Background. Doses of acetaminophen 40 mg kg\(^{-1}\) rectally and 15 mg kg\(^{-1}\) i.v. produce similar effect-site concentrations. However, the clinical effectiveness of these routes has not been compared. The aim of this study was to compare duration and efficacy of analgesia in children following adenotonsillectomy after acetaminophen either 40 mg kg\(^{-1}\) rectally or 15 mg kg\(^{-1}\) i.v.

Methods. Fifty children aged between 2 and 5 yr were recruited. They received a standardized anaesthetic, including 2 mg kg\(^{-1}\) of fentanyl. Children were randomized to receive either rectal or i.v. acetaminophen. Postoperative pain was assessed regularly with the Children and Infants Postoperative Pain Scale score and rescue analgesia provided if scores were 4 or greater. The primary outcome measure was time to first analgesia. Results were plotted with a Kaplan–Meier analysis and median time to rescue analgesia compared between the groups.

Results. The protocol was successfully completed in 46 children. Forty-five children required rescue medication. The time to first rescue analgesia was longer in children receiving rectal acetaminophen (median 10 h, inter-quartile range 9–11 h) compared with those receiving i.v. acetaminophen (7, 6–10 h) with a \(P\)-value of 0.01 by log-rank test for equality in survivor function. Few children in either group required rescue analgesia within the first 6 h with differences between the groups being most prominent in the period from 6 to 10 h.

Conclusions. Rectal acetaminophen 40 mg kg\(^{-1}\) provides longer analgesia for moderately painful procedures when compared with 15 mg kg\(^{-1}\) acetaminophen i.v.

Br J Anaesth 2008; 100: 251–5

Keywords: analgesia, paediatric; analgesic techniques, i.v.; analgesics non-opioid, acetaminophen; drug delivery, rectal; surgery, otolaryngological

Accepted for publication: November 22, 2007

Adenoidectomy with or without tonsillectomy is among the most common surgical procedures carried out in children. These procedures are associated with an increased risk of respiratory adverse events, bleeding, pain after surgery, and postoperative nausea and vomiting (PONV).\(^1\)–\(^3\) Analgesia is often provided with a combination of small doses of opioids along with non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, as acetaminophen and NSAIDs have an opioid-sparing effect. However, the optimum route of administration of acetaminophen is unclear. Oral acetaminophen produces an unpredictable plasma concentration,\(^4\) may not be accepted by all children, and administration after surgery may be limited by PONV and inability to swallow. Alternatively, the
rectal route can be used after induction of anaesthesia; however, it may be less acceptable to some patients and plasma concentrations may be unpredictable and may not achieve therapeutic levels in some cases.\textsuperscript{5–7} IV acetaminophen provides less variability in plasma concentrations.\textsuperscript{8–11} Although plasma levels are more predictable with i.v. acetaminophen, there are few studies actually comparing the clinical efficacy of i.v. acetaminophen with other routes. This randomized observer blind controlled trial was designed to compare efficacy and duration of analgesia in children after adenoidectomy with or without tonsillectomy randomized to receive either 40 mg kg\textsuperscript{-1} rectal or 15 mg kg\textsuperscript{-1} i.v. acetaminophen. These doses of acetaminophen were chosen as they produce equivalent plasma levels.

**Methods**

After approval by the ethics committee of the Ospedali Riuniti di Bergamo, informed written consent was obtained from the parents of 50 children with American Society of Anesthesiologists physical status I–II, aged 2–5 yr, weighing <30 kg, and undergoing elective adenoidectomy or adenotonsillectomy. Children were selected at the preoperative anaesthetic evaluation the day before surgery. Exclusion criteria were: emergency surgery; known hypersensitivity to the drugs under study; a known history of active and severe renal, hepatic, respiratory, or cardiac disease; a history of seizures; neurological or neuromuscular disorders; and history of chronic pain or analgesic drug use. All children were fasted and received rectal premedication with atropine 0.01 mg kg\textsuperscript{-1} and midazolam 0.5 mg kg\textsuperscript{-1} 30–45 min before surgery. EMLA cream\textsuperscript{®} (Astra Zeneca, Milan, Italy) was applied on both hands and arms. Peripheral i.v. access was secured and anaesthesia was induced with propofol 3–5 mg kg\textsuperscript{-1} and fentanyl 1–2 μg kg\textsuperscript{-1}. Succinylcholine 1 mg kg\textsuperscript{-1} was given to facilitate endotracheal intubation with a cuffed endotracheal tube. Anaesthesia was maintained with sevoflurane 2–2.5% in oxygen/air mixture. All children received dexamethasone 0.1 mg kg\textsuperscript{-1} before surgery as an antiemetic. Blood pressure (BP), heart rate (HR), respiratory rate (RR), and oxygen saturation were continuously monitored. The surgery was performed by one of the two staff surgeons who use similar surgical techniques.

After induction, patients were randomized to receive either acetaminophen 15 mg kg\textsuperscript{-1} i.v. (Perfalgan\textsuperscript{®} 10 mg ml\textsuperscript{-1}, Bristol-Myers Squibb, Sermoneta, Italy) (IV group) or 40 mg kg\textsuperscript{-1} rectally (PR group). Combinations of different dose suppositories (Tachipirina Angelini\textsuperscript{®}, Roma, Italy; 125, 250, 500, 1000 mg) were used to deliver the total amount.

After surgery, patients were transferred to the recovery room. HR, systolic arterial BP, RR, and oxygen saturation were monitored continuously. Pain intensity, emergence agitation,\textsuperscript{12} and Aldrete score were recorded every 10 min until an Aldrete Score of 8 was achieved. Behaviour after operation was evaluated using a four-point agitation scale: (1) calm child, no intervention required; (2) consolable child, requires only physical contact with the parents; (3) agitated child, a screaming and crying child; and (4) aggressive child, must be physically restrained in order to avoid harm. We defined significant postoperative agitation as an agitation scale 3 or 4.

Postoperative pain was evaluated using the Children and Infants Postoperative Pain Scale (CHIPPS),\textsuperscript{13} Pain intensity was assessed every 15 min in the recovery room, every 2 h during the first 6 h after surgery, and every 4 h after that by the ward nursing staff. Children were evaluated more frequently if any member of staff or the parents indicated that they thought the child may be in pain. If a CHIPPS score of ≥4 was found in the recovery room, the child received rescue analgesia as a bolus of fentanyl 0.5 μg kg\textsuperscript{-1}. After discharge from the recovery room, any children with a CHIPPS score ≥4 received rescue medication of acetaminophen 20 mg kg\textsuperscript{-1} rectally. The primary outcome of the study was time to first rescue analgesia, which was defined as time from tracheal extubation to the first request or indication for supplemental analgesia because of CHIPPS score ≥4.

Children were discharged home the day after surgery and contacted via telephone during the next 24 h. The child’s comfort at home was assessed using a previously described scale designed to assess recovery after adenotonsillectomy. The scale comprises six separate measures, each of which is assigned a score and the score then summed: spontaneous pain and pain at swallowing (verbal scale 0–4 each), occurrence of PONV (0 or 1), disturbed feeding (0 or 1), sleep (0 or 1), and play (0 or 1).\textsuperscript{14} A total score of 4 or less points is considered as very satisfactory.

Preoperative evaluation and data collection were carried out by an anaesthetist not primarily responsible for the conduct of the anaesthesia. This anaesthetist obtained consent, confirmed validity of the inclusion criteria, and allocated the patients using computer-generated random number sequence to the study groups. The anaesthetists and nurses who recorded study measures in the postanaesthesia care unit, during recovery, and during the follow-up telephone interview were unaware of the study group assignment. Pain was assessed by a number of different nurses and anaesthetists who were all familiar with the CHIPPS scale and all unaware of treatment allocation.

Previous studies have demonstrated that the mean analgesic duration of rectal acetaminophen is of 4–6 h with a standard deviation of 2 h.\textsuperscript{15} We considered a 30% decrease in analgesic time to be clinically significant. On the basis of the formula for normal theory and assuming a two-sided type I error of 0.05 and a power of 0.90, an estimated sample size of 21 children per group was required. Twenty-five children were enrolled in each group to allow for protocol violations. The primary outcome is time to rescue medication. Median and inter-quartile ranges of
time to rescue medication are described and Kaplan–Meier survival curves generated with equality of survivor functions between the groups compared with a log-rank test. Other secondary outcomes are compared between the groups with \( \chi^2 \) analysis. All analysis was done with STATA version 9.0 (Stata Corporation, College Station, TX, USA).

Results

Fifty children were enrolled in the study and four were excluded because of protocol violations. One child received a double dose of rectal acetaminophen and three (one in PR and two in IV) did not receive fentanyl during induction. There were no substantial differences in age, weight, type of surgery, surgical time, intraoperative fentanyl, wake-up time, or incidence of postoperative agitation (Table 1). One child (IV group) needed rescue fentanyl in the recovery room with a CHPPS >4 15 min after extubation. Forty-five children (98%) received rescue analgesia within 13 h after surgery. One child (PR group) did not receive any rescue analgesia during the first 24 h after surgery.

The Kaplan–Meier survival curves (Fig. 1) for the two groups show that the time to first analgesic request was longer in children receiving rectal acetaminophen (median 10 h, inter-quartile range 9–11 h) compared with those receiving i.v. acetaminophen (7, 6–10 h) (\( P \)-value 0.01 by log-rank test for equality in survivor function). Very few children needed rescue analgesia in the first 6 h with differences between the groups being most prominent in the period from 6 to 10 h.

There was no evidence for any difference between the groups in the score of comfort at home. Fourteen children (61%) in the IV group and 18 children (78%) in PR group had a global comfort score at home of three or less points (\( P = 0.3 \)) (Table 2). Interestingly, seven of 14 children with a global comfort scale >4 did not receive analgesia at home. Parents of those children did not give analgesics to their child because of fear of the adverse effects of analgesics or because they wanted their child to ‘resist’ pain.

### Table 1

Patient characteristics. Data are mean (SD) for weight, dose of fentanyl, duration of surgery, and wake-up time; mean (SD) (range) for age; number of children (%) for type of surgery, gender, or incidence or significant postoperative agitation. A, adenoidectomy; AT, adenotonsillectomy

<table>
<thead>
<tr>
<th></th>
<th>PR (n=23)</th>
<th>IV (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>48.9 (6.8) (28–60)</td>
<td>46.9 (9.3) (26–60)</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>12 (52%)/11 (48%)</td>
<td>8 (35%)/15 (65%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>19 (3)</td>
<td>18 (3)</td>
</tr>
<tr>
<td>Operation type (A/AT)</td>
<td>14 (61%)/9 (39%)</td>
<td>15 (65%)/8 (35%)</td>
</tr>
<tr>
<td>Fentanyl dose (µg kg(^{-1}))</td>
<td>1.6 (5)</td>
<td>1.6 (5)</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>17 (8)</td>
<td>22 (12)</td>
</tr>
<tr>
<td>Wake-up time (min)</td>
<td>18 (8)</td>
<td>14 (6)</td>
</tr>
<tr>
<td>Significant postoperative agitation</td>
<td>8 (35%)</td>
<td>11 (48%)</td>
</tr>
</tbody>
</table>

### Discussion

In this study, we demonstrated longer analgesic effectiveness with rectal acetaminophen 40 mg kg\(^{-1}\) compared with i.v. acetaminophen 15 mg kg\(^{-1}\). IV acetaminophen is a new method to deliver acetaminophen, which has the theoretical advantage of greater predictability and acceptability compared with oral or rectal routes of delivery. However there are few, if any studies directly comparing routes of delivery for actual analgesic effectiveness.

The ideal effect-site concentration of acetaminophen for adequate analgesia remains unclear. The relationship between plasma levels, effect-site levels, and analgesia is complex and incompletely understood. An effect-site concentration of around 10 mg litre\(^{-1}\) has been suggested to provide effective analgesia for minor to moderate pain. Several studies have suggested that a single rectal dose of 45 mg kg\(^{-1}\) provides plasma concentrations of 10–20 mg litre\(^{-1}\) and therefore this dose is often used as the appropriate loading dose if acetaminophen is given rectally. There are some data on i.v. acetaminophen; however, much of them pertain to propacetamol. One gramme of propacetamol is hydrolysed to 0.5 g acetaminophen and therefore 15 mg kg\(^{-1}\) of acetaminophen is equivalent to 30 mg kg\(^{-1}\) of propacetamol. Thirty milligrammes per kilogramme of propacetamol given 6 hourly provides a plasma concentration of 10 mg litre\(^{-1}\) and a pain reduction of 2.6/10 after tonsillectomy and acetaminophen 15 mg kg\(^{-1}\) i.v. is well tolerated and has a similar efficacy to propacetamol 30 mg kg\(^{-1}\) for providing pain relief in children. Therefore, the recommended initial dose for i.v. acetaminophen is 15 mg kg\(^{-1}\). We chose to compare single doses of acetaminophen 40 mg kg\(^{-1}\) rectally and 15 mg kg\(^{-1}\) i.v. as these are the often used doses associated with similar plasma levels.

We acknowledge that information on plasma levels could have added to our understanding of the pharmacokinetic and pharmacodynamic properties of acetaminophen; however, the primary research question of this trial was clinical effectiveness of the two recommended doses, and questions of pharmacokinetics or pharmacodynamics...
would be best answered in trials specifically designed to address these. In addition, taking blood can be difficult in children and for ethical reasons should be done only when the information gleaned is most likely to be useful. The doses used in this study were also based on previously published pharmacokinetic data which had produced plasma levels well below toxic levels.

Contrary to our findings, previous studies have found rectal acetaminophen to provide erratic and inconsistent analgesia after tonsillectomy.22–24 This variation may be explained by differing analgesic requirements with different surgical techniques, different doses of acetaminophen, or the concurrent use of other analgesic agents. The observation that rectal acetaminophen provided good analgesia in spite of previously described erratic absorption might indicate that either the effect-site concentration needed to provide effective analgesia in this population is low or that the relationship between effect-site concentration and analgesia is more complex than expected.9 Rectal acetaminophen would be expected to have a slower onset than i.v. acetaminophen. In our study, acetaminophen was given after induction and at least 20 min before the end of the procedure. All but one child had effective analgesia early after recovery, indicating that this period was sufficient to achieve adequate effect-site concentrations after rectal administration of this dose of acetaminophen. No further conclusions are possible with respect to analgesia onset times.

A possible confounding factor in the study could be if adenoidectomy is less painful than adenotonsillectomy. However, there was no significant difference between the groups in the type of surgery, and six of the eight children who required rescue analgesia during the first 6 h after surgery had adenoidectomy. All children received dexamethasone, giving some analgesic effect which should be considered when extrapolating these results to other populations. The patients in the ER group had also received a rectal premxed with midazolam and atropine. This may have altered the absorption situation for the acetaminophen in a way that it improved the efficacy of rectal acetaminophen.

Our study suggests that the duration of analgesia is shorter with 15 mg kg⁻¹ paracetamol i.v. than with 40 mg kg⁻¹ rectally. Both routes provided good analgesia for the first 6 h with differences between the groups being most prominent in the period from 6 to 10 h. Presumably, the effect-site concentration is maintained for a longer period with the larger rectal dose in spite of lower bioavailability. For continuing analgesia, i.v. acetaminophen is recommended to be repeated every 6 h, and the results from this study would support this recommendation. In contrast, a longer period may be possible before rectal acetaminophen is repeated. In conclusion, if acetaminophen is given as a single dose to provide analgesia for moderate–mild pain for a period of more than 6 h rectal rather than i.v. administration should be considered.

**Funding**

The study was funded by the department of Anesthesia and Intensive care of the Ospedali Riuniti di Bergamo and the Dipartimento di medicina sperimentale, ambientale e biotecnologie mediche of the Milan Bicocca University.

**Table 2 Comfort at home. Data are number of children (%) unless otherwise specified**

<table>
<thead>
<tr>
<th></th>
<th>PR (n=23)</th>
<th>IV (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous pain 0/1/2/3/4</td>
<td>6 (26%)/9 (39%)/8 (35%)/0/0</td>
<td>4 (17%)/13 (57%)/6 (26%)/0/0</td>
</tr>
<tr>
<td>Pain on swallowing 0/1/2/3/4</td>
<td>1 (4%)/5 (22%)/13 (57%)/3 (13%)/1 (4%)</td>
<td>0/5 (22%)/16 (70%)/2 (9%)/0</td>
</tr>
<tr>
<td>PONV at home</td>
<td>2 (9%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Disturbed sleep</td>
<td>7 (30%)</td>
<td>11 (48%)</td>
</tr>
<tr>
<td>Disturbed feeding</td>
<td>7 (30%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Disturbed play</td>
<td>3 (13%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Total score, mean (SD) (range)</td>
<td>3.8 (2.0) (1–8)</td>
<td>4.2 (1.8) (2–8)</td>
</tr>
<tr>
<td>Number with score ≤4</td>
<td>18 (78%)</td>
<td>14 (61%)</td>
</tr>
</tbody>
</table>

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