The Pharmacokinetics and Analgesic Efficacy of Larger Dose Rectal Acetaminophen (40 mg/kg) in Adults: A Double-Blinded, Randomized Study

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Analgesic acetaminophen plasma concentrations are not known. We investigated in a randomized, double-blinded study the pharmacokinetics and analgesic efficacy of small- (AS; 20 mg · kg^{-1}) and larger- (AL; 40 mg/kg) dose rectal acetaminophen and compared it with the combination (C) of rectal diclofenac (100 mg) and acetaminophen (20 mg/kg) in 65 women undergoing hysterectomy. Suppositories were administered after the induction of a standardized general anesthesia. Pain (measured by using a 10-cm visual analog scale) and morphine consumption (patient-controlled analgesia) were repeatedly assessed for 24 h. Acetaminophen plasma concentrations were measured by using a fluorescence polarization immunoassay. Antipyretic plasma concentrations (10–20 mg/L) after 40 mg/kg acetaminophen were not associated with improved analgesia or decreased opioid requirements; 20 mg/kg acetaminophen produced subtherapeutic plasma levels (<10 mg/L). Maximal plasma concentrations of 17.2 and 10.4 mg/L ($P < 0.01$, analysis of variance) were achieved after 4.2 and 3.6 h for the AL and AS groups, respectively. The only difference in clinical outcome was lower visual analog scale scores after acetaminophen/diclofenac (C: 2.0 versus AS: 3.2 and AL: 3.4) 4 h after the induction ($P < 0.05$, analysis of variance). Acetaminophen pharmacokinetics in adults were similar to those observed in children. Analgesic plasma concentrations are likely to be higher than antipyretic plasma levels, which were only attained after twice the recommended rectal dose was administered. Analgesic plasma concentrations have yet to be determined but may be higher than those associated with antipyresis. **Implications:** Acetaminophen pharmacokinetics were comparable in adults and children. Plasma concentrations known to reduce fever did not produce better pain relief and were only achieved after twice the conventional dose was administered. Analgesic plasma concentrations have yet to be determined but may be higher than those associated with antipyresis.

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Coadministration of acetaminophen and nonsteroidal antiinflammatory drugs has been advocated for decreasing postoperative opioid requirements and opioid-related side effects. Analgesic acetaminophen plasma concentrations have not been defined. Dosing recommendations are based on the assumption that antipyretic and analgesic effects occur at a similar range of plasma concentrations. Several authors (1–3) have investigated various acetaminophen dosing regimens, but did not attempt or were unable to establish a relationship between plasma concentrations and analgesia.

The recommended dose of rectal acetaminophen (15–20 mg/kg) may not be sufficient to attain analgesic plasma levels. In children, more than twice this dose (45 mg/kg) was required to achieve antipyretic plasma concentrations (2); a dose of 20 mg/kg produced subtherapeutic plasma concentrations (1). The combination of rectal diclofenac and small-dose acetaminophen (20 mg/kg) resulted in the largest reduction in postoperative opioid consumption in adults, compared with the same dose of either drug alone (3). However, the decreased opioid consumption in this group may merely reflect an additive analgesic effect

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because "twice" the amount of nonopioid analgesics had been administered. In children, 40 mg/kg of rectal acetaminophen produced antipyretic plasma concentrations and satisfactory postoperative analgesia (4). We hypothesized that the same rectal dose of 40 mg/kg acetaminophen, given to adults, may have analgesic effects comparable to those observed after addition of diclofenac to small-dose acetaminophen.

We therefore investigated the pharmacokinetics of small- and larger-dose rectal acetaminophen in women scheduled for gynecological surgery and compared their analgesic efficacy with that of diclofenac combined with small-dose acetaminophen.

Methods

The study was approved by the local ethics committee, and written, informed consent was obtained from all patients 1 day before the operation. Seventy women, ASA physical status I and II, scheduled for vaginal or abdominal hysterectomies, were randomly assigned to one of three groups to receive a single dose of 20 mg/kg (AS: $n = 24$) or 40 mg/kg (AL: $n = 23$) rectal acetaminophen or a combination of diclofenac (100 mg) and acetaminophen (20 mg/kg) suppositories (C: $n = 23$). Exclusion criteria were coagulation disorders, renal and liver disease, asthma, chronic obstructive airway disease, a history of peptic ulceration, and a body mass index greater than 32 kg/m^2. Patients receiving a regular medication containing any analgesic drugs were also excluded.

Oral midazolam (0.1 mg/kg) was given for premedication. After the induction of anesthesia with propofol (2 mg/kg) and alfentanil (10–20 μg/kg), the suppositories were administered. Cisatracurium (0.15 mg/kg) was administered IV to facilitate tracheal intubation. Anesthesia was maintained by continuous IV infusion of propofol and alfentanil (1–3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and 60% nitrous oxide in oxygen. We used commercially available lipophilic-based acetaminophen (1000 mg, 500 mg, 250 mg) and diclofenac (100 mg) suppositories. In order to achieve the desired acetaminophen target dose, patients were given the smallest possible number, but no more than three, acetaminophen suppositories, so that none of the women received more than four suppositories. Diclofenac was administered as a fixed dose of 100 mg.

Twenty minutes before the anticipated end of surgery, the alfentanil infusion was discontinued, and an IV dose of 1.25 mg droperidol was administered. After surgery, patients were tracheally extubated and transferred to the recovery room where they received a programmable patient-controlled analgesia (PCA) system, the use of which had been explained to them in detail during the premedication visit. The PCA pumps were set to deliver a bolus of 2 mg of morphine without a background infusion. The lockout period was 10 min. Before the commencement of the PCA infusion, increments of IV morphine (3–5 mg) were given as required to ensure satisfactory analgesia.

The cumulative amount of PCA morphine administered was recorded at 2, 4, 6, 8, 10, 12, and 24 h after the suppositories had been given. At the same time, quality of analgesia was assessed by using a 10-cm visual analog scale. Sedation and nausea scores were recorded on 4-point ordinal scales (sedation: 0 = awake, 1 = awake, but drowsy, 2 = asleep, but responsive to verbal commands, 3 = asleep, rousable only by painful stimuli; nausea: 0 = no nausea, 1= nausea, 2 = nausea and retching, 3 = vomiting and retching). The study protocol precluded the administration of opioids other than alfentanil and morphine; the use of rescue antiemetics in the postoperative period was restricted to IV droperidol (1.25 mg).

Blood samples for the measurement of acetaminophen plasma concentrations were obtained from an indwelling peripheral venous cannula, which was only used for blood sampling, at 1, 2, 3, 4, 6, 8, 10, and 12 h after drug administration. The first 3 mL of each specimen was discarded. After separation of the plasma by centrifugation, the samples were stored at −4°C and analyzed within 24 h by using a fluorescence polarization immunoassay (TDxFLx™; Abbott Laboratories, Abbott Park, IL). The detection concentration range of the assay was 1–200 mg/L. Values below the lowest measurable concentration, equivalent to the sensitivity of the assay, were excluded from data analysis.

Noncompartmental analysis of pharmacokinetic estimates was performed by using a computer program (WinNonlin™ 2.1; Scientific Consulting Inc., Mountain View, CA). The area under the plasma concentration-time curve (AUC_{0-12}) was determined for each individual for data points up to 12 h, applying the log-linear trapezoidal rule. The log-linear regression line used for extrapolation of the AUC_{0-12} to infinity was based on the last three measured concentrations at 8, 10, and 12 h. The slope of the regression line represents the elimination half-life. Computation of the area under the regression line from the last data point (12 h) to infinity yields the extrapolated AUC_{extr}. The total area under the curve is the sum of AUC_{0-12} and AUC_{extr}. Maximal plasma concentration (C_{max}) and the time to achieve maximal concentration were determined for each patient. Values for AUC_{0-12} and C_{max} were normalized for dose before statistical analysis was performed. For instance, if the dose administered was equivalent to 37 mg/kg, but the target dose was 40 mg/kg, the value for C_{max} was multiplied by 40/37. The relative bioavailability (F) of our suppositories was 90% of the corresponding oral dose (5). Drug clearance (Cl) was calculated using a standard formula: Cl = F × (rectal dose/total area under the curve).

Table 1. Demographic Characteristics and Data Related to the Surgical Procedure

	AL (n = 21)	AS (n = 22)	C (n = 22)
Age (yr)	45 (31–58)	45 (32–62)	51 (31–76)
Body mass index (kg/m^{-2})	24.4 (2.9)	26.5 (3.9)	25.4 (4.1)
Abdominal operations (n)	6	6	7
Duration of surgery (min)	101 (51)	97 (34)	108 (48)
Duration of anesthesia (min)	134 (53)	132 (43)	137 (56)
Estimated blood loss (mL)	300 (300)	300 (170)	390 (370)
Intraoperative fluids (mL)	1770 (960)	1730 (620)	1700 (840)
Preoperative Hb (g/L)	12.3 (1.1)	12.0 (1.5)	12.3 (1.5)
Postoperative Hb (g/L)	11.4 (1.2)	10.9 (1.5)	10.8 (1.6)

Values are mean (SD) or mean (range).
AL = larger-dose acetaminophen (40 mg/kg), AS = small-dose acetaminophen (20 mg/kg), C = combination (acetaminophen 20 mg/kg + diclofenac 100 mg), Hb = hemoglobin concentration.
There were no significant differences between the groups.

Opioid consumption, pharmacokinetic estimates, and visual analog scale measurements (6,7) were compared by using one-way analysis of variance and Bonferroni's test for multiple comparisons. Analysis of variance on ranks (Kruskal-Wallis test) and Dunn's test were applied for the analysis of sedation and nausea scores. P values < 0.05 were considered to be statistically significant. Based on previous investigations (3,8), the sample size was determined to provide a 80% probability of demonstrating a 25% difference in postoperative morphine requirements at the 5% significance level.

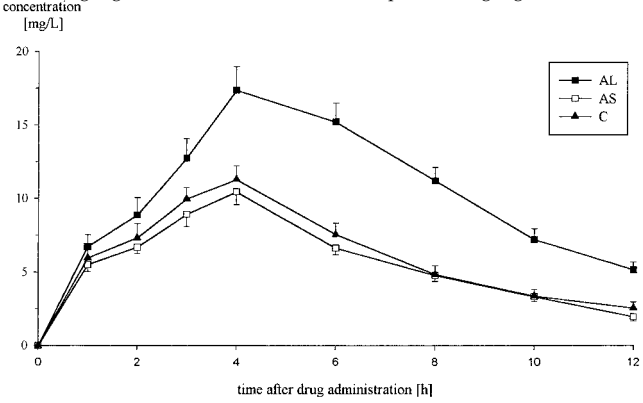

Figure 1. AL = acetaminophen (40 mg/kg) (■), AS = acetaminophen (20 mg/kg) (□), C = combination (▲). Error bars represent the SEM; for clarity unidirectional error bars were used. Plasma concentrations for the AL group were significantly greater than for both other groups (analysis of variance, $P < 0.01$).

Results

Seventy patients were enrolled in the investigation. Five patients were excluded, three because of protocol violations: one patient (AL) received a tramadol infusion, and two patients (AS) were given meperidine on the ward. Another patient (C) required a massive blood transfusion because of surgical complications. Another woman (AL) requested alternative analgesics 16 h after the operation because of severe vomiting and withdrew consent for further participation in the study.

Demographic characteristics and data related to the surgical procedure were similar for all groups (Table 1). Three patients (C: n = 2; AL: n = 1) required IV morphine increments (5 mg) in the recovery room before the commencement of PCA. We obtained 98% of the planned blood samples (n = 510) for the determination of acetaminophen plasma levels. Acetaminophen concentrations of six samples (1%) were below the detection range of the assay and were excluded from analysis. Five samples (1%) could not be collected because of difficult venous access. The highest measured acetaminophen plasma concentration was 31 mg/L. Plasma levels associated with liver toxicity (>150 mg/L) did not occur (9).

Larger-dose acetaminophen resulted in significantly higher plasma concentrations throughout the time of observation. Antipyretic plasma levels were sustained for approximately 6 h. Plasma concentrations after small-dose acetaminophen were below accepted therapeutic values. The concentration-time curves for small-dose acetaminophen were almost identical with a maximal value just exceeding 10 mg/L (Figure 1). Opioid requirements, sedation and nausea scores, and the request for rescue antiemetics were similar among the treatment groups (Table 2). The only difference in clinical outcomes was lower pain scores ($P < 0.01$) in the C group 4 h after the induction (Table 3). Six hours after the induction and later, more than 95% of all patients had pain scores <3. Pharmacokinetic estimates are presented in Table 4. To obtain reliable values, the extrapolated AUC should not exceed 25% of the total area under the concentration-time curve. For our data, the AUC_{extr} ranged from 14% to 20% and was within the accepted limits.

Discussion

Pharmacokinetics of rectal acetaminophen in adults were comparable to those observed in children. A rectal dose of 20 mg/kg acetaminophen produced

Table 2. Opioid Requirements and Opioid-Related Side Effects

	AL (n = 21)	AS (n = 22)	C (n = 22)	P value[a]
Alfentanil (mg)	3.6 (4.3)	2.5 (0.8)	2.8 (1.5)	0.992
Morphine (mg)	47.9 (23.7)	41.5 (20.4)	47.4 (24.6)	0.215
Droperidol (mg)	1.4 (0.5)	1.7 (0.9)	1.3 (0.3)	0.188
Incidence of PONV	4/21	6/22	3/22	0.523

Values are mean (SD) of total dose of morphine, alfentanil and droperidol or proportion.
[a] Analysis of variance except for PONV (χ^2 test).
AL = larger-dose acetaminophen (40 mg/kg), AS = small-dose acetaminophen (20 mg/kg), C = combination (acetaminophen 20 mg/kg + diclofenac 100 mg), PONV = postoperative nausea and vomiting.

subtherapeutic plasma levels; antipyretic plasma concentrations after 40 mg/kg did not result in lower pain scores or decreased morphine consumption.

An oral dose of 15 mg/kg typically results in peak plasma concentrations of 10–20 mg/L (10), which is considered to be the therapeutic antipyretic range (11). Seidemann et al. (12) suggested that, in particular with the rectal route of administration, higher doses are required because the relative bioavailability of rectal acetaminophen is 80% to 90% of the oral medication. Hopkins et al. (1), comparing 15 mg/kg oral and rectal acetaminophen, found that, after nasogastric administration, 50% of the children achieved plasma concentrations in the antipyretic range. The same rectal dose produced plasma concentrations of greater than 10 mg/L in only 2 of 28 patients. Analgesic effects were not measured, but mild antipyresis occurred in both groups. Cullen et al. (13) used a rectal dose of 15–20 mg/kg, which resulted in a mean peak plasma concentration of 9.3 mg/L in children after cardiac surgery. Two studies investigated the pharmacokinetics of rectal acetaminophen in children, but did not examine the relationship between measured plasma concentrations and analgesic effects. Birmingham et al. (14) reported a C_{max} of 14.2 mg/L after 3.5 hours using 30 mg/kg acetaminophen, whereas 20 mg/kg produced a subtherapeutic peak concentration of 8.8 mg/L, which was achieved with a delay of almost five hours. In another study, a dose of 45 mg/kg resulted in a maximal plasma level of only 13 mg/L after an average time of 3.3 hours (2). In both studies, almost twice the recommended dose was needed to achieve accepted therapeutic plasma concentrations.

These observations in pediatric patients agree with our findings in adults; 40 mg/kg rectal acetaminophen resulted in a maximal concentration of 17.2 mg/L after 4.2 hours. C_{max} (10.4 mg/ L) after a dose of 20 mg/kg just exceeded the lower limit of the antipyretic range. Antipyretic plasma concentrations after larger-dose acetaminophen were not associated with superior analgesia or decreased morphine requirements. The only investigation demonstrating a relationship between plasma concentrations and analgesic efficacy used 40 mg/kg oral acetaminophen as the sole analgesic in children undergoing tonsillectomy. Plasma concentrations of 25 mg/L provided satisfactory analgesia to 60% of children (4). A computer simulation based on these data showed that a loading dose of 50 mg/kg followed by 25 mg/kg once every four hours would be required to sustain these plasma concentrations (15).

The pharmacokinetic estimates after 40 mg/kg acetaminophen for our population were close to those observed in children, who had received the same rectal dose of the drug (16); C_{max} was 17.2 vs 17.7 mg/L, elimination half-life was 4.4 vs 4.7 hours and AUC_{inf} was 161 vs 140 mg $\cdot$ h^{-1} $\cdot$ L^{-1}, for adults and children, respectively. Compared with 2.3 hours for children, the time to maximal concentration (4.2 hours) was prolonged in adults. These findings are explicable by dose-related differences in the absorption characteristics of suppositories, resulting from different rates of dissolution. Smaller-dose suppositories dissolve more rapidly, but once the process of dissolution is completed, the bioavailibility of the "free" drug is independent from the suppository dose size (14). Our results show that the pharmacokinetics of rectal acetaminophen are comparable in adults and children.

Reduced opioid requirements are often used as an indicator of the efficacy of adjuvant nonopioid analgesics, but decreased opioid consumption as such is not necessarily of benefit, unless it is associated with better analgesia or fewer opioid-related side effects. The wide spectrum of responses to nonopioid analgesics given in conjunction with PCA morphine illustrates the limitations of this methodology; Montgomery et al. (3) showed a 30% decrease in morphine consumption after the administration of rectal diclofenac (100 mg) combined with acetaminophen (20 mg/kg) without observing any differences in pain scores among the groups. Conversely, better analgesia in the absence of reduced morphine intake was reported after coadministration of ibuprofen to PCA morphine (17). Reduced morphine requirements by 30% after diclofenac IM were associated with significantly lower pain scores four hours after surgery, but not later (8).

Because pain scores were low in our patients, the failure to detect analgesic effects of acetaminophen may be a result of the lack of sensitivity of the method used. Evaluation of the potency of acetaminophen for postoperative analgesia would be greatly facilitated

Table 3. Postoperative Analgesia, Morphine Consumption and Acetaminophen Plasma Concentrations

	T: 2 h	T: 4 h	T: 6 h	T: 8 h	T: 10 h	T: 12 h	T: 24 h
Pain scores (VAS) (cm)							
AL	2.8 (2.4)	3.4 (1.7)	2.4 (1.7)	1.4 (1.3)	1.0 (1.1)	0.8 (1.0)	0.9 (1.5)
AS	4.7 (3.2)	3.2 (1.7)	1.9 (1.3)	1.2 (1.0)	0.6 (0.8)	0.7 (0.8)	0.4 (0.7)
C	1.9 (2.2)	2.0 (1.6)*	1.4 (1.5)	0.7 (1.0)	0.5 (0.9)	0.4 (1.0)	0.4 (1.0)
Acetaminophen plasma concentrations (mg/L)							
AL	8.9 (5.6)	15.8 (6.4)†	14.2 (6.1)	11.1 (4.4)†	7.2 (3.4)	6.1 (4.9)†	—
AS	6.7 (2.1)	9.5 (3.7)	6.6 (2.1)	4.8 (1.9)	3.3 (1.6)	1.9 (1.4)	—
C	7.3 (4.5)	10.5 (4.3)	7.6 (3.5)	4.8 (2.8)	3.4 (2.1)	2.6 (1.8)	—
Cumulative morphine consumption (mg)							
AL	2.4 (3.5)	12.7 (7.1)	20.6 (10.0)	23.1 (9.9)	28.2 (14.4)	29.6 (12.9)	47.9 (23.7)
AS	2.1 (3.3)	11.7 (5.3)	16.5 (8.2)	20.2 (10.3)	22.7 (11.9)	25.2 (14.0)	41.5 (20.4)
C	1.6 (2.8)	12.5 (7.3)	17.8 (7.4)	21.1 (9.4)	24.1 (11.7)	27.1 (13.1)	47.4 (24.6)

Values are mean (SD).
T = time of measurement after the application of rectal acetaminophen, VAS = 10-cm visual analog scale, AL = larger-dose acetaminophen (40 mg/kg) (n = 21), AS = small-dose acetaminophen (20 mg/kg) (n = 22), C = combination (acetaminophen 20 mg/kg + diclofenac 100 mg) (n = 22).
* Significantly lower than in both other groups ($P < 0.05$, analysis of variance).
† Significantly higher than in both other groups ($P < 0.01$, analysis of variance).

Table 4. Pharmacokinetic Estimates by Noncompartmental Analysis

	AL (n = 21)	AS (n = 22)	C (n = 22)	P value
C_{max}	17.2 (6.1)*	10.4 (3.6)	11.9 (4.4)	<0.001*
T_{max}	4.2 (1.7)	3.6 (1.4)	3.2 (1.1)	0.02†
$t_{1/2\beta}$	4.5 (4.2)	3.9 (2.8)	3.4 (1.3)	0.31
Clearance	0.262 (0.10)	0.240 (0.07)	0.245 (0.11)	0.76
AUC_{inf}	156.3 (51.1)*	82.3 (24.9)	92.4 (35.6)	<0.001*
$AUC_{0–12}$	118.2 (34.1)*	66.9 (15.9)	74.7 (25.8)	<0.001*
$\%AUC_{extr}$	20.8 (16.6)	16.1 (13.2)	14.0 (8.3)	0.13

Values are mean (SD).
* Difference between AL and both other groups.
† Difference between AL and C groups.
AL = larger-dose acetaminophen (40 mg/kg), AS = small-dose acetaminophen (20 mg/kg), C = combination (acetaminophen 20 mg/kg + diclofenac 100 mg), C_{max} = maximal plasma concentration (mg/L), T_{max} = time to maximal concentration (h), $t_{1/2\beta}$ = elimination half-life (h), Clearance = for computation, the bioavailability of the suppositories was assumed to be 0.9 ($L \cdot kg^{-1} \cdot h^{-1}$). AUC_{inf} = total area under the concentration-time curve extrapolated to infinity ($mg \cdot h^{-1} \cdot L^{-1}$). $AUC_{0–12}$ = area under the curve for measured plasma concentrations from 0 to 12 h ($mg \cdot h^{-1} \cdot L^{-1}$). $AUC_{extr} = AUC_{inf} - AUC_{0–12}$, expressed in % of AUC_{inf}.

by a model that avoids the use of any additional opioid analgesics. Such a method, however, may not reflect the clinical practice in adults.

We showed that the pharmacokinetics of rectal acetaminophen are comparable in adults and children. Twice the conventional dose of rectal acetaminophen was required to attain accepted therapeutic concentrations. Larger-dose rectal acetaminophen of 40 mg/kg produced antipyretic plasma concentrations, which were not associated with improved analgesia. Effective acetaminophen plasma concentrations for postoperative analgesia in adults have yet to be determined but may be larger than the levels known to produce antipyresis.

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