Acetaminophen, ibuprofen, and tramadol analgesic interactions after adenotonsillectomy

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Summary

Background: The impact of tramadol in children given acetaminophen-ibuprofen combination therapy is uncertain in acute pediatric pain management. A model describing the interaction between these three drugs would be useful to understand the role of supplemental analgesic therapy.

Methods: Children undergoing tonsillectomy were given oral paracetamol and ibuprofen perioperatively. Blood was taken for paracetamol and ibuprofen drug assay on up to six occasions over 6 h after the initial dose. Tramadol was administered by caregivers for unacceptable postoperative pain. Pain was measured using the Parent's Postoperative Pain Measurement rating two hourly on the first postoperative day. A first-order absorption, one-compartment linear model with first-order elimination was used to describe acetaminophen and ibuprofen disposition. Analgesia was described using an E\text{MAX} model extended for three drugs, assuming additive effects. Curve fitting was performed using nonlinear mixed effects models.

Results: Pharmacodynamic parameter estimates, expressed using fractional Hill equation, were maximum effect (E\text{MAX}) 0.65 (95%CI 0.54, 0.74), the concentration of acetaminophen associated with 50% of the maximal drug effect (C\text{50,ACET}) 7.06 (95% CI 7.03, 7.72) mg/L, and the ibuprofen C\text{50} (C\text{50,IBU}) 3.95 (95%CI 2.57, 7.53) mg/L. The Hill coefficient was 1.48 (95%CI 0.92, 2.62) and an interaction term was fixed at zero (additivity). The half-time (t\text{1/2,keo}) for equilibration between the plasma and effect site was 0.34 hour (95%CI 0.23, 1.98) for acetaminophen and 1.04 hour (95% CI 0.75, 1.77) for ibuprofen. Tramadol had a C\text{50,TRAM} of 0.07 (95%CI 0.048, 1.07) mg/L with a t\text{1/2,keo,TRAM} 1.78 hour (95%CI 1.06, 1.96).

Conclusion: Ibuprofen has an EC50 for analgesia in children similar to that of adults (3.95 mg/L; 95%CI 2.57-7.53, vs 5-10 mg/L adults). The maximum effect from combination therapy (ie, 65% reduction in pain score) achieves satisfactory analgesia with commonly used doses but increased dose adds little additional benefit. The addition of tramadol to this analgesic mixture prolongs analgesia duration.

KEYWORDS

drug interactions, drugs, pharmacodynamics, pharmacokinetics, response surface models
1 | INTRODUCTION

Acetaminophen (paracetamol) and ibuprofen are established therapies for postoperative pain management in adults and children. Both drugs display analgesic and antipyretic effects, and do so via distinct mechanisms of actions.\(^1\) They can be safely combined without increases in their associated adverse effect profiles and combination therapy is used for analgesia after tonsillectomy in children.\(^2\)\(^—\)\(^5\) A maximal analgesic effect (E\(_{\text{MAX}}\)) of approximately 5/10 using a visual analog scale (VAS 0-10) has been reported for acetaminophen in children after tonsillectomy\(^6\) and for dental pain relief in adults given ibuprofen;\(^7\) however an E\(_{\text{50}}\) for ibuprofen (effective concentration for 50% maximal effect) has yet to be reported in children. When paracetamol and ibuprofen are used as combination therapy, a similar maximal analgesic effect but with prolonged duration has been observed in adults suffering dental pain.\(^8\)\(^—\)\(^9\) Similar results have been reported in children given diclofenac and acetaminophen for postoperative tonsillectomy pain.\(^10\)

Despite the use of paracetamol and nonsteroidal anti-inflammatory drug combination therapy children continue to suffer pain after adenotonsillectomy.\(^11\)\(^—\)\(^13\) Medications such as tramadol,\(^13\) codeine,\(^14\) morphine,\(^15\) oxycodone,\(^16\) and hydrocodone\(^12\) have all been used to supplement analgesia. Tramadol 1 mg/kg may have less potential to cause respiratory depression than equivalent doses of other opioid analgesics,\(^7\)\(^—\)\(^18\) but the drug’s impact as a supplemental analgesic after adenotonsillectomy is poorly quantified.

The aim of this current study was to quantify the combination ibuprofen-acetaminophen analgesia relationship after adenotonsillectomy in children, obtaining an estimate of ibuprofen potency (C\(_{\text{50}}\), ibu), and to assess the impact of supplemental tramadol in those children. In addition, we had opportunity to pool data using an external dataset from adults given ibuprofen and acetaminophen for molar extraction\(^19\) that allowed exploration of differences between adult and child and the different pain types.

2 | MATERIALS AND METHODS

Data were available from a study sponsored by AFT Pharmaceuticals (Auckland, New Zealand). The study was conducted in three sites in New Zealand (n = 179), one in Australia (n = 18), and one in Mexico (n = 60). The study was approved by the NZ Health and Disability Ethics Committee (5/CEN/50/AM06), the Mexican Regulatory Authority, Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS 163300CT190195) and the Human Research Ethics Committee in Australia (HREC/15/RCHM/75). Trial registration was with (ACTRN 12615000456550) Australia New Zealand Clinical Trials Registry.

2.1 | Formulations

The doses used in this study were based either on an acetaminophen dose of 48 mg/kg/day or 60 mg/kg/day in four divided doses which are combined with a corresponding ibuprofen dose in a 3.3:1 ratio.\(^20\)\(^—\)\(^21\) The ‘low dose’ regimen comprised a loading dose of a combination oral suspension (paracetamol 24 mg/kg and ibuprofen 7.2 mg/kg) followed by 4-6 hourly doses of paracetamol 12 mg/kg and ibuprofen 3.6 mg/kg. The ‘high dose’ regimen was a preoperative loading dose of a combination oral suspension (paracetamol 30 mg/kg and ibuprofen 9 mg/kg) followed by 4-6 hourly doses of paracetamol 15 mg/kg and ibuprofen 4.5 mg/kg. Doses were capped at a maximum of four doses within any 24-hour period.

2.2 | Patients

Children, 2-12 years of age, presenting to a study center for elective tonsillectomy or adenotonsillectomy were eligible for inclusion. Participants were excluded if they weighed less than 10 kg, had taken any NSAID or paracetamol in the 12 hours prior to surgery, suffered a neurological disorder related to pain perception, participated in another clinical trial in the previous 30 days, had a known hypersensitivity to NSAIDs or paracetamol, severe hemopoietic, renal or hepatic disease, immunosuppression, gastric disorders (ulceration, bleeding indigestion or stomach pain) or bleeding disorders, dehydrated, or suffering from diarrhea and/or vomiting or severe asthma.

2.3 | Study design

All parents or caregivers provided written informed consent and the children, where appropriate, provided written assent before inclusion in the study. Participants were randomized to either the ‘high’ or ‘low’ dose regimen using a computer-generated list prior to commencement. A researcher calculated the participant’s dose, based on their weight. This was confirmed and then administered by a study nurse. Participants were not advised of their dose regimen.
Participants were given a loading dose approximately 30 minutes before the start of surgery (Day 0). Dosing was then continued in hospital and at home for up to 11 days, every 4-6 hours, with a maximum of 4 doses in a 24-hour period.

Blood samples for paracetamol and ibuprofen assay were collected during the participants hospital stay: Sample 1 was taken as soon as the participant had undergone intraoperative venous cannulation and sample 2 immediately before leaving the operating room. A further three samples were taken at 1-2, 3-4, and 5-6 hours after the loading dose.

Pain assessments were recorded on the first postoperative day (Day 1). Parents/caregivers assessed their children's pain using the Parent's Postoperative Pain Measurement (PPPMP). Pain scores were assessed on swallowing. The first pain score was recorded on waking, immediately before the study drug was administered, then 2 hours thereafter until 2 hours after the last dose on Day 1.

2.4 | Rescue medication

Rescue medication was prescribed following the study sites’ own standard practices. In the event of rescue drug administration parents/caregivers were required to record the time and dose of each drug. If rescue was required on Day 1 parents/caregivers were also asked to complete a PPPMP, on swallowing, immediately before administration of rescue. A cursory analysis of the data revealed that tramadol was the predominant rescue medication used by study centers.

2.5 | Drug assay

Plasma extraction was by centrifugation at approximately 1300 g for 10 minutes. Approximately 2 mL of plasma was transferred into cryotubes and stored at −80°C before drug assay.

The procedure for acacetaminophen involved direct precipitation extraction of the drug and its internal standard acetaminophen-D4. The chromatographic separation employing C18 column, the mobile phase consisted of de-ionized water, formic acid, and acetonitrile. Detection was carried out using API-3000 and Quattro premier mass spectrometer in multiple reaction monitoring (MRM) mode using turbo ion spray with positive ionization. The method showed good linearity over the range at (50 – 20,000) mcg/L. The accuracy was within 20.00% at LLOQ (50 mcg/L) and 15.00% at other concentrations.

Liquid chromatography coupled to tandem mass spectrometric (LC-MS/MS) was used for determination of ibuprofen in human plasma (Li-heparin). It was developed using a Sciex API 4000 & API 3000 triple quadrupole mass spectrometer in multiple reactions monitoring (MRM) mode, with turbo ion spray in negative ionization using ibuprofen-D3 as an internal standard. The selective analysis of ibuprofen was achieved on Symmetry C18 Column, by using a mobile phase consisting of ammonium formate, methanol and acetonitrile. The method showed good linearity over the range at (50 – 35,000) mcg/L. The accuracy was within 20% at LLOQ (50 mcg/L) and 15% at other concentrations.

2.6 | Adult data comparator

Data were pooled with a published adult data. We identified a large, randomized, double blind, placebo-controlled trial comparing effectiveness of acetaminophen and ibuprofen, alone and in combination, for postoperative pain relief following the removal of impacted molars in adults. Patients were given an oral dose of either acetaminophen 250 mg with ibuprofen 100 mg, acetaminophen 500 mg with ibuprofen 200 mg, acetaminophen 1000 mg with ibuprofen 400 mg, acetaminophen 500 mg alone, acetaminophen 1000 mg alone, ibuprofen 200 mg alone, ibuprofen 400 mg alone, or placebo. The primary endpoint was the pain relief and pain intensity difference score (PRID, 0-10) from 0 to 8 hours postoperatively, displayed as the mean changes from baseline in PRID over the eight hour period. Mean time-PRID data were extracted from the published plot using the freeware Graph Extract version 2.1 (Quadtech Associates Inc, Sussex, USA). A total of 85 mean observations were extracted from time points 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hour. PRID scores from adults were scaled to PPPM equivalence (0-15) for analysis.

We have interrogated this dataset in the past and have reused it in this current analysis in order to compare pharmacodynamic parameter estimates in children and adults.

2.7 | Pharmacokinetic-pharmacodynamic analysis

2.7.1 | Pharmacokinetics (PK)

Data were analyzed using nonlinear mixed effects models (NONMEM 7.3, Globomax LLC, Hanover, MD, USA). Acetaminophen and ibuprofen PK were described using first-order absorption, one-compartment distribution, and first-order elimination. The model was parameterized in terms of clearance (CL), volume of distribution (V), and absorption half-time (Tabs). Theory based allometric scaling was used to scale parameter estimates for size. All patients were older than 2 years so we made no attempt to include maturation in the PK model.

Because tramadol was the predominant rescue medication, it was included in our analysis to account for its angesic effects. Tramadol concentrations were not available and PK (CL and V) estimates were taken from those reported in the literature. The absorption parameter (Tabs) was estimated.

2.7.2 | Pharmacodynamic interaction model

Pain scores on the first postoperative day (Day 1) were treated as continuous variables and analyzed. Predicted effect site concentrations were related to pain scores using a fractional E_max model expressing combined drug response. The PK and PD data were initially analyzed simultaneously. This method can distort PK model parameter estimates when pharmacodynamic or effect compartment model misspecification is present. Consequently, a second modeling process was undertaken whereby the PK parameters...
were estimated separately and then fixed in the PKPD model (known as the Population PK Parameters and Data, PPPD method).25,26

2.7.3  Effect compartment model for pain

The observed delay in analgesic response was described for each drug by the use of an effect compartment. The temporal relationship between concentrations in effect and plasma compartments was described using an equilibration rate constant (keo), parameterized as an equilibration half-time ($t_{1/2keo}$):

$$t_{1/2keo} = \frac{\ln(2)}{keo}$$

2.7.4  Pharmacodynamic interaction model

The model described by Greco et al27 was used to describe combined drug effects. This requires normalization of effect compartment concentrations of ibuprofen, acetaminophen and tramadol to a relative potency (or unit, U), ie,

$$U = \frac{C_{E_{IBU}}/C_{50IBU}}{C_{E_{ACET}}/C_{50ACET}} = \frac{U_{TRAM}}{C_{50TRAM}}$$

where $C_{Ex}$ is the predicted effect site concentration of drug x and $C_{50x}$ is the concentration of drug x associated with 50% of the maximal drug effect (or $E_{MAX}$). $E_{MAX}$ was constrained between 0 and 1, while a logistic distribution was used for its variability in order to maintain estimates within these limits (ie, avoid pain score estimates below zero). Drug effect $(Effect_{drug})$ was modeled for the normalized drug concentrations as:

$$Effect_{drug} = E_0 \cdot \left(1 - E_{MAX} \cdot \frac{U^{Hill}}{1 + U^{Hill}}\right)$$

where Hill is a parameter describing the steepness of the curve and $E_0$ is calculated for the Greco model as:

$$U = U_{IBU} + U_{ACET} + U_{TRAM} + \beta \cdot TB_{IBU} \cdot U_{ACET} \cdot U_{TRAM}$$

where $\beta$ is an interaction parameter. Fixing $\beta$ to a value of zero denotes no interaction (additive effects). The interaction parameter was a priori fixed at 0 based on a pragmatic approach (insufficient data of monotherapy and coverage of combination concentration pairs). As part of the final model validation, inclusion of a nonadditive interaction term ($\beta > 0$ = supra-additivity and $\beta < 0$ = infra-additivity) was tested by looking for a statistically significant improvement in NONMEM’s objective function.

2.7.5  Pain resolution

We noted that there were lower pain scores toward the end of the study period. This pain score change was modeled using an additional $E_{MAX}$ model that functioned as a disease (pain) progression score:

$$Effect_{disease} = E_{MAX,DIS} \cdot \frac{TIME^{HILLDIS}}{T_{SO,DIS} + TIME^{HILLDIS}}$$

where $E_{MAX,DIS}$ is the maximal decrease in pain score attributable to disease progression (pain resolution), $T_{SO,DIS}$ is the half-time describing this change, and $HILLDIS$ describes the slope for this change.

2.7.6  Pharmacodynamic parameter comparison between children and adults

An additional factor ($F_{ADDULT}$) was applied to pediatric pharmacodynamic parameters (eg, $E_{MAX}, C_{50}$) in order to discern differences between child and adult by seeking a change in the objective function for these nested models.

Final pharmacodynamic model

The final pharmacodynamic model comprised both the drug effect and disease progression models:

$$Pain \ Score = E_0 \cdot (1 - Effect_{drug}) \times (1 - Effect_{disease})$$

where $E_0$ was assumed a parent postoperative pain measure (PPPM) of 15 pain units (Appendix S1).

Parameter estimation

Population parameter variability was described using exponential models, which is equivalent to assuming a log-normal distribution and avoids biologically inappropriate parameter values of zero or less. Additive and proportional error models were used to describe unknown PK residual error. An additive error model was used for PD residual error. Population parameters, covariate effects, and variances were estimated using the first order conditional estimation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>CI 95%</th>
<th>Shrinkage%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{LACET}$ (L/h.70 kg$^{-1}$)</td>
<td>13.2</td>
<td>0.122, 0.147</td>
<td>28.6</td>
<td>12.6, 13.8</td>
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<tr>
<td>$V_{ACET}$ (L.70 kg$^{-1}$)</td>
<td>72.2</td>
<td>0.313, 0.42</td>
<td>22.5</td>
<td>67.8, 76.6</td>
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<tr>
<td>$TB_{ACET}$ (h)</td>
<td>0.18</td>
<td>1.53, 0.29</td>
<td>37</td>
<td>0.128, 0.23</td>
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<td>$ERR_{ADDULT,ACET}$ (mg/L)</td>
<td>2.61</td>
<td>0.178, 0.29</td>
<td>54.9</td>
<td>1.13, 2.74</td>
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<td>$ERR_{PROP,ACET}$ (%)</td>
<td>4.3</td>
<td>0.4, 0.9</td>
<td>0.4, 17.9</td>
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<tr>
<td>$CL_{IBU}$ (L/h.70 kg$^{-1}$)</td>
<td>3.83</td>
<td>0.259, 0.45</td>
<td>19</td>
<td>3.55, 4.01</td>
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<tr>
<td>$V_{IBU}$ (L.70 kg$^{-1}$)</td>
<td>16.5</td>
<td>0.381, 0.56</td>
<td>16.4</td>
<td>14.77, 18.13</td>
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<tr>
<td>$TB_{IBU}$ (h)</td>
<td>0.316</td>
<td>1.414, 0.64</td>
<td>23.9</td>
<td>0.22, 0.40</td>
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<tr>
<td>$ERR_{ADDULT,IBU}$ (mg/L)</td>
<td>1.13</td>
<td>0.235, 0.53</td>
<td>33.2</td>
<td>0.55, 2.15</td>
</tr>
<tr>
<td>$ERR_{PROP,IBU}$ (%)</td>
<td>21.3</td>
<td>0.4, 0.9</td>
<td>0.4, 14.1, 25.3</td>
<td></td>
</tr>
<tr>
<td>$CL_{TRAM}$ (L/h.70 kg$^{-1}$)</td>
<td>33.9 FIX</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>$V_{TRAM}$ (L.70 kg$^{-1}$)</td>
<td>185 FIX</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>$TB_{TRAM}$ (h)</td>
<td>1.61</td>
<td>0.045, 0.95</td>
<td>99.7</td>
<td>0.707, 1.98</td>
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</tbody>
</table>
method with interaction. Model equations were integrated using ADVAN = 13 with TOL = 9.

Model selection required a statistically significant improvement in the NONMEM objective function between nested models, equating to a reduction >3.84 based on a Chi-square distribution with one degree of freedom ($\alpha < 0.05$).

Quality of fit
The quality of fit of the pharmacokinetic model to the data was assessed by NONMEM’s objective function and visual examination of plots of observed vs predicted concentrations. Nonparametric bootstrap methods provided a means to evaluate parameter uncertainty. A total of 1000 simulations were used to estimate confidence intervals. A prediction corrected visual predicted check, a modeling tool that estimates the prediction intervals and graphically superimposes these intervals on observed data after a standardized dose, was used to evaluate how well the model predicted the distribution of observations (concentration or pain score).

In any model, the quality of the individual parameter estimate will depend heavily on the observed data available. For example, sparse data can result in reduced variance ($\omega^2$) of parameter estimates and distortions of the distribution shape. If no data are available on a particular individual, the individual’s estimate will be equal to the population value; the variance is shrinking toward zero as the quantity of information at the individual level diminishes, a phenomenon defined as shrinkage ($sh$). When there is no shrinkage the model is correct and individual data are sufficiently abundant for individual parameter estimation. Data contain virtually no information about these parameters when shrinkage is 100% and the individual parameter values approach the typical parameter value.

3 | RESULTS
There were 251 children available for study with 1168 ibuprofen and 1168 acetaminophen concentration data taken after the initial...
dose of the ibuprofen-paracetamol suspension. All concentrations were above the lower limit of quantification. Approximately one-third of the children (n = 80) were given tramadol (0.5–1 mg/kg) on the day after surgery to control pain; 34 children were given a single dose and 46 children were given multiple doses. More children given the ‘low dose’ regimen required tramadol rescue (n = 45) and 27 of these children required more than one dose. There were 35 children in the ‘high dose’ regimen that required rescue tramadol and 19 of these children required more than one dose.

There were five children given rescue medication other than tramadol on the day after surgery; oxycodone (three children from the ‘low dose’ group and one from the ‘high dose’ group), and codeine (one child from the ‘high dose’ group). These children were excluded from analysis after administration of these drugs. There were 3886 pain scores available for analysis.

Final pharmacokinetic parameter estimates and their associated population parameter variability (PPV) are shown in Table 1. The addition of a pain resolution model decreased the objective function by 167.6 points (P < 0.001). The correlation of between-subject variability for PK parameters is shown in Table S1.

Shrinkage was high for parameters such as the equilibration half-times (t½ keoACET, t½ keoIBU, t½ keoTRAM) and the EMAX for the disease progression model. These parameters also had low between-subject variability and fixing variance to zero had no impact on structural parameter estimates. There was imprecision in the estimate of the interaction term (Beta, 95%CI −0.2, 1.2) and fixing this parameter to 0 (additive interaction) did not alter the objective function, confirming our a priori assumption of additivity for this dataset. The correlation of between-subject variability for PK parameters is shown in Table S1. Prediction corrected VPCs are shown in Figure 1.

Final pharmacodynamic parameter estimates and their associated population parameter variability (PPV) are shown in Table 2. The correlation of between-subject variability for PD parameters is shown in Table S2. Prediction corrected VPCs are shown in Figure 2. We were unable to demonstrate any differences between pediatric and adult pharmacodynamic parameter estimates.

### 3.1 Simulation

Simulation was used to demonstrate the time-effect profile for various dosage regimens (12–30 mg/kg acetaminophen with 3.6–9 mg/kg

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>PPV</th>
<th>Shrinkage%</th>
<th>95% CI</th>
</tr>
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<tr>
<td>EMAX</td>
<td>0.648</td>
<td>0.503</td>
<td>22.3</td>
<td>0.542, 0.739</td>
</tr>
<tr>
<td>HILLEFFECT</td>
<td>1.48</td>
<td>-</td>
<td>-</td>
<td>0.919, 2.618</td>
</tr>
<tr>
<td>Beta (β)</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-0.2, 1.2</td>
</tr>
<tr>
<td>t½ keoACET (h)</td>
<td>0.34</td>
<td>-</td>
<td>-</td>
<td>0.23, 1.98</td>
</tr>
<tr>
<td>C50,ACET (mg/L)</td>
<td>7.06</td>
<td>0.352</td>
<td>56.9</td>
<td>7.03, 7.72</td>
</tr>
<tr>
<td>t½ keoIBU (h)</td>
<td>1.04</td>
<td>-</td>
<td>-</td>
<td>0.75, 1.77</td>
</tr>
<tr>
<td>C50,IBU (mg/L)</td>
<td>3.95</td>
<td>0.711</td>
<td>27.7</td>
<td>2.57, 7.53</td>
</tr>
<tr>
<td>t½ keoTRAM (h)</td>
<td>1.77</td>
<td>-</td>
<td>-</td>
<td>1.06, 1.96</td>
</tr>
<tr>
<td>C50,TRAM (mg/L)</td>
<td>0.0703</td>
<td>2.51</td>
<td>80.4</td>
<td>0.048, 1.07</td>
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<tr>
<td>EMAXDIS</td>
<td>0.983</td>
<td>-</td>
<td>-</td>
<td>0.934, 1.38</td>
</tr>
<tr>
<td>HILLDIS</td>
<td>5.9</td>
<td>-</td>
<td>-</td>
<td>3.92, 9.01</td>
</tr>
<tr>
<td>T50,DIS (h)</td>
<td>46</td>
<td>0.481</td>
<td>41.5</td>
<td>39.7, 53.7</td>
</tr>
<tr>
<td>ERRADD (pain units)</td>
<td>1.66</td>
<td>0.771</td>
<td>9.0</td>
<td>1.11, 1.86</td>
</tr>
</tbody>
</table>

**TABLE 2** Pharmacodynamic parameter estimates for the drug interaction model investigating the acetaminophen-ibuprofen-tramadol response surface (CI is the confidence interval; t½ keo describes the equilibration half-time; ERRADD is residual unknown variability; PPV is the apparent coefficient of variation of between-subject variability estimated with a exponential random effect (sqrt NONMEM Omega))
ibuprofen). Simulation of effect profiles over time was performed using Berkeley Madonna™ modeling and analysis of dynamic systems software (Robert Macey and George Oster of the University of California, Berkeley, USA). We used the PK and PD parameter estimates from this current analysis to simulate mean response profiles for a variety of dose combinations (Figures 3-5).

4 | DISCUSSION

Combination therapy with acetaminophen and ibuprofen mixture is more effective than either drug used alone, consistent with other reports from adults given this combination.8,20 This analgesic effect is additive, but there was a ceiling effect (E_max 0.648). Although more children given the ‘low dose’ regimen required tramadol rescue, we were unable to demonstrate important differences in pain scores between the ‘high’ and ‘low’ dose regimens using simulation (Figure 3), even with twice the dose used as a loading dose preoperatively, because this ceiling effect was approached by both regimens (Figure 4). The “high dose” regimen did have more prolonged effect. The principal effect of rescue tramadol was further prolongation of analgesia.

Tonsillectomy causes considerable postoperative pain with mean PPPM scores of 10/15 common on the first postoperative day,30,31 although tonsillectomy patients are often under-dosed; a median of only three doses of analgesia on each of the first 2 days after surgery has been reported.30 Simulation suggests that regular medication with acetaminophen and ibuprofen 4 hourly would benefit these children. Only one-third of the children required rescue medication when the drugs were given regularly in this current study. Supplementation with tramadol prolongs analgesia and would benefit children at bedtime. We noted a decrease in individual time-pain scores toward the end of the observations on the first postoperative day, a time close to that when children retire for the night. This
reduction of pain is not indicative of pain resolution because others have reported that severe pain persists for several days after surgery.\textsuperscript{30,31} It is possible that comfort measures given by caregivers before the onset of sleep contributed to this observation. Accounting for this temporary pain loss improved the model.

Pharmacokinetic parameter estimates were similar to those reported by others for both acetaminophen\textsuperscript{32,33} and ibuprofen\textsuperscript{34-37} in children. Pharmacodynamic parameter estimates were also similar to those published by others. Literature reports for an acetaminophen C$_{50,ACET}$ (7.39 mg/L) range from 2 to 13.3 mg/L\textsuperscript{6,8,10,38} while those for ibuprofen C$_{50,IBU}$ (3.39 mg/L) range from 5.07 to 10.2 mg/L\textsuperscript{7,8,39} We were unable to demonstrate any differences in pharmacodynamic parameters between children and adults. The idea that children’s (but not neonates or infants) responses to drugs differ to those of adults probably relates more to methodology issues of research in pediatric populations (failure to account for size, maturation and disease, among others).\textsuperscript{40} We had anticipated that the pain type (tonsil or dental pain) might differ, but could not demonstrate this effect.

There are few PKPD data parameter estimates available for tramadol in children. Tramadol proved to be about 1/6 to 1/10 as potent an analgesic as morphine when both intensity and duration of effect were considered.\textsuperscript{41} A steady-state plasma concentration of tramadol 0.1 mg/L and its active metabolite O-demethyltramadol (M1) 15 mcg/L was associated with a 95% probability of adequate pain relief.\textsuperscript{42} We report a C$_{50,TRAN}$ of 0.088 (95%CI 0.043, 1.01) mg/L that is consistent with these reports.

It may be possible that ibuprofen drives tramadol (M1) disposition through its effect on renal function, the clearance pathways for the M1 metabolite. However, the effect of short-term treatment with NSAIDs on healthy kidneys is transient and negligible.\textsuperscript{43} Any effect due to M1 metabolite or variability in M1 metabolite concentration attributable to single nuclear polymorphisms of the P450 enzyme CYP2D6 is encompassed by the C$_{50,TRAN}$ variability (PPV 2.5). Codeine is also metabolized by CYP2D6 and large variability has also been reported with codeine 60 mg after dental surgery in adults where the number needed to treat was 21 (95%CI 12 to 96) for one participant to experience at least 50% pain relief over 4 to 6 hours.\textsuperscript{44}
Simulation in Figure 5 demonstrates the importance of regular analgesic dosing in children after tonsil surgery; the mean pain score was maintained below 6 (visual analog scale; VAS 0-10). This threshold at which pain requires management also varies between individuals and may be an unsuitable measure as an end point. If analgesic remedication is initiated at a threshold of a pain score of 6/10, then some children may be given analgesic medication unnecessarily. Gauthier et al. reported a pain treatment threshold of 5.3
units on a VAS (0-10) with a coefficient of variation of 30% after minor uncomplicated surgery in children. The use of regular tramadol has little benefit for the typical individual. However, the administration of tramadol after the fourth dose of regular paracetamol and ibuprofen prolongs the duration of analgesia and may contribute to better overnight pain relief.

**CONFLICT OF INTEREST**

Dr. Jacqueline Hannam declares no conflicts of interest. Prof Brian Anderson is a Section Editor for the journal 'Pediatric Anesthesia'. Dr. Amanda Potts received payment from the sponsor for clinical trial management.

**CONTRIBUTIONS**

The sponsor contributed to protocol design, provided monitoring during the study, and maintained the trial database. The authors had complete access to all data. The sponsor reviewed the final draft of the manuscript and was allowed to make suggestions. The composition and content of the manuscript were determined entirely by the academic authors.

**DRUG ASSAYS**

Paracetamol and ibuprofen assays were performed by the International Pharmaceutical Research Center, 1 Queen Rania Street, Sport City Circle, Amman 11196, Jordan.

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**REFERENCES**


SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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