REVIEW ARTICLE

Drugs 2006; 66 (10): 1339-1350
0012-6667/06/0010-1339/$44.95/0

Experience with Remifentanil in Neonates and Infants

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Abstract

Remifentanil is a relatively new synthetic opioid, which is not licensed worldwide for neonates and infants. Because of its unique pharmacokinetic properties with a short recovery profile, it could be the ideal opioid for neonates and infants, who are especially sensitive to respiratory depression by opioids. Therefore, we conducted a MEDLINE search on all articles dealing with the use of remifentanil in this important subgroup of patients. Most experience with remifentanil in neonates and infants is as maintenance anaesthesia during surgery. In approximately 300 neonates and infants, remifentanil proved to be an effective and safely used opioid for this indication. However, very limited data exist on remifentanil for analgesia and sedation of mechanically ventilated paediatric intensive care patients. Further research with remifentanil in neonates and infants should focus on this group of patients because remifentanil, with its very short context-sensitive half-life, could result in shorter extubation times compared with commonly used opioids such as morphine or fentanyl.

Effective analgesia for painful procedures in newborns and infants is essential, not only for ethical reasons but also to reduce complications. It has been shown that preterm and term infants with repeated pain exposure and insufficient analgesia can exhibit different long-term sequelae, such as an al-

tered pain perception with hyperalgesia, an increased risk for neurological impairment, attention-deficit hyperactivity disorder or patterns of self-destructive behaviour.[1-4] Minor pain can be largely managed with paracetamol (acetaminophen), dipyrone or NSAIDs such as ibuprofen or diclofenac. Intense pain, on the other hand, should be treated with potent opioids. The most frequently used opioids in paediatric anaesthesia and paediatric intensive care medicine are morphine and fentanyl. Other regularly used opioids include alfentanil, sufentanil, piritramide and tramadol.[5-8]

In the last few years, there have been increasing reports about the use of the relatively new synthetic opioid remifentanil in children. Compared with other opioids, remifentanil offers two important advantages. Firstly, it has a very short context-sensitive half-time (i.e. the time required for a 50% reduction in the effect site concentration after a continuous infusion designed to maintain a constant effect site concentration), which is independent of infusion duration.[9,10] This allows rapid dose titrations according to the desired clinical effect and fast extubation of patients after cessation of the opioid infusion. Secondly, the pharmacokinetics and pharmacodynamics of remifentanil are not altered in patients with renal failure or liver disease; this makes it especially suitable for intensive care patients who often have impaired renal or liver function.[11-13]

Remifentanil is currently not licensed worldwide for use in neonates and infants (aged <1 year). However, neonates and infants represent a subgroup of paediatric patients that could benefit considerably from the advantages of remifentanil. At this age, the terminal elimination half-life ($t_{1/2}\beta$) of common opioids is prolonged compared with in older children or adults, and this can cause prolonged respiratory depression after cessation of an opioid infusion.[14,15] In addition, neonates and infants are especially vulnerable to respiratory depression caused by opioids because of the distinct distribution of opioid binding sites in their CNS.[16]

We conducted a MEDLINE search on articles dealing with the use of remifentanil in neonates and infants. Specifically, medical literature published in any language since 1991 on remifentanil was identified using MEDLINE. Additional references were identified from the reference lists of published articles, and unpublished data were also requested from the company developing the drug. MEDLINE search terms used were 'remifentanil' or 'remifentanyl' and the search was last updated 18 June 2006. Every article with an abstract reporting the use of remifentanil in children was further evaluated for the use of remifentanil in preterm infants, term neonates and infants <1 year. In this review, we discuss its potential role for this important subgroup of patients. Particular emphasis was placed on efficacy and safety aspects.

1. Pharmacology of Remifentanil

1.1 Pharmacokinetic Data

Remifentanil is structurally unique among currently available opioids because of its ester linkage, which makes it susceptible to hydrolysis by nonspecific esterases in blood and tissues. Pharmacokinetic investigations in adults revealed a short half-life ($t_{1/2}$) for equilibration between plasma and effect compartment of 1.3 minutes, a small volume of distribution (Vd) of 0.39 L/kg and a fast clearance of 41 mL/kg/min. The distribution half-life ($t_{1/2}\alpha$) is 0.9 minutes and the $t_{1/2}\beta$ is 9.5 minutes.[9,10] In patients with renal failure or liver disease, these pharmacokinetic properties remain essentially the same.[11,12] In contrast to that of other μ-opioid receptor agonists, the context-sensitive half-time of remifentanil is only 3–5 minutes and independent of the duration of infusion. The major metabolite of remifentanil, GI 90291, is almost inactive with a potency of 1 : 300–1 : 4600 compared with remifentanil and is eliminated primarily by the kidneys.[17,18]

Three studies investigating the pharmacokinetics of remifentanil in children have been published. Davis et al.[19] report on six neonates and infants, aged between 5 and 60 days, undergoing surgery. After intubation, a single remifentanil dose of 5 μg/kg was administered over 1 minute. In this young population, $t_{1/2}\alpha$ was 0.42 minutes, $t_{1/2}\beta$ was 4.38 minutes, clearance was 80 mL/kg/min, Vd at steady

state (Vd_{ss}) was 325 mL/kg and the volume of central compartment (V_c) was 125 mL/kg.

Another study by Davis et al.[20] was performed to determine the effects of cardiopulmonary bypass on the pharmacokinetics of remifentanil in paediatric patients undergoing open-heart surgery for atrial septal defect repair. Twelve children, aged between 10 months and 15 years, received remifentanil 5 μg/kg administered over 1 minute with subsequent blood sampling prior to the onset of cardiopulmonary bypass and after cardiopulmonary bypass had been completed. Vd_{ss}, V_c, $t_{1/2}\alpha$ and $t_{1/2}\beta$ were unaffected by cardiopulmonary bypass, while clearance increased by 20%. Overall, it seems that cardiopulmonary bypass does not have a big influence on remifentanil pharmacokinetics, while cardiopulmonary bypass is associated with marked changes in the pharmacokinetic properties of alfentanil, fentanyl and sufentanil (drugs that undergo hepatic biotransformation and elimination). The average pharmacokinetic parameters of all patients are not listed here, since they are provided as a summary of children with very different ages and it is known that the metabolic activity of children is age dependent.[21]

The most extensive investigations on remifentanil pharmacokinetics in children are those by Ross et al.,[22] who examined 34 children of different ages (5 days to 17 years). The children were undergoing elective surgical procedures and received remifentanil 5 μg/kg infused as a single bolus dose over 1 minute. The patients were divided into six different age groups and analysed separately. Neonates and infants had the largest Vd and the highest clearance rate. The $t_{1/2}\beta$ was within the range of 3.4–5.7 minutes and comparable in all age groups.

1.2 Pharmacodynamic Data

Opioid-binding studies demonstrated that remifentanil has a strong affinity for the μ-opioid receptor and a less strong affinity for the δ- and κ-receptors.[23,24] The potency of remifentanil is approximately equal to that of fentanyl, 15–60 times greater than the potency of alfentanil and around one-tenth the potency of sufentanil.[17,25,26] The main adverse effects of remifentanil are those usually associated with opioids and include bradycardia, hypotension, respiratory depression, skeletal muscle rigidity, nausea and vomiting.[25,27-32] As with the other opioids, the clinical effects of remifentanil can be antagonised by naloxone.[33]

2. Clinical Experience of Remifentanil

2.1 Maintenance of General Anaesthesia During Surgery

Most experience with remifentanil in neonates and infants derives from its use during surgery. Davis et al.[34] and Galinkin et al.[35] report on 60 neonates and young infants undergoing pylorotomy (aged ≤8 weeks). Anaesthesia was performed either with remifentanil and nitrous oxide (n = 38) or halothane and nitrous oxide (n = 22). The mean rate of remifentanil infusion was 0.55 μg/kg/min (range 0.39–1 μg/kg/min), which, like halothane, did not cause any bradycardia or dysrhythmias. Of the remifentanil-anaesthetised patients, 11% required treatment for hypotension (systolic blood pressure [SBP] <60mm Hg) compared with 32% in the halothane group. In both treatment arms, the children could be extubated approximately 7.5 minutes after discontinuation of anaesthesia. Of the subjects with normal preoperative pneumocardiograms, new-onset postoperative apnoea occurred in 23% of patients who received halothane-based anaesthetics compared with 0% of patients who received remifentanil-based anaesthetics. Postoperative vomiting, a common adverse event in patients with pylorotomy, occurred in 34% of the children anaesthetised with remifentanil compared 45% in children anaesthetised with halothane.

Wee et al.[36] anaesthetised 20 neonates and infants (age 7 days to 3 months) with remifentanil, isoflurane and epidural ropivacaine for major abdominal surgery. The first patients received a remifentanil bolus of 1 μg/kg, which led to bradycardia and hypotension. Therefore, the bolus dose was eliminated from the protocol and the remifentanil infusion started with a dose of 1 μg/kg/min, which also caused bradycardia and hypotension.

Finally, they started with an infusion rate of 0.25 μg/kg/min, which was then titrated according to haemodynamic response and clinical requirement. The resulting utilised dose range was 0.05–1 μg/kg/min with good perioperative analgesia and good overall haemodynamic stability. After cessation of the remifentanil infusion, neonates aged <7 days took 21 minutes to be extubated and infants aged ≥7 days took 6 minutes.

Schmidt et al.[37] describe 120 children aged 6 months to 16 years scheduled for minor lower abdominal surgery (number of infants aged <1 year not mentioned). Anaesthesia was either performed with propofol and remifentanil or sevoflurane and remifentanil. The mean remifentanil infusion rate was 0.37 μg/kg/min in the propofol group and 0.32 μg/kg/min in the sevoflurane group. In both groups, SBP decreased to some extent, while the heart rate decreased only in the propofol group (exact amount not mentioned). Overall, there were no serious adverse events. The extubation time was 11.8 minutes in combination with propofol and 15.0 minutes in combination with sevoflurane.

Weale et al.[30] analysed 49 infants and children aged <5 years undergoing elective cardiac surgery (number of infants aged <1 year not mentioned). The patients were randomised to receive one of four remifentanil infusion rates (0.25 μg/kg/min, 1 μg/kg/min, 2.5 μg/kg/min or 5 μg/kg/min). Recordings of blood glucose, plasma cortisol and heart rate alterations indicated that intraoperative remifentanil at infusion rates of ≥1 μg/kg/min can suppress the stress response in paediatric cardiac surgery, while a rate of 0.25 μg/kg/min was insufficient. Nine patients exhibited significant bradycardia or hypotension requiring intervention; four of these were neonates. The authors point out that three neonates with transposition of the great arteries needed epinephrine (adrenaline) [two were receiving remifentanil 1 μg/kg/min and one 2.5 μg/kg/min]. Overall, the cardiovascular depression observed was judged to be relatively minor in all treatment groups with the exception of the neonatal patients undergoing correction of either truncus arteriosus or transposition of the great arteries.

The efficacy of remifentanil has also been investigated by Bell et al.[38] They report on 17 children aged 3 months to 9 years undergoing cardiac surgery anaesthetised either with remifentanil or fentanyl/morphine (the remifentanil group included only one infant aged <1 year). Remifentanil was infused at a rate of 0.1 μg/kg/min with additional boluses of 1 μg/kg, titrated according to the clinical requirement. Both techniques produced broadly similar perioperative control of stress response during surgery, measured by alterations of blood glucose, serum cortisol and physiological variables such as blood pressure and heart rate.

Akpek et al.[39] compared the effects of remifentanil and fentanyl in 33 children aged 3 months to 6 years undergoing heart surgery for left-to-right shunt lesions (number of infants aged <1 year not mentioned). In addition to midazolam, patients received either remifentanil with a bolus of 2 μg/kg followed by a maintenance infusion at a rate of 2 μg/kg/min or fentanyl with a bolus of 10 μg/kg followed by a maintenance infusion at a rate of 20 μg/kg/h. Pre-bypass heart rate and mean arterial pressures changed significantly over time in the fentanyl group but not in the remifentanil group. Post-bypass heart rate and mean arterial pressures did not change over time in the fentanyl group, while in the remifentanil group only heart rate did not change and mean arterial pressures increased significantly. In summary, remifentanil was not associated with decreases in heart rate or arterial blood pressure, nor did it have clinically significant adverse effects on respiratory variables.

Roulleau et al.[40] describe 40 infants aged 2–12 months scheduled for cleft palate surgery. Anaesthesia was performed with either remifentanil or sufentanil as part of a balanced anaesthesia regimen with isoflurane and nitrous oxide. Remifentanil was started at a rate of 0.25 μg/kg/min and on average the infants needed a rate of 0.36 μg/kg/min. The mean heart rate decreased from approximately 140 bpm in both groups to 110 bpm in the remifentanil group and 125 bpm in the sufentanil group. SBP was less affected than heart rate by opioid injection; the baseline value of around 85mm Hg decreased only

to mean values between 75 and 80mm Hg. Overall, consistent haemodynamic stability was achieved throughout the surgical period in both groups. Only one 3-month-old infant developed sustained bradycardia and hypotension in the remifentanil group, which resolved within a few minutes after administration of atropine and a decrease in the infusion rate (the infusion rate causing bradycardia and hypotension is not mentioned). The median time from last suture to tracheal extubation was 12.5 minutes in the remifentanil group and 15 minutes in the sufentanil group. Postoperative EDIN (Échelle Douleur Inconfort Nouveau-Né) scale measurements provided no evidence of hyperalgesia and there was no enhanced morphine consumption in the remifentanil group compared with the sufentanil group.

In a study by Pietrini et al.,[41] remifentanil was used in combination with isoflurane or sevoflurane in 22 infants undergoing surgical correction of craniosynostosis. The mean remifentanil dose was 0.45 μg/kg/min in the sevoflurane group and 0.41 μg/kg/min in the isoflurane group. In both groups, patients had effective pain control and were haemodynamically stable, although heart rate and SBP decreased in both groups by approximately 20%. The extubation time was 16 minutes in the sevoflurane group and 13 minutes in the isoflurane group. No adverse effects such as respiratory depression or nausea were detected in the postoperative period, but there was moderate psychomotor agitation.

Chambers et al.[42] report on 62 children, including 13 neonates and 24 infants, receiving either remifentanil 1 μg/kg/min or saline as a bolus over 1 minute just before the tunnelling phase of ventriculoperitoneal shunt insertion. Isoflurane and nitrous oxide were used for general anaesthesia. Eight neonates and 13 infants received remifentanil, which caused good attenuation of haemodynamic and endocrine markers of stress, no delay in recovery and no additional postoperative respiratory depression. Clinically unimportant bradycardia and mild hypotension were frequent following administration of remifentanil.

Sammartino et al.[43] anaesthetised six premature infants undergoing laser therapy for retinopathy of prematurity with midazolam and remifentanil (gestational age 25–28 weeks, postnatal age 33–38 weeks). Remifentanil infusion was started at a rate of 0.75–1 μg/kg/min and titrated according to haemodynamic changes and clinical requirement. The mean infusion rate needed was 4 μg/kg/min and in a single case it was even increased to a rate of 20 μg/kg/min. Remifentanil provided good anaesthesia and analgesia, and no adverse effects were observed. The preterm infants were back to their preoperative status approximately 2 hours after the surgical procedure. The authors point out that preterm infants with earlier opioid consumption required 2- to 3-fold higher doses of remifentanil than those without earlier opioid therapy.

Finally, there are four case reports[44-47] on remifentanil for anaesthetic management of infants with rare medical problems. In all cases, the general medical condition supported the use of remifentanil as an opioid with short recovery time. All patients remained stable during the various surgical procedures and, where mentioned, there was fast recovery from anaesthesia.

2.2 Analgesia and Sedation During Short-Term Diagnostic and Therapeutic Procedures Under Mechanical Ventilation

The use of remifentanil for analgesia and sedation during short-term diagnostic and therapeutic procedures under mechanical ventilation is comparable to its use for anaesthesia during surgery.

Kessler et al.[48] report on 111 neonates and infants undergoing diagnostic bronchoscopy in total anaesthesia performed with remifentanil, propofol and mivacurium chloride. Patients remained haemodynamically stable under a mean remifentanil infusion rate of 0.77 μg/kg/min. Six infants exhibited a period of bradycardia and eight infants a brief episode of hypoxaemia (oxygen saturation [SpO_2] <90%), neither of which were related to anaesthesia. The mean extubation time was 8.8 minutes.

Foubert et al.[49] anaesthetised 30 mechanically ventilated children, aged 1–20 months, with

sevoflurane and remifentanil while they were undergoing cardiac catheterisation (number of infants aged <1 year not mentioned). The patients received remifentanil either 0.2 or 0.3 μg/kg/min, which caused a decrease in heart rate from 129 bpm to 101 bpm and 132 bpm to 112 bpm, respectively. The mean arterial pressure decreased from 53mm Hg to 48mm Hg and from 53mm Hg to 49mm Hg, respectively. In one patient, bradycardia was treated with atropine, while two patients needed therapy for arterial hypotension. The extubation time in both groups was around 7 minutes and there was no postoperative respiratory depression. On the basis of these results, they performed a comparable study[50] with 45 children, aged 1–36 months, receiving glycopyrronium bromide (glycopyrrolate) or saline with sevoflurane and remifentanil 0.15 μg/kg/min. Glycopyrronium bromide prevented bradycardia but not a blood pressure decrease of around 15–20%.

2.3 Analgesia and Sedation During Short-Term Diagnostic and Therapeutic Procedures Under Spontaneous Breathing

The most frequent indications for the use of remifentanil in spontaneously breathing children are short-term diagnostic or therapeutic procedures such as cardiac catheterisation, bone marrow aspiration or bronchoscopy. However, most experience derives from the toddlers-to-adolescents age range,[51-58] and there are very few reports on the use of remifentanil in spontaneously breathing neonates and infants.

Donmez et al.[59] report on 55 children aged 2 months to 12 years receiving remifentanil for cardiac catheterisation (number of infants aged <1 year not mentioned). After premedication with a mixture of midazolam (0.5 mg/kg) and hydroxyzine (1 mg/kg), remifentanil was started at a rate of 0.1 μg/kg/min. In the first patients, 0.02 μg/kg bolus doses of remifentanil were administered if the patient reacted to pain, but this resulted in bradypnoea and apnoea. This led the authors to change their protocol and after the initial five patients, midazolam 0.05 mg/kg was administered intravenously when a patient reacted to pain. When this proved to be inadequate, ketamine 1 mg/kg was also administered intravenously. This procedure did not cause any significant changes in SBP, heart rate or arterial oxygen saturation. Overall, in 23 patients, remifentanil on its own maintained a satisfactory level of analgesia and sedation; however, 18 children required additional midazolam and 14 children required midazolam plus ketamine. Mean recovery time was 2 minutes in patients receiving only remifentanil, while it was 4.3 minutes in patients with additional midazolam, and 4.1 minutes in patients with additional midazolam and ketamine.

Tsui et al.[60] performed light general anaesthesia with remifentanil and propofol in 56 children aged 1 month to 11 years undergoing magnetic resonance imaging (MRI) [number of infants aged <1 year not mentioned]. The mean infusion rate was 0.06 μg/kg/min for remifentanil and 60 μg/kg/min for propofol. Complications included seven children with spontaneous movements during the MRI scan, two children with brief episodes of hypoxaemia (SpO_2 <90%) and one case of mild airway obstruction. A respiratory rate decrease from 27 to 16 was judged to be not clinically significant. Patients of all age classes had a short mean recovery time of 8.9 minutes.

2.4 Analgesia and Sedation of Mechanically Ventilated Intensive Care Patients

In total, there are only five reports on remifentanil for analgesia and sedation of mechanically ventilated paediatric intensive care patients. The study by Akinci et al.[61] and the two case reports of German et al.[62] do not include any neonates or infants aged <1 year, but both authors judged remifentanil to be safe and effective for this indication with short recovery and extubation times.

Stoppa et al.[63] describe 18 mechanically ventilated neonates (gestational age >32 weeks) receiving remifentanil for analgesia and sedation. Remifentanil was started at a rate of 0.25 μg/kg/min and then titrated according to sedation score. After the critical phase of respiratory failure, the infusion rate was reduced to restore spontaneous breathing. The exact criteria used to end the remifentanil infusion are not mentioned. The mean infusion time was

67 hours, with a mean infusion rate of 0.15 μg/kg/min for the entire treatment time. Deeper analgesia required a mean dose of 0.17 μg/kg/min. Compared with baseline, heart rate decreased by around 20% during remifentanil infusion, while blood pressure remained unchanged. Eight patients required <2 hours (mean 1.8 hours) to restore spontaneous breathing under a reduced infusion rate of 0.06 μg/kg/min, while ten patients required >2 hours (mean 2.8 hours) under an reduced infusion rate of 0.1 μg/kg/min. The mean extubation time after discontinuing remifentanil was 18 minutes. Overall, there were no serious adverse effects.

Eck and Lynn[64] report on a 7-week-old, former 35-week-premature infant with cirrhosis and severe liver failure undergoing surgical ligation of a patent ductus arteriosus in preparation for liver transplantation. During surgery, anaesthesia was performed with propofol and remifentanil 0.5–0.75 μg/kg/min. In the intensive care unit, remifentanil was commenced at 0.38 μg/kg/min for postoperative analgesia. The infusion was stopped after removal of the chest tube and within 5–6 minutes, the patient opened her eyes. Extubation could be performed after 20 minutes.

Pereira e Silva et al.[65] administered remifentanil to a premature infant of 34 weeks gestation, who was mechanically ventilated for infant respiratory distress syndrome. Intubation was performed under excellent intubating conditions after premedication with midazolam and a remifentanil bolus dose of 1 μg/kg. Subsequently, a continuous infusion of remifentanil was started at 0.75 μg/kg/min, surfactant applied and remifentanil decreased to 0.5 μg/kg/min, under which the infant remained deeply sedated. After 6 hours, it was decided to extubate the child and decrease remifentanil to 0.2 μg/g/min, under which the infant developed spontaneous breathing after 20 minutes. The drug was then discontinued and 30 minutes later, the child was successfully extubated. Potential adverse effects such as bradycardia, hypotension or chest-wall rigidity were not seen at any stage.

2.5 Tracheal Intubation

There is only one published study, by Crawford et al.,[66] which evaluated remifentanil for tracheal intubation in infants. This included 32 children aged 2–12 months. Besides glycopyrronium bromide 10 μg/kg and propofol 4 mg/kg, patients received remifentanil either 1.25, 1.5, 1.75 or 2.0 μg/kg over 30 seconds to facilitate tracheal intubation. The proportion of intubating conditions judged excellent or good increased in proportion to increasing remifentanil dose, but even with a dose of 2.0 μg/kg, the intubating conditions were unacceptable in 25% of patients. On the basis of these results, another 24 infants were randomised to receive either remifentanil 3.0 μg/kg or succinylcholine 2.0 mg/kg in addition to glycopyrronium bromide and propofol for tracheal intubation. Intubating conditions were judged to be excellent in all 12 patients in the succinylcholine group and in 11 patients in the remifentanil group (good in 1 patient). There were no complications associated with tracheal intubation and no episodes of bradycardia, hypotension or chest wall rigidity.

Remifentanil has been used in other studies to facilitate intubation in neonates and infants without directly investigating the intubation conditions.[30,37,41,49,50]

3. Discussion

This review shows that there is already quite a lot of experience with remifentanil in neonates and infants aged <1 year, despite the fact that remifentanil is not licensed for children of this age.

The available pharmacokinetic data in children are similar to the data in adults. Neonates and children aged <2 years show a larger Vd and a larger clearance compared with older children or adults (table I). The $t_{1/2}\beta$ is very short being within ~5 minutes in all paediatric age classes.[10,19,22] This indicates that the pharmacodynamic advantages of remifentanil with a short recovery time from anaesthesia could also be valid for neonates and infants. However, it should be emphasised that very few pharmacokinetic data about neonates exist and there are no data about preterm infants.

Table I. Pharmacokinetic profile of remifentanil by age group after a single bolus dose of 5 μg/kg[a]

Parameter	0–2mo	2mo–2y	2–6y	7–12y	13–16y	16–18y	Reference
C_{max} (ng/mL)	24.2 ± 10.2	25.4 ± 3.7	34.8 ± 8.2	42.5 ± 13.7	35.0 ± 10.2	42.7 ± 12.9	22
Vd_{ss} (mL/kg)	453 ± 145	308 ± 89	240 ± 131	249 ± 91	223 ± 31	243 ± 109	22
	325 ± 90						19
CL (mL/kg/min)	90.5 ± 36.8	92.1 ± 25.8	76.0 ± 22.4	59.7 ± 22.5	57.2 ± 21.1	46.5 ± 2.1	22
	80.4 ± 22.6						19
$t_{1/2\beta}$ (min)	5.4 ± 1.8	3.4 ± 1.2	3.6 ± 1.2	5.3 ± 1.4	3.7 ± 1.1	5.7 ± 0.7	22
	4.4 ± 1.3						19
$t_{1/2\alpha}$ (min)	0.42 ± 0.17						19

a Data shown are mean results ± SD.

CL = clearance; **C_{max}** = peak plasma concentration; **$t_{1/2\alpha}$** = distribution half-life; **$t_{1/2\beta}$** = terminal elimination half-life; **Vd_{ss}** = volume of distribution at steady state.

Most of the clinical experience with remifentanil in neonates and infants derives from its use for maintenance of general anaesthesia during surgery and short-term diagnostic/therapeutic procedures under mechanical ventilation (table II).

Remifentanil proved to be an effective analgesic for neonates and infants. The adverse effects include bradycardia and hypotension, in particular, which were mostly without clinical significance. Caution has been recommended in neonatal patients undergoing correction of either truncus arteriosus or transposition of the great arteries, especially at higher doses (≥1 μg/kg/min). For this subgroup of patients, severe cardiovascular depression has been reported, which required the use of epinephrine.[30] It is not clear whether only patients with certain congenital heart defects might have an increased risk for severe bradycardia and hypotension, or whether neonates in general are susceptible to severe cardiovascular depression in the higher dose range. The exact mechanisms for both bradycardia and hypotension are unclear, but it seems that they are not only caused by an activation of the parasympathetic autonomic nervous system, and cannot be fully prevented by atropine or glycopyrronium bromide.[31,32,50]

Controversy exists regarding the safety of bolus doses remifentanil. Wee et al.[36] report on an increased risk for bradycardia and hypotension after giving a bolus dose of 1 μg/kg, while others registered no increased-bolus-related haemodynamic instability.[39,41,66] A possible explanation may be the fact that Wee et al.[36] did not apply the bolus dose over 60 seconds, as was the case in other studies.

In summary, remifentanil can cause typical adverse effects of μ-receptor binding opioids, but there are no reports about serious adverse effects when doses <1 μg/kg/min are used. We would recommend commencing at an infusion rate of 0.25 μg/kg/min and titrating according to haemodynamic response. Many reports pointed out the short recovery profile of remifentanil; after termination of a remifentanil infusion, it takes only a few minutes until the patient develops spontaneous breathing, which results in short extubation times. There are no reports of postoperative respiratory depression.

The experience to date with remifentanil in spontaneously breathing older children indicate there is a wide range of infusion rates that can cause respiratory depression, but usually a dose of ≤0.05 μg/kg/min is not associated with significant respiratory adverse effects,[51-58] which is similar to adults.[67] This dose range does not usually cause any haemodynamic problems. Whether such a small dose provides sufficient analgesia and sedation seems to depend on the type of procedure and the use of concomitant hypnotics. Nevertheless it is questionable whether the results from older children and adults can be transferred to neonates and infants, who respond more sensitively to opioid-induced respiratory depression.[16]

The very few available data about the use of remifentanil in spontaneously breathing neonates and infants do not allow us to comment on the safety of remifentanil for this group of patients.

There is very little published experience with the use of remifentanil for analgesia and sedation of

Table II. Summary of experience with remifentanil in preterm infants, term neonates and infants

Experience	Preterm infants (<37wk of gestation)	Term neonates (0–28d)	Infants (1–12mo)	Conclusions
Pharmacokinetic data	No data available	Data from 5 patients available[19,22]	Data from 16 patients available[19,20,22]	Data in neonates and infants are comparable to those in adults. Data from preterm infants are missing
Surgery or short-term diagnostic and therapeutic procedures under mechanical ventilation	8 preterm infants with a gestational age of 25–29 weeks and a postconceptional age of 33–40 weeks are described[43,44,46]	Exact number of neonates is not mentioned in the literature, but overall the reports include approx. 40–60 children of this age[30,34-36,42,48]	Exact number of infants is not mentioned in the literature, but overall the reports include approx. 240–270 children of this age[30,34-42,45,47-50]	Remifentanil proved to be an effective and safely used analgetic at the common dose (<1 μg/kg/min)
Short-term diagnostic and therapeutic procedures under spontaneous breathing	No experience	No experience	Experience with approx. 20–30 infants[59,60]	The limited experience allows no recommendation at this time
Analgesia and sedation of mechanically ventilated paediatric intensive care patients	A study with 17 preterm and term infants includes an unknown number of preterm neonates, in addition there are two case reports[63-65]	A study with 17 preterm and term infants includes an unknown number of term neonates[63]	No experience	Remifentanil could be the ideal opioid for this indication with a short extubation time, but further research is needed
Intubation conditions	No reports	No reports	One study included 32 infants[66]	The limited experience allows no recommendation at this time

mechanically ventilated neonates and infants. However, this indication is particularly interesting in our opinion because neonates and infants show a long recovery time after prolonged administration of common opioids, such as fentanyl or sufentanil,[68] which is associated with delayed extubation, higher morbidity, longer stay in intensive care and increased costs. The prolonged respiratory depression is caused by the long context-sensitive half-time of the common opioids, which increases with the duration of the opioid infusion. Remifentanil offers a promising alternative, with a context-sensitive half-time of 3–5 minutes, independent of the infusion duration.[9] In the few existing reports in mechanically ventilated children, remifentanil provided effective analgesia and sedation with short extubation times after discontinuation of the opioid infusion. Because of its short recovery profile, remifentanil is especially suited for selected paediatric neurosurgical patients (for example, infants with serious head trauma and mechanical ventilation), who have to be sedated but also need serial neurological examinations.[62] Further research is needed because remifentanil could be the ideal opioid for long-term analgesia and sedation of mechanically ventilated paediatric intensive care patients.

Studies in adults raised some concern about the possible induction of acute opioid tolerance and hyperalgesia by remifentanil,[69-71] while many studies could not demonstrate this phenomenon.[72-76] The exact mechanism remains unclear but the stimulation of NMDA receptors could play a major role.[77] However, acute opioid tolerance is also seen with other opioids, and seems to be related to long infusion durations and high doses.[78] To date, there have been no reports of the induction of acute opioid tolerance or hyperalgesia by remifentanil in neonates or infants.

4. Conclusion

At the usual dose (<1 μg/kg/min), remifentanil proved to be an effective and safely used opioid for surgery in neonates and infants with a short recovery profile. The limited experience with remifentanil in

spontaneously breathing neonates and infants allow no recommendation at this time.

Further research should focus on mechanically ventilated paediatric intensive care patients, for whom remifentanil could offer important advantages. With its short context-sensitive half-time, remifentanil could result in shorter extubation times, especially in neonates.

Acknowledgements

This review was developed without any funding and the authors have no conflicts of interest directly relevant to its contents. Besides the authors, no other persons made substantial contributions to the work.

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