Acetaminophen analgesia in children: placebo effect and pain resolution after tonsillectomy

Abstract Background: Pharmacodynamic models of acetaminophen analgesia in children have not explored the efficacy of single oral doses greater than 40 mg/kg. Methods: Children aged 9.0 ± 3.0 years (±SD) and weight 37.9 ± 16.6 kg undergoing outpatient tonsillectomy were randomised to receive acetaminophen elixir 40 mg/kg (n = 12), high dose acetaminophen elixir 100 mg/kg (n = 20) or placebo (n = 30) 0.5–1 h preoperatively. No other analgesics were given. Individual acetaminophen serum concentrations and pain scores [visual analogue scale (VAS) 0–10] were measured over a 4–8 h postoperative period. These data were pooled with data from a previous study investigating acetaminophen pharmacodynamics (n = 120) and analysed using a non-linear mixed effect model. Placebo effects and drug effects were modelled using effect-site concentration models.

Results: A one-compartment model with first-order input, lag time and first-order elimination was used to describe the population pharmacokinetics of acetaminophen. Pharmacokinetic parameter estimates were similar to those previously described. Pharmacodynamic population parameter estimates [population variability coefficient of variation (CV)] for a maximum analgesic effect (Emax) model, in which the greatest possible pain relief (VAS 0–10) equates to an Emax of 10, were Emax 5.17 (64%) and 50% effective concentration 9.98 mg/l (107%). The equilibration half-life (teq) of the analgesic effect compartment was 53 min (217%). A placebo drug model for the effects of placebo response had a teq of 1.96 h (40%), an elimination half-life of 2.06 h (50%) and a potency of 1.54 pain relief units (24%).

Conclusions: High dose acetaminophen (100 mg/kg) was no more effective than 40 mg/kg and was associated with increased nausea and vomiting. A target effect concentration of 10 mg/l is expected to produce a pain reduction of 2.6 units. The placebo model accounted for a maximum pain reduction of 5.6 units at 3 h. The combination of placebo effect and preoperative acetaminophen 40 mg/kg results in pain scores below 4 units for 5 h postoperatively.

Keywords Analgesia · Allometric size model · Paracetamol

Introduction

It is hard to find a quantitative description of either the time course of pain resolution after tonsillectomy in children or the effect of simple analgesics on the pain. Lavy [1] has reported the time course of pain resolution between day 1 and day 14 after tonsillectomy, but the pain’s natural history in the immediate postoperative period is unknown. Serious ethical concerns often preclude the mapping of such pain using placebo controls in paediatric analgesic trials. We have recently described the postoperative time course of acetaminophen analgesia in children after tonsillectomy using a pharmacokinetic–pharmacodynamic model, however that study had three potential drawbacks [2]. First, it was not placebo controlled and therefore could not account for
the placebo effect that could contribute significantly to analgesia. Second, the pain stimulus was assumed to remain constant over the 4-h postoperative observation period. Lastly, using a dose of 40 mg/kg we were able to measure a mean analgesic effect intensity of only 68% of the predicted maximum analgesic effect ($E_{max}$), which creates uncertainty in the estimate of the true efficacy of acetaminophen.

Korpela et al. [3] have shown a linear relationship between acetaminophen dose and postoperative rescue morphine requirement in children undergoing day-stay surgery. Eighty percent of children given acetaminophen 60 mg/kg rectally had no need for rescue morphine. Efficacy (maximum possible analgesia) was not determined.

In order to identify more clearly the efficacy of acetaminophen, we studied a further group of children undergoing tonsillectomy given either placebo or high doses of acetaminophen (100 mg/kg) preoperatively as a single dose. The usual daily dose of acetaminophen is 90 mg/kg [4, 5, 6]. Single doses of 200 mg/kg in children are not associated with hepatotoxicity [7, 8, 9]. Opioids are thought to have greater efficacy than acetaminophen but are associated with an incidence of postoperative vomiting of 50–70% after tonsillectomy [10, 11, 12]. We wished to test whether high doses of acetaminophen could produce pain relief similar to opioids but with a lower risk of vomiting. Data from Lavy [1] were used to quantify pain resolution after the day of surgery in children under 10 years and in young adults.

**Materials and methods**

**Study design**

Approval from the Regional Health Authority ethics committee was obtained for all three studies included in this current analysis. Parental consent was given for each child in each study. All studies were very similar in design, exclusion criteria and population demographics. The studies were:

a. Current high-dose acetaminophen study patients. Children with an American Society of Anesthesiologists physical status (ASA) 1 and 2, age 6–15 years and scheduled for outpatient tonsillectomy with or without adenoidectomy were enrolled into the study. Children with hepatic or renal disease, acetaminophen allergy or already receiving acetaminophen within 24 h of surgery were excluded. Children were randomised to receive either acetaminophen elixir 40 mg/kg ($n = 12$) or acetaminophen elixir 100 mg/kg ($n = 20$), given between 0.5 h and 1 h preoperatively. No other premedicant or analgesic agents were administered. Anaesthesia was induced with either propofol 3 mg/kg intravenously or inhalation of halothane and 70% nitrous oxide in oxygen. Anaesthetic maintenance consisted of halothane in 70% nitrous oxide in oxygen. Tonsil dissection was carried out using monopolar coagulation diathermy, and any subsequent bleeding was arrested with packing or bipolar diathermy. Children were extubated once the surgical field was dry and laryngeal reflexes had returned. They were then transported to the post-anaesthetic care unit (PACU). All children received 20 ml/kg of a balanced salt solution intravenously. The oral elixir was supplied as a sugar-free, alcohol-free preparation with a standard strength of 250 mg/5 ml (SmithKline Beecham Ltd, Auckland, New Zealand).

b. Previous acetaminophen study patients. We have reported the perioperative pharmacodynamics of acetaminophen in children undergoing outpatient tonsillectomy [2]. These children (ASA 1 and 2, age 2–15 years) were administered acetaminophen either orally, 0.5–1.0 h preoperatively ($n = 20$), or per rectum at induction of anaesthesia ($n = 100$). No other premedicant or analgesic agents were administered. Individual concentrations of acetaminophen in serum and pain scores (0–10) were measured over a 4-h postoperative period. The rectal suppositories were an acetaminophen slurry contained in a glycoegalatin capsule and are available in two sizes 125 mg and 250 mg [Sanofi Winthrop (NZ) Ltd, Auckland, New Zealand].

c. Placebo patients. Observations in children receiving a placebo (and rescue medication with morphine) were available from an unpublished study we have completed, with the same design, investigating diolenoac analgesia after tonsillectomy. Sera from this study have not yet been assayed for diolenoac concentrations, but the study included a group of 30 children randomised to receive black currant fruit juice as placebo between 0.5 h and 1 h preoperatively.

d. Validation patients. The above unpublished study also included 25 children (ASA 1 and 2, age 2–15 years) given acetaminophen elixir 40 mg/kg 1 h preoperatively with an additional rectal acetaminophen suppository 20 mg/kg at the end of adenotonsillectomy surgery, approximately 1.5 h after elixir dosing.

**Observations**

Postoperative pain was assessed using a visual analogue scale (VAS, 0–10) [13]. A score of 10 is the worst pain imaginable to the individual child. In this current high-dose acetaminophen study, pain scores were made at hourly intervals after admission to the PACU and continued until discharge from the day-stay facility approximately 4–8 h after surgery. Blood samples for acetaminophen concentrations were taken from indwelling venous canulae. All children (including those given placebo) had the first blood sample taken following anaesthetic induction and then 3–5 samples were taken over the subsequent 4–8 h study period. Pain score recordings and blood sampling were performed by a research nurse. Pain scores and blood samples were collected at 30-min intervals in our previous study [2]. Once awake and alert all children were offered flavoured blocks of ice. They were kept a minimum of 4 h prior to discharge home.

Children in severe pain (as assessed by nursing staff) had a blood sample drawn for acetaminophen assay and were then given rescue morphine 0.05 mg/kg as needed. No further pain scores were collected from this subgroup of children. The data from children enrolled into the current study ($n = 32$) were combined with those from the placebo group ($n = 30$) and those 120 children studied previously [2]. These pooled data ($n = 182$) were analysed together. Children from the validation group given the combination of acetaminophen elixir (40 mg/kg) and subsequent suppository (20 mg/kg) had pain scores and blood samples collected at 30-min intervals for 2.5 h after surgery. The data from these children were used to validate the pooled data analysis.

**Assessment of adverse effects in current study patients**

At the end of the study period children were given alternative analgesic drugs (diolenoac, ibuprofen, codeine) to use overnight. No further acetaminophen was used until the following morning. Prescriptions for subsequent acetaminophen dosing were no greater than 90 mg/kg/day.

All children were followed up by telephone on the day after surgery, and the occurrence of postoperative vomiting was sought. A request was made for children to present for phlebotomy on day 2 or day 3 after surgery to measure hepatic transaminase concentrations.