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Narrative review shows that the short-term use of ketorolac is safe and effective in the management of moderate to severe pain in children

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Short title: Using ketorolac for childhood pain

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ABSTRACT

In June 2013, the European Medicine Agency recommended limiting codeine use in paediatric patients, creating a void in managing moderate pain. We reviewed literature published in English (1985-June 2017) on the pharmacokinetic, pharmacodynamic and safety profile of ketorolac, a possible substitute for codeine and opioids, for treating moderate to severe pain. We found that gastrointestinal side effects were mainly reported with prolonged use, significant bleeding was reported in adenotonsillectomies and adverse renal effects appeared to be limited to patients with specific coexisting risk factors. **Conclusion**. The short-term use of ketorolac appears to be safe for children in many situations.

Key words: Children; ketorolac; pain; pharmacodynamics; side effects.

Key notes

- In June 2013, the European Medicine Agency advice limiting codeine use in paediatric patients created a void in managing moderate pain.
- We reviewed literature published in English from 1985 to June 2017 on the pharmacokinetic, pharmacodynamic and safety profile of ketorolac, a possible substitute for codeine and opioids.
- The short-term use of ketorolac in children appears to be safe, but prolonged use or coexisting risk factors can increase the risk of side effects.

Abbreviations

EMA, European Medicine Agency; FDA, US Food and Drug Administration; NSAIDs, nonsteroidal anti-inflammatory drugs

INTRODUCTION

Pain is a common symptom in children attending emergency departments and ambulatory settings (1). Drugs such as paracetamol and ibuprofen are commonly and safely used in the management of mild pain (2). Treatment options for moderate pain are limited, as paracetamol or ibuprofen may not be effective and major opioids may be considered excessive or inconvenient in terms of side effects (1). In June 2013 the European Medicine Agency (EMA) recommended that codeine should not be used for postoperative pain control in children undergoing adenoidectomies or tonsillectomies for obstructive sleep apnoea and restricted the use of this drug in the paediatric population. This created a void in the management of moderate pain (3). Codeine is no longer recommended due to low efficacy in poor metabolisers and possible life-threatening events in ultra-rapid metabolisers (3,4). There is some evidence that tramadol could be safe and effective in treating moderate pain in paediatric inpatients and outpatients (4). Even though, tramadol is a prodrug, some experts have suggested limiting its use in monitored settings for children with specific risk factors for respiratory depression, while waiting for more safety data (4). As a matter of fact, in April 2017 the US Food and Drug Administration (FDA) banned the use of codeine and tramadol in children under 12 years of age and recommended that breastfeeding mothers did not take these drugs due to the risk of serious adverse reactions in breastfed infants. In addition, the FDA warned against using codeine and tramadol for patients aged 12 to 18 years if they had a history of obesity, obstructive sleep apnoea or severe lung disease. In particular, neither codeine nor tramadol should be given to children or adolescents as pain

medication after a tonsillectomy or adenoidectomy (5). Complying with these recommendations has led to changes in clinical practice and in treatment strategies to assure that adequate pain control could be provided for paediatric patients (3-5).

Ketorolac is a drug that could be considered for the treatment of moderate to severe pain. Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the short-term, up to a maximum of five days, management of moderate to severe acute pain in adults (6). Ketorolac exerts its analgesic, anti-inflammatory and antipyretic actions by inhibiting cyclo-oxygenase, resulting in a reduction in the synthesis of prostaglandins, thromboxanes and prostacyclin (7). Presently, it is not indicated for paediatric use (6), except for moderate to severe post-operative pain, according to the British National Formulary, but a growing number of reports in the literature suggest that it provides good efficacy and safety when it is properly used in other settings. The aim of this review was to examine the available evidence on the pharmacokinetic, pharmacodynamics, efficacy and safety profile of ketorolac in children and adolescents and to discuss its possible use as an alternative to tramadol and opioids for managing moderate to severe acute pain.

Search strategy and selection criteria

This was a narrative review. The Cochrane Library, Medline, PubMed and relevant specialist journals were searched from 1985 to June 2017. We searched for the combination of ketorolac and the following words and phrases: paediatric, children, infants, pharmacokinetics, metabolism, sublingual administration, intranasal administration, post-operative pain, safety, toxicity, bleeding, gastrointestinal bleeding and kidney injury. In addition we searched for pain management and children.

Publications from the past 30 years were selected with an emphasis on the past five years, but commonly referenced, relevant and influential older publications were not excluded. The reference lists in the papers identified by our search strategy were also searched. Searches

were restricted to publications in English. Randomised controlled trials, observational studies, retrospective studies, meta-analyses and case reports were included. Abstracts were excluded. Book chapters, guidelines, review articles and editorials in English were also included, as well as online English resources such as Medscape and UpToDate, because they provided comprehensive overviews that met the scope of this review.

Elements of pharmacokinetics

Absorption

Ketorolac tromethamine is well absorbed when administered either orally or via the intramuscular route. The maximal plasma concentration is attained between 20 and 60 minutes (8), which is faster for the intramuscular than the oral route (9). For the intravenous route, the time to peak concentration is 1-3 minutes (10). The systemic bioavailability of the oral and intramuscular administration is 100% ±20 and 100% ±22%, respectively (10). Food intake delays, but does not reduce, ketorolac absorption when administered orally (9). When ketorolac is administered as tablets, the rate at which the tablets dissolve is a limitation of the absorption velocity and the onset of action (11). The use of fast dissolving tablets improves the dissolution and absorption rate (11). Sublingual administration may have several advantages, such as improved bioavailability and more comfortable administration compared to the intravenous route. Children from the age of six years and above have been shown to be able to take sublingual drugs with adequate support from nurses (12). Ketorolac is absorbed more rapidly after sublingual than intramuscular administration: the sublingual route takes about half an hour to achieve an increase in peak concentration, and a reduction in the time to attain this, compared to one hour for the intramuscular route (Figure 1 and Table 1). In addition, the extent of absorption has been shown to be similar for both of these routes, with no important change in the area under the curve and elimination half-life, and there appears to be no difference in the duration of the analgesic activity of the drug (13).

The intranasal formulation provides several benefits, such as rapid absorption across the nasal mucosa and ease of administration (14). Another study showed that administering 15mg of ketorolac (weight <50kg) or 30mg (weight >50kg) by the intranasal route using a metered spray resulted in a rapid increase in plasma concentration. The mean time to peak concentration using the intranasal route was 52 minutes, with a standard deviation of six minutes. A target concentration of 0.37mg/L in the effect compartment was achieved within 30 minutes and remained above that target for 10 hours (15). An analysis of the postoperative analgesia provided by ketorolac in adults showed an estimated effect compartment with 50% effective concentration of 0.37mg/L. The pharmacokinetics of intranasal ketorolac has been shown to be similar in adolescents and adults, assuming the use of the same nasal administration device. Intranasal ketorolac may be a useful therapeutic alternative to intravenous injections in adolescents, because the plasma concentrations attained with the device are likely to be analgesic (15). Most of the ketorolac administered intranasally is deposited in the nasal cavity and pharynx, with less than 20% in the oesophagus and stomach and less than 0.5% in the lungs (6,16). The reduction in the time to achieve a maximum concentration did not differ significantly between a single dose of 30mg intranasal ketorolac and a single dose of 30mg intramuscular ketorolac in healthy volunteers, while the systemic availability of the intranasal ketorolac was lower than the intramuscular ketorolac. Ketorolac is rapidly and well absorbed via the intranasal route, with a reduced bioavailability compared to the intramuscular route. Intranasal administration, therefore, offers a therapeutic alternative to other routes of administration in different clinical settings (16).

Distribution

After intravenous administration, the volume of distribution at a steady state was 113 ±33mL/kg (17). The body weight normalised paediatric pharmacokinetics variables for children aged one to 16 years are similar to adult values (10,17,18). On the other hand, studies in neonates and young infants indicated a volume of distribution at a steady state of

290mL/kg, which was greater than that of children older than one year and adults (19,20). Ketorolac has been shown to be extensively bound (>99%) to plasma proteins and had a volume of distribution of 0.1 to 0.3L/kg in healthy young volunteers and 0.36L/kg in children comparable with those of other nonsteroidal anti-inflammatory drugs (NSAIDs) (8). There is evidence that ketorolac does not readily penetrate the central nervous system in children, with less than 0.05% of the ketorolac plasmatic concentrations found in the cerebrospinal fluid (21). Higher ketorolac cerebrospinal fluid concentrations have been reported in younger children, particularly those under two years of age (21).

Metabolism and elimination

The elimination clearance has been reported to be 0.57 ±0.17mL/min/kg in children aged one year and above, which was similar in adults (17,18). The clearance is higher in neonates and infants, reaching values of 1.52mL/min/kg (19-21). Ketorolac has an elimination half-life of about 4-6 hours (8). In order to maintain ketorolac plasma levels that were consistent with adult analgesic concentrations in most infants, a dosing regimen of a bolus every four to six hours would be reasonable (19,22). Ketorolac is extensively metabolised in the liver to inactive or mainly inactive metabolites. The metabolic products are hydroxylated and conjugated forms of the parent drug. The major metabolite of ketorolac is the acyl-glucuronide (23). The other important ketorolac metabolite is the *p*-hydroxyl-ketorolac, presenting 20% of the anti-inflammatory activity and 1% of the analgesic activity of ketorolac (8). The principal route of the elimination of ketorolac and its metabolites is the renal route. About 92% of a given dose is found in the urine, approximately 40% as metabolites and 60% as unchanged ketorolac. About 6% of the dose is excreted in the faeces (6,24) (Table 2).

Stereoselective pharmacokinetics

Ketorolac is a chiral substance with (S)-enantiomers and (R)-enantiomers and *in vitro* and animals studies have suggested that its pharmacological activity is mainly related to (S)-ketorolac (25-27). Hamunemn et al showed that the clearance, volume of distribution and elimination half-life were higher for (S)-enantiomers than (R)-enantiomers (28). The volume of distribution at the steady state and elimination half-life of the (S)-enantiomer were higher in children than in adolescents and adults, but the clearance was similar (28). The pharmacokinetics of the (R)-enantiomer was essentially unaffected by age (28). Therefore, children, adolescents and adults require similar maintenance doses (28). Moreover, infants aged 6-18 months showed rapid elimination of the analgesic (S)-enantiomer and, therefore, in this age group, shorter dose intervals to maintain (S)-enantiomer concentrations might seem indicated, but will result in (R)-enantiomer accumulation with unknown clinical implications (22,23,29). In conclusion, the (S)-enantiomer has been shown to have greater analgesic and anti-inflammatory activity than the (R)-enantiomer.

Elements of pharmacodynamics

Ketorolac is an NSAID and exerts its analgesic, anti-inflammatory and antipyretic actions by inhibiting cyclo-oxygenase, resulting in a reduction in the synthesis of prostaglandins, thromboxanes and prostacyclin (7). The mechanisms by which ketorolac may exert a central effect are still unclear. Ketorolac does not directly bind to mu-opiod, kappa-opiod or delta-opioid receptors, but it could indirectly activate opioid receptors by inducing the release of endogenous opioids (30). It has also been reported that ketorolac is associated with mitochondrial calcium release, local nitric oxide synthesis and interaction with the cannabinoid receptor and all these processes may be involved in its analgesic effect (30). In several clinical trials, ketorolac, administered by different routes, produced analgesia to a similar extent as morphine and other opioids, but was not associated with sedative or

anxiolytic effects and did not have any effects on gut motility (7,29,30). When ketorolac was co-administered with morphine, it produced a higher analgesic effect than that obtained with either drug alone or together (30). The pharmacological drug interactions of ketorolac with concomitant treatments (14) are presented in Table 3.

There is no evidence in animal or human studies that ketorolac induces or inhibits any of the hepatic enzymes that are involved in its metabolism or that of other drugs (6).

Side effects

The most important adverse effects of ketorolac are bleeding and gastritis and these typically occur after repeated doses (30). The gastrointestinal side effects of ketorolac and other NSAIDs are due to the inhibition of gastric mucosal prostaglandin synthesis with subsequent mucosal damage caused by stomach acid. The risk of upper gastrointestinal bleeding increases with the use of long-acting forms of NSAIDs and seems to be higher with ketorolac when compared with ibuprofen or other NSAIDs, such as indomethacin and diclofenac (31,32). In adults, the mucosal injury caused by ketorolac, when it is administered at doses of 10 to 30mg four times daily, has been reported to be remarkably less than that caused by 650mg aspirin administered four times a day (33). Due to the possible increase in the risk of bleeding events, many surgeons may prefer not to use ketorolac perioperatively. In a retrospective analysis of 1,451 children that had undergone neurosurgical procedures, including 955 who received perioperative ketorolac, there was no significant association between clinically significant bleeding events or radiographic haemorrhages and the perioperative administration of ketorolac (34). Although, several reports have associated an increased incidence of bleeding after tonsillectomies with the perioperative use of ketorolac, a retrospective study of 310 children who underwent tonsillectomy found that using ketorolac did not increase the incidence of post-tonsillectomy haemorrhage and was associated with a shorter length of hospital stay (35). Chan et al (36) showed that ketorolac could be used

safely for tonsillectomies in children, but not in adults. On the other hand, a prospective study on 96 children receiving intravenous morphine or ketorolac showed that patients who received ketorolac had more major bleeding requiring intervention and more bleeding episodes in the first 24 hours after surgery, but no greater overall incidence of bleeding when compared to the morphine treated subjects (37). Although, it is true that bleeding time seems to be increased, even after a single dose of ketorolac (38), clinically important bleeding is usually not reported (39). In another retrospective review conducted on 221 children who underwent operative fracture care, including 169 who received ketorolac perioperatively and 52 who did not receive the drug, there was no difference in overall complication rates and the need for blood transfusion between the two groups (40). Furthermore, in a retrospective study on 208 children that underwent spine surgery, the postoperative use of ketorolac did not significantly increase complications, including transfusions and reoperations (41).

As with any other NSAID, ketorolac inhibits the synthesis of prostaglandin and is mainly excreted by the kidney, making the risk of adverse renal effects relevant. In a retrospective analysis of 1,015 children over a 10-year period, NSAIDs accounted for 2.7% of acute kidney injuries (42). A retrospective case-control study showed that the concomitant administration of aspirin and ketorolac could increase renal morbidity in young infants of less than six months of age after cardiac surgery (43). There are single case reports of acute renal failure associated with ketorolac administration, but it is not commonly seen unless risk factors are present. For this reason, the use of ketorolac should be avoided in patients with risk factors for nephrotoxicity, such as hypo-perfusion, a history of volume depletion, a history of reduced urine output, renal failure, known NSAID intolerance, treatment with angiotensin-converting enzyme inhibitors, sartanics and diuretics (30,42,43). In a retrospective review of 118 children who underwent ureteroneocystostomy, in which 50 received narcotic analgesics postoperatively while another 68 received ketorolac postoperatively, there was no statistical difference between postoperative creatinine (0.68

and 0.65mg/dl) and haematocrit levels (33 and 34%) between the groups and no major complications (44). Besides the gastrointestinal and renal adverse reactions, other less common adverse effects reported after multiple doses of intramuscular ketorolac include somnolence, pain at the injection site, increased sweating, nausea, headache, dizziness, vomiting, pruritus and vasodilation (45). Ketorolac, unlike opioids, has not been associated with respiratory depression or tolerance (30, 45).

Use of ketorolac in children

Ketorolac has been reported to be an efficacious analgesic alternative to opioids in neonates, especially in conditions where there are high risks of respiratory depression. One study of a group of 18 preterm neonates with chronic lung disease examined the use of ketorolac to control postsurgical pain and pain from invasive procedures. It found that there was a significant reduction in the Neonatal Infant Pain Scale after the administration of 1mg/kg of intravenous ketorolac as a bolus over 10 minutes, with total pain relief being achieved in 94.4% of cases. None of the neonates had significant changes in haematological, renal or hepatic indices after treatment or a systemic haemorrhage, gastric bleeding or haematuria. Meanwhile, the hourly urinary output remained constant and normal after the administration of the drug (46). In another study, ketorolac was safely used in 53 neonates and infants after cardiac surgery and was not associated with any adverse haematologic or renal effects or clinically significant bleeding episodes (47). The blood urea nitrogen and serum creatinine levels increased from baseline at 48 hours of therapy in all infants but remained within normal limits (47).

Ketorolac is effective in the treatment of moderate to severe pain in children and it is used for the treatment of several pain conditions, such as postoperative or chronic pain, renal colic pain, cancer pain and oral surgery pain and as an adjuvant therapy in anaesthesia and in patient-controlled analgesia (30). Ketorolac seems to be more useful as an analgesic than

as an anti-inflammatory agent, since the dose required to produce its anti-inflammatory effect is about 15 times higher than the dose required to produce its analgesic effect (30).

Several studies have shown that ketorolac was better tolerated than morphine and other opioid drugs with similar effectiveness, in the treatment of moderate to severe postoperative pain, without producing opioid-related side effects, especially respiratory depression (48). Venous access in children presenting to an emergency department with pain requiring analgesia is not always easy. Pain relief needs to be provided reasonably quickly and the oral route is not ideal in the this setting for procedural sedation or analgesia, because there are often delays before the drug is absorbed in the small intestine and before the drug in plasma reaches its site of action. Alternative early analgesic administration delivery routes in young children, such as the intranasal route or the sublingual route, are available (49). A study by Neri et al (50) showed that a single dose of ketorolac administered through the sublingual route was as effective as sublingual tramadol for pain management in children with suspected fractures or dislocations and had fewer side effects. The pain reduction for sublingual ketorolac or sublingual tramadol given to children aged 4-17 years was similar to that described for intranasal fentanyl (49-51). Consequently, sublingual ketorolac may be a valid therapeutic alternative to intravenous injections for children requiring analgesia in the emergency department. Both sublingual and intranasal routes offer ease of administration, rapid systemic absorption and they avoid hepatic first-pass metabolism (49,50). Opioid-related side effects, such as nausea, vomiting and respiratory depression, is avoided with ketorolac and other NSAIDs, while tramadol is associated with nausea and vomiting in a significant percentage of cases (49-51).

Numerous adult studies (51-54) have compared the analgesic effects of ketorolac versus tramadol and other opioids in surgical settings, showing similar efficacy, reduced adverse effects and a morphine-sparing effect (52-55). In multiple-dose studies, ketorolac has showed an equivalent or superior profile when compared with either opioids or other NSAIDs in relieving moderate to severe pain (30). Ketorolac is also used as a therapy for renal colic

pain. In adults, providing 60mg of intramuscular ketorolac was better at reducing patients' renal colic pain than 150-100mg of intramuscular meperidine (56).

Migraines are one of the most common causes of recurrent pain in children. Effective medication that is commonly used to treat acute migraine headache in the emergency department includes ketorolac, prochlorperazine and metoclopramide. A retrospective study showed that intravenous migraine therapy, with just ketorolac, ketorolac plus metoclopramide or prochlorperazine, just prochlorperazine or metoclopramide or just ondansetron, reduced posttraumatic headache pain scores for children within 14 days of a being treated for a mild traumatic brain injury in the emergency department (57). The treatment was successful in 86% of the 254 patients who were treated, defined as a reduction in their pain score of greater than or equal to 50%, with 52% experiencing a complete resolution of their headache. The medication combinations that were most frequently given were ketorolac and metoclopramide or prochlorperazine (n = 152), with a high rate of treatment success (89%). Of the 55 patients who were just treated with ketorolac, 80% experienced treatment success (57). Another retrospective study showed the safety and efficacy of a standardised paediatric migraine practice guideline for reducing pain in children with migraine headaches in the emergency department (58). Children with a verbal numeric pain score of greater than six received 0.5mg/kg ketorolac (maximum 30mg), 2mg/kg diphenhydramine (max 50mg), and either 0.2mg/kg metoclopramide (max 20mg) or 0.1mg/kg prochlorperazine (max 10mg). After 40 minutes, another verbal numeric pain score was obtained, and, if there was no improvement, a repeat dose of metoclopramide or prochlorperazine was administered. A total of 533 patients were identified with a discharge diagnosis of migraine headache and 266 were enrolled. The mean initial verbal numeric pain score was 7.8 and the mean discharge verbal numeric pain score was 2.1, representing a 73% reduction of pain (58).

Details of recommended ketorolac doses are given in Table 4.

DISCUSSION

Pain is a common symptom in emergency departments and ambulatory settings. Paracetamol and ibuprofen are useful for mild pain, but are not indicated for treating major pain. Tramadol and opioids are indicated for the treatment of moderate to severe pain and are licensed for use in children, but they are not devoid of possible adverse effects, such as nausea, vomiting and respiratory depression. The June 2013 EMA recommendations limiting codeine use, and the April 2017 warning by the FDA against using codeine and tramadol, have created a void in managing moderate pain in children. Ketorolac is only licensed for treating moderate to severe post-operatory pain in children. The major adverse effects of ketorolac are well known and a short-term use is indicated, particularly due to possible gastrointestinal involvement,.

The issue we need to consider is if, in the light of the actual evidence, it is reasonable to limit the use of ketorolac to treating moderate to severe pain in the post-operative field or if it is possible to consider its short-term use in other settings as well. In our experience in the emergency department, which is in agreement with the evidence in the literature, the short-term use of ketorolac, alone or in association with other drugs such paracetamol and opioids, appears to be safe and useful in many situations.

CONCLUSION

Our review of the literature showed that ketorolac had a good safety profile for short-term use in children. Gastrointestinal side effects were mainly reported when there was prolonged use or in cases of pre-existing conditions, such as gastritis. For short-term use, bleeding was mainly reported in adenotonsillectomies, while adverse renal effects appeared to be limited to patients with coexisting specific risk factors, such as hypoperfusion, volume depletion or

pre-existing kidney damage. More studies are needed in emergency departments and ambulatory settings to confirm the safety and efficacy of ketorolac for children.

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Parameter	Sublingual Administration	Intramuscular Administration	p value
C_{max} (ng/ml)	3275.9 ± 170.6	2442.9 ± 135.8	0.0013
t_{max} (h)	0.468 ± 0.032	0.981 ± 0.122	0.0008
AUC (ng.h/ml)	12119.6 ± 1198.7	11897.0 ± 832.3	0.7967
$t_{1/2}$ (h)	5.44 ± 1.25	4.23 ± 0.51	0.2555

Table 1. Comparative pharmacokinetic parameters of ketorolac after sublingual or intramuscular administration of 30 mg ketorolac tromethamine to 13 female healthy volunteers. Modified from Urizar et al (13)

ABSORPTION
Bioavailability: 80-100%
Onset: 10 min (intramuscular); 30-60 min (oral)
Duration: 4-6 hours (analgesia)
Peak serum time: 1-3 min (intravenous); 30-60 min (intramuscular); ~1 hour (oral)
Peak plasma concentration: varies with dose and route
DISTRIBUTION
Protein bound: >99%
Volume distribution: ~13 L
METABOLISM
Metabolized in liver
Metabolites: p-hydroxyketorolac, unidentified polar metabolites
ELIMINATION
Half-life: 2-6 hours
Dialyzable: yes, with unknown effect
Excretion: urine (91%), feces (6%)

Table 2: Ketorolac pharmacokinetics (modified from reference 24)

Concomitant drug or drug class	**Recommendations and effects when coadministered with ketorolac**
ACE inhibitors, ARB	Consideration advised: increased risk of renal impairment (especially in volume-depleted pts)[a], reduced antihypertensive effect of ACE inhibitors/ARB[a,b]
Antiepileptic drugs (phenytoin, carbamazepine)	Sporadic cases of seizures reported
Aspirin	Not generally recommended: increase in adverse events [a]; reduction in KET protein binding
Diuretic drugs	Patients should be observed for signs of renal failure: reduction in natriuretic effect of FUR and thiazides in some patients (data from clinical studies and postmarketing observations)[a]
Lithium	Patients should be observed for signs of LIT toxicity: reduction in renal LIT clearance, increase in LIT plasma levels [b]
Methotrexate	Caution advised: increase MET toxicity;[a,b] competitive inhibition of MET accumulation in kidney reported (data from animal studies)[b]
Nondepolarizing muscle relaxants	increased risk of apnoea (data from postmarketing observations)[a]
Pentoxifylline	Contraindicated: increased bleeding tendency
Probenecid	Contraindicated: reduction in oral KET clearance and volume of distribution, significant increase in oral KET plasma levels and terminal half-life
Psychoactive drugs (fluoxetine, thiothixene, alprazolam)	Hallucinations reported
Salicylate	reduction in KET protein binding (potential 2-fold increase in unbound KET plasma levels) [data from in vitro studies]
SSRIs	Caution advised: increased risk of GI bleeding
Warfarin	Synergistic effects on GI bleeding;[b] slight reduction in WAR protein binding

a Potential effect.

b Class effect of NSAIDs.

ARB= angiotensin receptor blockers; FUR = furosemide; GI = gastrointestinal; KET = ketorolac; LIT = lithium; MET= methotrexate; pts = patients; SSRI = selective serotonin reuptake inhibitor; WAR= warfarin;

Table 3: summary of pharmacological drug interactions with ketorolac (modified from reference 14)

Age	Route		First administration	Note
6 months-16 years	**Parenteral***	**<2years**	0.25-0.5mg/kg (repeatable every 6-8 hours) possible continuous infusion continuing the administration of 0.83µg/h for 24 hours	Licensed from 6 months; not licensed <6 months but efficacy and tolerability demonstrated in several studies
		≥2years	0.5-1mg/kg (max 15mg) (repeatable every 6-8 hours)	
	Intranasal[1]		0.5mg/kg (max 30mg but 15mg if weight <50kg)	Not licensed. Clinical trial about intranasal administration with n°NCT02297906 in progress. Not yet available sufficient evidence about intranasal administration for the clinical use in children
	Oral/Sublingual		0.5mg/kg (max 20mg) (repeatable every 6 h)	Not licensed but evidence about its safety are available in literature
16-18 years	**Parenteral***	**<50kg**	15mg (repeatable every 6 hours; max 60mg/day) possible continuous infusion continuing the administration of 2.5mg/h for 24 hours)	Licensed
		≥50 kg	30mg (repeatable every 6hours; max 120mg/day) possible continuous infusion continuing	Licensed

			the administration of 5mg/h for 24 hours	
	Intranasal[2]	**<50kg**	15mg (repeatable every 6-8 hours; max 4 doses per day)	Licensed
		≥50 kg	30mg (repeatable every 6-8 hours; max 4 doses per day)	Licensed
	Oral/Sublingual	**<50kg**	10mg (repeatable every 4-6 hours; max 40 mg/day)	Licensed
		≥50 kg	20mg (repeatable every 4-6 hours; max 40 mg/day)	Licensed

The minimum effective dose should be always preferred. The duration of the treatment should not be longer than 5 days

[*]Intramuscular route should not be preferred in order to minimize stressful procedures in childhood.

[1]Using MAD device

[2] Alternatively, with MAD device can be administered 0.5mg/kg (max. 30 mg).

Table 4: Ketorolac dosages in paediatric age (modified from references 6,30,48,49,50,51,59)