ABSTRACT

Background: Parecoxib is a cyclooxygenase-2 selective inhibitor used in management of postoperative pain in adults. This study aimed to provide pediatric pharmacokinetic information for parecoxib and its active metabolite valdecoxib.

Methods: Thirty-eight children undergoing surgery received parecoxib (1 mg/kg IV to a maximum of 40 mg) at induction of anesthesia, and plasma samples were collected for drug measurement. Population pharmacokinetic parameters were estimated using nonlinear mixed effects modeling. Area under the valdecoxib concentration-time curve and time above cyclooxygenase-2 in vitro 50% inhibitory concentration for free valdecoxib were simulated.

Results: A three-compartment model best represented parecoxib disposition, whereas one compartment was adequate for valdecoxib. Age was linearly correlated with parecoxib clearance (5.0% increase/yr). There was a sigmoid relationship between age and both valdecoxib clearance and distribution volume. Time to 50% maturation was 87 weeks postmenstrual age for both. In simulations using allometric-based doses the 90% prediction interval of valdecoxib concentration-time curve was similar to that in adults (40 mg), and simulated free valdecoxib plasma concentration remained above the in vitro 50% inhibitory concentrations for more than 12 h. In children younger than 2 yr, a dose reduction is likely required due to ongoing metabolic maturation.

Conclusions: The final pharmacokinetic model gave a robust representation of parecoxib and valdecoxib disposition. Area under the valdecoxib concentration-time curve was similar to that in adults (40 mg), and simulated free valdecoxib concentration was above the cyclooxygenase-2 in vitro 50% inhibitory concentration for free valdecoxib for at least 12 h.

Development of a Population Pharmacokinetic Model for Parecoxib and Its Active Metabolite Valdecoxib after Parenteral Parecoxib Administration in Children


What We Already Know about This Topic

- Parecoxib is a produg that is converted to valdecoxib, a cyclooxygenase-2 inhibitor, by carboxylesterases
- Parecoxib is administered parenterally to adults to manage postoperative pain

What This Article Tells Us That Is New

- The elimination clearance of parecoxib increased by approximately 5% per year of age in children ages 1.1–12.7 yr
- The volume of distribution and elimination clearance of valdecoxib also increased with age
- Simulations predict allometrically-based parecoxib dose recommendations for children aged 2 to 12 yr and weighing 10 to 70 kg will produce analgesic plasma valdecoxib concentrations for a median duration of at least 12 h

PARECOXIB is a nonsteroidal antiinflammatory drug (NSAID) that specifically inhibits the enzyme cyclooxygenase-2 (COX-2). It is administered parenterally to adults as a single 40-mg dose for the management of acute postoperative pain. In adults, it has been shown to be as effective or more effective than the older NSAIDs, and also more efficac...
tive than placebo. When used in conjunction with opioids peroperatively, COX-2 specific inhibitors were opioid sparing and increased patient satisfaction. The adverse effects of parenteral parecoxib in adult clinical trials are similar to those for NSAIDs, with serious adverse effects such as acute renal failure, Stevens-Johnson syndrome, and hypersensitivity reactions including anaphylaxis and angioedema occurring at low incidence. Advantages of parecoxib over other NSAIDs are that it does not impair platelet function, gastrointestinal ulceration is less likely, and it does not induce hypersensitivity reactions in patients who have NSAID-induced urticaria or angioedema. In addition, the ability to give the drug parenterally means a more reliable NSAID dose (i.e., 100% bioavailability in children with an IV cannula in place), compared with traditional perioperative per rectum NSAID, or where oral dosing is inappropriate.

Parecoxib is a prodrug that is rapidly and almost completely converted (half-life \( t_{1/2} \) approximately 0.5 h in adults) to its active moiety valdecoxib by carboxylesterases in plasma, liver, and other tissues. Valdecoxib is highly bound to plasma proteins (98%) and metabolized primarily by cytochrome P450 3A4 (CYP3A4) and secondarily by cytochrome P450 2C9 (CYP2C9) to a variety of metabolites that are excreted in the urine as conjugates. In adults, its volume of distribution is approximately 55 l and elimination \( t_{1/2} \) is approximately 8–9 h. Valdecoxib also exhibits linear kinetics over a dose range of 1–100 mg IV. However, in children older than 1 yr, significantly higher weight-corrected doses than those used in adults are often required for drugs that are metabolized via cytochrome P450 isozymes.

Neither parecoxib nor its metabolite valdecoxib are licensed for use in children, and their pharmacokinetics and analgesic efficacies have not been studied. To investigate pediatric dose prediction and duration of action, we administered parecoxib IV intraoperatively to children undergoing surgery and applied nonlinear mixed effects modeling to define the population pharmacokinetics of both parecoxib and valdecoxib. We suggest that parecoxib is potentially useful for pediatric analgesia and that the acceptable safety profile of the drug in the adult population justifies a pharmacokinetic trial in children.

**Materials and Methods**

**Patients**

This prospective observational study was approved by the Human Research and Ethics Committee of Princess Margaret Hospital for Children (Subiaco, Western Australia, Australia; # 890/EP) and registered with the Australian Government Department of Health and Ageing, Therapeutic Goods Administration (Canberra, Australian Capital Territory, Australia) under the Clinical Trial Notification Scheme (#2008/0442). Children likely to benefit from an NSAID for postoperative pain were identified and written informed consent obtained from their guardians. Exclusion criteria included genetic syndromes, major organ dysfunction, hypersensitivity to NSAIDs, or asthma, or receipt of NSAIDs or drugs that interact with cytochrome P450 before surgery. All the guardians consented that a single IV dose of parecoxib would be administered for postoperative analgesia. Demographic data collected included sex, age, weight, past medical history, regular medications, intraoperative medications, and the nature of the surgical procedure. We aimed for a total of 40 patients in the trial on the basis that this sample size and our rich sampling schedule (Blood Sampling, paragraph 1, second sentence) would enable a robust population pharmacokinetic analysis.

**Parecoxib Dose and Administration**

Children were given parecoxib sodium (Dynastat, 40 mg base/2 ml, Pfizer Australia Pty. Ltd., West Ryde, New South Wales, Australia) on a mg/kg basis by IV injection (over approximately 10 s, and followed by a 5-ml saline flush) shortly after anesthesia was established and the patient’s medical condition was stable. In the study design phase, dose calculations were investigated using weight, body surface area, and allometry, with a 40 mg/70 kg adult reference dose. Body surface area for children was calculated from weight as previously described. Using body weight (pediatric dose = adult dose \( \times \) weight \( \text{pediatric/weight}\text{adult} \)), body surface area (pediatric dose = adult dose \( \times \) body surface area \( \text{pediatric/body surface area}\text{adult} \)) and allometry (pediatric dose = adult dose \( \times \) weight \( \text{pediatric/weight}\text{adult}^{0.75} \)) gave mean (range) pediatric doses of 0.57 (fixed) mg/kg, 0.71 (1.05–0.55) mg/kg and 0.68 (0.93–0.57) mg/kg, respectively over the pediatric weight range of 10–70 kg (1-kg increments). Nevertheless, on the basis of the experience of previous use of the drug in our hospital, a pediatric dose of 1 mg/kg was adopted, with capping at the adult dose at 40 mg for children weighing 40 kg or greater.

**Blood Sampling**

For the purpose of anesthesia an IV catheter (BD Insyte®, Becton Dickinson Australia, North Ryde, New South Wales, Australia) was placed and used subsequently for blood sampling. Blood (1 ml each) for parecoxib and valdecoxib analysis was collected immediately before drug administration, and at nominal times of 0.05, 0.25, 0.75, 1, 1.5, 3, 6, 12, 18, and 24 h after the dose (exact times recorded for each sample in relation to dose). A discard blood sample (5 ml) was withdrawn immediately before each retained blood sample, and the discard was later returned (ensuring complete asepsis) to minimize blood loss. Samples were collected in fluoride-oxalate tubes (Becton Dickinson Australia), placed in ice (4°C), then promptly separated by centrifugation, and the plasma
stored at −80°C until assayed. A rich-sampling schedule was chosen because some difficulty was anticipated in the recruitment of patients, and because it would facilitate definition of a suitable pharmacokinetic model. Preliminary experiments established that there was no in vitro conversion of parecoxib to valdecoxib under the sample collection conditions (data not shown). The measurement of parecoxib and valdecoxib in plasma is detailed in the appendix.

**Population Pharmacokinetic Analysis**

Log concentration versus time datasets of parecoxib and valdecoxib were analyzed simultaneously by nonlinear mixed effects modeling using NONMEM (version 6.2.0, ICON Development Solutions, Ellicott City, MD) with an Intel Visual FORTRAN 10.0 compiler. User-defined linear manifolds models (ADVANS) within NONMEM, first-order conditional estimation (LAPLACE) with η-ε interaction, and the objective function value (a NONMEM-calculated global goodness-of-fit indicator equal to −2 log-likelihood value of data) were used to construct and compare plausible models. It was assumed that parecoxib was exclusively eliminated by metabolic conversion to valdecoxib. Models with two and three compartments for parecoxib coupled with one and two compartments for valdecoxib were tested. A large fraction of the parecoxib concentrations were below the limit of quantification (BLQ) of the assay (29% of all samples, 20% of those taken before 6 h and 87% of those taken after 6 h) and preliminary model building compared models that excluded parecoxib samples taken after 6 h (only seven samples from three children) with those that did not. In addition, models that excluded BLQ data were compared with those that used a method previously described to adequately account for BLQ concentrations. This method (referred to in the context of dealing with BLQ data in NONMEM as M3)13 maximizes the likelihood that BLQ samples from three children) with those that did not. In addition, models that excluded BLQ data were compared with those that used a method previously described to adequately account for BLQ concentrations.13 This method (referred to in the context of dealing with BLQ data in NONMEM as M3) maximizes the likelihood that BLQ data are BLQ, while treating data above the BLQ as normal predictions.

All volume terms were allometrically scaled with ((weight/70)0.75) and all clearance terms with ((weight/70)0.75).14 Interindividual variability (IIV) was added to parameters for which it could be estimated reasonably from the available data. An additive residual unexplained variability model was applied to the log transformed concentration data, approximately representing a proportional error on the normal scale.

Because the study population included children with a wide range of ages, the influence of age on volume and clearance terms was assessed using linear, exponential asymptotic, and sigmoid hyperbolic relationships by multiplying the parameter with a parameter representing the effect of age (\(F_{AGE}\)). For a linear relationship, the effect of age was centered on the average age of the population as follows:

\[
F_{AGE} = (1 + SLOPE) \times (AGE - \overline{AGE})
\]

where SLOPE is the percentage increase per year of age, AGE is the age in years and \(\overline{AGE}\) is the average age of the population in years (6.9 in this population).

The effect of age for an exponential asymptotic relationship was defined as:

\[
F_{AGE} = (1 - (1 - \beta) \times EXP(- (PMA - 40) \times \frac{\ln(2)}{T})
\]

where PMA is postmenstrual age, \(\beta\) is the fractional parameter estimate at 40 weeks PMA, and \(T\) is the maturational half-life of the age-related process.

Finally, a sigmoid hyperbolic relationship the effect of age was defined as:

\[
F_{AGE} = \frac{PMA_{Hill}}{PMA_{Hill} + TM_{50}}
\]

where PMA is postmenstrual age, Hill is the Hill coefficient for the relationship, and \(TM_{50}\) is the time to 50% maturation of the age-related process.

Because PMA was not known for the children, the Australian national average gestation of 38.8 weeks†† (0.744 yr) was assumed, and added to postnatal age to estimate PMA for each child. Once relationships between model parameters and age had been established, the effect of coadministered medications was investigated. These relationships were identified by inspection of correlation plots and subsequently evaluated within NONMEM with the effect size (%) of the medication on the parameter estimated. Inclusion of the covariate required a significant decrease in objective function value, a decrease in the variability of that parameter and biologic plausibility of the identified relationship. Correlations among IIV terms were also investigated.

A bootstrap using Perl speaks NONMEM with 1,000 samples was performed. The resulting parameters from the analysis of the new datasets were then summarized as median and 2.5th and 97.5th percentiles (95% empirical CI) to facilitate evaluation of the final model parameter estimates. In addition, visual predictive checks were performed with 1,000 datasets simulated from the final model. The observed 10th, 50th, and 90th percentiles were plotted with their respective simulated 95% CIs to assess the predictive performance of the model. The observed fraction of BLQ observations was compared with the median (95% CI) of BLQ observations from the simulated datasets. Because age was an influential covariate for some pharmacokinetic parameters, numeric predictive checks were performed (stratified according to age) and assessed by comparing the actual with the expected number of data points within the 20, 40, 60, 80, 90, and 95% prediction intervals. See Supplemental Digital Content 1, http://links.lww.com/ALN/A839, for the NONMEM code for the pharmacokinetic model.


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concentration (Cmax). In addition, the duration of COX-2 inhibition and the duration of COX-2 inhibition (and therefore analgesia) by valdecoxib was estimated using the in vitro 50% inhibitory concentration (IC50; 1.57 µg/l for unbound drug) and the fraction of unbound drug in plasma for healthy adults (0.0211) to calculate the time for the free concentration of valdecoxib in the simulated subjects to fall below this level. Macro constants for the three compartment model were calculated from the modeled parameters using previously published equations, whereas

\[ C_{\text{max}} \]

and duration of action were determined from simulated subjects and their drug concentrations obtained at 6-min intervals. For the simulations, 1,000 male and 1,000 female subjects for each age between 1.1 and 12.7 yr (the range of age in the study population) were used. Weights for each age group were based on sex, and simulated from the 2000 Centers for Disease Control and Prevention growth charts data. The dosing regimen used for the simulations was based on allometry (pediatric dose = adult dose \times \frac{\text{weight}_{\text{pediatric}}}{\text{weight}_{\text{adult}}}^{0.75}). Simulated data for boys and girls were combined and the resulting median and 90% prediction interval were plotted for each age group.

### Results

A total of 40 patients were recruited for the study; however, two were lost due to cancellation of surgery. The demographic characteristics of the 38 remaining children are summarized in table 1. The mean parecoxib dose of 0.89 mg/kg for the group was slightly lower than the intended 1 mg/kg because the dose in patients 40 kg and over was capped at 40 mg. Surgical procedure types (and % in group) carried out in the children were tonsillectomy or adenotonsillectomy (50%), orthopedic operations (15.8%), plastics (13.2%), general surgery (13.1%), and other (7.9%). Anesthesia was induced with propofol or volatile, and maintained with volatile (mostly isoflurane or sevoflurane). The commonly used anesthetic were infrequent and unacceptable. The median number of blood samples collected from the patients was 10 with a range of 3–11.

A model with three compartments for parecoxib and a single compartment for valdecoxib with first-order elimination was found to adequately describe the concentration-time data (fig. 1). A model with only two compartments for valdecoxib resulted in significant model misspecification, and the addition of the extra compartment was accompanied by a significant drop in the objective function value (−85.985, P < 0.001 chi-square df = 2). Parecoxib samples taken more than 6 h after the dose were excluded as the parameter estimates did not change greatly (less than 4%), the samples only represented 3% of the observed parecoxib data and were only from 3 of the 38 children, and the low levels of parecoxib after 6 h are unlikely to be clinically significant. When BLQ data were excluded from the dataset, significant model misspecification of the parecoxib data were evident and therefore a method previously shown to enable good parameter estimation in the presence of a large fraction of BLQ data (10–40%) was used. The parameter estimates of the base and final models are summarized in table 2. IVV was able to be estimated on \( \text{CL}_{\text{parecoxib}} \), \( V_{\text{P1,parecoxib}} \), \( \text{CL}_{\text{valdecoxib}}/F^* \) and \( V_{\text{valdecoxib}}/F^* \) with a band matrix used to estimate correlations between IVV terms. Age was found to be correlated with \( \text{CL}_{\text{parecoxib}} \), \( V_{\text{valdecoxib}}/F^* \), and \( \text{CL}_{\text{valdecoxib}}/F^* \) with a significant decrease

### Table 1. Demographic Characteristics and Parecoxib Dose for the 38 Children

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>29.6 (9.7, 84.2)*</td>
</tr>
<tr>
<td>Sex</td>
<td>26 males, 12 females</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>6.9 (1.1, 12.7)*</td>
</tr>
<tr>
<td>Parecoxib dose (mg)</td>
<td>22 (14, 40)†</td>
</tr>
<tr>
<td>Parecoxib dose (mg/kg)</td>
<td>0.89 (0.84, 0.95)‡</td>
</tr>
</tbody>
</table>

* Mean (range), † median (interquartile range), ‡ mean (95% CI).

### Simulations

Once a final model had been established, simulations were performed to assess the effect of age on secondary pharmacokinetic parameters including area under the curve (AUC0–∞), elimination half-life of valdecoxib (\( t_{1/2} \)), and maximum valdecoxib concentration (Cmax). In addition, the duration of COX-2 inhibition and the duration of COX inhibition (and therefore analgesia) by valdecoxib was estimated using the in vitro 50% inhibitory concentration (IC50; 1.57 µg/l for unbound drug) and the fraction of unbound drug in plasma for healthy adults (0.0211) to calculate the time for the free concentration of valdecoxib in the simulated subjects to fall below this level. Macro constants for the three compartment model were calculated from the modeled parameters using previously published equations, whereas

\[ C_{\text{max}} \] and duration of action were determined from simulated subjects and their drug concentrations obtained at 6-min intervals. For the simulations, 1,000 male and 1,000 female subjects for each age between 1.1 and 12.7 yr (the range of age in the study population) were used. Weights for each age group were based on sex, and simulated from the 2000 Centers for Disease Control and Prevention growth charts data. The dosing regimen used for the simulations was based on allometry (pediatric dose = adult dose \times \frac{\text{weight}_{\text{pediatric}}}{\text{weight}_{\text{adult}}}^{0.75}). Simulated data for boys and girls were combined and the resulting median and 90% prediction interval were plotted for each age group.

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Table 2. Population Pharmacokinetic Estimates Parecoxib and Valdecoxib in Plasma in Base and Final Models with Results of the Nonparametric Bootstrap

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Base Model Estimate (%RSE)</th>
<th>Final Model Estimate (%RSE)</th>
<th>Bootstrap Median [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Matrix Objective Function Value</td>
<td>-464.808</td>
<td>-488.185</td>
</tr>
<tr>
<td>Parecoxib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{CL}_{\text{parecoxib}}$ (l h$^{-1}$ 70 kg$^{-1}$)</td>
<td>21 (6)</td>
<td>21 (5)</td>
<td>21 [19, 24]</td>
</tr>
<tr>
<td>$\text{V}_{\text{C, parecoxib}}$ (l/70 kg)</td>
<td>5.1 (6)</td>
<td>5.1 (5)</td>
<td>5.1 [4.6, 5.7]</td>
</tr>
<tr>
<td>$Q_1$, parecoxib (l h$^{-1}$ 70 kg$^{-1}$)</td>
<td>5.9 (15)</td>
<td>6.0 (10)</td>
<td>5.9 [4.2, 7.8]</td>
</tr>
<tr>
<td>$V_{\text{P1, parecoxib}}$ (l/70 kg)</td>
<td>240 (43)</td>
<td>260 (36)</td>
<td>260 [120, 580]</td>
</tr>
<tr>
<td>$Q_2$, parecoxib (l h$^{-1}$ 70 kg$^{-1}$)</td>
<td>5.1 (17)</td>
<td>5.3 (16)</td>
<td>5.3 [3.7, 7.9]</td>
</tr>
<tr>
<td>$V_{\text{P2, parecoxib}}$ (l/70 kg)</td>
<td>1.8 (12)</td>
<td>1.8 (10)</td>
<td>1.8 [1.4, 2.3]</td>
</tr>
<tr>
<td>Maturation slope $\text{CL}_{\text{parecoxib}}$ (%)</td>
<td>5.0 (22)</td>
<td>4.8 [2.2, 7.1]</td>
<td></td>
</tr>
<tr>
<td>RUV$_{\text{parecoxib}}$ (%)</td>
<td>30 (7)</td>
<td>30 (6)</td>
<td>30 [25, 35]</td>
</tr>
<tr>
<td>Valdecoxib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{CL}_{\text{valdecoxib/F}}$ (l h$^{-1}$ 70 kg$^{-1}$)</td>
<td>8.1 (7)</td>
<td>8.6 (6)</td>
<td>8.7 [7.7, 9.7]</td>
</tr>
<tr>
<td>$\text{V}_{\text{valdecoxib/F}}$ (l/70 kg)</td>
<td>53 (7)</td>
<td>62 (11)</td>
<td>63 [52, 87]</td>
</tr>
<tr>
<td>Hill coefficient - $\text{CL}_{\text{valdecoxib/F}}$</td>
<td>3.0 (4)</td>
<td>3.0 [3.0, 3.0]</td>
<td></td>
</tr>
<tr>
<td>TM$<em>{50}$ - $\text{CL}</em>{\text{valdecoxib/F}}$ (yr)</td>
<td>1.7 (15)</td>
<td>1.7 [1.1, 2.4]</td>
<td></td>
</tr>
<tr>
<td>Hill coefficient - $\text{V}_{\text{valdecoxib/F}}$</td>
<td>1.6 (54)</td>
<td>1.6 [0.6, 3.2]</td>
<td></td>
</tr>
<tr>
<td>TM$<em>{50}$ - $\text{V}</em>{\text{valdecoxib/F}}$ (yr)</td>
<td>1.7 (23)</td>
<td>1.7 [1.0, 3.7]</td>
<td></td>
</tr>
<tr>
<td>RUV$_{\text{valdecoxib}}$ (%)</td>
<td>24 (7)</td>
<td>24 (5)</td>
<td>24 [21, 28]</td>
</tr>
<tr>
<td>IIIV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{CL}_{\text{valdecoxib/F}}$ (%)</td>
<td>30 (21)</td>
<td>27 (14)</td>
<td>25 [13, 35]</td>
</tr>
<tr>
<td>$\text{V}_{\text{valdecoxib/F}}$ (%)</td>
<td>30 (16)</td>
<td>25 (12)</td>
<td>24 [14, 37]</td>
</tr>
<tr>
<td>$\text{CL}_{\text{parecoxib}}$ (%)</td>
<td>30 (13)</td>
<td>23 (13)</td>
<td>23 [16, 29]</td>
</tr>
<tr>
<td>$V_{\text{P1, parecoxib}}$ (l/70 kg)</td>
<td>194 (11)</td>
<td>150 (15)</td>
<td>142 [95, 196]</td>
</tr>
<tr>
<td>Correlation parameters and terms</td>
<td>$r(\text{CL}<em>{\text{valdecoxib/F}}, \text{V}</em>{\text{valdecoxib/F}}^*)$</td>
<td>0.39</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>$r(\text{V}<em>{\text{valdecoxib/F}}, \text{CL}</em>{\text{parecoxib}})$</td>
<td>0.51</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>$r(\text{CL}_{\text{P1, parecoxib}})$</td>
<td>0.22</td>
<td>0.12</td>
</tr>
</tbody>
</table>

* Parameters are: $\text{CL}_{\text{parecoxib}} = \text{parecoxib clearance}$—centered on 6.9 yr of age; $\text{CL}_{\text{valdecoxib/F}} = \text{valdecoxib clearance}$, where $F^*$ is the fractional metabolic conversion of parecoxib to valdecoxib; Hill = $\text{CL}_{\text{valdecoxib/F}}$ and $\text{V}_{\text{valdecoxib/F}}$; Hill coefficient for $\text{CL}_{\text{valdecoxib/F}}$ and $\text{V}_{\text{valdecoxib/F}}$ maturation, respectively; Maturation slope $\text{CL}_{\text{parecoxib}}$ = percentage increase in $\text{CL}_{\text{parecoxib}}$ per year of age; $Q_{\text{p, parecoxib}}$ = parecoxib intercompartmental clearance for $V_{\text{P1, parecoxib}}$ and $V_{\text{P2, parecoxib}}$, respectively; TM$_{50}$ for $\text{CL}_{\text{valdecoxib/F}}$ and $\text{V}_{\text{valdecoxib/F}}$ = time to 50% maturation for $\text{CL}_{\text{valdecoxib/F}}$ and $\text{V}_{\text{valdecoxib/F}}$ respectively; $\text{V}_{\text{C, parecoxib}}$ = parecoxib central volume of distribution; $V_{\text{P1, parecoxib}}$ and $V_{\text{P2, parecoxib}}$ = parecoxib peripheral volumes of distribution; $\text{V}_{\text{valdecoxib/F}}$ = valdecoxib volume of distribution.

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The nonparametric bootstrap showed robust parameter estimates with bias less than 4% for structural model parameters and a bias of less than 7% for random model parameters. The population predicted and individual predicted versus observed plots for parecoxib (fig. 2A) and valdecoxib (fig. 2B) showed adequate model performance, despite some bias in the population predicted versus observed plot for parecoxib in the 10–100 μg/l range. The latter is most likely an artifact due to BLQ data that were not able to be represented in these plots. The visual predictive checks for parecoxib (fig. 3A) and valdecoxib (fig. 3B) compartments did not show evidence of model misspecification. The numeric predictive checks performed with age stratification for both parecoxib and valdecoxib showed good predictive performance, with the expected number of data points above and below all prediction intervals tested (data not shown).

The results from the simulations are summarized for valdecoxib (fig. 4A–D) with the dose regimen presented in figure 5 with approximate dosing (mg/kg) shown in table 3. Simulations are limited to the age range for the children in the study (1.1–12.7 yr). The AUC plots show the pooled average (6640 g/l) as a horizontal dotted line and the pooled 90% prediction interval (3,775–9,498 μg l/h) as a...
pink shaded area calculated from adult studies for a single
dose of 40 mg valdecoxib, whereas the analgesia duration
plots show a target (minimum) duration of action of 12 h as
a horizontal dotted line. There was an increase in t1/2 and a
decrease in Cmax with increasing age as a result of changes in
CLvaldecoxib/F* and Vvaldecoxib/F*. There was little change in
AUC in children older than 2 yr while in children younger
than 2 yr there was a significant increase due to the incom-
plete maturation of valdecoxib metabolism. In children older
than 2 yr the median AUC was slightly below (within 18%)
of the target concentration; however, the 90% prediction
interval largely overlapped that of pooled adult data. With
increasing age there was an initial decrease in the duration of
action with a nadir at 3 yr, followed by a gradual rise. The
median duration of action was longer than 12 h for all ages.
Simulations were also undertaken to characterize the t1/2 for
parecoxib. The median t1/2 was 4.4 min and was indepen-
dent of age whereas the median t1/2 and t1/2 were 14 min
and 29 h, respectively, and both increased with age. Overall,
across all ages the t1/2 and t1/2 disposition phases ac-
counted for a mean of 77% of the AUC for parecoxib. No adverse effects that might be attributed to parecoxib were
encountered during the trial.

Discussion

Our study has defined a nonlinear mixed-effects pharmaco-
kinetic model for the simultaneous disposition of parecoxib
and valdecoxib in children after IV parecoxib. Parecoxib was
best represented by a three-compartment model with very
rapid mean t1/2 and t1/2 values of 4.4 and 14 min, respec-
tively, that accounted for 77% of the AUC. The model for
parecoxib included a maturation slope term indicating that
its overall metabolism increased linearly by approximately
5.0% per year of age. Unlike the maturation of other clear-
ance pathways there is evidence that activity of carboxyle-
sterase metabolism increases throughout childhood, with
adults having a greater activity than children ages 0 –10 yr.21
This makes extrapolation of our finding to adult values dif-
ficult because it is unlikely that the observed relationship
would continue into adult years where the expression and
activity of carboxylesterases is unaffected by age. Although a
linear relationship was found to best describe the relationship
of parecoxib clearance with age in our population (1.1–12.7
yr) extrapolation above or below this age range may not be
appropriate. The most influential simulated half-lives for
parecoxib, namely t1/2 (4.4 min) and t1/2 (14 min) in
children, were much shorter than reported in the literature.

22, 2012.
values of 23 min and 28 min for parecoxib half-life obtained from noncompartmental analyses in adults; however, the expected median t\textsubscript{1/2} for a 70 kg adult using the derived model was similar (19 min). The differences in t\textsubscript{1/2} values are likely a result of different study designs particularly with our study having three additional samples taken in the first hour after dose, and the ability of our compartmental analysis to support a three-compartment model for parecoxib.

In our model, valdecoxib was best represented by a single compartment with first-order absorption and elimination. Overall, the model met the required evaluation criteria in the form of population and individual predicted versus observed data plots, as well as visual and numeric predicted checks. The bootstrap procedure also confirmed the lack of bias in the model parameters. We used previous information of the maturation of midazolam to stabilize our estimates of TM\textsubscript{50} and Hill coefficient for CL/F*valdecoxib. Given that our initial unsupported estimates were not significantly different to those reported for midazolam and that both drugs have similar metabolic pathways (primarily CYP3A4 with some contribution from CYP2C9) the use of these supporting data are warranted. Our inability to better define TM\textsubscript{50}, without previous data to support it, most likely results from the fact that we had only four children in our cohort who were younger than 2 yr when significant maturation is still occurring.

Mean TM\textsubscript{50} for the clearance of morphine (metabolized by glucuronidation), paracetamol (metabolized by glucuronidation and sulfation), and midazolam (metabolized primarily by CYP3A4) in children are 54.6, 50.1, and 73.6 weeks PMA, respectively, whereas corresponding values for the Hill coefficient were 3.83, 3.4, and 3, respectively. Our TM\textsubscript{50} estimates for CL\textsubscript{valdecoxib}/F* and V\textsubscript{valdecoxib}/F* (87 weeks PMA for both) were closer to those for midazolam, and our respective estimates for the Hill coefficients (3 and 1.6, respectively) were not significantly different to those reported previously. However, given the low numbers of children younger than 2 yr in this study, these values should be interpreted with caution and dose recommendations cannot be made with certainty in this age group with the current data.

The simulated t\textsubscript{1/2} estimates for valdecoxib in children were age-dependent, ranging from medians of 2.7 h at age 2 yr and up to 4.2 h at age 12 yr, while based on our model it would be 5.0 h in an average 70-kg adult. This compares with literature values ranging from 6.8–7.4 h in studies of adults. The model predicted a distribution volume of 62 l for a 70-kg adult for valdecoxib, which is comparable with the 55 l reported in the manufacturer’s product information, whereas valdecoxib clearance of 8.61 l/h for a 70-kg

### Table 3. Suggested Dose Regimen Approximating Allometry with a Power of 0.75 for Children Older Than 2 Years

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–14 kg</td>
<td>0.9</td>
</tr>
<tr>
<td>15–24 kg</td>
<td>0.8</td>
</tr>
<tr>
<td>25–39 kg</td>
<td>0.7</td>
</tr>
<tr>
<td>40–69 kg</td>
<td>0.6</td>
</tr>
<tr>
<td>≥70 kg</td>
<td>Maximum dose = 40 mg</td>
</tr>
</tbody>
</table>

Fig. 4. Results from the simulations showing the median (red lines) and 90% simulation interval (black lines) for area under the plasma concentration-time curve (AUC) (A), valdecoxib half-life (t\textsubscript{1/2}) (B), valdecoxib maximum plasma concentration (C\textsubscript{max}) (C), and estimated valdecoxib duration of action (D), as the time (h) for free valdecoxib concentration above the in vitro 50% inhibitory concentration (IC\textsubscript{50}). Solid lines represent smoothed data averaged from 2000 simulated children from both sexes in yearly age increments. Plots are limited to the age range for the children in the study (1.1–12.7 yr). The horizontal dashed line in A shows a value of 6640 μg · h/l being the pooled average AUC for 40 mg parecoxib in adults and a pink shaded area from 3775–9498 μg · h/l representing the pooled 90% prediction interval AUC for 40 mg parecoxib in adults. The horizontal dotted line in D shows time at 12 h after dose.

Fig. 5. Suggested dosing regimen based on allometry (pediatric dose = adult dose × [weight_pediatric/weight_adult]\textsuperscript{0.75}) showing dose (mg) versus weight (kg). The maximum dose was capped at the usual adult dose of 40 mg/70 kg body weight.

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The simulations demonstrated a valdecoxib $C_{\text{max}}$ that was age-dependent, varying from a median of approximately 1,025 μg/l at age 2 yr down to a median of approximately 652 μg/l at age 12 yr. $C_{\text{max}}$ in older children was comparable with the reported 768 μg/l in adults that can be calculated for a 40-mg IV parecoxib dose. The higher $C_{\text{max}}$ in younger children is primarily due to changes in valdecoxib volume that are related to body size and age (particularly for those younger than 2 yr). Both of these factors become less influential as children approach the age of 12 yr.

The secondary aim of the study was to evaluate whether our chosen dose regimen was appropriate, and to use the pharmacokinetic model to predict dose. We chose to consider this aim by a series of simulations of age versus key valdecoxib pharmacokinetic factors (AUC, $C_{\text{max}}$, and $t_{1/2}$) and a pharmacodynamic measure (time above COX-2 IC$_{50}$ for free valdecoxib). A robust comparator of active drug exposure in adults that we could relate to our children’s pharmacokinetic dataset was valdecoxib AUC$_{0-\infty}$. We calculated that AUC$_{0-\infty}$ in adults, adjusted for a 40-mg parecoxib single dose of 6640 μg h/l, and this dose has been shown to have a high analgesic efficacy in adults. As shown in the simulations (fig. 4A), although the median valdecoxib AUC was slightly lower for children older than 2 yr compared with the adult comparator target value, the 90% prediction interval was within that calculated from published adult values. We conclude from these data that a parecoxib IV dose calculated using an allometric power of 0.75 and an adult dose of 40 mg (for a 70 kg adult) is appropriate for children older than 2–12 yr age range (fig. 5 and approximated in table 3). As noted previously (Discussion, paragraph 2, lines 6–7), our dataset had only four children younger than 2 yr and therefore further studies are needed to define dosing in this age group where maturation of metabolism is still occurring. It is evident, however, that the dose in these children would need to be lower than that predicted by allometry alone and be adjusted depending on the age of the child. For example, if the maturation profile from our final model were to be confirmed in future investigations, a child with a PMA of 92 or 118 weeks (approximately 1 and 1.5 yr old) would need a dose reduction of 46% or 28%, respectively, to achieve the same median AUC as in older children.

Although we had no measure of analgesic efficacy in our study, the likely duration of analgesia was estimated from consideration of the free valdecoxib IC$_{50}$ (1.57 μg/l) for COX-2 enzyme inhibition in vitro and the knowledge that in adults the protein binding of valdecoxib is approximately 2.1% and independent of concentration. Using these data and our pharmacokinetic parameters from the final model, we were then able to simulate the time that the free plasma valdecoxib concentration would remain above the IC$_{50}$ value. Our suggested target of keeping above this concentration for at least 12 h after dose was easily met in all subjects. Nevertheless, our free valdecoxib IC$_{50}$ analysis assumes that receptor response is similar in adults and children. Given that our assessment of likely analgesic efficacy is theoretical, we suggest that pediatric studies of the effective duration of analgesia after surgery, and/or the need for breakthrough pain medication should be the next step in further evaluation of parecoxib use.

Conclusions

The final pharmacokinetic model gave a robust representation of parecoxib and valdecoxib disposition in children. Simulations showed that our parecoxib IV dose regimen (1 mg/kg with 40 mg maximum) gave valdecoxib AUC values that were similar to those in adults given a single 40-mg IV dose, and that valdecoxib concentrations were above the IC$_{50}$ for COX-2 for at least 12 h. Based on our modeling, we present allometrically-based dose recommendations for parecoxib in children older than 2 yr and weighing 10–70 kg. Finally, we suggest that formal assessment of the analgesic efficacy of parecoxib in children is warranted.

Appendix: Parecoxib and Valdecoxib Measurement by Ultra Performance Liquid Chromatography-Tandem Mass Spectrometry

Samples of parecoxib sodium and valdecoxib used as standard materials in the assay were provided by Pfizer Australia Pty Ltd., North Ryde, Australia. Parecoxib and valdecoxib were extracted from plasma, using a liquid-liquid extraction procedure. Aliquots of plasma (250 μl) and internal standard (50 μl valdecoxib-13C$_2$; 100 ng/ml) were extracted with 100 μl 1M HCl and 5 ml dichloromethane. After centrifugation (2,000 g for 5 min), the top aqueous layer was aspirated to waste. The dichloromethane layer was transferred to clean glass tubes, and dried a gentle stream of nitrogen at 50°C. The residue was reconstituted with 1 ml methanol and 20-μl aliquots were injected onto the ultraperformance liquid chromatography-tandem mass spectrometry system.

The analytical system consisted of a Waters Acquity ultraperformance liquid chromatograph (Milford, MA) coupled with a Waters Premier XE tandem mass spectrometer. The ultraperformance liquid chromatography mobile phases were (A) 25% acetonitrile in 2 mM ammonium acetate/0.1% formic acid and (B)50/50 methanol and 2 mM ammonium acetate in 0.1% formic acid. Elution of the analytes through a Waters OASIS HLB 20 mm column (Wexford, Ireland) was effected by an initial gradient flow of 0.6 ml/min 50% A and 50% B, then ramped up to 100% B over 0.8 min, followed by 0.1-min reconditioning. In positive electrospray ionization mode, the multiple reaction protonated adduct transitions m/z 315.2 to 222.2 and m/z 317.1 to 234.2 for valdecoxib and parecoxib, respectively, and m/z 318.2 to 222.2 for valdecoxib-13C$_2$ were monitored. Capillary voltage was set at 1.2kV for both analytes, whereas cone voltages of 30V and 35V and collision energies of 25eV
and 20eV were used for valdecoxib and parecoxib, respectively. The source temperature was 400°C for both analytes. Under these conditions, the retention time for valdecoxib and its labeled internal standard was 1.3 min and for parecoxib was 1.3 min. Linearity was established for both valdecoxib and parecoxib over the concentration range of 10 μg/l to 1869 μg/l (r² = 0.999) and 9 μg/l to 2010 μg/l (r² = 0.999), respectively.

Matrix effects, absolute recovery, process efficiency and interpatient (intraday) variability, and intraday relative SD for the assay were investigated as previously described with five blank plasma samples from different patients that were spiked with parecoxib at 10 μg/l and 100 μg/l and 2,000 μg/l or valdecoxib at 10 μg/l, 100 μg/l, and 1,000 μg/l, and valdecoxib-13C2,15N1 at 100 μg/l. For sample set 1, plasma was spiked with parecoxib at 10 μg/l, 100 μg/l, and 2,000 μg/l, and with valdecoxib at 10 μg/l, 100 μg/l, and 1,000 μg/l. Internal standard valdecoxib-13C2,15N1 at was spiked into plasma at 100 μg/l. For sample set 2 spiked postextraction addition extracts for the same five samples were also prepared (at concentrations equivalent to sample set 1) by using a fixed volume of the extracts obtained after the methanol-precipitation. Finally, for sample set 3 “pure solutions” of all analytes (at concentrations equivalent to sample set 1) were prepared by diluting with methanol. The results are summarized in table 4. The interday relative standard deviations at 200 μg/l, 400 μg/l, and 800 μg/l (n = 5) were 3.3%, 5.2%, and 1.7%, respectively, for parecoxib, and 2.3%, 1.9%, and 1.1% respectively for valdecoxib. The intraday relative standard deviations for valdecoxib (10 μg/l) and parecoxib (10 μg/l) were 2.2% and 7.3%, respectively, and these latter concentrations were considered satisfactory as lower limits of quantitation (i.e., < 20%) for both compounds. Frozen, freeze-thaw, and on-bench stability has been previously demonstrated.

The authors acknowledge cooperation from the anesthetic staff at Princess Margaret Hospital, Subiaco, Western Australia, Australia.

References
1. Anonymous: Dynastat; MIMS abbreviated prescribing information. E-MIMS Ver 5.01.0100 2010; MultiMedia Australia Pty Limited, St Leonards, Australia

Table 4. Matrix Effects, Recovery, Process Efficiency and Intraday Variability of Parecoxib and Valdecoxib Assay in Plasma (Data as Mean ± SD [Range])

<table>
<thead>
<tr>
<th>Analyte</th>
<th>10 μg/l</th>
<th>100 μg/l</th>
<th>2,000 μg/l</th>
<th>Internal Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parecoxib</td>
<td></td>
<td></td>
<td></td>
<td>13C2,15N1-Valdecoxib</td>
</tr>
<tr>
<td>Matrix effect (%)*</td>
<td>89 ± 2 (86–91)</td>
<td>84 ± 5 (78–90)</td>
<td>59 ± 5 (50–73)</td>
<td>—</td>
</tr>
<tr>
<td>Absolute recovery (%)†</td>
<td>103 ± 4 (95–107)</td>
<td>97 ± 7 (89–104)</td>
<td>108 ± 10 (92–117)</td>
<td>—</td>
</tr>
<tr>
<td>Process efficiency (%)‡</td>
<td>91 ± 5 (83–96)</td>
<td>81 ± 4 (76–84)</td>
<td>63 ± 7 (52–72)</td>
<td>—</td>
</tr>
<tr>
<td>Intraday RSD (%)</td>
<td>7.3</td>
<td>10.9</td>
<td>2.0</td>
<td>—</td>
</tr>
<tr>
<td>Valdecoxib</td>
<td></td>
<td></td>
<td></td>
<td>13C2,15N1-Valdecoxib</td>
</tr>
<tr>
<td>Matrix effect (%)*</td>
<td>75 ± 6 (66–82)</td>
<td>64 ± 6 (56–70)</td>
<td>82 ± 3 (78–85)</td>
<td>64 ± 6 (56–71)</td>
</tr>
<tr>
<td>Absolute recovery (%)†</td>
<td>104 ± 11 (93–119)</td>
<td>97 ± 8 (85–107)</td>
<td>97 ± 6 (92–107)</td>
<td>97 ± 8 (84–106)</td>
</tr>
<tr>
<td>Interpatient RSD (%)</td>
<td>2.2</td>
<td>3.1</td>
<td>1.7</td>
<td>—</td>
</tr>
</tbody>
</table>

* Matrix effect = response for sample set 2 ×100/response for sample set 3; † absolute recovery = response for sample set 1 × 100/response for sample set 2; ‡ process efficiency = response for sample set 1 × 100/response for sample set 3. RSD = relative standard deviation.


