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Morphine-sparing Effect of Acetaminophen in Pediatric Day-case Surgery

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Background: **Postoperative pain is a major problem in day-case surgery in children. Nonsteroidal antiinflammatory drugs have gained popularity in management of pediatric surgical patients to reduce the need for opioids. The aim of this study was to evaluate the efficacy of different doses of rectal acetaminophen in day-case surgery in children.**

Methods: **A randomized, double-blinded, placebo-controlled study design was used. Patients (n = 120) were randomized to receive a single dose of 0, 20, 40, or 60 mg/kg of rectal acetaminophen after induction of anesthesia. General anesthesia was induced by mask ventilation with sevoflurane (7%) in nitrous oxide and oxygen and maintained with 2.5–4.0% end-tidal sevoflurane. Opioids or local anesthetics were not used. Postoperative pain was evaluated by behavioral assessment and physiologic measurements every 10 min after arrival at the postanesthesia care unit. The pain intensity was scored using a 0–100 visual analog scale used in the authors' clinic. The need for rescue medication, intravenous morphine 0.1 mg/kg, was decided by the nurse, who was unaware of the rectal acetaminophen dose. The parents were interviewed by phone after 24 h regarding pain and its treatment, nausea, and vomiting. Rescue analgesia at home was rectal ibuprofen, 10 mg/kg.**

Results: **In the postanesthesia care unit pain scores were significantly lower in the 40- and 60-mg/kg groups compared with placebo and 20-mg/kg groups. Acetaminophen resulted in a dose-related reduction in the number of children who required postoperative rescue opioid, with significance reached with 40 or 60 mg/kg doses. Calculated dose of acetaminophen at which 50% of the children not requiring a rescue opioid was 35 mg/kg. The need for rescue analgesia at home during the first 24 h after surgery was also significantly less in patients in the 40- or 60-mg/kg groups than in the 0- or 20-mg/kg groups (20–17 *vs.* 80–63%). Thirty-three percent of patients receiving placebo had postoperative nausea and vomiting, compared with 0–3% in groups receiving 40 or 60 mg/kg acetaminophen.**

Conclusions: **A single dose of 40 or 60 mg/kg of rectal acetaminophen has a clear morphine-sparing effect in day-case surgery in children if administered at the induction of anesthesia. Moreover, children with adequate analgesia with acetaminophen have less postoperative nausea and vomiting. (Key words: Acetaminophen; analgesia; children; day-case surgery; potency; rectal administration.)**

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PAIN following surgical procedures in children has aroused growing concern in the past 15 years.[1–3] Awareness of undertreatment of surgical pain has led to clinical trials to study if part of the need for analgesics can be covered with regular administration of nonsteroidal antiinflammatory drugs. These drugs have a morphine-sparing effect if administered intravenously[4] or intrarectally.[5] However, the reduced use of opioids following pretreatment with nonsteroidal antiinflammatory drugs may not diminish the postoperative nausea and vomiting as expected.[6]

Acetaminophen is the most commonly used analgesic and antipyretic in childhood. Acetaminophen is also frequently used as an adjuvant for postoperative analgesia in pediatric patients.[7] Unfortunately, clinical trials with commonly used dosages (10–15 mg/kg every 6–8 h[8,9] or as single bolus[10,11]) have not confirmed its antinociceptive efficacy. The analgesic effect of a larger dose of rectal acetaminophen has been studied only in few reports. Anderson *et al.*[12] found 40 mg/kg of rectal acetaminophen to be less effective than the same dose orally. Rectal doses of 20 or 35 mg/kg were unsatisfactory to treat pain associated with tonsillectomy.[13,14] However, in these studies there was only one dose group for acetaminophen. Also, the absence of a control group limited the ability to quantitate analgesia.

A metaanalysis has shown that in adults 1000 mg of oral acetaminophen produces a 50% pain relief in one of

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Table 1. **Patient Data and Surgery Performed in the Study Groups**

	Acetaminophen (mg/kg)			
	0	20	40	60
Sex (M/F)	16/14	20/10	21/9	25/5
Weight (kg)	17.1 (5.2) [9–27.6]	14.7 (4.3) [9–22]	15.8 (5.0) [9–28]	16.4 (7.4) [9–44]
Age (yr)	4.4 (2.1) [1.1–7.7]	3.1 (1.9) [1.0–7.2]	3.8 (2.2) [1.0–7.2]	4.2 (2.3) [1.1–7.8]
Herniorrhaphy (n)	24	15	19	13
Orchidopexy (n)	1	3	5	3
Hydrocoelectomy (n)	1	3	1	7
Adenoidectomy (n)	2	3	4	4
Excision of subcutaneous tumor (n)	2	6	1	3

Values are mean (SD) [range], or number of children. There were no significant differences.

every four patients with moderate to severe postoperative pain.[15] However, it has not been clarified which dose of rectal acetaminophen has an opioid-sparing effect in children. Therefore, we designed a randomized, double-blinded, placebo-controlled study using acetaminophen to establish a clinically effective dose of acetaminophen for postoperative pain management in children.

Materials and Methods

Forty-two boys and 78 girls from 1 to 7 years of age, with American Society of Anesthesiologists physical status 1, undergoing elective day-case surgery, were included in the study (table 1). The study was approved by the Ethics Committee of the Hospital for Children and Adolescents, University of Helsinki. The parents of the patients gave written informed consent. Patients were excluded if they had known allergy to acetaminophen, kidney or liver dysfunction, or hemorrhagic diathesis.

A randomized, double-blinded, placebo-controlled study design was used. The patients had no premedication. General anesthesia was induced by mask ventilation with sevoflurane (7%) in nitrous oxide and oxygen or, in cases of patient preference, with intravenous thiopental (n = 26) . Patients who underwent an adenoidectomy had endotracheal intubation facilitated by succinylcholine (1 mg/kg). Following the induction of anesthesia children were randomized by a sealed-envelope method to receive a single dose of acetaminophen (SmithKline Beecham, Midy, Herouville, France) rectally, either 0, 20, 40, or 60 mg/kg. Suppositories were administered by a nurse not involved in the surgical procedure and not participating in postoperative care of the child. A minimum of 24 children in a group was needed to detect a 40% reduction in morphine requirement at a power of 90%, and 28 children in a group was needed to detect a 30% reduction in morphine requirement at a power of 80%, by assuming that 90–100% of children in the smallest dose group would require morphine.

Anesthesia was maintained with 2.5–4.0% end-tidal sevoflurane in nitrous oxide and oxygen (2:1) under spontaneous breathing. Hemoglobin oxygen saturation, end-tidal carbon dioxide, and electrocardiogram were monitored during the anesthesia. Opioids or local anesthetics were not used. If there was a rise of 10% in the heart rate, sevoflurane was increased as indicated by the response of the child. At the end of the operation the inspired gas mixture was switched to 100% oxygen and the patients were transferred to the postanesthesia care unit (PACU) for continuous monitoring of vital signs and pain assessment.

In the PACU, hemoglobin oxygen saturation, heart rate, and spontaneous rate of breathing were recorded. The investigator, who was unaware of the dose of acetaminophen, followed each child for 2 h. Data were recorded every 10 min after arrival at the PACU.

The pain was evaluated by behavioral assessment and physiologic measurements.[16] The pain intensity was "translated" to a score on a visual analog scale used in daily clinical practice in our institution: 0–9 = no pain; 10–29 = slight pain; 30–49 = moderate pain; 50–79 = severe pain; and 80–100 = extreme pain. Because of the young age of most of the children, self-assessment of pain was not used. As the same observer continuously assessed the child, the assessments were in relation to each other. Rescue pain medication in the PACU, intra-

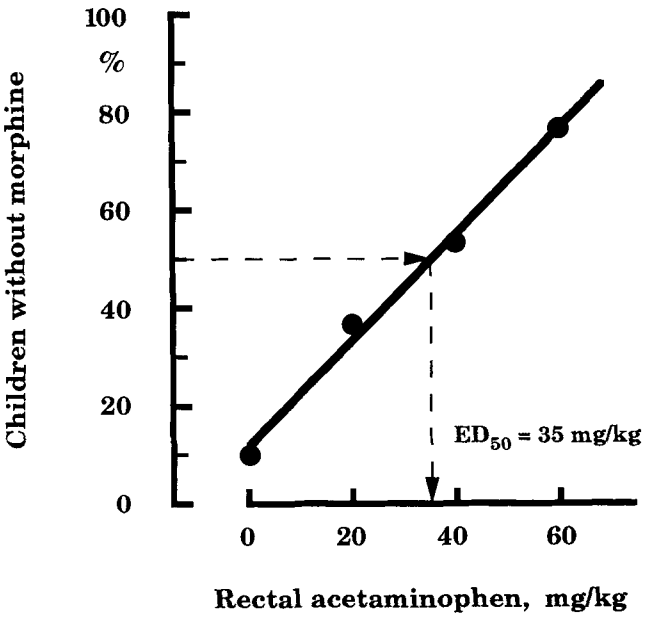

Fig. 1. Correlation between the dose of rectal acetaminophen in a pediatric day-case surgery and the percentage of children who did not need postoperative rescue morphine.

venous morphine 0.1 mg/kg, was administered at the discretion of the nursing staff, which was unaware of the acetaminophen dose. The minimum dose interval of morphine was 5 min.

The patients were kept in the PACU for a minimum of 2 h and until they were comfortable. Patients were then discharged home if they were alert and cooperative with normal motor activity and had only slight pain without nausea or vomiting. The investigator interviewed the parents by phone after 24 h for postoperative pain and its treatment (rescue medication at home was always rectal ibuprofen 10 mg/kg), nausea and vomiting, or any other untoward events.

Kruskal-Wallis analysis, Mann-Whitney U tests, the exact chi-square test, and analysis of variance were used for statistical analyses when appropriate. Differences in the number of patients requiring rescue morphine and in overall morphine consumption were analyzed with the Mantel-Cox test. Between-group comparisons were made at 30, 60, and 120 min after children arrived at the PACU. A dose-response curve of acetaminophen was created by least-squares linear regression analyses of the dose of acetaminophen and the percentage of children not requiring postoperative morphine. A P value less than 0.05 was considered significant.

Results

Demographic data of the patients and the type of operative procedure matched well between the groups (table 1). The children whose anesthesia was induced with thiopental were evenly distributed in the study groups. The time from the induction of anesthesia to arrival into the PACU averaged 24 min (SD 6 min, range 15-41 min; no between-group differences).

Acetaminophen had a clear dose-dependent morphine-sparing effect. There was a good correlation between the dose of acetaminophen and percentage of children who did not require morphine in the PACU ($y = 1.08x + 12$, $r^2 = 0.993$, $P < 0.001$) (fig. 1). Dose-response analysis showed that the dose of acetaminophen at which 50% of the children did not require a rescue opioid (ED_{50}) in the day-care setting was 35.4 mg/kg. Ninety percent of the patients who received placebo required morphine, with an average of 1.2 doses (figs. 2 and 3). Of patients receiving 60 mg/kg of acetaminophen, only 23% required postoperative morphine (fig. 2); the average number of morphine doses in this group was 0.27 (fig. 3). Patients receiving placebo or 20 mg/kg of acetaminophen were the only ones who experienced severe pain (fig. 4), and they frequently needed more than a single dose of morphine (table 2). The differences in pain between the study groups became apparent already within the first 20 min in the PACU (within 45 min after giving the rectal acetaminophen; see fig. 2).

Eighty percent of the patients who received placebo had pain at home as opposed to 17-20% of those who

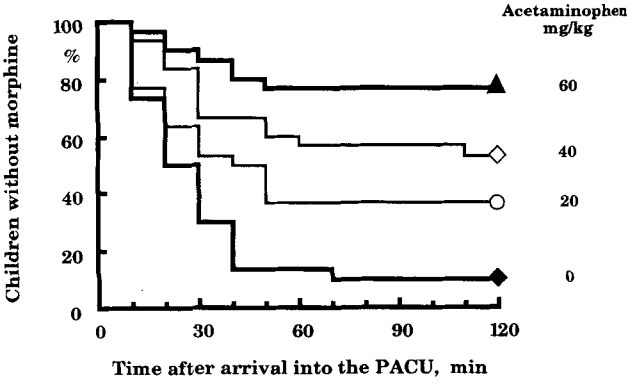

Fig. 2. Percentage of children who did not require postoperative morphine after receiving acetaminophen 0, 20, 40, or 60 mg/kg rectally. Acetaminophen had a clear morphine-sparing effect: The proportion of pain-free children was greater with the higher acetaminophen doses.

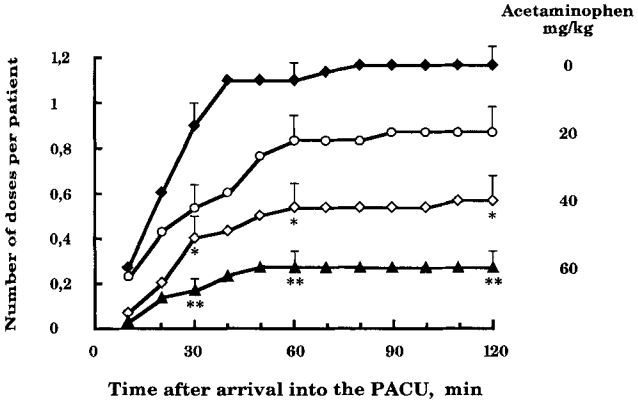

Fig. 3. Average number of morphine doses required in children who received acetaminophen 0, 20, 40, or 60 mg/kg rectally. Acetaminophen had a clear morphine-sparing effect: The number of morphine doses was smaller with the greater acetaminophen doses. Single asterisk denotes difference from the 0-mg/kg group, and double asterisk denotes significant difference from 0- and 20-mg/kg groups. Bars indicate SEM.

received 40 or 60 mg/kg of acetaminophen ($P < 0.01$) (table 2). Thirty-three percent of the patients receiving placebo had postoperative nausea and vomiting as compared with 0–3% in groups receiving 40 or 60 mg/kg of acetaminophen ($P < 0.01$) (table 2). Children who received morphine had a greater frequency of postoperative nausea and vomiting than children who did not receive morphine (18 *vs.* 2%, $P < 0.01$). Sixty-nine percent of children who experienced postoperative nausea or vomiting had received at least two separate doses of morphine. No other side effects were recorded.

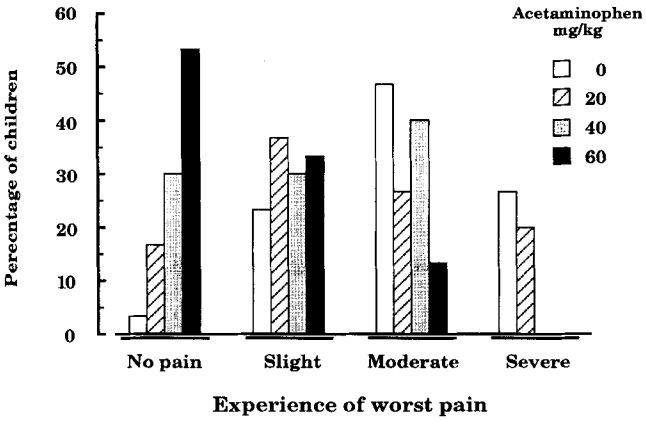

Fig. 4. Percentage of children who experienced no, slight, moderate, or severe pain as their worst pain experience after receiving acetaminophen 0, 20, 40, or 60 mg/kg rectally. The severity of pain was closely related to the acetaminophen dose.

Table 2. Incidence of Pain, Its Treatment, and Postoperative Nausea and Vomiting in the Study Groups

	Acetaminophen (mg/kg)			
	0	20	40	60
Severe pain (% of children)	27*	20*	0	0
Received morphine in PACU (%)	90*	63†	47	23
At least two doses (%)	23	20	10	3
Received ibuprofen at home (%)	80*	63*	20	17
PONV				
In PACU (%)	23†	3	3	0
By 24 h (%)	33*	7	3	0

PACU = postanesthesia care unit; PONV = postoperative nausea and vomiting.

* Significantly different from the 40- and 60-mg/kg groups.

† Significantly different from the 60-mg/kg group.

Discussion

We have demonstrated that rectal acetaminophen has a clear dose-dependent morphine-sparing effect in children, with significance reached with a 40- or 60-mg/kg dose. These relatively high single doses reduced the overall 24-h requirement of postoperative pain medication. No previous study has shown similar effects, even though the current clinical dose recommendations of acetaminophen exceed the manufacturers' guidelines.[7] Our finding that the ED_{50} of rectal acetaminophen is 35 mg/kg strongly supports Birmingham *et al.*[17] in their recommendation that the initial dose of rectal acetaminophen should be approximately 40 mg/kg.

The currently recommended doses for oral and rectal administration of acetaminophen are the same. However, the rectal dose should perhaps be higher than the oral dose because of poor and erratic absorption of acetaminophen from suppositories.[18,19] Montgomery *et al.*[20] found that plasma concentrations following a single 45-mg/kg rectal dose of acetaminophen (13 ± 6 μg/ml [mean ± SD]) are comparable with those resulting from 10–15 mg/kg of oral acetaminophen. Birmingham *et al.*[17] studied the pharmacokinetics and bioavailability of acetaminophen after 10, 20, and 30 mg/kg of rectal administration. Serum concentrations obtained over a 24-h period after the doses of 10 and 20 mg/kg were less than the range generally associated with an antipyretic effect (10–20 μg/ml). The dose of 30 mg/kg resulted in a mean maximum serum concentration of 14.2 μg/ml. These results corroborate the findings of Anderson *et al.*[19] reporting a maximum concentration of 17.2 μg/ml following a rectal dose of 40 mg/kg.

Although plasma concentrations of acetaminophen required for analgesia have not been defined, the accepted

therapeutic plasma concentration range for an antipyretic effect is 10–20 μg/ml.[8] Following oral administration of acetaminophen the peak concentration is usually achieved between 30 min and 1 h.[21–23] In contrast, several authors have reported that the peak plasma concentration occurred in an average of 2 to 3 h after rectal suppository insertion.[17,19,20] We found that there was a clear decrease of pain already within 45 min after drug administration when a single dose of 40–60 mg/kg of acetaminophen was used. This may be explained by the zero-order dissolution and first-order absorption of acetaminophen from the rectal cavity soon after insertion of a suppository.[17] Rusy *et al.*[13] found no detectable plasma concentration of acetaminophen in 20 min but a clear concentration at 40 min after rectal administration of 35 mg/kg of acetaminophen. Hopkins *et al.*[24] found detectable plasma concentration within 30 min after a dose of 15 mg/kg of rectal acetaminophen. The vehicle base of the suppository has been shown to have a profound effect on the absorption of poorly soluble drugs such as acetaminophen.[25] We used lipid-soluble suppositories that produce higher plasma concentrations than water-soluble suppositories.[26] This may explain the fast onset of effect following large single acetaminophen doses in our study.

The finding that a single high dose of acetaminophen reduced the need for a rescue pain-killing medication for an extended period at home was not expected. Only 17–20% of the patients who received 40 or 60 mg/kg of acetaminophen required ibuprofen at home within 24 h postoperatively, as opposed to 80% of those who received placebo, even though each child left for home free of pain. This indicates that a single effective dose of acetaminophen seems to have significant beneficial effects far beyond its expected pharmacokinetic profile. This means that if a high-enough peak concentration is reached the effect may be longlasting.

The experience of postoperative pain is the most important single cause for longlasting postoperative temper tantrums and untoward behavioral changes in children.[27] Therefore, it is of crucial importance to find the dosages of drugs that may prevent this experience. A single high dose of acetaminophen is a very promising agent for further studies. This is important, as postoperative pain also seems to be a clear predictor of postoperative nausea and vomiting in children.[28] Ten of the 30 patients who did not receive acetaminophen had postoperative nausea and vomiting, as opposed to only 1 child of the 60 who received either 40 or 60 mg/kg of acetaminophen. This difference may partially be explained by the more frequent use of morphine in the placebo group, as even a single dose of morphine is documented to increase the incidence of postoperative nausea and vomiting in children.[29] However, as postoperative pain even without opioids is associated with nausea and vomiting,[10,11,28] it is important to treat postoperative pain as effectively as possible.

Our findings on the efficacy of acetaminophen in pediatric postoperative pain treatment are clinically important if pain is mild or moderate. It is noteworthy that 10% of the children in the placebo group did not need any pain medication at all. Opioids finally have an important role in controlling severe pain. However, generally used rectal doses of acetaminophen (10–15 mg/kg) should clearly be replaced with higher single doses of 40–60 mg/kg to achieve better pain control. The higher doses are not only more effective than the smaller doses but also seem to cause less untoward events. There are no guidelines for maintenance doses of acetaminophen following these single high rectal doses, and a daily maximum dose should be limited to 90–120 mg/kg.[7]

We found that 20 mg/kg of rectal acetaminophen did not significantly reduce the pain in the PACU compared with placebo. The dose of 40 mg/kg of acetaminophen reduced the incidence of pain, and 60 mg/kg was most effective. These results clearly indicate that a single high dose of acetaminophen (60 mg/kg) is superior to any smaller dose. However, further studies are indicated to document the safety and efficacy of this dose in a larger patient population, in other surgical conditions, and in situations in which acetaminophen therapy is to be continued for several days. Nahata *et al.*[30] have shown the possibility of cumulation after repeated doses of acetaminophen in 2 to 3 days. We always prescribed ibuprofen as a rescue analgetic for home and do not recommend several daily high doses of acetaminophen be administered until more studies on the safety of acetaminophen have been conducted.[31,32]

In conclusion, we found that acetaminophen has a clear dose-related potency for postoperative pain in pediatric day-case surgery. Based on our results, it is not good clinical practice to administer acetaminophen as an analgesic for postoperative pain at recommended rectal doses of 10–15 mg/kg, because the ED_{50} of rectal acetaminophen is 35 mg/kg.

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