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Perioperative use of high-dose rectal acetaminophen

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The use of acetaminophen in the perioperative period has been suggested as a method to improve analgesia and reduce opioid requirements following surgery. While high-dose rectal acetaminophen has become routine in many institutions, the efficacy of this therapy has been debated in the medical literature. This issue of *Pediatric Pharmacotherapy* will review the literature both supporting and refuting this technique, as well as the pharmacokinetics and safety profile of rectal acetaminophen in pediatric surgical patients.

Pharmacokinetic considerations

Many standard pediatric dosing texts cite identical doses for oral and rectal acetaminophen administration, typically 10 to 15 mg/kg given up to every 4 hours.[1] It is well known, however, that absorption from the rectal route is slow and often erratic. Several factors may account for this variability, including the placement of the suppository, the degree of lipophilicity of the vehicle, and the pH within the rectum. This erratic absorption pattern frequently results in serum acetaminophen concentrations that fail to reach the target for antipyresis of 10 to 20 mcg/ml.[2] The ideal serum concentration for analgesia remains largely undefined.

Because of this delayed absorption, several investigators have suggested using higher doses when administering acetaminophen by the rectal route in children, as well as adults.[3-12] If the optimal dose for rectal administration could be determined, the use of this route might prove ideal for the perioperative setting. The slower rate of absorption could provide a prolonged analgesic effect during recovery.

In 1995, Montgomery and colleagues evaluated the pharmacokinetics of high-dose rectal acetaminophen in 10 children (average age 3.4±0.5 years).[3] A single 650 mg suppository, providing a dose of approximately 45 mg/kg, was administered immediately after induction of anesthesia. Serum samples were collected over a 4-hour period in the first five patients, but extended to 7 hours in the remaining patients after a prolonged absorption phase was identified. The average maximum serum concentration for the 10 children was 13.3±5.9 mcg/ml. The time to maximum concentration occurred at 198±70 minutes. Based on their results, the authors suggested that a 45 mg/kg rectal acetaminophen dose was roughly equivalent to a 10 to 15 mg/kg oral dose.

The results of Montgomery's group were subsequently reproduced in a larger dose-ranging study. Birmingham and colleagues at Children's Memorial Hospital in Chicago conducted a trial of rectal acetaminophen in 28 children (ages 2 to 12 years) undergoing orthopedic surgery.[4] Patients were randomized to receive a single 10, 20, or 30 mg/kg dose after induction of anesthesia. Serum sampling was performed over a 24-hour period and the results analyzed with nonparametric mixed-effects modeling (NONMEM). Pharmacokinetic analysis showed considerable patient variability and wide differences in dissolution rates. In the patients receiving the two larger (325 and 650 mg) suppositories, the average time to complete dissolution was 3 hours. Only the 30 mg/kg dose produced serum concentrations within the predetermined target range of 10-20 mcg/ml, with an average maximum serum concentration of 14.2±5.1 mcg/ml. While this study was not designed to evaluate analgesic efficacy, the

authors concluded that a rectal acetaminophen dose of 40 mg/kg would likely be needed to provide adequate serum acetaminophen concentrations in the perioperative setting.

Similar results were observed by Hansen and coworkers in a study of 17 infants given rectal acetaminophen 25 mg/kg during induction of anesthesia.[5] The average maximum serum acetaminophen concentration (10.9±5.1 mcg/ml) was considered by the authors to be subtherapeutic. Average time to maximum concentration was 102.4±59.1 minutes.

Potential for accumulation

While these initial studies support the need for higher rectal doses (ie, 25-45 mg/kg) when acetaminophen is given intraoperatively, they have not addressed the potential risk for drug accumulation if dosing is continued. Hahn and colleagues recently reported the results of a trial of repeated dosing of rectal acetaminophen using 25 mg/kg.[7] Twenty-three children between the ages of 9 weeks and 11 years were enrolled in this open-label trial. Acetaminophen doses were given every 6 hours for up to 5 days after surgery. In these patients, the average serum concentration at steady state was 15.2±6.8 mcg/ml. The authors found no potentially toxic serum concentrations and no evidence of drug accumulation. While these findings are reassuring, children receiving high-dose rectal therapy beyond 24 hours should be closely monitored for signs of toxicity. Serum acetaminophen concentrations can also be measured in children requiring longer treatment to detect any drug accumulation.

Continuing controversy over efficacy

Although the initial pharmacokinetic studies produced consistent findings, the few efficacy studies conducted in children to date have provided mixed results. In 1996, Anderson and coworkers reported the results of a prospective, randomized, double-blind trial comparing oral and rectal acetaminophen in children undergoing tonsillectomy.[8] One hundred children (aged 3-15 years) were randomized to receive a single 40 mg/kg dose of either acetaminophen elixir or a suppository. The oral dose was given 30 minutes prior to surgery and the suppository was given at induction. Pain scores, from 0 (least pain) to 10 (worst pain), were assessed 30 minutes after the end of surgery. A serum sample was also taken at that time to determine the acetaminophen concentration. Children in the elixir group had a significantly higher mean acetaminophen serum concentration than the group given suppositories (22.7±9.1 versus 7.6±4.5 mcg/ml) and a lower median pain score (5 versus 7). More of the children receiving suppositories required morphine postoperatively. While these results appear to demonstrate a clear benefit from oral therapy, it should be remembered that the doses used in this study were not equivalent.

Despite their early concerns about the efficacy of rectal administration, in 1999 these same investigators used both oral and rectal acetaminophen in 120 children undergoing tonsillectomy to develop a pharmacokinetic-pharmacodynamic dosing model.[6] Twenty children were given 40 mg/kg acetaminophen elixir and 100 were given approximately the same dose rectally, using 125 or 250 mg suppositories. The pharmacokinetic parameters determined in these patients were similar to earlier studies. Pain was assessed with a visual analog scale (0 to 10 points) four hours after surgery. The authors found that, regardless of route, serum acetaminophen concentrations between 10 and 20 mcg/ml were associated with pain scores of 2.8 to 3.6, indicating that the same range used for antipyretic effect may be used to assess analgesic efficacy. Based on the pharmacodynamic model developed from this study, the authors also concluded that higher serum concentrations were not likely to result in significant improvement in pain relief and increased the potential for adverse effects. In their simulation, a preoperative oral dose 40 mg/kg followed by a rectal dose of 20 mg/kg two hours later provided optimal serum concentrations for pain control.

Several additional efficacy studies have been published this year. In March, Birmingham's group published another pharmacokinetic study of perioperative rectal acetaminophen.[9] In this trial, the authors chose a target serum acetaminophen concentration range of 10-20 mcg/ml. Based on their previous work, an initial dose of 40 mg/kg was given to 16 children undergoing orthopedic surgery, followed by doses of 20 mg/kg given at 6 hour intervals for up to 24 hours. Using this regimen, serum concentrations remained within the target range 60% of the time. The highest serum concentration reached was 38.6 mcg/ml, well below the 120 mcg/ml threshold for toxicity. The authors concluded that this regimen provided adequate serum concentrations for analgesia without evidence of accumulation.

In *Anesthesia and Analgesia* the following month, Bremerich and colleagues compared the opioid-sparing effects of rectal acetaminophen given in doses of 10, 20, or 40 mg/kg versus

placebo in 80 children less than 2 years of age.[10] All patients were undergoing cleft palate repair. Pain was assessed with a five-item scale evaluated by an independent observer. In this trial, acetaminophen provided no significant improvement in pain scores in the first hour after surgery, even with mean serum concentrations of 13 and 21 mcg/ml in the 20 and 40 mg/kg groups, respectively. In addition, acetaminophen failed to reduce opioid use compared to placebo.

Unfortunately, differences in methods for pain assessment, unequal dose and dosing regimen comparisons, and the unavoidable difficulties in conducting analgesic trials in children make comparisons of these trials impractical. There is still much to be learned. It is possible that even the initial assumptions about an analgesic "therapeutic range" may not be sound.

In July of this year, van der Marel and coworkers published the results of a trial comparing oral and rectal acetaminophen in children undergoing craniofacial surgery.[12] Forty children between the ages of 8 and 20 months received a loading dose of 40 mg/kg acetaminophen given rectally during surgery, followed by 20 mg/kg given either orally or rectally every 6 hours postoperatively. Unlike previous studies, serum acetaminophen concentrations were higher in the group receiving drug by the rectal route. Ninety percent of the patients in the rectal group achieved a serum concentration greater than 10 mcg/ml versus 65% in the oral group. Pain scores, as evaluated by trained nurses using a standardized scale, were also better in rectal-dosing group. When the patients who vomited after receiving the oral acetaminophen were excluded, however, the differences were no longer significant. Interestingly, the authors did not find a correlation between serum acetaminophen concentrations and pain scores. In the group of patients who failed to achieve serum concentrations > 10 mcg/ml, 92.5% of their VAS scores were less than 4 cm, indicating adequate pain control.

Summary

The administration of high-dose rectal acetaminophen in the perioperative period appears to be a safe and effective therapy for children. While some research suggests a significant degree of pain relief may be provided by this therapy alone, it should be anticipated that children undergoing surgery are likely to require additional analgesia in the immediate postoperative period. The optimal dosing and target serum concentrations for rectal acetaminophen in this patient population remain controversial, and additional research is needed to set standards for this practice.

References

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Pharmacology Literature Review

Experience with infliximab in children

The authors of this paper report their experience with infliximab, a monoclonal antibody to tumor necrosis factor, in 18 children with inflammatory bowel disease. The patients, ranging in age from 7 to 21 years, had either Crohn's disease or ulcerative colitis and had failed conventional therapy. These patients received from one to five infusions of infliximab at a dose of 5 mg/kg. All patients were reported to have experienced clinical improvement. Adverse reactions included one patient who developed a rash and another who developed recurrent infections. Serrano M, Schmidt-Sommerfeld E, Kilbaugh TJ, et al. Use of infliximab in pediatric patients with inflammatory bowel disease. **Ann Pharmacother 2001;35:823-8**.

Fetal demise after valsartan and atenolol

The first suspected case of fetal death resulting from valsartan, with atenolol, is described in this report. The authors describe a 40 year old woman who was taking both agents for chronic

hypertension. An ultrasound at 24 weeks' gestation revealed anhydramnios. At that time, valsartan was discontinued. Amniotic fluid levels returned to normal, but interuterine death occurred at 33 weeks. Postmortem examination revealed a small placenta and hypoplastic lungs. Valsartan, a selective angiotensin II receptor antagonist, appears to have the potential to cause fetal toxicity similar to the traditional angiotensin-converting enzyme inhibitors, resulting in decreased perfusion of the fetal kidney, anuria, oligohydramnios, and pulmonary hypoplasia. Briggs GG, Nageotte MP. Fatal fetal outcome with the combined use of valsartan and atenolol. **Ann Pharmacother 2001;35:859-61**.

Montelukast dosing

Montelukast, a leukotriene receptor antagonist, has become an important component of asthma management. The authors of this study evaluated the pharmacokinetics of montelukast in 15 children between the ages of 2 and 5 years following a dose of a new 4 mg chewable tablet. This dose produced an area under the concentration curve similar to that of adults given a standard 10 mg dose. Average time to peak serum concentration was shorter than that observed in adults (2.07±0.3 versus 3.36±0.6 hrs); average maximum concentration was higher (471±65 versus 283±54 ng/ml). The authors concluded that the new tablet appears to be an appropriate dosage formulation for younger children. Knorr B, Nguyen HH, Kearns GL, et al. Montelukast dose selection in children ages 2 to 5 years: comparison of population pharmacokinetics between children and adults. **J Clin Pharmacol 2001;41:612-9.**

Prolonged QT interval

The ability of drugs to prolong the QT interval has come under increasing attention from both health care professionals and the FDA. This article provides a background on the mechanisms for this effect, then focuses on how the risk for prolonged QT can be evaluated in new drugs prior to marketing. Malik M, Camm AJ. Evaluation of drug-induced QT interval prolongation: implications for drug approval and labelling. **Drug Safety 2001;26:323-51.**

Vancomycin in infants

This pharmacokinetic study was designed to identify those indices of maturation most predictive of vancomycin elimination. Using NONMEM modeling techniques and data from 374 infants, the authors identified weight and serum creatinine as having the greatest influence on vancomycin clearance. Postnatal age and prematurity were also predictive, but were of less significance. This is the first study of vancomycin in infants to recommend the use of serum creatinine as a reliable predictor of drug elimination. If routinely adopted, these results could have a considerable impact on clinical practice. Capparelli EV, Lane JR, Romanowski GL, et al. The influences of renal function and maturation on vancomycin elimination in newborns and infants. **J Clin Pharmacol 2001;41:927-34.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 8/24/01:

1. Argatroban (Argatroban®) was added to the Formulary for prophylaxis and treatment of thrombosis in patients with heparin-induced thrombocytopenia. It is restricted to use by the Hematology division.
2. Fomepizole (Antizol®) was added as an antidote for ethylene glycol or methanol poisoning. It serves as a competitive inhibitor of alcohol dehydrogenase. The use of fomepizole is restricted to Medical Toxicology.
3. Pioglitazone (Actos®) and a long-acting formulation of metformin (Glucophage XR®) were added for the management of patients with type 2 diabetes mellitus. The immediate release form of metformin was deleted.
4. Insulin glargine (Lantus®), a once daily formulation, was also added with restriction to Endocrinology.
5. The newest of the atypical antipsychotics, ziprasidone (Geodon®), was added to the Formulary, with restriction to Psychiatry. For more information about the role of this agent in pediatric patients, please refer to the August issue of *Pediatric Pharmacotherapy*.
6. An immunoglobulin Fab fragment for snake venom, crotalidae polyvalent immune Fab (CroFab®), was also added to the Formulary.

Correction

The dose of Rhinocort Aqua® was inadvertently omitted from article on intranasal steroids in the May issue (*Pediatric Pharmacotherapy* 2001;7(5):1-4). The starting dose for this product in adults and children ≥ 6 years of age is one spray (32 mcg) per nostril once daily. The dose may then be titrated to response, with a maximum dose in adults of 4 sprays per nostril once daily and a maximum in children < 12 years of 2 sprays per nostril once daily.

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