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Use of Intravenous Ketorolac for Postoperative Analgesia in Infants

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Ketorolac was approved by the Food and Drug Administration (FDA) in 1989, making it the first parenteral nonsteroidal anti-inflammatory drug (NSAID) available in the United States.[1,2] It was initially indicated only for the treatment of moderate to severe pain in adults, but was subsequently approved for use in children 2 years of age and older based on the results of several studies documenting its safety and efficacy in this population. As in adults, ketorolac has been shown to provide effective postoperative pain relief in children, often decreasing opioid requirements. It is generally well tolerated, but the risk for bleeding and renal dysfunction must always be taken into consideration. Although not currently approved for use in infants, several recent studies suggest a role for ketorolac in this population as well.[3-7] This issue of *Pediatric Pharmacotherapy* will review these studies and provide recommendations for patient selection, dosing, and monitoring.

Mechanism of Action

Ketorolac tromethamine, (±)-5-benzyol-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, 2-amino-2-(hydroxymethyl)-1,3-propanediol, is a heterocyclic acetic acid derivative. Like other NSAIDs, it decreases prostaglandin synthesis by non-selective competitive inhibition of cyclo-oxygenase (COX-1 and COX-2), producing peripherally-mediated analgesia. Ketorolac is marketed as a racemic mixture of S- and R-enantiomers, but only the S-enantiomer has pharmacologic activity.[1,2]

Pharmacokinetics

Ketorolac may be administered orally and by IV or IM injection. Oral bioavailability approaches 100%. It is widely distributed throughout the body and highly (99%) bound to serum albumin. The average volume of distribution in adults is 0.18-0.21 L/kg. Ketorolac is both metabolized and excreted in the urine as unchanged drug. The half-life of the R-enantiomer is approximately 300 min (5 hrs) in adults, while the average half-life of the active S-enantiomer is only 150 min (2.5 hrs). Renal dysfunction prolongs the clearance of ketorolac and increases the unbound (active) fraction of drug in the serum, resulting in an overall increase in the area under the concentration-time curve (AUC).[1,2]

Four studies have recently been published describing the pharmacokinetic profile of ketorolac in infants.[3,4,9,10] In 2007, Lynn and colleagues conducted a pharmacokinetic analysis as part of their randomized, double-blind, placebo-controlled study of ketorolac efficacy and safety in 37 infants and toddlers (ages 6-18 months).[3] Twenty-five patients received ketorolac, either 0.5 or 1 mg/kg given IV over 10 minutes. Serum sampling was performed over 12 hours in all patients to maintain the blind. Stereo-specific pharmacokinetic differences were found for clearance, with a mean of 7.52 mL/min (equivalent to 0.7 mL/min/kg) for the inactive R-enantiomer and 45.3 mL/min (4.8 mL/min/kg) for the active S-enantiomer. The mean values for elimination half-life were 238 ± 48 min and 50 ± 42 min for the R- and S-enantiomers.

In 2009, Zuppa and colleagues reported the results of an intraoperative ketorolac pharmacokinetic study in 3 neonates and 9 infants (ages 1-33 weeks).[9] Each patient received a single 0.5 mg/kg IV dose after induction of general anesthesia. Effective ketorolac serum concentrations (≥ 0.37 mg/mL) were maintained for 3-4 hours after dosing. The authors found an average racemic ketorolac clearance of 2.8 mL/min/kg, more rapid than that reported previously in older children (1.6 mL/min/kg). However earlier this year, Cohen and colleagues reported a clearance of 1.49 ± 1.12 mL/min/kg in their study of 14 infants (mean age 6.2 months, range 2-11 months) given a single 0.5 mg/kg IV ketorolac dose, similar to earlier pediatric studies.[10] The average elimination half-life in their study was 236 ± 169 minutes. Serum ketorolac concentrations ≥ 0.37 mcg/mL were present in only 50% of the patients at 4 hours, suggesting that a shorter dosing interval may be necessary.

An additional study was published this year by Lynn and colleagues in *Pediatric Anesthesia*.[4] The authors performed a second pharmacokinetic analysis of ketorolac, this time in 14 younger infants (2-6 months of age) given either a single 0.5 or 1 mg/kg IV dose. Clearance values for the R- and S-enantiomers were 1.04 mL/min/kg and 5.0 mL/min/kg. Mean elimination half-lives were 191 and 33 minutes, respectively. Although the four pharmacokinetic studies used differing methodology, the overall results suggest a more rapid clearance of the active S-enantiomer in young infants, compared to older infants, children, and adults.

Clinical Trials in Infants

In 2002, Burd and colleagues performed a retrospective study comparing morphine requirements in 10 infants given both ketorolac and morphine and 8 controls who received morphine alone.[5] The patients (all less than 6 months of age) underwent abdominal surgery by the same surgeon and were extubated immediately after surgery. Both groups received morphine 0.1 mg/kg IV every 2-3 hours based on standardized neonatal pain scores. Ketorolac was administered at doses of 0.5 mg/kg every 8 hours in 8 patients and every 12 hours in 2 patients. The average amount of ketorolac given was 1.1 $\pm$ 0.4 mg/kg/day. Infants who received ketorolac required significantly less morphine during the first 48 hours after surgery (0.04 $\pm$ 0.05 mg/kg/day vs. 0.15 $\pm$ 0.06 mg/kg/day, $p < 0.01$). Four of the ketorolac patients required no supplemental morphine.

Two years later, Gupta and colleagues from the Children's Hospital Los Angeles conducted a prospective randomized, controlled trial of ketorolac in 70 infants and children following cardiac surgery to evaluate potential adverse effects.[6] The patients, ranging in age from 2.5 months to 14 years, were randomized to receive morphine alone or morphine plus ketorolac given in doses of 0.5 mg/kg IV every 6 hours for up to 48 hours. Ketorolac patients received between 6 and 8 doses. The authors reported no significant differences in bleeding complications between the groups. Among their secondary outcome measures, there was a trend towards less morphine use in the ketorolac-morphine group, but the results were not significantly different (0.3 mg/kg/day vs. 0.4 mg/kg/day in the morphine group, $p = 0.13$).

That same year, Papacci and colleagues conducted an observational study of 18 neonates (average gestational age 33 $\pm$ 4 weeks, average postconceptional age 37 $\pm$ 4 weeks) given ketorolac for pain associated with surgery or invasive procedures.[7] Pain scores, based on the Neonatal Infant Pain Scale (NIPS), were assessed before and after a single 1 mg/kg IV ketorolac dose. Pain control was achieved in 94.4% of the neonates. None of the patients experienced bleeding or adverse renal or hepatic effects.

As described earlier, Lynn and colleagues conducted a safety and efficacy study of ketorolac in 37 infants and toddlers undergoing surgery.[3] On postoperative day 1, patients were randomized to receive a single 0.5 or 1 mg/kg ketorolac dose or placebo given IV over 10 minutes. Morphine requirements following ketorolac or placebo administration revealed no significant difference between the groups (total morphine given over 12 hours: 1.4 $\pm$ 1.2 mg/kg in the 0.5 mg/kg ketorolac group vs. 2.3 $\pm$ 1.7 mg/kg in the 1 mg/kg ketorolac group and 2.2 $\pm$ 1.4 mg/kg in the placebo group, $p = 0.33$). The authors suggested that these results may not reflect lack of ketorolac efficacy, but rather their current practices to continue morphine infusions as long as patients had satisfactory pain scores and no evidence of adverse effects.

In their second study, which included younger infants, the authors randomized 14 infants less than 6 months of age to receive ketorolac or placebo in the same manner.[4] As in their previous study, ketorolac was well tolerated, but there was no significant difference in cumulative morphine administration between groups (total morphine given over 12 hours: 0.123 $\pm$ 0.28 mg/kg in the ketorolac group vs. 0.077 $\pm$ 0.12 mg/kg in the placebo group, $p = 0.68$).

In 2009, Dawkins and colleagues performed a retrospective study of the safety profile of ketorolac in 19 infants less than 6 months of age who had undergone cardiac surgery, comparing them to 19 matched controls.[8] Patients in the ketorolac group received doses of 0.5 mg/kg IV every 6-8 hours. The mean length of therapy was 3.1 days (range 1-6 days). Although the primary purpose of the study was to examine bleeding and changes in renal function, the authors also examined concurrent analgesic use. There was no difference in the amounts of morphine, fentanyl, acetaminophen, and ibuprofen used between the groups.

Adverse Effects

All of the NSAIDs carry a black box warning for cardiovascular events (hemorrhage, myocardial infarction, and stroke) and gastrointestinal bleeding. Ketorolac has also been associated with renal impairment, hepatic dysfunction, and serious dermatologic reactions, including Stevens Johnson syndrome and toxic epidermal necrolysis. The risks for bleeding and renal dysfunction require close attention when considering treatment in infants. Ketorolac inhibits platelet aggregation and may prolong

bleeding time. Unlike aspirin, the effect of ketorolac on platelets is transient, resolving within 24-48 hours after discontinuing therapy. In adults, the risk for clinically significant postoperative bleeding is approximately 0.4%. In pediatric trials, the incidence of any postoperative bleeding has been reported to be between 6 and 17%, compared to 4-17% in controls receiving only opioids.[1,2]

Renal toxicity associated with ketorolac administration is typically seen in patients with decreased renal blood flow, where renal prostaglandins are a necessary component in maintaining renal perfusion. Administration of an NSAID reduces renal prostaglandin synthesis and may precipitate acute kidney failure. Prior to treatment with ketorolac, patients should be evaluated for dehydration or the presence of underlying renal dysfunction. Reduced cardiac output and the use of diuretics, situations often encountered in infants after cardiac surgery, have the potential to increase the risk for renal toxicity. Discontinuing ketorolac typically leads to a return to baseline renal function.

In the studies conducted in infants to date, complications have largely been avoided by careful patient selection. Most prospective studies, as well as retrospective case series, have described exclusion of premature infants, as well as those with underlying coagulopathy, gastrointestinal bleeding, and renal or hepatic dysfunction.[4-8] In their 2004 prospective study, Gupta and colleagues found that median chest tube drainage was no different in the ketorolac-morphine group and the morphine only group (13.3 mL/kg/day and 16.6 mL/kg/day, respectively).[6] One patient in the morphine group had wound bleeding, and one patient in the ketorolac group had evidence of gastrointestinal bleeding (a coffee-ground gastric aspirate). The authors concluded that ketorolac was a reasonable option for improving analgesia after pediatric cardiac surgery without increasing the risk for postoperative bleeding.

Lynn and colleagues reported no changes in surgical drain output or oxygen saturation over a 12-hour monitoring period in their 2007 prospective study.[3] There were no changes in serum creatinine, BUN, or urine output in any of the three groups during the assessment period. One patient in the placebo group and one patient given ketorolac had mild increases in AST and ALT which resolved within 2-3 days. Similarly, no adverse effects were reported in their 2011 study in younger infants.[4]

Other papers have shown similar results. In 2006, Moffett and coworkers found only minor elevations in serum creatinine and BUN in a review of 53 neonates and infants given ketorolac after cardiac surgery.[11] Four patients had evidence of minor bleeding, without hemodynamic instability or the need for transfusion.

Gupta and colleagues conducted a retrospective review of 94 infants and children who received ketorolac after cardiac surgery and 94 matched controls.[12] None of the patients in the ketorolac group had postoperative bleeding, compared to 4 patients in the control group who experienced bleeding requiring surgical exploration. Similarly, in the study by Dawkins described earlier, there were no statistically significant differences between the groups in renal function or bleeding, including the number of blood transfusions between the groups.[8] Kay and colleagues also found no increase in postoperative bleeding in their retrospective study of 169 infants and children who received ketorolac after orthopedic surgery compared to controls who received other analgesics.[13]

In contrast, Aldrink and colleagues found a 17.2% incidence of bleeding in a chart review of 57 neonates and infants (0-3 months of age) who received ketorolac after surgery.[14] Their paper, published in the June issue of the *Journal of Pediatric Surgery*, found that the patients who experienced bleeding had received ketorolac at a mean age of 20.7 days, with the majority (70%) receiving it prior to 2 weeks of age. This is in contrast to the patients who did not experience a bleeding event, who received ketorolac at a mean age of 31.9 days ($p = 0.04$). In all but one patient, the bleeding events were also correlated with reduced renal function or concomitant use of medications which also carry a risk for bleeding. Based on their findings, the authors suggest that ketorolac not be used in infants less than 21 days of age and less than 37 weeks corrected gestational age.

Drug Interactions

Careful consideration should be given to the use of ketorolac in infants receiving anticoagulants or other antiplatelet agents. Concurrent use of ketorolac and furosemide may reduce the latter's diuretic effect by approximately 20%. Use of ketorolac with angiotensin converting enzyme (ACE) inhibitors may produce additive adverse effects on renal perfusion. Administration of NSAIDs may inhibit the clearance of lithium and methotrexate, leading to toxicity. Giving probenecid at the same time as ketorolac reduces its clearance and increases the half-life in adults to approximately 15 hours. In addition to these documented drug interactions, there are also isolated case reports of increased seizure frequency in patients given ketorolac while taking antiepileptics.[1,2]

Availability and Dosing Recommendations

Ketorolac injection is available as a generic product from several manufacturers in 15 mg/mL and 30 mg/mL syringes or vials. The recommended IV dose of ketorolac is 30 mg every 6 hours in adults and 0.5 to 1 mg/kg in children, with a maximum dose of 15 mg. In patients with renal impairment, the dose should be decreased by 50%. There are no specific guidelines for dosing in hepatic impairment.[1,2]

The studies of ketorolac use in infants published to date suggest that an IV dose of 0.5-1 mg/kg given every 6 to 8 hours is appropriate.[2-7] Although the recommended duration of therapy for adults is 5 days, a shorter duration of 24 hours is recommended for children and may be more appropriate for postoperative analgesia in infants in order to minimize the risk for adverse effects.

Summary

Management of postoperative pain in infants is complicated by both difficulties in pain assessment and concerns for drug-related adverse effects. Opioids, the mainstay of analgesic therapy in this population, are associated with respiratory depression, emesis, pruritus, and ileus. Ketorolac provides a useful alternative to the opioids, but is associated with its own risks, including bleeding and renal dysfunction. Careful attention to patient selection, dosing, and monitoring is necessary to optimize therapy while minimizing the risk for adverse effects.

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Pharmacology Literature Review

Clevidipine Use in Infants and Children

Clevidipine, a short-acting calcium channel blocker, is used for the control of perioperative hypertension in adults. The authors of this retrospective study describe the use of clevidipine in 14 pediatric patients (11 months-15 years) following cardiac surgery. Clevidipine was administered intraoperatively or following surgery. In patients treated after surgery, the infusion was started at 1 mcg/kg/min and increased to an average dose of 7 mcg/kg/min. Target blood pressures were reached within 5 minutes. Clevidipine was not effective during cardiopulmonary bypass or cooling. **Tobias JD, et al. Clevidipine for perioperative blood pressure control in infants and children undergoing cardiac surgery for congenital heart disease. J Pediatr Pharmacol Ther 2011;16:55-60.**

Correction

There was an error in the October 2009 issue of the newsletter (Pediatric Pharmacotherapy 2009;5(10):1-4). The first sentence of the second paragraph on page 3 should read "When ganciclovir is administered simultaneously with, or within 2 hours prior to, didanosine, the AUC of didanosine may be increased by approximately 100%."

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