Plasma concentrations after high-dose (45 mg · kg⁻¹) rectal acetaminophen in children

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Although the recommended dose of rectal acetaminophen (25–30 mg · kg⁻¹) is twice that for oral administration (10–15 mg · kg⁻¹), the literature justifies the use of a higher dose when acetaminophen is administered via the rectal route. We measured venous plasma acetaminophen concentrations resulting from 45 mg · kg⁻¹ of rectal acetaminophen in ten ASA 1, 15 kg paediatric patients undergoing minor surgery with a standardized anaesthetic. After induction of anaesthesia, a single 650 mg suppository (Abenol®, SmithKline Beecham Pharma Inc.) was administered rectally. Plasma was sampled at $t = 0, 15, 30, 45, 60, 90, 120, 180, 240$ min in the first five patients and at $t = 0, 30, 60, 90, 120, 180, 240, 300, 420$ min in the subsequent five. Acetaminophen plasma concentrations were determined using a TDxFLx® fluorescence polarization immunoassay (Abbott Laboratories, Toronto, Ontario). The maximum plasma concentration was $88 \pm 39 \mu\text{mol} \cdot \text{L}^{-1}$ ($13 \pm 6 \mu\text{g} \cdot \text{mL}^{-1}$) and the time of peak plasma concentration was 198 ± 70 min (mean $\pm$ SD). At 420 min, the mean plasma concentration was $46 \pm 18 \mu\text{mol} \cdot \text{L}^{-1}$ ($7.0 \pm 0.9 \mu\text{g} \cdot \text{mL}^{-1}$). No plasma concentrations associated with toxicity ($>800 \mu\text{mol} \cdot \text{L}^{-1}$) were identified. A 45 mg · kg⁻¹ rectal dose of acetaminophen resulted in peak plasma concentrations comparable with those resulting from 10–15 mg · kg⁻¹ of oral acetaminophen at three hours after suppository insertion. It is concluded

that the delayed and erratic absorption of acetaminophen after rectal administration leads to unpredictable plasma concentrations. Rectal acetaminophen will not be consistently effective for providing rapid onset of analgesia in children.

La dose rectale d'acétaminophène conseillée (25–30 mg · kg⁻¹) est le double de la dose orale (10–15 mg · kg⁻¹); les publications confirment la pertinence de cette dose lorsque l'acétaminophène est administré par la voie rectale. Les auteurs ont mesuré la concentration plasmatique veineuse de l'acétaminophène 45 mg · kg⁻¹ administré chez dix enfants ASA 1 de 15 kg soumis à une chirurgie mineure sous anesthésie standardisée. Après l'induction de l'anesthésie, un suppositoire de 650 mg d'acétaminophène (Abenol®, SmithKline Beecham Pharmacologique Inc.) est administré par la voie rectale. Le plasma est analysé au $t = 0, 15, 30, 45, 60, 90, 120, 240$ min chez les cinq premiers patients et au $t = 30, 60, 90, 120, 180, 240, 300, 360, 420$ min chez les cinq patients suivants. Les concentrations plasmatiques d'acétaminophène sont mesurées au moyen de l'épreuve d'immunofluorescence par polarisation TDxFLx® (Laboratoires Abbott, Toronto, Ontario). La concentration plasmatique maximale est de 88 ± 39 ($13 \pm 6 \mu\text{g} \cdot \text{mL}^{-1}$) et elle survient à 198 ± 70 min (moyenne $\pm$ ET). A 420 min, la concentration plasmatique moyenne est de $46 \pm 18 \mu\text{mol} \cdot \text{L}^{-1}$ ($7,0 \pm 0,9 \mu\text{g} \cdot \text{mL}^{-1}$). Aucune concentration plasmatique ne peut être associée au niveau toxique ($>800 \mu\text{mol} \cdot \text{L}^{-1}$). La dose rectale de 45 mg · kg⁻¹ d'acétaminophène produit des concentrations plasmatiques comparables à celles de la dose orale de 10–15 mg · kg⁻¹ trois heures après l'insertion du suppositoire. Les auteurs concluent que l'absorption retardée et irrégulière de l'acétaminophène rectal entraîne des concentrations plasmatiques imprévisibles. L'acétaminophène rectal ne procure pas toujours un analgésie rectale efficace et rapide chez les enfants.

Key words

ANAESTHESIA: paediatric;

ANALGESICS: acetaminophen;

PHARMACOKINETICS: acetaminophen, rectal absorption.

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Acetaminophen is frequently used as an adjuvant for postoperative analgesia in paediatric patients. It is thought to act through inhibition of cyclo-oxygenase in the central nervous system producing analgesia comparable with that

of non-steroidal anti-inflammatory drugs. Inhibition of prostaglandin synthesis in other tissues does not occur, thus acetaminophen produces no anti-inflammatory effects or effects on platelet function that may be associated with the use of non-steroidal anti-inflammatory drugs.¹

While the plasma concentrations required for analgesia have not been defined, the "accepted" therapeutic plasma concentration range for an antipyretic effect is 35–130 $\mu\text{mol} \cdot \text{L}^{-1}$ (5–20 $\mu\text{g} \cdot \text{ml}^{-1}$).² Optimal analgesic plasma concentrations may be higher than this as clinical studies have shown that a typical oral dose of 10 $\text{mg} \cdot \text{kg}^{-1}$ of acetaminophen may be no more effective than placebo for analgesia.^{3,4}

The preoperative oral administration of acetaminophen syrup may be difficult in an awake uncooperative toddler. The rectal route of administration of acetaminophen may be simpler as the drug can be given after induction of anaesthesia.

A commonly recommended paediatric dose of the synthetic, lipophilic, triglyceride-based rectal acetaminophen suppository (Abenol®, SmithKline Beecham Pharma Inc.) ranges from 10–22 $\text{mg} \cdot \text{kg}^{-1}$.⁵ This dose range was determined by dividing the dose recommended for a given age group in the Abenol® product monograph by typical weights for the age ranges provided. The manufacturer's dose recommendations are based on an unpublished adult study in which a rectal dose of 8–10 $\text{mg} \cdot \text{kg}^{-1}$ resulted in maximum plasma concentrations which ranged from 9.4–36.2 $\mu\text{mol} \cdot \text{L}^{-1}$ (1.4–5.4 $\mu\text{g} \cdot \text{ml}^{-1}$), 45 to 360 min after administration. Data from that study also showed that the absorption of Abenol® suppositories compared with oral tablet administration ranged from 24–98% with a mean of 52%, thus confirming erratic absorption with this route.*

Several authors have proposed that the recommended rectal dose should be higher because of this poor and erratic absorption.^{6–8} Their recommendations of 25–30 $\text{mg} \cdot \text{kg}^{-1}$ are based on extrapolations of data from studies using conventional doses of 15–20 $\text{mg} \cdot \text{kg}^{-1}$ rectally. In these studies, with these doses, mean peak plasma concentrations in these studies were low: 13.4–7.2 $\mu\text{mol} \cdot \text{L}^{-1}$ (2.0–10.8 $\mu\text{g} \cdot \text{ml}^{-1}$).^{7,8} These recommendations need to be confirmed with accurate pharmacokinetic data.

The purpose of this study was to examine prospectively the plasma concentrations resulting from the rectal administration of a lipophilic acetaminophen suppository (Abenol®) in a dose of 45 $\text{mg} \cdot \text{kg}^{-1}$. The dose of 45 $\text{mg} \cdot \text{kg}^{-1}$ (three times 15 $\text{mg} \cdot \text{kg}^{-1}$) was chosen, based on the work of Hopkins and Cullen.^{7,8} We expected

plasma levels of three times those resulting from rectal administration of 15 $\text{mg} \cdot \text{kg}^{-1}$ which would be consistent with the currently described therapeutic levels. Administration of a single suppository was chosen to control the surface area of drug presented to the rectal mucosa. The lipophilic, readily available, commercial preparation was studied.

Methods

After Institutional Review Board approval, informed, written, parental consent was obtained. Ten ASA Class I paediatric patients weighing 13–15 kg and undergoing peripheral surgical procedures requiring general anaesthesia were enrolled in the study. Patients who had received acetaminophen within the previous 24 hr, had a history of acetaminophen intolerance or allergy, or had an objection to the rectal route of administration were excluded from the study.

The anaesthetic protocol consisted of an intravenous induction using propofol 5.0 $\text{mg} \cdot \text{kg}^{-1}$, intubation and controlled ventilation facilitated with vecuronium 0.1 $\text{mg} \cdot \text{kg}^{-1}$ and morphine 0.1 $\text{mg} \cdot \text{kg}^{-1}$. Anaesthesia was maintained with isoflurane with nitrous oxide in oxygen. Perioperative fluid administration was standardized such that each patient received normal saline, 10 $\text{ml} \cdot \text{kg}^{-1}$, during the first hour of the study and then a maintenance hourly rate according to body weight. Immediately after induction, dedicated vascular access via the saphenous vein was obtained and an initial control ($t = 0$) blood sample was collected. A single 650 mg (45 $\text{mg} \cdot \text{kg}^{-1}$) acetaminophen suppository (Abenol®) was inserted rectally. Subsequent venous blood samples (0.5 ml per sample) were collected into heparinized tubes at the following intervals after suppository insertion: $t = 15, 30, 45, 60, 90, 120, 180, 240$ min.

All patients underwent tracheal extubation when awake in the operating room after completion of the surgery. Retention of the suppository was confirmed by visual inspection before the end of the anaesthetic. Additional analgesia consisted of morphine 0.1 $\text{mg} \cdot \text{kg}^{-1}$ *iv* or codeine 1.5 $\text{mg} \cdot \text{kg}^{-1}$ *po* as required. The intravenous catheter placed for blood sampling during the anaesthetic remained *in situ* for the duration of the study.

A study duration of 240 min was initially chosen based on the data of Hopkins and Cullen. However, the plasma concentration results of the initial five patients demonstrated considerably delayed absorption.^{7,8} The study duration was then extended to include samples at 300, 360, and 420 min and early sampling at 15 and 45 min was discontinued for the subsequent five patients. As these were healthy toddlers undergoing minor peripheral surgery, this extended study period required up to seven awake sample collections per subject and it was thought

*Personal communication Nancy Bishop BSc Pharm, SmithKline Beecham Pharma. June, 1993.

FIGURE Plasma acetaminophen concentration.

unacceptable to extend the sampling period beyond 420 minutes.

After collection, plasma was separated by centrifugation and then frozen at -70°C for subsequent batch analyses. Acetaminophen plasma concentrations were determined by the Biochemistry Research Division laboratory, using a TDxFLx[®] fluorescence polarization immunoassay (Abbott Laboratories, Toronto, Ontario). The detection range of this assay is $10\text{--}1320\text{ }\mu\text{mol}\cdot\text{L}^{-1}$. The within runs precision of this assay is 3% and the between runs precision is 4% at these plasma concentrations.⁹

Normally distributed demographic data were summarized using means and standard deviations. Skewed demographic data were expressed using medians and ranges. Pharmacokinetic data were determined by plotting the mean plasma concentrations versus time. The C_{max} was determined by averaging the maximum plasma concentrations and T_{max} was determined by averaging the times of maximum concentration. Due to erratic or delayed absorption, the duration of the sampling time was insufficient to determine an AUC accurately.

Results

Ten patients were evaluated. The average age was 3.4 ± 0.5 yr and weight was 14.4 ± 0.8 kg. The mean dose of acetaminophen given was 45.2 ± 2.7 $\text{mg}\cdot\text{kg}^{-1}$ (Table I). The resulting plasma concentrations are shown in the

TABLE I Demographic data

Variable	
Age (yr)*	3.4 ± 0.5
Height (cm)*	97 ± 3
Weight (kg)*	14.4 ± 0.8
Sex (M/F)†	7/3
Duration of anaesthesia (min)†	90 (30–135)
Acetaminophen dose ($\text{mg}\cdot\text{kg}^{-1}$)*	45.2 ± 2.7

*mean $\pm$ SD.

†median (range).

‡count.

Figure. Samples were not obtained in subject 4 at 240 min and in subject 8 at 90 min. Samples at 300 min were obtained in subjects 4 and 5. Eight patients had detectable plasma concentrations at 30 min. The mean maximum concentration (C_{max}) was $88 \pm 39\text{ }\mu\text{mol}\cdot\text{L}^{-1}$ ($13 \pm 6\text{ }\mu\text{g}\cdot\text{kg}^{-1}$) and occurred at 198 ± 70 mins (T_{max}). All data points are shown in the Figure and mean plasma concentrations are shown in Table II. Mean plasma concentration at 420 min in the five patients studied was $46 \pm 18\text{ }\mu\text{mol}\cdot\text{L}^{-1}$ ($7 \pm 0.9\text{ }\mu\text{g}\cdot\text{ml}^{-1}$). Plasma concentrations were not obtained for long enough to calculate an elimination half-life or an area under the curve.

Mean plasma concentrations greater than $60\text{ }\mu\text{mol}\cdot\text{L}^{-1}$ occurred only later 90 min and remained at

TABLE II Plasma acetaminophen concentrations

Time (min)	Plasma concentration ($\mu\text{mol} \cdot \text{L}^{-1}$)*	Number of samples†
30	19 $\pm$ 12	10
60	46 $\pm$ 29	10
120	78 $\pm$ 48	10
180	88 $\pm$ 39	10
240	82 $\pm$ 30	9
300	77 $\pm$ 28	7
420	46 $\pm$ 18	5

*mean $\pm$ SD.

†count.

this concentration or greater for six hours after administration. Plasma concentrations associated with toxicity ($>800 \mu\text{mol} \cdot \text{L}^{-1}$) did not occur.¹⁰

Discussion

While the plasma concentrations required for analgesia have not been defined, the accepted therapeutic plasma concentration range for an antipyretic effect is 35–130 $\mu\text{mol} \cdot \text{L}^{-1}$ (5–20 $\mu\text{g} \cdot \text{ml}^{-1}$).² Peak plasma concentrations after administration of an oral elixir of acetaminophen 10 $\text{mg} \cdot \text{kg}^{-1}$, are $45 \pm 15 \mu\text{mol} \cdot \text{L}^{-1}$ ($6.7 \pm 2.3 \mu\text{g} \cdot \text{ml}^{-1}$) at 60 min.¹⁰ Recent paediatric studies have shown that administration of oral acetaminophen, 10 $\text{mg} \cdot \text{kg}^{-1}$ for analgesia, may be no more effective than placebo. Watcha demonstrated that oral acetaminophen 10 $\text{mg} \cdot \text{kg}^{-1}$ given 30 min before induction of anaesthesia was no more effective than placebo for the treatment of surgical pain after myringotomy tube insertion.³ In contrast, oral acetaminophen 15 $\text{mg} \cdot \text{kg}^{-1}$ was an effective analgesic when pharyngitis was used as a pain model, using a self-reporting "smiley face" scale as a tool to evaluate analgesic efficacy.¹¹ In that study, plasma concentrations were not reported but an oral dose of 15 $\text{mg} \cdot \text{kg}^{-1}$ typically results in peak plasma concentrations of 67–134 $\mu\text{mol} \cdot \text{L}^{-1}$ (10–20 $\mu\text{g} \cdot \text{ml}^{-1}$).¹²

Three previous studies have examined plasma concentrations after rectal administration of acetaminophen using conventional doses of 10–20 $\text{mg} \cdot \text{kg}^{-1}$. Hopkins studied a rectal dose of 15 $\text{mg} \cdot \text{kg}^{-1}$ formulated in a paraffin suppository in nine children (mean age 2.7 yr), after cardiac surgery. Plasma concentrations of greater than 67 $\mu\text{mol} \cdot \text{L}^{-1}$ (10 $\mu\text{g} \cdot \text{ml}^{-1}$) occurred in only one patient.⁷ Cullen compared acetaminophen concentrations resulting from the use of lipophilic with those from hydrophilic suppositories, in a dose of 15–20 $\text{mg} \cdot \text{kg}^{-1}$ in postoperative cardiac patients. The mean peak plasma concentration was 62.3 $\mu\text{mol} \cdot \text{L}^{-1}$ (9.3 $\mu\text{g} \cdot \text{ml}^{-1}$) two hours after administration of the lipophilic suppository and was effective for antipyresis.⁸ Lipophilic suppositories

resulted in higher rectal bioavailability compared with that from a hydrophilic base. Dange reported a C_{max} of 16.8 $\mu\text{mol} \cdot \text{L}^{-1}$ (2.5 $\mu\text{g} \cdot \text{ml}^{-1}$) and T_{max} of 180 min after rectal administration of acetaminophen 8.6–10.7 $\text{mg} \cdot \text{kg}^{-1}$ to six children age 10–12 yr. These concentrations were 30% of those obtained after a comparable oral dose.¹³ These studies suggest that low and delayed plasma concentrations result from the rectal use of lipophilic suppositories when conventional acetaminophen doses of 10–15 $\text{mg} \cdot \text{kg}^{-1}$ are given.

Even when an aqueous solution of acetaminophen 0.4% in a dose of 20 $\text{mg} \cdot \text{kg}^{-1}$ was given rectally after induction of anaesthesia in 20 healthy children (age 1–8) undergoing adenotonsillectomy, the mean concentration was only 35 $\mu\text{mol} \cdot \text{L}^{-1}$, 30 min after administration.¹⁴ The mean peak plasma concentration was 72 $\mu\text{mol} \cdot \text{L}^{-1}$ (10.8 $\mu\text{g} \cdot \text{ml}^{-1}$) and occurred only at 120 min after administration. Although higher concentrations were achieved with the use of an aqueous solution, absorption was still delayed and incomplete when compared with the oral route.

In this study, a 45 $\text{mg} \cdot \text{kg}^{-1}$ rectal dose of acetaminophen resulted in plasma concentrations comparable with those resulting from 10–15 $\text{mg} \cdot \text{kg}^{-1}$ of oral acetaminophen. The peak plasma concentrations occurred on average three hours after suppository insertion. The use of this higher dose did not result in the more rapid achievement of the presumed therapeutic concentrations.

In conclusion, rectal administration of acetaminophen leads to slow absorption and erratic blood levels and the time to achieve therapeutic levels is long. The rectal route of acetaminophen administration cannot be recommended when rapid onset of analgesia is desired. A single rectal dose of acetaminophen 45 $\text{mg} \cdot \text{kg}^{-1}$ may be appropriate if a delayed and sustained effect is required. If clinicians choose to use repeated higher doses of rectal acetaminophen, they should be aware of the possibility of a longer duration of action, the need for increased dosing intervals and the possibility of drug accumulation.

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