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Initial and Subsequent Dosing of Rectal Acetaminophen in Children

A 24-Hour Pharmacokinetic Study of New Dose Recommendations

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Background: **Recent studies have determined that an initial rectal acetaminophen dose of approximately 40 mg/kg is needed in children to achieve target antipyretic serum concentrations. The timing and amount of subsequent doses after a 40-mg/kg dose has not been clarified for this route of administration. Based on the authors' previous pharmacokinetic data, they examined whether a 40-mg/kg loading dose followed by 20-mg/kg doses at 6-h intervals maintain serum concentrations within the target range of 10–20 μg/ml, without evidence of accumulation.**

Methods: **Children (n = 16) received rectal acetaminophen (40 mg/kg) and up to three additional doses of 20 mg/kg at 6-h intervals. Venous blood samples were taken every 30 min for 4 h, then every 60 min for 4 h, and every 4 h for 16 h. The authors assessed whether their published pharmacokinetic parameters predicted the acetaminophen concentrations in the present study. They also assessed their dosing regimen by determining the fraction of time each individual maintained the target concentration.**

Results: **All patients received the initial loading dose; 10 of 16 patients received three subsequent doses. Serum concentrations with the initial dose were in the target range 38 ± 25% of the time. With subsequent dosing, the target range was maintained 60 ± 29% of the time. The highest serum concentration with initial or subsequent dosing was 38.6 μg/ml. Pharmacokinetic parameters from the earlier study predicted the serum concentrations observed for both initial and subsequent doses.**

Conclusions: **A rectal acetaminophen loading dose of 40 mg/kg followed by 20-mg/kg doses every 6 h results in serum concentrations centered at the target range of 10–20 μg/ml. There was large interindividual variability in pharmacokinetic characteristics. There was no evidence of accumulation during the 24-h sampling period.**

ACETAMINOPHEN is often given to children during surgery for analgesia or antipyresis. When the oral route is not an option, acetaminophen may be administered as a rectal suppository. Several studies have investigated initial rectal dosing of 30,[1] 35,[2] 40,[3,4] 45,[5] and 60 mg/kg.[4] The timing and amount of subsequent doses to maintain a target antipyretic serum of 10–20 μg/ml by this route of administration has not been clarified. This is important because additional acetaminophen dosing may be desired in the postoperative period for analgesia or antipyresis, and hepatotoxicity has been reported after multiple as well as single dosing.[6] Based on our previous study, in which doses of 10–30 mg/kg were given, we recommended an initial dose of 40 mg/kg, but made no recommendations regarding subsequent dosing. In the present study, we determined the serum concentrations of acetaminophen attained with a regimen of an initial dose of 40 mg/kg followed by doses of 20 mg/kg every 6 h. In addition, we evaluated whether the pharmacokinetic parameters that we determined previously from acetaminophen doses of 10–30 mg/kg predict the serum concentrations of acetaminophen attained with that regimen.

Materials and Methods

With Institutional Review Board approval (Children's Memorial Hospital, Chicago, IL) and parental informed consent, patients received an initial dose of 40 mg/kg rectal acetaminophen after induction of anesthesia and between zero and three subsequent 20-mg/kg doses at 6-h intervals. This dosing regimen was determined using previous pharmacokinetic parameter estimates. FeverAll suppositories (Upsher-Smith Laboratories, Minneapolis, MN; distributed by Ascent Pediatrics, Inc., Wilmington, MA) were used. In this suppository formulation, acetaminophen is suspended in a hydrogenated vegetable oil base. Combinations of the four commercially available doses (80, 120, 325, and 650 mg) were used to deliver a dose for each patient as close as possible to the desired dose. Suppositories were not cut, because acetaminophen may not be distributed evenly throughout the suppository.

Children aged 2–12 yr undergoing elective orthopedic surgery were eligible if they were to be hospitalized after surgery, weighed more than 12 kg, were classified as American Society of Anesthesiologists physical status 1–3, and had a preoperative hematocrit more than 30%. Children were excluded if they received acetaminophen within 24 h before the study; had clinically important

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hepatic, renal, or cardiac disease; had rectal dysfunction that may impair their ability to retain the suppository; or if blood loss was anticipated to be large. Children underwent intravenous or inhalation induction of anesthesia. Nitrous oxide with halothane or isoflurane was used to maintain anesthesia. Intravenous opioids provided supplementary analgesia in the perioperative period.

After a baseline blood sample was obtained, unlubricated suppositories were inserted several centimeters into the rectum. Peripheral venous blood was sampled at 0, 30, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 720, 960, 1,200, and 1,440 min. Serum was separated from erythrocytes and refrigerated at 4°C until drug concentrations were measured using fluorescence polarization immunoassay (TDx System; Abbot Laboratories, North Chicago, IL). The TDx system was operated according to the manufacturer's published recommendations. Assay controls (Liquichek TDM; Bio-Rad Laboratories, Hercules, CA) at 12.2 and 121 μg/ml (81 and 801 mM) were performed with each batch of samples. The level of quantification of the assay was 1.0 μg/ml. The coefficients of variation were 7.5% and 4.3%, respectively, during the study.

Statistical Analysis

To assess whether our dosing regimen achieved the target concentration of 10–20 μg/ml, we determined the fraction of time that each individual maintained a serum acetaminophen concentration between 10 and 20 μg/ml from initial administration until 6 h after the final dose (or until the final sample was obtained). To determine the fraction of time that each individual maintained the target concentration, we assumed that serum concentrations of acetaminophen varied in a linear manner in the period between measured values. For example, we assumed that a concentration of 3.0 μg/ml at 3 h and one of 13.0 μg/ml at 5 h yielded a concentration of 8.0 μg/ml at 4 h.

We also assessed whether our published pharmacokinetic parameters predicted the acetaminophen concentrations in the present study. In the previous study, children aged 2–12 yr received 10, 20, or 30 mg/kg of the same acetaminophen suppositories as in the present study. Serum was sampled during 24 h, and acetaminophen concentrations were measured using the same assay.[1] That analysis demonstrated that a one-compartment model was adequate to describe the distribution and elimination of acetaminophen. The absorption model for acetaminophen had two components. The first component was a zero-order rate constant that differed for each size suppository; we postulated that this rate constant corresponded to the dissolution rate of each size suppository. The second component was a first-order rate constant that we assumed corresponded to absorption of acetaminophen from the rectal vault. Because all doses were administered rectally and there was no control group given intravenous acetaminophen, we could not estimate a typical value for bioavailability (*F*), and hence reported clearance and volume of distribution divided by *F*.

Table 1. Study Population Demographics

Number of patients	16
Age (yr)	6.6 ± 2.8 (3.2–12.3)
Weight (kg)	22.2 ± 8.7 (13.6–46.0)
Gender	13 F/3 M
Intravenous fluids (ml/kg)	22.9 ± 9.7 (13–52.5)
Estimated blood loss (% estimated blood volume)	2.9 ± 4.6 (0–14.2)
Anesthesia time (min)	186.2 ± 47.2 (95–280)

Values are mean ± SD (range).

Using the pharmacokinetic parameters from that model and the dosing information for each patient (quantity and dose of suppositories), we predicted the serum concentrations of acetaminophen expected for each patient (NONMEM, version 5, Level 1.0L4, 1995, University of California, San Francisco, CA). For each patient, the ratio of measured to predicted concentration was determined and plotted against time. The similarity between observed and predicted concentrations was assessed by comparing the plotted ratios with the target value (1.0).

Results

Sixteen children were enrolled in the study (table 1). Six patients received only the initial acetaminophen dose; 10 received all four doses. All initial doses were within 6% of the desired dose (table 2); subsequent doses were within 18% of the desired dose.

One hundred ninety of the 272 planned blood samples were obtained. The 16 baseline samples and two samples after suppository insertion had concentrations less than the level of quantification of the assay and were excluded from analysis. The remaining 172 data points were used in the pharmacokinetic analysis. Fifty-five of these samples were collected more than 300 minutes after initial dosing. Sampling was incomplete because of factors such as early hospital discharge, loss of intravenous access, inability to obtain an adequate blood sam

Table 2. Acetaminophen Dosing

Initial acetaminophen dose (mg/kg)	39.8 ± 1.2 (37.6–41.7)
Number of suppositories in initial dose	2.8 ± 1.1 (1–5)
Subsequent acetaminophen doses (mg/kg)	19.8 ± 2.0 (16.3–23.5)
Number of suppositories in subsequent doses	1.5 ± 0.6 (1–3)

Values are mean ± SD (range).

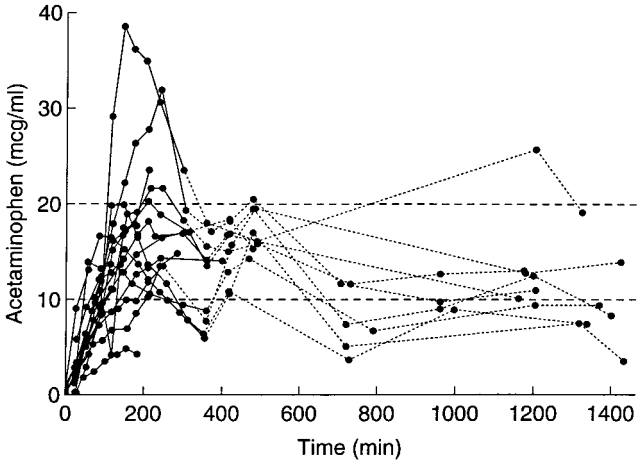

Fig. 1. Values for serum concentration of acetaminophen are plotted against time for each patient. Solid lines represent serum concentrations resulting from initial 40-mg/kg dosing. Dashed lines represent serum concentrations in patients resulting from subsequent 20-mg/kg doses at 6-h intervals. Six patients received only the initial 40-mg/kg dose.

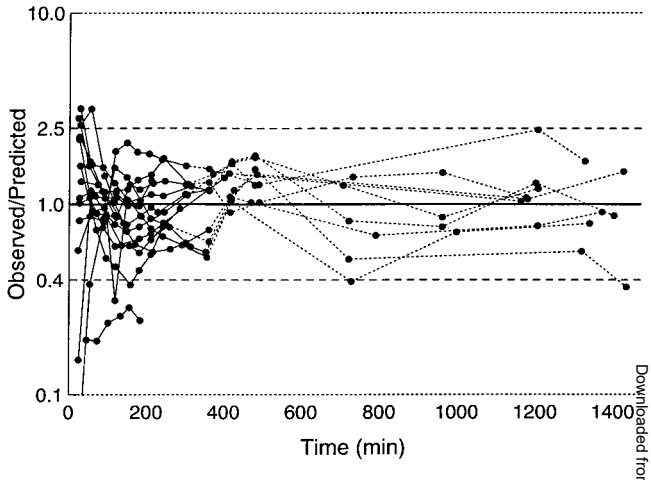

Fig. 2. Quality of fit of the measured serum concentrations to those predicted from our published pharmacokinetic model, which assumes dissolution of suppositories is a zero-order process and absorption is a first-order process. The *y* axis displays the ratio of measured concentrations to those predicted from our published pharmacokinetic analysis. Solid lines represent values resulting from the initial 40-mg/kg dose. Dashed lines represent values resulting from subsequent 20-mg/kg doses at 6-h intervals. Six patients received only the initial 40-mg/kg dose.

ple from the intravenous line, or parental or patient objection to further sampling.

For six patients given only the initial 40 mg/kg dose of acetaminophen, serum acetaminophen concentrations were in the target range 38 ± 25% of the time (fig. 1). For 10 patients given more than one dose of acetaminophen, serum acetaminophen concentrations were in the target range 60 ± 29% of the time (fig. 1). Excluding baseline levels drawn before suppository insertion, 48% of the observed concentrations were within the therapeutic range during the study period. After 5 h, 67% of the observed concentrations were within the desired range. One patient given a single dose of 40.2 mg/kg had serum concentrations that never exceeded 5 μg/ml during 3 h of sampling. The highest serum concentration was 38.6 μg/ml, obtained 150 min after the patient received an initial dose of 41.1 mg/kg. One other patient had a serum concentration more than 30 μg/ml (31.9 μg/ml) 4 h after a 41.7-mg/kg dose; peak concentrations were less than 24 μg/ml in the remaining patients. Pharmacokinetic parameters from the earlier study predicted the serum concentrations observed in this study for both the initial dose and all doses (fig. 2).

Discussion

Using single or multiple uncut combinations of a commercially available acetaminophen suppository in a hydrogenated vegetable oil base, an initial dose of 40 mg/kg and subsequent doses of 20 mg/kg at 6-h intervals achieved and maintained acetaminophen serum concentrations of 10–20 μg/ml during more than 50% of the period surveyed. Because the initial absorption of rectal acetaminophen has considerable interpatient variability, early sampling times (first 2 h) would be expected to demonstrate many sample concentrations below the target range. This explains in part the wide percentage variation in time (38 ± 25%) during which patients remained outside the target concentration range with initial dosing. Although serum concentration exceeded 20 μg/ml in five patients, the peak serum concentration observed at any time during the 24-h sampling period was less than 40 μg/ml, and only two patients had peak serum concentrations more than 30 μg/ml. The side effect of greatest concern after acetaminophen ingestion is hepatotoxicity. The relationship between acetaminophen serum levels and hepatotoxicity is best understood after single oral dosing. Concentrations more than 300 μg/ml 4 h after oral ingestion are associated with severe liver damage, whereas toxicity is generally not seen with concentrations less than 120 μg/ml.[7]

The pharmacokinetic parameters from our previous study predicted the serum concentrations in the present study well. Some patients had serum concentrations larger than the predicted values, whereas others had concentrations smaller than predicted. This variability in pharmacokinetics is consistent with that seen in our previous study. During the 24-h study period, the acetaminophen values tended to converge. Although one may expect rectal dosing would produce larger interindividual variability, the later data are surprisingly consistent between individuals.

Our previously published pharmacokinetic parameter for volume of distribution, normalized for bioavailability, was recently questioned as lower than would be expected based on other studies.[8] The finding that the

pharmacokinetic parameters from our previous study predict the serum concentrations in the present study appears to refute this concern. A possible explanation for the difference between our pharmacokinetic parameters and those of Holford *et al.* is that the dissolution and absorption of acetaminophen rectal suppositories can differ between manufacturers because of differences in formulation (acetaminophen slurry and polyethadene glycols in a glycogelatin capsule [Winthrop Sterling Pharmaceuticals, NZ Ltd., New Zealand] *vs.* acetaminophen in a hydrogenated vegetable oil base [Upsher-Smith Laboratories, Minneapolis, MN], distributed by Ascent Pediatrics, Inc.).[1,3] Panadol brand acetaminophen suppositories (SmithKline Beecham Consumer Health Care, Ermington, Australia) were recently shown by Coulthard *et al.*[9] to have a mean relative rectal bioavailability of 78%. The authors of that study caution against "extrapolation of dosing regimens . . . when non-equivalent products are administered." Indeed, depending on suppository formulation, rectal bioavailability of acetaminophen has been shown to vary between 6.5 and 92.2%.[10] This may also lead to differences in both initial and subsequent dosing recommendations. As a result, we limit our dosing recommendations to those institutions in which FeverAll suppositories are used.

We selected a target range of 10–20 μg/ml because that serum concentration is reported to produce antipyresis. However, because acetaminophen is more typically given as an analgesic during the postoperative period rather than as an antipyretic, the target acetaminophen concentration should be that necessary to produce analgesia rather than antipyresis. We did not collect pharmacodynamic data in our study subjects because our focus and study design was on pharmacokinetics. Several recent studies have examined the serum concentrations of acetaminophen associated with analgesia.[2,11] Anderson *et al.*[11] performed a pharmacokinetic and pharmacodynamic study of rectally administered acetaminophen in children undergoing tonsillectomy with or without adenoidectomy. They demonstrated superior analgesia and an opioid-sparing effect in children with a serum concentration more than 10.5 μg/ml and with additional analgesia as serum acetaminophen concentration increased. It thus appears that the target serum concentration for antipyresis will also provide analgesia.

Our dosing recommendations can also be compared with those of Korpela *et al.*,[4] who examined whether rectal acetaminophen (doses of 20–60 mg/kg) demonstrated a morphine-sparing effect in outpatient pediatric surgery. The rectal acetaminophen dose (SmithKline Beecham, Midy, Herouville, France) that decreased morphine consumption 50% was 35 mg/kg. This supports our previous recommendation and current use of an initial dose of approximately 40 mg/kg. Our results in this small patient cohort further suggest that subsequent doses of 20 mg/kg at 6-h intervals are appropriate. A computer simulation supports this 6-h dosing interval, but suggests even higher initial and subsequent dosing. A 50-mg/kg loading dose and 30-mg/kg follow-up doses are postulated, but have not been examined in a clinical study.[12]

The age range in our study population was 3–12 yr. Dosing guidelines based on our study may not apply to preterm infants, full-term neonates, and infants early in the first year of life. Lin *et al.*[13] measured rectal acetaminophen concentrations in preterm infants given 20 mg/kg, but cautioned that further study is required to clarify the relationship between age and clearance.[14]

Differences exist between oral and rectal bioavailability, although data are limited. Rectal doses necessary to achieve the same desired target concentrations are larger than with oral doses.[15] In turn, total daily oral dose recommendations for acetaminophen may not apply to rectal dosing. Our rectal dosing regimen totals 100 mg/kg during the first 24 h, close to the recommended upper limits of oral dosing.[16] The potential for toxicity would appear to be minimal with this formulation, route of delivery, and dose recommendations, although our study is limited by sample size and study time period. We saw no evidence of drug accumulation during the 24-h study period. It is possible that administration of acetaminophen over longer periods or in certain patient subsets could result in higher serum levels.

In summary, an acetaminophen regimen of 40 mg/kg as an initial dose followed by 20 mg/kg every 6 h results in serum concentrations centered at the target range of 10–20 μg/ml. Some patients have larger serum concentrations, others smaller, a result of interindividual variability in pharmacokinetic characteristics. Unless pharmacokinetic studies can identify those characteristics that yield larger or smaller concentrations, any standardized dosing regimen will result in some individuals having concentrations exceeding target and others at less than the target. The results obtained could also be specific to this manufacturer, suppository composition, or both.

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