Pediatric Anesthesia 2005 **15**: 1041–1047 doi:10.1111/j.1460-9592.2005.01738.x

Review article

Use of tramadol in children

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Keywords: tramadol; anesthesia; pain treatment

Introduction

Some progress has been made in alleviating pain in children in the last two decades. A growing body of knowledge about the nature of pain from intrauterine life to childhood has changed practices in pediatric pain treatment. However, the availability of potent analgesic medications labeled for children is limited. These medications include paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids; NSAIDs have restricted approval for children and may cause a bleeding tendency, renal impairment and aggravate asthma, and opioids have the risk of respiratory depression. Thus, pediatric anesthesiologists mainly depend on paracetamol and regional techniques, especially in day-case surgery of children. A drug with different formulations, which would enable proper dosing and be effective in relieving moderate to severe pain in children, is still needed. Although tramadol was launched in the area of pain practice 30 years ago in Germany, its use is still limited to those over the age of 12 in some countries, whereas it is licenced for use in children older than 1 year in some others. Also, a new oral tablet form, which is a combination of paracetamol and tramadol, has been introduced to the market but is not yet approved for use in children. This review focuses on the pharmacokinetic and pharmacodynamic profile of tramadol in children and its use in the treatment of postoperative and chronic pain.

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Pharmacodynamic profile

Tramadol is a synthetic 4-phenyl-piperidine analog of codeine which is marketed as a racemic mixture of (+) and (−) enantiomers. Two complementary mechanisms are defined for its mode of action. The opioid activity of tramadol results from low affinity binding of the (+) enantiomer to μ-opioid receptors. Tramadol acts like a weak or partial agonist with no affinity for δ- or κ-opioid receptors. The central analgesic effects of tramadol are partially reversed by naloxone. In addition, the (+) enantiomer inhibits serotonin uptake and has a direct serotonin-releasing action while the (−) enantiomer is a more effective inhibitor of norepinephrine reuptake and increases its release by autoreceptor activation (1). Therefore, the analgesic efficacy of tramadol is extended by both opioid and monoaminergic mechanisms in opioid-sensitive and -insensitive pain. O-desmethylated metabolite (M1) also contributes to the analgesic effect because of its 300-fold higher affinity to bind to μ-opioid receptors (Table 1) (2–6). Studies of animals and humans have suggested that tramadol may have selective spinal and local anesthetic action on peripheral nerves (7,8).

The analgesic potency of tramadol is considered to be medium: it has one-tenth the potency of morphine, one-fifth the potency of nalbuphine and the equivalent of pethidine, oxycodone and at least the equivalent of ketamine and NSAIDs (9–12). Its advantages over opioids are mainly the lower incidence of side effects such as ventilatory depression, nausea-vomiting, and constipation and sedation (13). Tramadol has no clinically relevant effects on heart rate and blood pressure. The overall

Table 1
Comparative affinity of opioid receptor and inhibition of monoamine uptake by tramadol, its enantiomers and metabolite, codeine, morphine and imipramine modified from the literature (4–6)

	Affinity to opioid receptors			*Inhibition of uptake*	
Drugs	μ	δ	κ	*Norepinephrine*	*Serotonin*
+/− Tramadol	++	NA	NA	+++	+++
+Tramadol	++	NA	NA	++	+++
−Tramadol	NA	NA	NA	+++	++
M1 metabolite	++++	ND	ND	ND	ND
Morphine	+++++	++++	+++	NA	NA
Codeine	++	+	+	NA	NA
Imipramine	++	NA	++	+++++	++++
Naloxone	− − − − −	−	− −	ND	ND

+, agonist, −, antagonist.
Scoring: NA, not active; active concentration >10 μmol·l^{-1}; (+) 5–10 μmol·l^{-1}; (++) 1–5 μmol·l^{-1}; (+++) 0.1–1 μmol·l^{-1}; (++++) 0.001–0.1 μmol·l^{-1}; (+++++) 0.0001–0.001 μmol·l^{-1}; ND, no data.

incidence of adverse effects in adults is >15%; frequency increases with higher doses. Although the number of patients in the pediatric study groups is limited, the incidence of adverse events seems similar to that observed in adults. The overall side effects were 11.7% ($n = 77$, enteral or parenteral routes) in Kralinski's study; these effects were reportedly increased by chronic use (14,15). The incidence of nausea-vomiting is not enhanced by the use of tramadol in cases prone to this problem (16). There has been no report of respiratory depression and sedation in the pediatric age group in a wide literature search performed for this review. The incidences of nausea-vomiting, pruritus and rash reported by Finkel *et al.* (15) were 9–10%, 7% and 4%, respectively. Some other advantages over opioids are: the absence of effect on sphincter of Oddi, a low potential for dependence or abuse in i.v. clinical doses and reduced postoperative shivering (3,17,18). Unlike NSAIDs, tramadol does not inhibit prostaglandin synthesis. Patients with peptic ulceration, asthma and renal impairment may benefit from the substitution of tramadol for NSAIDs. The incidence of seizures in patients receiving tramadol is estimated to be <1% (3). Prescribing tramadol in patients taking psychoactive medications (monoamine oxidase inhibitors, neuropleptic agents and other drugs that lower the seizure threshold) and administering tramadol to patients with a known convulsive disorder or head injury increases the risk of seizures. Exceeding dosing guidelines may cause toxicity and the anticipated symptoms are lethargy, nausea, tachycardia, agitation, seizures, coma, hypertension and respiratory depression. Sedation and apnea can be reversed in 50% of cases by naloxone. Serious cardiotoxicity has not been observed with a tramadol overdose (3).

Pharmacokinetic profile

The extensive metabolization of tramadol in the liver by the cytochrome P450 enzyme CYP2D6 sparteine-oxygenase produces O-desmethylated metabolite (M1). Metabolism is affected by other drugs using the same pathway. When administered by the gastrointestinal route, there is an extensive first-pass metabolism in the liver. Parent drug and metabolites are primarily excreted via the kidneys (90%) (3). The 5-HT3 antagonist ondansetron may decrease the efficacy of tramadol because 5-HT3 receptors play a role in pain transmission at the spinal level (19).

In adults, oral tramadol has a bioavailability of 68% after a single dose and 90–100% after multiple doses. The time to the onset of action is 30 min to 1 h and the time to peak concentration is 2 h (20–22). In children aged 4–7 years, given 1.5 mg·kg^{-1} oral tramadol drops, absorption was rapid with the maximum measured serum concentration reported at 30 min (352 ± 83.4 ng·ml^{-1}). The concentration remained above the 100 ng·ml^{-1} analgesic level for approximately 7 h. Aside from the rapid rise in serum concentration, the elimination half-life, serum clearance and concentration of metabolites are similar to those seen in healthy young adults (23).

A study evaluating pharmacokinetics via the rectal route in children aged 1–6 years demonstrated

that tramadol was well-absorbed and showed low variability in absorption and clearance. The mean time to maximal serum concentration of tramadol and its metabolite was found to be 2.4 ± 1 and 3.9 ± 1.1 h. Contrary to Murthy's findings, because of the more alkaline pH of rectal mucosa in children a significantly higher clearance in children is attributed to differences in the degree of absorption between children and adults (24,25).

After i.v. injection, the highest mean serum concentration was achieved at 0.19 ± 0.06 h and the peak serum concentration M1 metabolite at around 5 h. Murthy *et al.* (26) reported that mean serum concentrations of tramadol and its metabolite after a single dose of i.v. injection in children aged 1–12 years were slightly higher than those in adults. According to the pharmacokinetic data presented by Murthy *et al.*, children require similar bodyweight-related doses to adults via the i.v. route.

In a recent study by Allegaert *et al.* (27), total clearance of tramadol reached 84% of the adult value by 44 weeks postconceptual age, although the central volume of distribution had a longer maturation half-time than the clearance. This presents slower changes in body composition when compared with clearance enzyme maturation with age. Allegaert *et al.* also documented the presence of *in vivo* CYP2D6 (the main enzyme in metabolization of tramadol) activity in early neonatal life. Whilst further studies are required, this information encourages the use of IV tramadol in infants.

The peak serum concentration of tramadol was achieved 0.5 ± 0.11 h after caudal administration in children which is somewhat similar to the time achieved by the i.v. route. Murthy *et al.* speculated that the analgesic efficacy after epidural administration could be attributed to the extensive systemic availability, and its prolonged duration to the sustained release of the drug from epidural fat and other relatively poorly perfused tissues.

Clinical use in pediatric anesthesia

Perioperative pain treatment

Tramadol is mainly used for postoperative pain treatment in children undergoing day-case surgery resulting in mild to moderate pain. For this purpose, the drug is administered preemptively, intraoperatively or postoperatively. The majority of the studies on this subject have been randomized, double-blind trials with some also being placebo-controlled. Other than case reports or small study groups, these studies have been performed on children from 1 to 16 years. Generally, pain intensity was assessed by investigators and/or nursing staff using modified Visual Analog Scale scores (such as the Hannallah Objective Pain Scale, the Oucher Six Faces Pain Scale and a modified Toddlers Preschooler Postoperative Pain Scale, and the Children's Hospital of Eastern Ontario Pain Scale).

The gastrointestinal route

In studies by Payne and Roelofse (28,29), oral tramadol drops 1.5 or 3 $mg \cdot kg^{-1}$ with concomitant oral midazolam of 0.5 $mg \cdot kg^{-1}$, given 30 min prior to induction provided postoperative analgesia superior to that of placebo ($P < 0.05$) in 71 children undergoing extraction of six or more teeth. In these patients, significantly fewer patients required rescue analgesic (paracetamol 120 mg) in the tramadol group (≈20%) compared with the placebo group (83–100%). There was no significant difference in the time to recovery and no events of respiratory, cardiovascular derangements or emetic incidents were reported in the two groups in either study. In a multicenter study performed postoperatively immediately after switching from morphine to oral analgesics, oral tramadol tablets were given in 1 $mg \cdot kg^{-1}$ ($n = 40$) or 2 $mg \cdot kg^{-1}$ ($n = 41$) doses to children aged 7–16 years. In the follow-up period of 8 h patients who had been administered 1 $mg \cdot kg^{-1}$ tramadol required more supplemental analgesics at an earlier time. Eighty percent of all cases assessed the treatment as being good or excellent. No significant adverse event profile was reported between the two doses (15).

Zwaveling *et al.* (24) studying the pharmacokinetics of rectal tramadol in children prepared suppositories consisting of 25 mg tramadol in the institutional pharmacy. Commercial suppositories containing 100 mg tramadol are available in some countries. They concluded that for the treatment of pain after minor surgery at least 1.5 $mg \cdot kg^{-1}$ of tramadol was required for therapeutic effect.

The parenteral route

Intramuscular. In the pioneering studies performed on children, tramadol was given intramuscularly at

0.75–1–2 mg·kg^{-1} to compare their relative analgesic efficacy with that of intramuscular pethidine 1 mg·kg^{-1} or nalbuphine 0.15–0.2–0.1 mg·kg^{-1} on moderate to severe postoperative pain following various surgical procedures. These studies presented that tramadol given intramuscularly at these doses provided equivalent analgesia to the opioids it was compared with (30,31). In children, the intramuscular route should be avoided whenever possible.

Intravenous. In dose finding studies, a 2 mg·kg^{-1} i.v. dose was found best for analgesic action with minimal side effects. In order to decrease the incidence of adverse effects, such as hemodynamic changes, fatigue and flushing, tramadol should be administered by slow intravenous injection. When a lower dose of 1 mg·kg^{-1} is used, an NSAID should be added to the analgesic regimen (Table 2) (13,32).

Adenotonsillectomy operations were chosen frequently for studying the analgesic efficacy of tramadol in children as surgery caused a standard pain. In a double-blind placebo-controlled study performed in 1- to 3-year-old children ($n = 80$, 40 each group) undergoing adenoidectomy, 2 mg·kg^{-1} of tramadol was given in combination with preoperative ibuprufen 10 mg·kg^{-1} rectally. Forty-five percent of the patients did not require a rescue analgesic compared with 15% of the patients in the placebo group. The duration of recovery and the incidence of adverse events were similar. Nevertheless, the elimination half-life of the parent drug and metabolite is 6–10 h and all patients required additional analgesia at home after discharge (33). In children aged 2–9 years undergoing tonsillectomy, the first group was given 3 mg·kg^{-1} of tramadol after induction, followed by rectal tramadol 2.5 mg·kg^{-1}. The second group was given proparacetamol 30 mg·kg^{-1}, followed by rectal paracetamol 15 mg·kg^{-1}. Both groups received similar dosage three times a day for 3 days. It was found that tramadol provided better analgesia with a similar incidence of adverse effects (34).

In a recent study performed on children undergoing unilateral hernia repair, the analgesic efficacy and side effects of preoperative i.v. tramadol 1.5 mg·kg^{-1} was compared with ilioinguinal–iliohypogastric nerve block with 0.5% bupivacaine (0.25 mg·kg^{-1}). It was found that tramadol provided at least the same analgesic effect as that of ilioinguinal-iliohypogastric nerve blocks, with a superior effect at the time of maximal analgesia (second and third hour after administration). Unfortunately, the incidence of emesis was significantly higher in the tramadol group (35).

Although the preemptive effect of analgesics and local anesthetics are controversial in children, Ozkose *et al.* (36) (0.5 or 1 mg·kg^{-1} of tramadol by slow injection, $n = 15$ each group, tonsillectomy) and Chiaretti *et al.* (37) (1 mg·kg^{-1} bolus tramadol or 0.5 mg·kg^{-1} of tramadol followed by 150 μg·kg^{-1}·h^{-1} infusion, $n = 14$ each, neurosurgery) suggested a preemptive analgesic effect with tramadol in children. Both studies seem to have technical problems; as tramadol was given at induction, not enough time had elapsed for the drug to reach peak effect before the surgical incision when i.v. pharmacokinetics are considered. The application time of tramadol in these studies does not cover the definition of preemptive 'antinociceptive treatment that prevents centralization' (38). Further studies should be performed to prove the preemptive analgesic effect of tramadol in children.

A continuous infusion of tramadol 0.25 mg·kg^{-1}·h^{-1} was given to 17 children aged 3 months to 13 years undergoing surgery for bladder exstrophy, the rate being decreased to 0.08 mg·kg^{-1} on the third day after surgery. Emesis occurred in three of 64 treatment days (4.7%), in 17.6% of patients. Oxygen saturation stayed within normal limits and pruritus and extreme sedation did not occur (39). Kralinski *et al.* (14) infused tramadol at 0.1–0.25 mg·kg^{-1}·h^{-1} to children aged 1–16 years ($n = 33$, polytrauma, burn, major surgery, malignancy) and recommended decreasing the dose to 0.07–0.15 mg·kg^{-1}·h^{-1} when benzodiazepines or barbiturates are coadministered. Tramadol at 0.1–0.2 mg·kg^{-1}·h^{-1} combined with boluses of 1–2 mg·kg^{-1} provided sufficient

Table 2
Recommended doses for children

Route; form	*Dose (repeated doses × 4–6 per day)*
Oral; drops	2–3 mg·kg^{-1}
Oral; tablets	1–2 mg·kg^{-1}
Rectal; suppositories	1.5–3 mg·kg^{-1}
i.v.; bolus	2–2.5 mg·kg^{-1}
i.v.; continuous infusion	0.1–0.25 mg·kg^{-1}·h^{-1}

postoperative analgesia in 13 newborns after medium-traumatic operations. Dose-dependent hypercapnia was reported in 80% of neonates with unassisted respiration. The authors concluded that this was indicative of tramadol affecting the respiratory center during the neonatal period and that it was necessary to monitor constantly their respiratory functions during and after tramadol therapy (40).

Although patient-controlled analgesia (PCA) with tramadol has been studied in adult patients, no comparable studies have been performed in children (41). However, nurse-controlled analgesia (NCA) has been studied in children ($n = 30$) with a mean age of 9.5 months, i.v. infusion (6 $mg \cdot kg^{-1}$ 24 h^{-1}). NCA (initial dose: 0.5 $mg \cdot kg^{-1}$, bolus injection 0.3 $mg \cdot kg^{-1}$ with an interval of 10 min for security and a highest dose of 1.2 $mg \cdot kg^{-1} \cdot 4\ h^{-1}$) was recommended for postsurgical pain as an alternative to morphine infusion or PCA in infants (42).

Novel routes

Caudal epidural. Several reports regarding the use of i.v. formulation tramadol via the epidural route in adults and the resulting longer duration of the analgesic effect have encouraged pediatric anesthesiologists to use this route since 1997 (8). The pediatric reports have parallel or contradictory results to each other; some report analgesic effects as good as morphine and local anesthetics or vice versa and some others prolongation of analgesic effect when added to local anesthetics (8,43–48).

The effects of drugs injected into the spinal or epidural space need to be tested in terms of histological, physiological and behavioral changes in several animal species before they are used in humans. There are a small number of reports regarding the neurotoxicity of tramadol in animals. Koç *et al.* (49) reported glial cell reaction in rats which were given intracerebroventricular tramadol 6 μg in 10 μl normal saline without behavioral changes. In rabbits, injection of 200 μg of tramadol in 0.2 ml of normal saline (pH 6.5–7) into the intracisternal subarachnoid space caused changes in the concentration and the numbers of fatty acids of the blood–brain barrier (disruption of membrane fluidity of the blood–brain barrier) which might set off neurotoxicity (50). Neither study proves neurotoxicity to be due solely and directly to tramadol but Gursoy *et al.* (51) reported neurotoxicity in rabbits caused by intrathecal tramadol at 1–8 $mg \cdot kg^{-1}$ in 1 ml volume after 24 h. This finding may clarify the myoclonus and death 48 h after an accidental intrathecal injection of tramadol in a case report (52). This issue was brought up for discussion by several colleagues (53–55). Safety and neurotoxicity in the epidural space has not yet been proved in animal studies, and the drug is not licenced for use by this route. Parallel to the findings and recommendations of Murthy *et al.* stating equal efficacy and duration between epidural and enteral–parenteral routes, this reviewer thinks that use by the epidural route should be abandoned.

Local infiltration and blocks. Specific analgesic effects of tramadol on peripheral nerves were postulated. This theory was proved in studies performed by prolongation of the analgesic effect of local anesthetics on the axillary brachial plexus blockade, psoas compartment block, and subcutaneous infiltration in adults (56–59). No local neural toxicity was observed in the absence of irreversible conduction blockade in rats by using somatosensory-evoked potential measurements (60). Unpublished study results by Demiraran *et al.* presented an equal analgesic effect through subincisional injection of 2 $mg \cdot kg^{-1}$ of tramadol and 0.2 $ml \cdot kg^{-1}$ 0.25% bupivacaine in children aged 1–6 undergoing herrniorrhaphy (≈6 h). Another local application of tramadol into joints showed no histopathological changes in the synovia of rabbits (61). As alternative routes such as local infiltration and blocks are introduced, several detailed studies should be performed to differentiate systemic and /or peripheral effect in animals and human.

Chronic pain treatment

Orally administered tramadol was found to be an effective analgesic in step 2 of the World Health Organization's guidelines for the treatment of patients with cancer pain. The effect of tramadol in the treatment of chronic pain was shown in one study where it was used for a short period in children. Rose *et al.* (62) reported that the use of oral tramadol (50 mg) at 1 $mg \cdot kg^{-1}$ every 4–6 h in 113 children aged 7–16 years for 7–30 days for various painful conditions was well tolerated. Pain relief was considered very good or excellent by 69% of parents.

The changes in serum chemistry and hematology variables were clinically insignificant and adverse events such as nausea-vomiting, abdominal pain, dizziness, headaches, somnolence, fatigue and pruritus were rated as mild to moderate. Only 12 patients discontinued the therapy because of an adverse event. There was no event of respiratory depression in this study group. The analgesic effect started and reached its anticipated peak as stated in the pharmacokinetics of the enteral route. Further randomized and controlled studies should be performed to clarify the chronic use of tramadol in children.

In summary, tramadol seems a very promising drug in pediatric pain treatment, having an analgesic potency intermediate between that of NSAIDs and opioids. Several forms of systemic preparations such as i.v., tablet, and drop make its use easier in children, although further clarification is required. Tramadol should be one of the options in the multimodal pain treatment approach in postoperative and chronic pain in children. Neuraxial administration has been studied without taking toxicity into consideration. Furthermore, as it is probable that caudally administered tramadol is absorbed systemically, and is no more efficacious or long lasting than when given intravenously, the use of this method of administration should be stopped forthwith.

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Accepted 3 June 2005