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REVIEW ARTICLE

Aspects of pharmacokinetics and pharmacodynamics of sufentanil in pediatric practice

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Summary

Sufentanil is a potent synthetic opioid. Like other opioids, sufentanil creates a stable hemodynamic environment in cardiovascularly compromised pediatric patients. Clearance, expressed as per kilogram, is increased in children compared to adults. The P450 CYP3A4 enzyme is responsible for the major metabolic *N*-dealkylation pathway. Enzyme activity is reduced in neonates but the maturation of sufentanil clearance is not described. The free active fraction is affected by age because of the reduced α_1-acid glycoprotein plasma concentrations in neonates. Intranasal administration of sufentanil is a possible option for premedication, procedural sedation and analgesia in children, as this option has been found to be safe and effective. Studies concerning the pharmacokinetics and dynamics of sufentanil administered as a bolus or continuous infusion in children are few.

Introduction

Sufentanil, first synthesized in 1974, is an opioid about five to ten times more potent than fentanyl, and yet has a shorter duration of action. Sufentanil has a high lipid solubility, which accounts for the fast onset when given intravenously. The commercial solution comes as preservative-free sufentanil citrate, injectable with a pH of 4.5–7.0 (Jansen-Cilag AB, Sweden). Sufentanil has been administered via various routes e.g., as intravenous, epidural, intrathecal, transdermal, and nasal applications.

The purpose of this review is to describe the pharmacokinetics and dynamics in the pediatric population. Published studies describing its use in children are limited and most from the last century. On the other hand, the experience and clinical use of sufentanil in the pediatric population is gathering momentum.

Pharmacokinetics

Normal children

Sufentanil has a rapid onset and a short duration of action after an intravenous dose. In adults, the terminal half-life is about 2.5 h. Sufentanil is about 90% bound to plasma proteins. Sufentanil is metabolized in the liver and to some extent in the small intestine by *N*-dealkylation and *O*-demethylation and the inactive metabolites are excreted in the urine and faeces. About 80% of a dose is excreted within 24 h, and 2% is eliminated as the unchanged drug. Sufentanil does cross the placenta and is excreted into breast milk (1).

The P450 CYP3A4 enzyme is responsible for *N*-dealkylation (2) and maturation of this enzyme, which is also responsible for fentanyl and alfentanil, may mature over the first month or so of postnatal life (3,4), but the maturation profile is not yet fully described. While CYP3A7 is expressed in the fetal liver and appears to have activity from as early as 50–60 days after conception, there appears to be a temporal switch in the immediate perinatal period and CYP3A4 expression increases dramatically after the first week of life (5).

Age seems to affect the pharmacokinetic profile. In a pharmacokinetic study in 20 normal children between 2 and 8 years of age (6), differences were demonstrated between children and adults. After an

intravenous bolus dose of sufentanil of 1–3 $\mu g \cdot kg^{-1}$, the mean distribution half-life ($t_{1/2\alpha}$) was 5.2 SD 2.2 min and the mean elimination half-life ($t_{1/2\beta}$) was 97 SD 42 min. The volume of distribution at steady state (V_{dss}) was 2.9 $l \cdot kg^{-1}$ and the mean clearance was 30.5 SD 8.8 $ml \cdot kg^{-1} \cdot min^{-1}$. The V_{dss} was one and a half times greater than reported in adults when expressed as a function of body weight but similar to that of adults when expressed as a function of body surface area. The clearance of sufentanil in normal children between 2 and 8 years was twice as rapid as described in adults and adolescence (7). These age-related changes in children are predictable from allometric size modeling (3). We might anticipate reduced clearance in neonates and perhaps infants and what is unknown is the clearance maturation profile from premature neonates through to infancy.

Chronic renal failure

Davis *et al*. (8) evaluated the metabolism of sufentanil in six adolescents, 10–15 years of age, with chronic renal failure undergoing renal transplant. This group of patients were compared with controls with normal renal function. This study did not show any differences in clearance, apparent volume of distribution, and terminal half-life between the two groups. Sufentanil clearance and elimination half-life were however more variable among the patients with chronic renal failure. Elimination half-life ($t_{1/2\beta}$) was 76 SD 33 min in normal adolescents, and 90 SD 15 in the group with renal failure. Clearance was 13 SD 12 $ml \cdot kg^{-1} \cdot min^{-1}$ and 16 SD 6, respectively. The authors concluded that renal failure had a minimal effect on the pharmacokinetic parameters of sufentanil but the dosing should be individualized in this group because of wide variability

Cardiovascular patients

Two studies in 1987 looked at the pharmacokinetics of sufentanil in pediatric patients undergoing cardiovascular procedures. Greeley *et al*.(9) studied 28 patients in four groups from neonates to adolescents (nine neonates, seven infants, seven children, and five adolescents). Typical procedures were shunt operations and partial resection of aorta because of the coarctation. Sufentanil 10–15 $\mu g \cdot kg^{-1}$ was given as a single bolus dose, and plasma concentrations were measured for up to 20 h after administration. Seven patients (one infant, three children, and three adolescents) underwent procedures requiring cardiopulmonary bypass. In these patients, no blood sampling was obtained during or after bypass. Clearance was significantly lower in the neonatal group, 6.7 SD 6.1 $ml \cdot kg^{-1} \cdot min^{-1}$ than the values of 18.1 SD 2.7, 16.9 SD 3.2, 13.1 SD 3.6 in infants, children, and adolescents, respectively. The volume of distribution was significant greater in neonates when compared to children and adolescents. The elimination half-life showed a comparable difference, significant longer in neonates (783 SD 346 min) than values of 214 SD 41, 140 SD 30, and 209 SD 23 min observed in infants, children, and adolescents, respectively. The results of this study clearly demonstrated that age-related differences in pharmacokinetic properties of sufentanil are evident in pediatric patients with major cardiovascular disease undergoing cardiovascular surgery.

Davis *et al*. (10) did examine the pharmacokinetics and dynamics of a high dose of sufentanil, 15 $\mu g \cdot kg^{-1}$, in 20 infants and children undergoing repair of congenital heart defects. Approximately 75% of the children were in compensated congestive heart failure controlled by medication with digitalis and diuretics. Pharmacokinetic parameter estimates were based on the measurements made before cardiopulmonary bypass. In infants younger than 10 months, and children over 10 months, who were not surface cooled, the elimination half-lives were similar 53 SD 15 min vs 55 SD 10 min, as were clearance values 27.5 SD 9.3 vs 18.1 SD 10.7 $ml \cdot kg^{-1} \cdot min^{-1}$. The volume of distribution was smaller in the infants compared to children in this study, 1.6 SD 0.5 vs 3.0 SD 1.3 $l \cdot kg^{-1}$. In infants who were surface cooled, the elimination half-life was prolonged and the volume of distribution was larger. The differences between elimination half-lives in the two studies with cardiac pediatric patients are noticeable. The dose used was similar so the difference needs another explanation, as e.g., disease-related conditions or contrasting pharmacokinetic modeling. Pharmacokinetic models also differed; Greeley (9) used a three compartment model while Davis (10) used a two compartment model.

Plasma protein binding

Sufentanil is highly bound to proteins as α_1-acid glycoprotein (AAG) in plasma. The free fraction of the drug is accountable for the analgesic and respiratory effects. Protein binding varies significantly with age. Meistelman *et al*.(11) showed in their study that the free fraction of sufentanil was significantly higher in newborns than in older age groups. In newborns, the mean free fraction was 19.5 SD 2.7%. The values in infants, children, and adults were 11.5 SD 3.2, 8.1 SD 1.4, and 7.8 SD 1.5%, respectively. The results are in accordance

with the lower concentrations of α_1-acid glycoprotein found in newborns and infants. It remains uncertain whether the increased free fraction of sufentanil has clinical implications in neonates and infants. Sufentanil has a high hepatic extraction ratio, and protein binding may have little effect because dose is commonly titrated to effect and reduced clearance in neonates and infants will have greater impact.

Total intravenous anesthesia

Sufentanil has a place in total intravenous anesthesia as a fast acting, potent opioid. Both sufentanil and alfentanil have advantages in comparison with fentanyl, i.e., faster onset and smaller volume of distribution. A concentration of 5–10 $ng \cdot ml^{-1}$ is suggested for total intravenous anesthesia and 0.2–0.4 $ng \cdot ml^{-1}$ for analgesia. However, pharmacokinetic studies in children and infants are rare or nonexistent, limiting the use in this age group (12). A summary of pharmacokinetic variables are shown in Table 1.

Pharmacodynamics and clinical use

Cardiovascular surgery. In the studies by Davis (10) and Greeley (9), high doses of sufentanil, 10–15 $\mu g \cdot kg^{-1}$ as a rapid bolus infusion, were used. In both studies, sufentanil attenuated changes in blood pressure and heart rate during the initial phase of surgery with incision and sternotomy, in a majority of patients. One neonate in the study by Greeley (9) required temporary chronotropic and inotropic support for severe bradycardia and hypotension after sufentanil administration. The changes in catecholamine concentrations in pediatric cardiac surgery were examined by Moore *et al*. (13). No significant changes were reported in concentrations during stress periods e.g., incision and sternotomy. However, the lack of statistical significance was attributed to major individual variability. Sufentanil in a high dose is an efficient analgesic in the initial phase of surgery in cardiac patients, but supplemental anesthesia is required intraoperatively.

Epidural and intrathecal administration

The effect of sufentanil on the duration of analgesia after a caudal block was studied by De Mey *et al*. (14). The aim was to evaluate whether the addition of sufentanil or clonidine, or both, prolonged the period of analgesia after a caudal block with bupivacaine. Sixty healthy boys, between 8 months and 13 years, undergoing hypospadias repair were examined in this prospective randomized study. Sufentanil was added to bupivacaine 0.25% in a dose of 0.5 and 0.25 $\mu g \cdot kg^{-1}$ when given together with clonidine. The results showed no additional clinical benefit with sufentanil or clonidine, or both, compared to bupivacaine alone. The findings are a bit surprising because the beneficial effect of clonidine added to local anesthetics have been demonstrated in several studies during the last decade (15).

The ventilatory response to carbon dioxide following epidural sufentanil in 15 children has been studied by Benlabed *et al*. (16). The mean onset (time from epidural administration to no pain) and duration (time from onset to moderate pain requiring an analgesic) of anal-

Table 1 Pharmacokinetic parameters

Study (ref) (number of patients)	Volume of distribution (V_{dss}) mean (SD) $l \cdot kg^{-1}$	Clearance (Cl) mean (SD) $ml \cdot kg^{-1} \cdot min^{-1}$	Elimination half-life ($t_{1/2\beta}$) mean (SD) min	Comment
Guay (6)				
2–8 years (n = 20)	2.9 (0.6)	30.5 (8.8)	97.0 (42)	Normal children
Davis (8)				
10–15 years				Renal failure and controls
controls (n = 6)	1.28 (0.62)	12.8 (12.0)	76.0 (32.8)	
renal failure (n = 6)	1.65 (0.6)	16.4 (6.1)	89.7 (15.7)	
Greeley (9)				
0–1 month (n = 9)	4.15 (1.0)	6.7 (6.1)	783 (346)	Cardiovascular surgery
1–24 month (n = 7)	3.09 (0.95)	18.1 (2.7)	214 (41)	
2–12 years (n = 7)	2.73 (0.5)	16.9 (3.2)	140 (30)	
12–18 years (n = 5)	2.75 (0.5)	13.1 (3.6)	209 (23)	
Davis (10)				
<10 month (n = 7)	1.6 (0.46)	27.5 (9.3)	53 (15)	Cardiovascular surgery
<10 month sc (n = 6)	3.7 (1.1)	21.5 (5.0)	120 (36)	Surface cooled
>10 months (n = 6)	3.0 (1.3)	18.1 (10.7)	55 (10)	

sc, surface cooled.

gesia were 3 SD 0.3 and 198 SD 19 min, respectively. Depression of ventilatory control was observed during the first hour after sufentanil administration. The authors concluded that the analgesic effect was rather short, and it is important to monitor the patients because of the risk of ventilatory depression. Lejus *et al*. (17) showed that time to peak plasma concentration after epidural administration of sufentanil occurred at about 20 min. The fast onset of analgesia showed by Benlabed (16) could be explained by a direct spinal effect and not by systemic uptake from the epidural space.

The use of epidural-administered sufentanil in children has been demonstrated by Kokki and coworkers (18–20). Their aim was not to explore the effect of sufentanil but more to show opioid sparing effects of additives as epinephrine given epidurally and the NSAID ketoprofen administered intravenously.

Intrathecal administration is occasionally used in children but here are no published studies in this area.

Cardiovascular response to intubation

Laryngoscopy and tracheal intubation is a very stressful procedure and often used as a pain indicator in studies. Xue *et al*. (21,22) have studied the effect of a dose of intravenous sufentanil on stress response on intubation. They demonstrated that a dose of 0.3 $\mu g \cdot kg^{-1}$, but not lower, could abolish the cardiovascular intubation response when propofol was used as induction agent. Liao and coworkers showed in 2009 a similar effect of remifentanil 2 $\mu g \cdot kg^{-1}$ given intravenously (23). In this study, remifenatnil was compared to sufentanil 0.2 $\mu g \cdot kg^{-1}$. Not surprisingly, the dose of sufentanil was not as effective. All the intubation studies are from the same group, and it would therefore have been more appropriate and interesting if remifentanil had been compared with sufentanil in a dose of 0.3 $\mu g \cdot kg^{-1}$.

Intranasal administered sufentanil

There has been a growing interest and use of intranasal sufentanil in children. Sufentanil does not create any pain or discomfort when applied to the nasal mucosa. The uptake has been studied in adults, and the bioavailability is about 80% (24). To this date, there are no studies in children but a group in Denmark at Copenhagen University Hospital is in the process of starting a study with sufentanil given as an aerosol. Pharmacokinetic parameters and pharmacodynamics are to be examined (personal communication).

Several studies have been performed with nasally administered sufentanil for premedication. Henderson *et al*. (25) examined eighty children aged 6 months to 7 years. The children were randomized to receive sufentanil (1.5, 3 or 4.5 $\mu g \cdot kg^{-1}$) or placebo. Sufentanil was given as drops from a syringe over 15–20 s. Patients given sufentanil were judged to have less anxiety at 10 min compared to those given placebo. The group receiving 4.5 $\mu g \cdot kg^{-1}$ showed a marked decreased ventilatory compliance during the induction of anesthesia and had a higher incidence of vomiting during the first postoperative day. Zedie and coworkers (26) compared intranasal midazolam (0.2 $mg \cdot kg^{-1}$) with sufentanil (2 $\mu g \cdot kg^{-1}$) premedication in 60 pediatric outpatients. Children who received midazolam were more likely to cry upon administration, compared with sufentanil. The sufentanil group appeared to be more sedated and more cooperative during induction. Bayrak *et al*. (2007) (27) also examined the effect of different drugs as premedication. The study was performed to evaluate the efficacy and safety of oral midazolam (0.5 $mg \cdot kg^{-1}$), tramadol drops (3 $mg \cdot kg^{-1}$), or intranasal sufentanil (2 $\mu g \cdot kg^{-1}$). The children were aged 3–10 years, 20 children in each group. Oxygen saturation, respiratory rate, and blood pressure significantly decreased in the sufentanil group relative to the patients receiving midazolam or tramadol. Anxiety scores and face mask acceptance were better in the sufentanil and midazolam group.

Roelofse *et al*. (28) evaluated the efficacy and safety of intranasal sufentanil (administered via a Go Medical® nasal spray) and intranasal midazolam (S/M), when compared with intranasal ketamine and intranasal midazolam (K/M), for sedation and analgesia in pediatric patients undergoing dental surgery. Fifty healthy ASA 1 status children aged 5–7 years, weighing 15–20 kg, and having six or more teeth extracted, were randomly allocated to two groups of 25 children each. In the S/M group, children received intranasal sufentanil 20 μg, and intranasal midazolam 0.3 $mg \cdot kg^{-1}$, 20 min before induction of anesthesia. In the K/M group, children received intranasal ketamine 5 $mg \cdot kg^{-1}$ and intranasal midazolam 0.3 $mg \cdot kg^{-1}$, 20 min before the induction of anesthesia. Sevoflurane in nitrous oxide oxygen was used for the induction of anesthesia. The study demonstrated the safety and efficacy of both methods, with ease of administration, combined with a rapid onset of action. A smooth mask induction of anesthesia was experienced in the majority of children. The Oucher facial pain scale (29) was used to measure pain postoperatively. Seventy-two percent of children in the S/M group were responders, as to 52% in the K/M group. The Oucher facial pain scale showed the

S/M group to experience less pain than those in the K/M group. The nasal administration of drugs for sedation and analgesia has some promising features, especially in children with fear of separation from parents and unfamiliar surroundings. Improvements of nasal sprayer devices and formulations may improve clinical outcome.

In a pilot study of 300 children (J. A. Roelofse, personal communication) (2010), sufentanil is used intravenously with midazolam, ketamine, and propofol, for procedural sedation and analgesia in children weighing 10–20 kg, undergoing painful dental procedures. More than 200 children have already been done with the above-mentioned combination of drugs. Sufentanil 10 mcg (μg), is mixed with ketamine 50 mg, and propofol 200 mg, in the same syringe. Sufentanil is administered at a dose of 0.2–0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$. No significant hemodynamic changes have been noticed in the children, nor serious adverse effects. None of the children had an oxygen saturation drop below 92%. Capnography is used to monitor the carbon dioxide concentrations - all values are below 5 kPa. This study shows sufentanil to be a promising agent for procedural sedation and analgesia.

The premedication studies illustrate several interesting findings. Midazolam given by the nasal route causes a high degree of irritation during instillation, which limits its use as a suitable drug. Commercially available Sufentanil 50 $\mu g \cdot ml^{-1}$ on the other hand does not cause major irritation when given nasally. On the other hand, opioids, and especially in higher doses over 2 $\mu g \cdot kg^{-1}$, increase the risk for ventilatory depression and vomiting.

At Astrid Lindgren Children's Hospital, Stockholm, Sweden we have used intranasal sufentanil for reducing procedural pain, and infrequently as premedication for more than a decade, and in over 1000 patients. Our clinical experience is that the dose of sufentanil could substantially be decreased when changing the mode of application from drops to an aerosol. The onset is also faster with the aerosol.

Different devices could be used for creating an aerosol but we favor the Mucosal Atomization Device, MAD^{TM} (Wolfe Tory Medical, Inc, Salt Lake City, UT, USA), for its simplicity and accuracy of dosing. The onset of sufentanil aerosol is about 5–10 min with a maximum sedative and analgesic effect at about 20–25 min. Depending on the dose used, the effect wears off at about 60 min. Doses used for procedural pain are usually 0.7–1 $\mu g \cdot kg^{-1}$ and very occasionally over 1.5 $\mu g \cdot kg^{-1}$. These doses (< 1.5 $\mu g \cdot kg^{-1}$) very seldom give adverse effects like nausea/vomiting and ventilatory depression. Lower doses of intranasal sufentanil can be used when combined with other drugs such as intranasal s-ketamine or dexmedetomidine.

Conclusion

Sufentanil has been used in pediatric anesthesia for several decades. Studies concerning the pharmacokinetics and pharmacodynamics of sufentanil administered as a bolus or continuous infusion in children are surprisingly few, and most from the last century. On the other hand, the experience and clinical use of sufentanil in the pediatric population for analgesia, and procedural sedation for painful procedures should be noted. Intranasal administration of sedatives and opioid analgesics provide a mechanism for more rapid drug absorption and more rapid onset of pain relief compared with oral dosing. Lipophilic agents i.e., sufentanil with a low molecular weight should produce plasma concentrations similar to those achieved by the intravenous route. Therefore, from a clinical point of view, sufentanil is a suitable and safe drug for premedication if used as a slow continuous infusion or given by the nasal route.

Sufentanil has about five to ten times the clinical potency of fentanyl. It is highly protein bound, and the active free fraction could increase especially in neonates and infants. In normal children, between 2 and 8 years, the clearance of sufentanil was twice as rapid as described in adults and adolescence. Similar to fentanyl and alfentanil, it has shown to be a suitable and effective opioid for cardiac comprised pediatric patients. Chronic renal failure does not alter the pharmacokinetics significantly but there seems to be a larger interindividual variability that has to be taken into concern.

The intranasal route of sufentanil is attractive because of a predictable onset of action and acceptance by the child when applied on the nasal mucosa. Intranasal sufentanil is favorable for premedication and the treatment of procedural pain when lacking an intravenous line. The experience of nasally administered use of sufentanil for procedures and sedation is large. Sufentanil is a very potent opioid and therefore should be administered by personnel with the knowledge of opioid use. Sufentanil may be a useful agent for analgesia in the postoperative period.

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