively. Both cases produced good quality sedation and analgesia as evaluated by the neonatal/infants pain scale (NIPS) and Comfort scores, but the time needed to awakening and extubation was 18.9 and 12.1 times longer in the morphine than in the remifentanil group (75).

Adequate analgesia with significant reduction in NIPS and Comfort scores was also obtained in 48 preterm neonates (GA 25–33 weeks) undergoing mechanical ventilation. The adequate dose for analgesedation in 97% of the newborns was 0.094 mcg·kg\(^{-1}\)·min\(^{-1}\) and allowed extubation after 36 min from discontinuation of remifentanil, following a treatment period of 5.9 SD 5.7 days. No respiratory or cardiovascular side effects were observed showing the manageability of remifentanil even in extreme low birth weight (ELBW) preterm neonates (76).

Lago et al. (77) tested the efficacy and safety of remifentanil 0.03 mcg·kg\(^{-1}\)·min\(^{-1}\) by using pain scores (NIPS and PIPP) and by measuring SpO\(_2\) and RR in 54 preterm neonates (28 SD 2 weeks undergoing peripherally inserted central catheters (PICC) placement and receiving 0.3 ml 12% sucrose and nonnutritive sucking. Both pain scores were lower in the remifentanil group than in the placebo group (5% dextrose) during skin preparation and needle insertion. No significant difference was found for HR, BP, and RR.

Remifentanil bolus

Early reports concerning the administration of remifentanil bolus was discouraging because of the high incidence of rigidity and respiratory depression. Over time, better knowledge of the drug has allowed encouraging results, and nowadays, there are several reports about the utility of remifentanil bolus. In fact, according to Johnson, remifentanil bolus can provide ‘intense levels of analgesia while the patient remains conscious and responds to commands’ (78). Slow bolus has been found very useful to avoid the pain related to local anesthesia in short surgical procedures. However, this technique is recommended in school-aged children able to interact and to understand orders such as the encouragement to breathe (68).

Conclusions

Nowadays, the dominant role of remifentanil in children and even in neonates is certified by increasing of reports about its unique PK characteristics. However, further studies are needed to evaluate the possible advantages of TCI models in children and infants.

Attention should be paid to the concerns about postoperative analgesic effect and to validation of the real risk of hyperalgesia, as clinical trials in humans are controversial (79,80) and do not support the findings in animal studies (81,82).

References


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254 M. SAMMARTINO ET AL.


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