Anesthesiology
1997; 87:244-52

Twenty-four–Hour Pharmacokinetics of Rectal Acetaminophen in Children

An Old Drug with New Recommendations

Patrick K. Birmingham, M.D., Michael J. Tobin, M.D.,* Thomas K. Henthorn, M.D.,† Dennis M. Fisher, M.D.,‡ Maura C. Berkelhamer, M.D.,§ Frederick A. Smith, M.D.,‖ Kaaren B. Fanta, R.N.,# Charles J. Coté, M.D.***

***Background*: Rectal acetaminophen is often administered during operation to provide supplemental analgesia or antipyresis in children. Recent studies examining current dose guidelines are limited by short sampling times. The authors extended the drug sampling period to more clearly define acetaminophen pharmacokinetics in children having surgery.**

***Methods*: Children (n = 28) were randomized to receive a single dose of 10, 20, or 30 mg/kg rectal acetaminophen after induction of anesthesia. Venous blood samples were taken every 30 min for 4 h, every 60 min for 4 h, and every 4 h for 16 h. Data were analyzed using a mixed-effects modeling technique (using NONMEM software) to determine the volume of distribution and clearance normalized for bioavailability. Additional models accounted for suppository dissolution followed by acetaminophen absorption.**

***Results*: Age, weight, estimated blood loss, volume of intravenous fluid administered, and anesthesia time were similar in the three groups. Most patients did not achieve peak or sustained serum values in the 10–20 μg/ml serum concentration range associated with antipyresis. The volume of distribution was 385 ml/kg, and clearance normalized for bioavailability, F, was 5.46 $ml \cdot kg^{-1} \cdot min^{-1}$. Pharmacokinetic models suggest that absorption of acetaminophen is a function of zero-order dissolution of suppositories and first-order absorption from the rectum. Suppository dose size also may affect absorption characteristics.**

***Conclusions*: The current recommended rectal acetaminophen dose of 10–15 mg/kg yields peak serum concentrations less than the antipyretic serum concentration of 10–20 μg/ml. Based on the observed kinetics, the authors recommend that the initial dose should be approximately 40 mg/kg. (Key words: Analgesics: acetaminophen. Anesthesia: pediatric. Pharmacokinetics: modeling. Pharmacology: acetaminophen; rectal.)**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

* Assistant Professor of Anesthesiology, Northwestern University Medical School at Children's Memorial Hospital.

† Associate Professor of Anesthesiology, Northwestern University Medical School.

‡ Professor of Anesthesia and Pediatrics, University of California San Francisco.

§ Assistant Professor of Anesthesia, Washington University School of Medicine at St. Louis Children's Hospital.

‖ Assistant Professor of Pathology, Northwestern University Medical School at Children's Memorial Hospital.

Research Nurse, Northwestern University Medical School at Children's Memorial Hospital.

** Professor of Anesthesiology and Pediatrics, Northwestern University Medical School at Children's Memorial Hospital.

Received from Children's Memorial Hospital, Chicago, Illinois. Submitted for publication June 25, 1996. Accepted for publication April 11, 1997. Presented in part at the annual meeting of the American Society of Anesthesiologists, Atlanta, Georgia, October 21-25, 1995.

Address reprint requests to Dr. Birmingham: Attending Anesthesiologist, Department of Anesthesia, #19, Children's Memorial Hospital, 2300 Children's Plaza, Chicago, Illinois 60614.

ACETAMINOPHEN is commonly used in children because of its analgesic and antipyretic effects and because of its safety. It is often administered rectally perioperatively to provide analgesia or antipyresis to infants and children for whom the oral route is not an option. Although an intravenous prodrug form of acetaminophen exists,[1] it is not available in the United States.

The currently recommended dose for oral and rectal administration of acetaminophen ranges from 10-15 mg/kg.[2-7] Several recent studies have examined this dose recommendation for rectal administration[8-10]; larger doses were required to achieve a serum concentration of 10-20 μg/ml (66-132 mM), a concentration known to be antipyretic.[11] The serum concentration required for analgesia has not been defined in children.

Absorption of acetaminophen suppositories may be irregular and prolonged. Recent studies have been limited in part by relatively short sampling times — as little as 40 min in one study.[10] Our study examined single-dose absorption over an extended sampling time of 24

h to more clearly define pharmacokinetics, and thus to develop better prescribing information.

Materials and Methods

With hospital Institutional Review Board approval and parental informed consent, we randomized patients into one of three groups to receive a single dose of approximately 10, 20, or 30 mg/kg rectal acetaminophen after induction of anesthesia. Feverall suppositories (Upsher-Smith Laboratories, Minneapolis, MN) were used. These are manufactured by suspending acetaminophen in a hydrogenated vegetable oil base, which then solidifies after being poured into a bullet-shaped mold. Combinations of the four commercially available doses (80, 120, 325, and 650 mg) were used to deliver an amount of drug as close as possible to the dose desired. Individual suppositories were not cut to approximate the desired dosage, because the acetaminophen may not be evenly distributed throughout the suppository.††

We included children who were aged 2–12 yr and who were having elective orthopedic surgery requiring postoperative hospital admission, classified as American Society of Anesthesiologists physical status 1–3, weighed more than 12 kg, and had a preoperative hematocrit concentration greater than 30%. Children were excluded if they had received acetaminophen within 24 h of the study period; had significant hepatic, renal, or cardiac disease; rectal dysfunction that might impair their ability to retain the suppository; a preexisting coagulopathy; or if blood loss was anticipated to be large. Children underwent intravenous or inhalation induction of anesthesia. Halothane or isoflurane was used to maintain anesthesia. Continuous epidural analgesia was not used because of uncertainty about its possible effect on rectal blood flow and drug uptake and metabolism. Intravenous opioids were used for supplementary analgesia in the perioperative period.

Combinations of one, two, or three suppositories were used to achieve the target dose for each patient. After obtaining a baseline blood sample, an unlubricated suppository(s) was inserted several centimeters into the rectum. Peripheral venous blood samples were obtained at 30, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 720, 960, 1,200, and 1,440 min. Serum was separated from blood cells and refrigerated at 4°C until drug concentrations were measured using fluorescence polarization immunoassay (TDx System; Abbott Laboratories, North Chicago, IL). The TDx System was operated according to the manufacturer's published procedures. 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 patient samples. The coefficients of variation were 6.4% and 4%, and analytical biases were 3.5% and 3.7%, respectively, during the study.

For each patient, we determined maximal plasma concentration (C_{max}) and time to maximal plasma concentration (T_{max}).

Pharmacokinetic Analysis

We initially assumed that the pharmacokinetics of acetaminophen could be described by a one- or two-compartment model with first-order absorption from the rectal depot and first-order elimination from the central compartment. These pharmacokinetic models were fit to the serum concentration *versus* time data using a population approach (mixed-effects modeling) that estimates a "typical" value for the population for each pharmacokinetic parameter and the extent of variability between patients. Analyses were performed with NONMEM.‡‡. In addition, we used NONMEM's *post hoc* step to estimate pharmacokinetic parameters for each patient.

Because all doses were administered into the depot (*i.e.*, there was no control group given acetaminophen intravenously), we could not estimate a typical value for bioavailability (F). In this context, parameters of the one-compartment model were volume of distribution divided by F (V/F), clearance divided by F (Cl/F), and the absorption rate constant (*k*a). The two-compartment model had two additional parameters, volume of distribution of the peripheral compartment divided by F (V_2/F) and clearance from the central to peripheral compartments divided by F ($Cl_{distribution}$/F). Interindividual variability was permitted for each of the pharmacokinetic parameters, including F. We assumed that this interindividual variability was log-normally distributed.

The quality of fit of the pharmacokinetic model to the data was judged by NONMEM's objective function (similar to the residual sum of squares in nonlinear regression) and by visual examination of plots of observed *versus* predicted concentrations. We also plotted the

†† Personal communication: Lori M. Freese, R.Ph., Professional Services Coordinator, Upsher-Smith Laboratories, Minneapolis, Minnesota.

‡‡ NONMEM Version V, Level 1.0L4, University of California, San Francisco, 1995.

post hoc estimates of the pharmacokinetic parameters against age, weight, dose of acetaminophen, and number of suppositories administered.

Because of systematic differences between dose groups in *post hoc* estimates in the pharmacokinetic parameters (see Results), we examined the effect of suppository size on absorption. For each patient, the dose administered as 80- or 120-mg suppositories was determined and compared with the total dose for that patient. These ratios were plotted against individual values for bioavailability (Fi/F where Fi is the value for bioavailability for the *ith* individual and F is the "typical" value for bioavailability that could not be determined in this analysis) determined during the *post hoc* step and analyzed by linear regression.

This analysis suggested that absorption characteristics of the smaller-dose suppositories differed from those of the larger-dose suppositories. In addition, the poor fit of the pharmacokinetic model to the serum concentration data led us to consider a more complicated absorption model in which there was zero-order dissolution of suppositories and first-order absorption of the dissolved material. Lacking specific information about the rate at which the suppositories dissolved†† (and assuming this varied as a function of such factors as patient temperature and the contents of the rectal vault), we permitted NONMEM to estimate the rate at which or duration over which each suppository dissolved.

Results

Twenty-eight children were enrolled in the study. We were able to administer drug amounts close to the calculated study dose using commercially available suppository doses alone or in combination (table 1). There were no statistically significant differences among the three groups with respect to age, weight, sex, intravenous fluid volume administered, estimated blood loss, and duration of anesthesia.

Three hundred sixty-five of the planned 476 blood samples were obtained (fig. 1). Eighty-one serum samples had concentrations less than 1 μg/ml (the level of quantification of the assay) and thus were excluded from the analysis. The remaining 284 data points were used for pharmacokinetic analysis. Sixty-three usable data points were collected at times more than 300 min after dosing. Complete sampling from all children was not possible because of factors such as parental/patient objection to further sampling, vasoconstriction, loss of intravenous access, or early hospital discharge.

Table 1. Study Population Demographics

	Target Dose		
	10 mg/kg	20 mg/kg	30 mg/kg
N	9	9	10
Dose (mg/kg)	9.9 ± 0.9 (8.4–11.1)	19.8 ± 1.5 (17.1–22.4)	30.7 ± 1.3 (28.9–32.5)
Age (yr)	7.5 ± 2.4 (4.7–12.6)	9.3 ± 3.9 (3.4–13)	9.2 ± 3.1 (4.1–12.4)
Weight (kg)	27.5 ± 14.4 (14.5–60)	37.3 ± 21.8 (12–71)	31.8 ± 14.6 (15–48.5)
Gender	6M/3F	4M/5F	6M/4F
IV fluids (ml/kg)	18.8 ± 6.5 (9.7–30.8)	24.1 ± 17.6 (4.7–58.3)	16.7 ± 3.9 (9.3–21)
EBL (% EBV)	1.1 ± 1.1 (0–3.6)	4.1 ± 5.5 (0.1–14.3)	1.3 ± 1.1 (0.2–3.3)
Anesthesia time (min)	147 ± 60 (30–230)	166 ± 89 (60–332)	164 ± 50 (95–245)

Values are mean ± SD (range).

EBL = estimated blood loss; EBV = estimated blood volume (70 ml/kg). Other than dose administered, the differences between groups did not achieve statistical significance in any category.

The time to C_{max} and the range of C_{max} varied widely (table 2). Dose-normalized serum concentrations peaked earlier and at a larger value and decreased more rapidly for the group given the 10 mg/kg dose compared with the two larger-dose groups (fig. 2).

We examined a series of pharmacokinetic models (table 3). The one-compartment model with first-order absorption (model 1, table 3) failed to fit the data well, with marked dose-related differences between the predicted and observed concentrations (fig. 3). The two-compartment model (model 2, table 3) demonstrated the same dose-related bias and was not associated with an improved fit. (The objective function improved less than 0.1 units [$P > 0.05$ by the likelihood ratio test], and plots of observed *vs.* predicted concentrations showed the same systematic bias as with the one- compartment model.) Plots of *post hoc* pharmacokinetic parameters *versus* age and weight failed to reveal a relation (data not shown). The percentage of the total dose administered as 80- and 120-mg suppositories correlated with *post hoc* values for *k*a ($P = 0.05$). In addition, *post hoc* estimates of *k*a varied with dose. There was no relation between the percentage of the total dose administered as 80- and 120-mg suppositories and *post hoc* values for bioavailability (Fi/F).

Because of the apparent relation between the smaller-dose compared with the larger-dose suppositories and *k*a, and because of the poor fit of the model to the data,

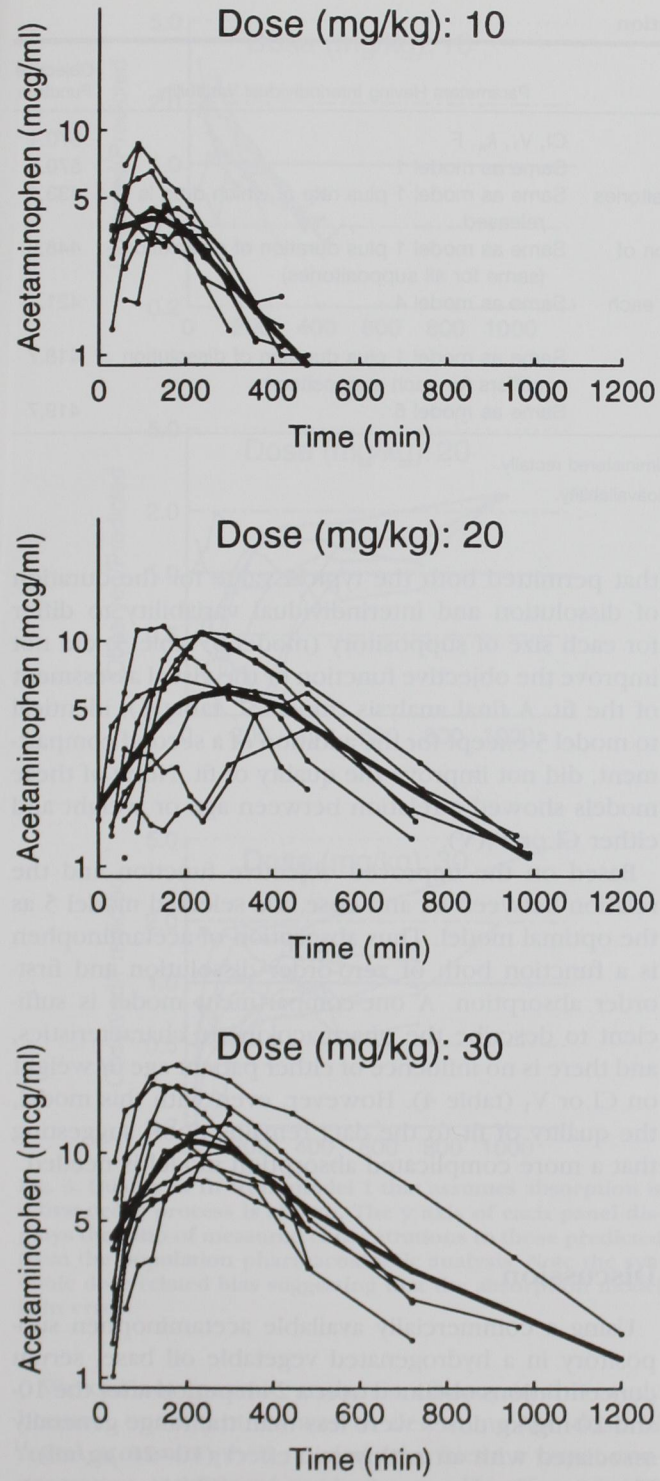

Fig. 1. Values for serum concentration of acetaminophen (circles, thin lines) are plotted against time for each patient. Thick lines indicate "average" values determined using a smoother (lowess) on the logarithms of the serum concentration values; this yields the central tendency when the time data are spaced unevenly.

Table 2. Maximal Concentration (C_{max}) and Time to Maximal Concentration (T_{max}) for Three Target Doses*

Target Dose (mg/kg)	C_{max} (μg/ml)	T_{max} (min)
10	5.5 ± 1.9 (3.5–8.7)	107 ± 52 (30–210)
20	8.8 ± 3.4 (4.1–13.6)	288 ± 126 (150–480)
30	14.2 ± 5.1 (7.5–22.7)	210 ± 71 (120–300)

Values are mean ± SD (range in parentheses).

*For each subject, C_{max} was adjusted for the target dose, *i.e.*, if a subject received 18 mg/kg instead of the target dose of 20 mg/kg, the peak concentration was multiplied by 20/18.

we evaluated a more complicated absorption model that permitted both zero-order dissolution of suppositories and first-order absorption from the rectum. First we assumed that the typical rate (expressed as milligrams per minute) at which each suppository released drug was similar (but variability was permitted among patients in the rate at which the drug was released). This resulted in a marked improvement in the objective function (model 3, table 3; 137 points, $P < 0.0001$ for two additional parameters in the model). However, plots of parameters determined in NONMEM's *post hoc* step *versus* covariates continued to suggest a relation between *k*a and weight-normalized dose (fig. 4).

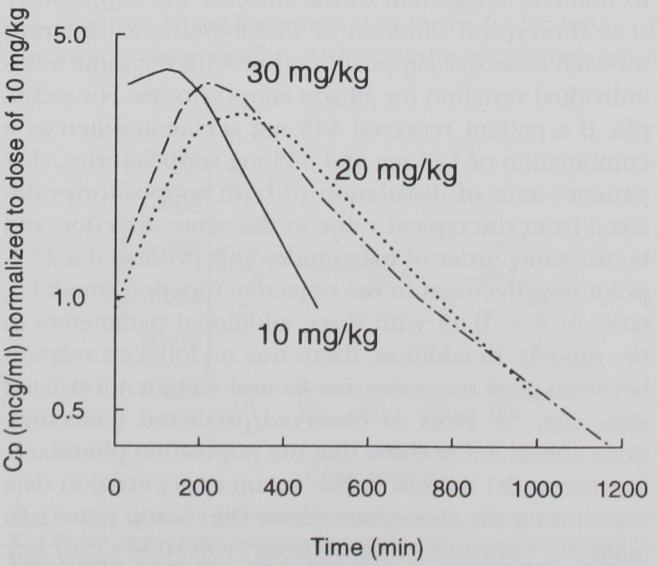

Fig. 2. "Average" serum concentration of acetaminophen for each dose group, normalized to a dose of 10 mg/kg, are plotted against time. Average values are determined using a smoother (lowess) on the logarithms of the serum concentration values; this yields the central tendency when the time data are spaced unevenly.

Table 3. Pharmacokinetic Models Tested and Their Objective Function

Model No.	Structural Model	Parameters Having Interindividual Variability	Objective Function
1	1 compartment, first-order absorption	Cl, V_1, k_a, F	570.1
2	2 compartments, first-order absorption	Same as model 1	570.1
3	Model 1 plus zero-order dissolution of suppositories, all suppositories release acetaminophen at same typical rate	Same as model 1 plus rate at which drug is released	433.1
4	Model 3 except that all suppositories have same typical duration of dissolution	Same as model 1 plus duration of dissolution (same for all suppositories)	448.8
5*	Same as model 4 except that duration of dissolution differs for each size suppository	Same as model 4	421.1
6	Same as model 5	Same as model 1 plus duration of dissolution (differs for each suppository)	418.7
7	Model 5 with two compartments	Same as model 5	419.7

*This is the optimal model to describe the pharmacokinetics of acetaminophen administered rectally.

Cl = clearance; V_1 = volume of distribution; k_a = absorption rate constant; F = bioavailability.

Another analysis was performed in which we permitted the typical value for duration of dissolution to be the same for all suppositories but permitted differences among individuals (model 4, table 3). Compared with the model with first-order absorption only, this model yielded a marked improvement in the objective function (123.1 points, $P < 0.0001$). In addition, this model yielded an improvement in the visual relation between *post hoc* values for *k*a and weight-normalized dose. Model 5 (table 3) permitted the duration of dissolution to differ as a function of the dose of the suppository (*i.e.*, the typical duration of dissolution was different for each dose size suppository) but with the same interindividual variation for all size suppositories. For example, if a patient received 445 mg acetaminophen as a combination of 120 mg and 325 mg suppositories, that patient's rate of dissolution of both suppositories differed from the typical value in the same direction and by the same order of magnitude. This produced a 27.7-point improvement in the objective function (model 5, table 3; $P < 0.05$ with three additional parameters in the model). In addition, there was no longer a relation between *post hoc* value for *k*a and weight-normalized dose (fig. 5). Plots of observed/predicted concentrations continued to show that the population pharmacokinetic model did not fit the serum concentration data well during the absorption phase (fig. 6, top panel). In addition, estimates obtained from NONMEM's *post hoc* step fit the model well (fig. 6, bottom panel) and there was no systematic relation between the *post hoc* pharmacokinetic parameters and the covariates. This suggested that more complicated pharmacokinetic models would not improve the quality of the fit. An analysis that permitted both the typical value for the duration of dissolution and interindividual variability to differ for each size of suppository (model 6, table 3) did not improve the objective function or the visual assessment of the fit. A final analysis (model 7, table 3), identical to model 5 except for the addition of a second compartment, did not improve the quality of fit. None of these models showed a relation between age or weight and either Cl or V_1(V).

Based on the improved objective function and the relation between *k*a and dose, we selected model 5 as the optimal model. Thus absorption of acetaminophen is a function both of zero-order dissolution and first-order absorption. A one-compartment model is sufficient to describe the pharmacokinetic characteristics, and there is no influence of either patient age or weight on Cl or V_1 (table 4). However, even with this model, the quality of fit to the data remains poor, suggesting that a more complicated absorption model is needed.

Discussion

Using a commercially available acetaminophen suppository in a hydrogenated vegetable oil base, serum concentrations obtained over a 24-h period after the 10- and 20-mg/kg doses were less than the range generally associated with an antipyretic effect (10–20 μg/ml).[11] The 30-mg/kg dose resulted in a mean maximum serum concentration (14.2 μg/ml) in the lower portion of the desired range. The maximum concentration obtained for any patient was 24.6 μg/ml (dose normalized = 22.7 μg/ml) in those receiving 30 mg/kg.

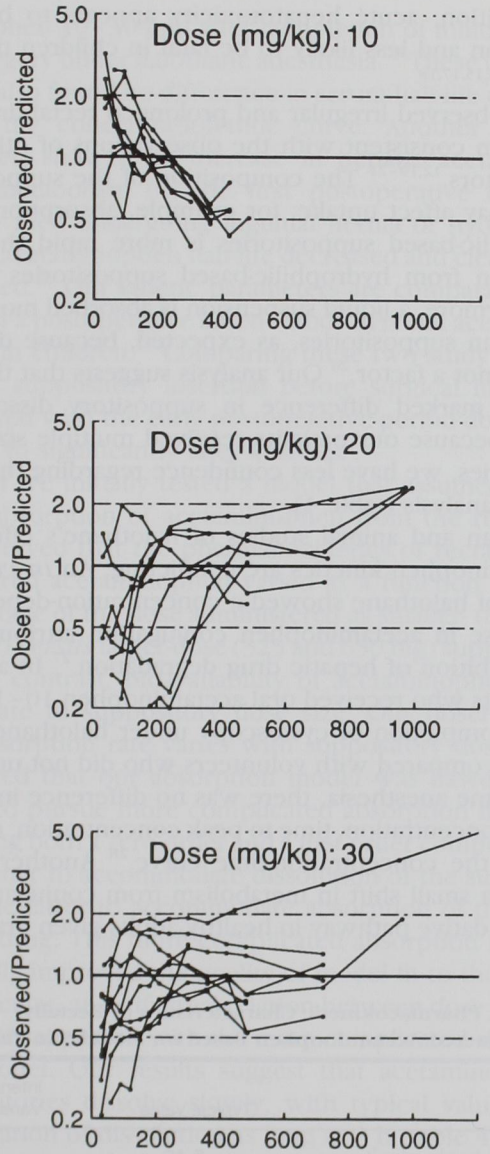

Fig. 3. Quality of fit from model 1 that assumes absorption is a first-order process is shown. The y axis of each panel displays the ratio of measured concentrations to those predicted from the population pharmacokinetic analysis. Note the systemic dose-related bias suggesting that the absorption model is in error.

We did not measure analgesic efficacy in this study because our intention was to determine the dose of rectal acetaminophen needed to achieve a target concentration. Additional studies controlling for surgical procedure and use of supplemental analgesics and local anesthetics are needed to correlate analgesia with the serum concentrations achieved after a given dose. Two studies have examined the analgesic effect of rectal acetaminophen perioperatively in children.[10,12] A 20-mg/kg liquid suspension of rectal acetaminophen was equianalgesic to 1 mg/kg intramuscular meperidine in children undergoing tonsillectomy with or without adenoidectomy.[10] In another study of children having the same procedure, a suppository dose of 35 mg/kg was equianalgesic to 1 mg/kg ketorolac.[12] The absence of a placebo group in either study limited the ability to quantitate analgesia. If acetaminophen's analgesic effect is associated with the antipyretic effect, then the mean C_{max} for our 30-mg/kg group was in the lower range of the target concentration. Although the mean peak value

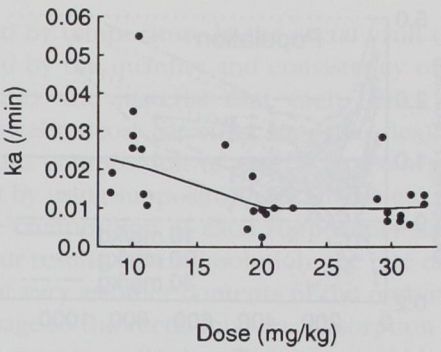

Fig. 4. The relation between *k*a and dose is shown for model 3. Circles represent values for each patient determined in NONMEM's *post hoc* step; the line is determined using a smoother (lowess). The apparent relation between *k*a and dose suggests that the pharmacokinetic model and, in particular, the absorption model, is flawed.

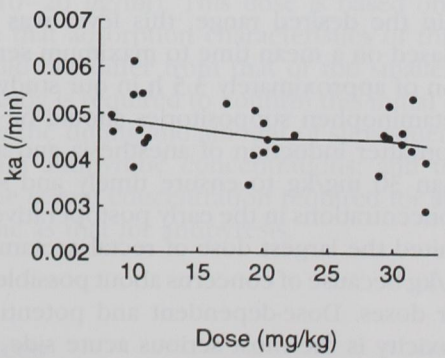

Fig. 5. The relation between *k*a and dose is shown for model 5. Circles represent values for each patient determined in NONMEM's *post hoc* step; the line is determined using a smoother (lowess). The lack of relationship between *k*a and dose suggests that the pharmacokinetic model (model 5) that permits both zero-order dissolution of suppositories and first-order absorption from the rectum is better than the model that does not permit zero-order dissolution of suppositories (model 3).

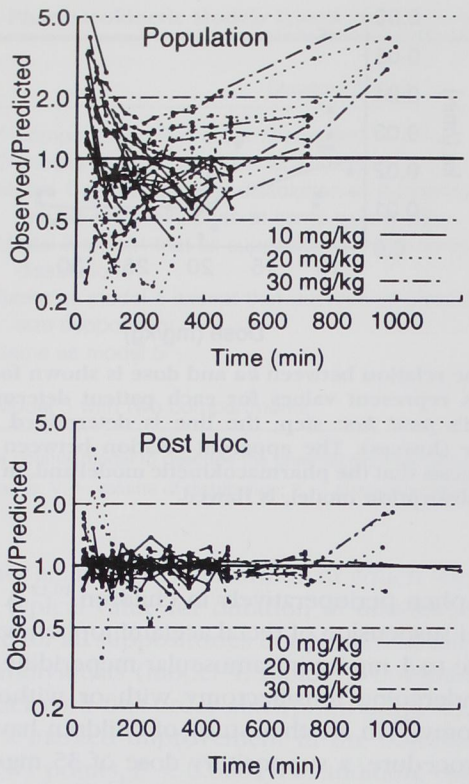

Fig. 6. Quality of fit from a model that assumes that dissolution of suppositories is a zero-order process and that absorption is a first-order process is shown. The y axis of each panel displays the ratio of measured concentrations to those predicted from the pharmacokinetic analysis. The upper panel displays values from the population analysis. The lower panel displays values from the *post hoc* analysis.

fell within the desired range, this level was not sustained. Based on a mean time to maximum serum concentration of approximately 3.5 h in our study population, acetaminophen suppositories should be administered soon after induction of anesthesia and at a dose larger than 30 mg/kg to ensure timely and sustained serum concentrations in the early postoperative period.

We limited the largest dose of rectal acetaminophen to 30 mg/kg because of concerns about possible toxicity at higher doses. Dose-dependent and potentially fatal hepatotoxicity is the most serious acute side effect of acetaminophen administration.[2,3,13-16] Serum half-life and serum concentration (area under the curve) contribute to toxicity. Toxicity after single-dose administration is generally not observed with concentrations less than 120 μg/ml 4 h after ingestion[16]; the highest dose normalized peak concentration obtained in our patients (22.7 μg/ml) was only 20% of the toxic concentration. In addition, acute hepatotoxicity appears to be less common and less likely to be fatal in children than in adults.[3,15,17,18]

We observed irregular and prolonged rectal drug absorption consistent with the observations of other investigators.[12,19-21] The composition of the suppository base may affect uptake; for example, absorption from lipophilic-based suppositories is more rapid than absorption from hydrophilic-based suppositories.[2,6,22-25] Furthermore, a liquid suspension is absorbed more rapidly than suppositories, as expected, because dissolution is not a factor.[26] Our analysis suggests that there is also a marked difference in suppository dissolution time; because our patients received multiple size suppositories, we have less confidence regarding this part of the analysis (table 4).

Human and animal studies of halothane's effect on acetaminophen kinetics are conflicting. An *in vivo* rat study of halothane showed a concentration-dependent decrease in acetaminophen conjugation attributed to an inhibition of hepatic drug degradation.[27] In a study of adults who received oral acetaminophen 10-15 min after completion of cystoscopy under halothane anesthesia compared with volunteers who did not undergo halothane anesthesia, there was no difference in mean peak concentration, time to peak concentration, or area under the concentration-time curve.[28] Another study found a small shift in metabolism from conjugation to the oxidative pathway in healthy adults given oral acet-

Table 4. Pharmacokinetic Characteristics of Rectally Administered Acetaminophen Based on Model 5 in Table 1

	Typical Value	Interindividual Variability (%)
Cl/F (ml · kg^{-1} · min^{-1})	5.46	24.7
V_1/F (ml/kg)	385	79.7
F (%)	Not estimated†	23.9
k_a/min	0.00468	17.8
Suppository dissolution time		
80 mg	40.3	104‡
120 mg	6.16	104‡
325 mg	187	104‡
650 mg	126	104‡

*Computed as $100\% \cdot \sqrt{\omega^2}$ where ω^2 = variance (η); 68% of the population lies within this range of the typical value.

†In the absence of data in this study population for intravenous administration, F cannot be estimated; however, its interindividual variability can be estimated.

‡Interindividual variability in the duration of dissolution of suppositories was assumed to be the same for all size suppositories.

aminophen 10–30 min after completion of minor elective surgery under halothane anesthesia.[29] These investigators also found no difference in serum half-life or area under the concentration-time curve. Another study, however, showed an increase in hepatic acetaminophen metabolism on the first postoperative day in healthy men undergoing inguinal hernia or hydrocele repair; acetaminophen half-life decreased and clearance increased.[30] Our kinetic parameters are comparable to those of a postoperative kinetic study of rectal acetaminophen in children.[19] Comparing these two study populations, suppository insertion before surgical incision compared with the early postoperative period does not appear to significantly alter kinetics.

When we initially tested a model that assumed first-order absorption of acetaminophen from the rectum, we observed that the pharmacokinetics of rectally administered acetaminophen varied as a function of the percentage of the dose administered as smaller- (80 and 120 mg) *versus* larger-dose (325 and 650 mg) suppositories. In contrast, bioavailability of acetaminophen did not relate to suppository dose size. Our observation that absorption rate varies with suppository dose size suggested that our absorption model was flawed and led us to pursue more complicated absorption models involving both a zero-order and a first-order component; the former to accommodate dissolution of the suppository, the latter to accommodate absorption of the dissolved drug. This more complicated absorption model markedly improved the quality of model fit to the data; in particular, an artifactual relation between dose group and k_a disappeared with the more complicated absorption model. Our results suggest that acetaminophen suppositories dissolve slowly, with typical values for the duration of dissolution as long as 3 h (table 4). Our results also suggest that the rate at which suppositories dissolve may be a function of suppository dose size; *i.e.*, smaller-dose suppositories dissolve more rapidly. However, the absence of an effect of suppository dose size on bioavailability suggests that once suppositories have dissolved, the same percentage of each suppository is available for absorption, regardless of suppository dose size.

By modeling absorption as having two components, a zero-order process to explain dissolution of the suppositories and a first-order process to explain absorption from the rectum, we markedly improved the quality of the data fit. Several complex and related factors, however, probably influence the rate of dissolution and absorption from the rectum. Rate of dissolution may be influenced by temperature in the rectal vault (possibly influenced by the quantity and consistency of stool in the rectum); the material that each tablet contacts (stool, bowel mucosa, or other suppositories); and the volume and composition of each suppository. We assume that by using suppositories from a single manufacturer, the composition of each suppository did not influence our results. After dissolution, the rate of absorption might vary as other contents of the rectum inhibit drug passage to the rectal mucosa. Absorption through the rectal mucosa might vary with intestinal blood flow. Even analysis with our "optimal" model (model 5, table 3) suggests that a more complicated absorption model may be needed to adequately describe the uptake of rectally administered acetaminophen.

In summary, we observed dose-related differences in the pharmacokinetic characteristics of rectally administered acetaminophen. A correlation between the percentage of dose administered with small-dose suppositories (80 and 120 mg) suggested that dose-related differences in k_a resulted from differences in the absorption characteristics of suppositories of different dose sizes, leading us to use a more complicated absorption model. Additional studies comparing dosing with multiple 80-mg-dose suppositories *versus* single 650-mg-dose suppositories might provide additional insights into factors influencing differences in dissolution and absorption.

Our pharmacokinetics suggest that an initial dose of 40 mg/kg is more likely to consistently achieve and sustain acetaminophen concentrations producing antipyresis (10–20 μg/ml). This dose is based on the assumption that absorption characteristics of this larger dose would not differ from that of the smaller doses. Further study is required to confirm this initial dose; to determine the timing and amount of subsequent doses to maintain antipyretic concentrations; and to determine if the serum concentration required for analgesia is the same as that for antipyresis.

References

1. Autret E, Dutertre JP, Breteau M, Jonville AP, Furet Y, Laugier J: Pharmacokinetics of paracetamol in the neonate and infant after administration of propacetamol chlorhydrate. Dev Pharmacol Ther 1993; 20:129–34

2. United States Pharmacopeial Dispensing Information: Drug Information for the Health Care Professional. Taunton, MA, Rand McNally, 1996, pp 3–10

3. Drug Information American Hospital Formulary Service:

Bethesda, MD, American Society of Health-System Pharmacists, 1995, pp 1410–16

4. Physician's Desk Reference. Montvale, NJ, Medical Economics Data Production Company, 1996, pp 1555–8

5. Temple AR: Pediatric dosing of acetaminophen. Pediatr Pharmacol 1983; 3:321–7

6. Keinänen S, Hietula M, Similä S, Kouvalainen K: Antipyretic therapy. Comparison of rectal and oral paracetamol. Eur J Clin Pharmacol 1977; 12:77–80

7. The Harriet Lane Handbook. Edited by Barone MA. St. Louis, MO, Mosby-Year Book, 1996, p 475

8. Houck CS, Sullivan LJ, Wilder RT, Rusy LM, Burrows FA: Pharmacokinetics of a higher dose of rectal acetaminophen in children. ANESTHESIOLOGY 1995; 83:A1126

9. Montgomery CJ, McCormack JP, Reichert CC, Marsland CP: Plasma concentrations after high-dose (45 mg.kg-1) rectal acetaminophen in children. Can J Anaesth 1995; 42:982–6

10. Rusy LM, Houck CS, Sullivan LJ, Ohlms LA, Jones DT, McGill TJ, Berde CB: A double-blind evaluation of ketorolac tromethamine versus acetaminophen in pediatric tonsillectomy: analgesia and bleeding. Anesth Analg 1995; 80:226–9

11. Rumack BH: Aspirin versus acetaminophen: a comparative view. Pediatrics 1978; 62:943–6

12. Gaudreault P, Guay J, Nicol O, Dupuis C: Pharmacokinetics and clinical efficacy of intrarectal solution of acetaminophen. Can J Anaesth 1988; 35:149–52

13. Rivera-Penera T, Gugig R, Davis J, McDiarmid S, Vargas J, Rosenthal P, Berquist W, Heyman MB, Ament M: Outcome of acetaminophen overdose in pediatric patients and factors contributing to hepatotoxicity. J Pediatr 1997; 130:300–4

14. Heubi JE, Bien JP: Acetaminophen use in children: more is not better. J Pediatr 1997; 130:175–7

15. Penna A, Buchanan N: Paracetamol poisoning in children and hepatotoxicity. Br J Clin Pharmacol 1991; 32:143–9

16. Rumack BH, Matthew H: Acetaminophen poisoning and toxicity. Pediatrics 1975; 55:871–6

17. Peterson RG, Rumack BH: Age as a variable in acetaminophen overdose. Arch Intern Med 1981; 141:390–3

18. Rumack BH: Acetaminophen overdose in young children. Treatment and effects of alcohol and other additional ingestants in 417 cases. Am J Dis Child 1984; 138:428–33

19. Anderson BJ, Woolard GA, Holford NHG: Pharmacokinetics of rectal paracetamol after major surgery in children. Paediatr Anaesth 1995; 5:237–42

20. Hopkins CS, Underhill S, Booker PD: Pharmacokinetics of paracetamol after cardiac surgery. Arch Dis Child 1990; 65:971–6

21. Mitchell IM, Jamieson MPG, Pollock JCS, Logan RW: Paracetamol suppositories after cardiac surgery. Arch Dis Child 1991; 66:1004

22. Kahela P, Laine E, Anttila M: A comparison of the bioavailability of paracetamol from a fatty and a hydrous suppository base and the effect of storage on the absorption in man. Drug Dev Indust Pharm 1987; 13:213–24

23. Cullen S, Kenny D, Ward OC, Sabra K: Paracetamol suppositories: a comparative study. Arch Dis Child 1989; 64:1504–5

24. van Hoogdalem EJ, de Boer AG, Breimer DD: Pharmacokinetics of rectal drug administration, Part I. General considerations and clinical applications of centrally acting drugs. Clin Pharmacokinet 1991; 21:11–26

25. Feldman S: Bioavailability of acetaminophen suppositories. Am J Hosp Pharm 1975; 32:1173–5

26. Moolenaar F, Olthof L, Huizinga T: Biopharmaceutics of rectal administration of drugs in man: 3. Absorption rate and bioavailability of paracetamol from rectal aqueous suspensions. Pharm Weeklab Scient Ed 1979; 1:25–30

27. Aune H, Bessesen A, Olsen H, Mørland J: Acute effects of halothane and enflurane on drug metabolism and protein synthesis in isolated rat hepatocytes. Acta Pharmacol et Toxicol (Copenh) 1983; 53:363–8

28. Reilly CS, Nimmo WS: Drug absorption after general anaesthesia for minor surgery. Anaesthesia 1984; 39:859–61

29. Lewis RP, Dunphy JA, Reilly CS: Paracetamol metabolism after general anaesthesia. Eur J Anaesthesiol 1991; 8:445–50

30. Ray K, Adithan C, Bapna JS, Kamatchi GL, Mehta RB: Effect of halothane anaesthesia on salivary elimination of paracetamol. Eur J Clin Pharmacol 1986; 30:371–3