Remifentanil–midazolam sedation for paediatric patients receiving mechanical ventilation after cardiac surgery†


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Background. Sedation of critically ill children requiring artificial ventilation remains a therapeutic challenge due to large individual variation in drug effects and a paucity of knowledge of pharmacokinetics in this population. This study aimed to determine the pharmacokinetics of remifentanil in children requiring ventilation after cardiac surgery.

Methods. Twenty-six ventilated children aged 1 month to 9.25 yr (median 1.77 yr) who had undergone cardiac surgery were sedated with a fixed rate infusion of midazolam 50 \( \mu \text{g kg}^{-1} \text{h}^{-1} \) and a remifentanil infusion that was commenced at 0.8 \( \mu \text{g kg}^{-1} \text{min}^{-1} \) for a minimum of 60 min and subsequently decreased by 0.1 \( \mu \text{g kg}^{-1} \text{min}^{-1} \) every 20 min until the patient awoke. Arterial blood concentrations of remifentanil and midazolam were measured using high-performance liquid chromatography. Mixed-effects population models were fitted to the remifentanil concentration–time data.

Results. Satisfactory sedation was achieved in all patients as assessed by Comfort score during the initial maintenance and reduction phase of the remifentanil infusion. One patient was withdrawn from the study due to hypotension. Remifentanil pharmacokinetics were best described using a two-compartment allometric model. For a typical child with a body weight of 10.5 kg, clearance was 68.3 ml kg\(^{-1}\) min\(^{-1}\), intercompartmental clearance was 80 ml kg\(^{-1}\) min\(^{-1}\), the central compartment volume was 91.7 ml kg\(^{-1}\), and the peripheral compartment volume was 141 ml kg\(^{-1}\).

Conclusions. A combination of remifentanil and midazolam provided satisfactory sedation for these patients. Owing to enhanced clearance rates, smaller (younger) children will require higher remifentanil infusion rates than larger (older) children and adults to achieve equivalent blood concentrations.


Keywords: analgesics opioid, remifentanil; children; hypnotics benzodiazepines, midazolam; pharmacokinetics remifentanil; sedation

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Children in intensive care require analgesia and sedation to tolerate artificial ventilation. The drugs most commonly used in the paediatric intensive care unit (PICU) are an opioid (morphine or fentanyl) in combination with a benzodiazepine (midazolam or lorazepam). There are only a limited number of drugs available for sedation on PICU, and they are all associated with significant side-effects. Opioid use is associated with ventilatory depression, delayed return of bowel function, withdrawal symptoms, and dose-dependent effects on immunity. Midazolam is

also associated with withdrawal and delayed recovery after longer-term use. Propofol was withdrawn as a sedative agent in PICU due to the risk of a syndrome characterized by bradycardia and rhabdomyolysis, the loss of this useful agent has increased the need for a new approach to sedation in PICU. A potential alternative is remifentanil which, in adults, has an onset of action of about 1 min and an elimination half-life of less than 10 min that is virtually independent of age, organ function, and infusion duration. Remifentanil has been used successfully as a sedative agent in children and adults, and has clinical potential in PICU.

This study aimed to determine the pharmacokinetics of remifentanil in children requiring ventilation after cardiac surgery and to seek correlations between processed electroencephalogram (EEG) derivatives, measured and predicted remifentanil concentrations, and a standard PICU sedation scale, the Comfort Score.

Methods

Patient population

The study population comprised children scheduled for elective cardiac surgery. The study was approved by the Local Ethics Committee, and written informed consent was given by the child’s parents or legal guardian. The study was conducted at Bristol Children’s Hospital between March 2003 and February 2005.

Children who were undergoing simple cardiac surgery were included in the study. Children with existing neurological deficits or significant cognitive impairment and children requiring postoperative muscle relaxants were excluded from the study. Patients were excluded if prolonged postoperative ventilation or major inotropic support was anticipated.

Conduct of anaesthesia

After premedication with oral diazepam (0.5 mg kg⁻¹), anaesthesia was induced with sevoflurane and maintained with isoflurane (0.1–0.5%) except during cardiopulmonary bypass (CPB). Fentanyl was administered on induction as a bolus dose of 5 μg kg⁻¹ followed by an infusion of 25 μg kg⁻¹ h⁻¹ reduced to 10 μg kg⁻¹ h⁻¹ after 1 h. Pancuronium 0.1 mg kg⁻¹ was administered on induction. For bypass cases, a standardized CPB circuit was used and midazolam 0.5 μg kg⁻¹ and pancuronium 0.1 μg kg⁻¹ added to the prime solution. The fentanyl infusion was increased to 15 μg kg⁻¹ h⁻¹ during CPB. After CPB had been discontinued, a loading dose of midazolam 0.1 μg kg⁻¹ was administered and the fentanyl infusion was discontinued. In non-bypass cases, fentanyl was given as above, but was maintained at 10 μg kg⁻¹ h⁻¹ until chest closure when the fentanyl was discontinued and midazolam (0.1 μg kg⁻¹) given. Hypothermic CPB was not used. Normothermia was maintained except in coarctation patients in whom temperature was allowed to ‘drift’ to no lower than 34°C.

Haemodynamic management

Arterial blood pressure was monitored invasively in all cases. Vasodilating drugs (sodium nitroprusside or milrinone) were given according to independent direction from the intensive care and cardiology teams. Hypotension was defined as a persistent reduction in mean blood pressure by more than 20%. Hypotension was treated either with volume replacement (in aliquots of 5 ml kg⁻¹) or according to central venous pressure management) or with inotropes (dopamine 5–10 μg kg⁻¹ min⁻¹ or epinephrine 0.1–0.5 μg kg⁻¹ min⁻¹) if there was evidence of impaired ventricular function (increased arterial lactate and decreased venous saturations).

Sedation on PICU

On arrival on PICU, midazolam was infused at 50 μg kg⁻¹ h⁻¹ and this was continued throughout the study period. A remifentanil infusion was commenced at 0.8 μg kg⁻¹ min⁻¹ and maintained at this rate for a minimum period of 1 h. After this time and when the patient was free from neuromuscular block, normothermic and stable haemodynamically, the rate of remifentanil infusion was decreased to 0.7 μg kg⁻¹ min⁻¹ and blood samples were collected during the subsequent 25 min. The remifentanil infusion rate was then decreased by 0.1 μg kg⁻¹ min⁻¹ every 20 min until the patient awoke.

Arousal was pre-defined as the combination of eye-opening and spontaneous limb movement. Immediately after arousal, the remifentanil infusion rate was increased to 0.3 μg kg⁻¹ min⁻¹, and sedation and analgesia increased with i.v. bolus doses of morphine 100 μg kg⁻¹ and midazolam 200 μg kg⁻¹. A morphine infusion was started at 20 μg kg⁻¹ h⁻¹. Remifentanil was discontinued 15 min after commencing the morphine infusion and the remifentanil infusion line flushed clear of drug.

Blood sampling

Pharmacokinetic simulations (WinNonlin v1.5, Pharsight Corporation, CA, USA) using parameter values derived from a similar study population were used to create an informative sampling scheme. The partial derivatives of the predicted function (i.e. the mathematical function describing a two-compartment pharmacokinetic model) with respect to each of the model parameters were plotted against time to reveal any turning points (local maxima or minima). Blood samples obtained at the time of these turning points will contribute the maximum information on that particular parameter. Having identified key sampling time zones, we then compared various sampling designs and selected those that were associated with smaller variance inflation factors (indicative of an
Remifentanil, fentanyl, and midazolam were extracted in liquid nitrogen and then stored at −80°C to prevent further metabolism of remifentanil by plasma esterases. The samples were immediately frozen (w/v) to prevent further metabolism of remifentanil by plasma esterases. The samples were then thawed and centrifuged. The resulting supernatant was used for drug assay.

Sample handling and drug assay

Whole blood samples (1 ml) were collected using lithium heparin blood gas analysis syringes and decanted into polypropylene tubes containing 20 μl of citric acid 50% (w/v) to prevent further metabolism of remifentanil by plasma esterases. The samples were immediately frozen in liquid nitrogen and then stored at −80°C before assay. Remifentanil, fentanyl, and midazolam were extracted from 900 μl whole blood using a liquid–liquid extraction technique and quantified using a novel high performance liquid chromatography method. See the appendix for details of the assay methodology. The assay had proven linearity for remifentanil in the range 1–25 ng ml⁻¹ (R²=0.997). Intra-day precision (coefficient of variation, n=5) for remifentanil was 9% at 1 ng ml⁻¹ and at 10 ng ml⁻¹ and 2% at 20 ng ml⁻¹. Inter-day precision was <10% at 5, 10, and 20 ng ml⁻¹ (n=7). The limit of quantification for remifentanil was 1 ng ml⁻¹.

Assessment of sedation

Sedation status was assessed approximately every 10 min using the Comfort Scale scoring system. Comfort scores are used routinely in our practice and data collection for the present study was restricted to one of two trained PICU research nurses.

EEG recordings were made continuously from electrodes at C3P3 and C4P4 using standard equipment (Nicolet Pathfinder).

Pharmacokinetic analysis

Mixed-effects population models were fitted to the remifentanil blood concentration vs time data. The program NONMEM version V was used. Models were fitted using the first order conditional estimation method with interaction between the interindividual error terms (ETAs) and the random residual error term allowed. The random residual error was described using an additive error model.

A proportional variance model was used to describe the interindividual variability. Next, guided by diagnostic plots and generalized additive modelling using S-PLUS and Xpose software, we examined models which allowed the structural pharmacokinetic parameters to differ with covariates. We systematically modelled each structural model parameter as a simple (proportional) and as complex (linear, power, and fixed allometric) functions of age and body weight. For the allometric function, parameter values were standardized for a body weight of 10.5 kg (the median patient weight in our study) as follows:

\[
P_i = P \times \left( \frac{WT_i}{WT_{MED}} \right)^{POWER}
\]

\(P_i\) describes the parameter value in the \(i\)th individual, \(WT_i\) is the weight of the \(i\)th individual, and \(P\) is the parameter
value in an individual with a body weight \((WT_{MED})\) of 10.5 kg. The value of the power exponent (POWER) was fixed to 0.75 for clearance parameters and to 1.0 for volume parameters in accordance with established biological scaling laws. CPB was examined as a dichotomous covariate. Hence, in models evaluating the influence of CPB, the pharmacokinetic parameters were allowed to assume different values in bypass and non-bypass patients.

The statistical significance of each proposed covariate–parameter relationship and the requirement for ETA parameters was assessed using the likelihood ratio test (where appropriate, i.e. for nested models) and by consideration of the Akaike Information Criterion (non-nested models) and the precision of the final parameter estimates (all models). For nested models, the justification for each additional effect was for it to improve the goodness-of-fit statistic \((-2 \log\text{-likelihood})\) by more than 3.84 (evaluated against the \(\chi^2\) distribution, this is equivalent to significance at the 0.05 level). The improvement (or lack of) in model goodness-of-fit was also assessed visually by the examination of diagnostic plots. After completing the model build, the necessity for each added component was assessed by removing it from the model and evaluating the impact on the resultant model fit.

**Model evaluation**

The median prediction error and median absolute prediction error were calculated for our final population model as described by Varvel and colleagues. The predictive performance of our model was also evaluated using leverage analysis and bootstrap simulations. For the leverage analysis, multiple data sets were produced each of which excluded one patient from the analysis, a different patient being excluded from each data set. Our final population model was applied to each data set and the parameter estimates compared with the estimates resulting from the analysis of the entire data set to identify any individuals who may have exerted a large influence on the parameter values. The software Wings for NONMEM (WFN v409, N. Holford, University of Auckland) was used to perform a bootstrap analysis. One thousand bootstrap data sets were created by sampling the data, with replacement, from the original data set. Our final pharmacokinetic model was then fitted to each of the resulting data sets. The mean parameter values and the 2.5 and 97.5 percentiles for all successful runs (where the model minimized successfully and the covariance step was completed) were determined, and the difference between the bootstrap mean and the NONMEM estimate obtained from original data set was calculated.

**Simulations**

To investigate our findings, pharmacokinetic simulations were performed using the typical population parameters of our final model. Concurrently, we performed simulations using previously published kinetic models for remifentanil. This allowed comparison of our model with a model developed from a similar patient population and with a model based on data from healthy adults. Remifentanil blood concentration vs time profiles resulting from a 60 min infusion of remifentanil at a constant rate of 0.8 \(\mu g kg^{-1} min^{-1}\) were simulated.

**Sample size**

Study size was determined pragmatically based on our previous experience with pharmacokinetic studies in small children, anticipated recruitment, and feasible number of samples for assay.

**Results**

We studied 26 children aged 0.08–9.25 (median 1.77 yr), weight range 3.1–39.8 kg (median 10.5 kg). Surgical procedures included ASD repair, VSD repair, Glenn Shunt, mitral valve repair, and atrial septectomy (Table 1). Twenty-one children underwent CPB. The CPB time ranged from 19 to 83 min [mean 46 (SD 15) min]. Remifentanil infusion duration ranged from 19 min to 20.6 h (median 194 min). Patient 2 required overnight sedation at a remifentanil infusion rate of 0.8 \(\mu g kg^{-1} min^{-1}\) before the criteria for the step-down rate sequence were met, hence the extended remifentanil infusion duration.

**Safety**

Patient 3 was withdrawn from the study. After commence ment of remifentanil, blood pressure decreased from 71/47 to 59/39 mm Hg in 3 min. Norepinephrine infusion at 0.1 \(\mu g kg^{-1} min^{-1}\) and fluid bolus (60 ml) were minimally effective and the remifentanil infusion was stopped after 19 min. Two minutes after stopping the infusion, blood pressure returned to 72/49 mm Hg. The early blood samples obtained from this child, before withdrawal from the study, were assayed and included in the pharmacokinetic analysis.

A further two children became hypotensive after commencement of remifentanil infusion (Table 1). One settled spontaneously, the other responded to fluids.

**Sedation scores**

Satisfactory sedation was achieved and maintained in all patients. During the stepped withdrawal of remifentanil, the children’s level of sedation progressively lightened and this was reflected in the Comfort scale scores (Fig. 2).

**EEG data**

EEG data were analysed using median power frequency, spectral edge frequency, and power band ratios.
Preliminary exploration revealed no discernible correlation between these EEG indices and remifentanil blood concentrations, remifentanil infusion rate, or Comfort Score. Hence, these data were not analysed further.

**Blood sample analysis**

Arterial remifentanil concentrations were closely correlated to the rate of remifentanil infusion ($R^2=0.6$, $P<0.001$) (Fig. 3). At the commencement of remifentanil infusion, the median residual fentanyl blood concentration was 6.4 ng ml$^{-1}$ [minimum 0 (i.e. undetectable), maximum 15.1, and inter-quartile range 3.1]. The median midazolam concentration at the beginning of the remifentanil infusion was 87 ng ml$^{-1}$ (minimum 20, maximum 560, and inter-quartile range 111).

Remifentanil concentrations in samples taken at the point of arousal ($n=22$) showed considerable interpatient variability. The median concentration at arousal was 3.7 ng ml$^{-1}$ (minimum 1.4, maximum 15.2, and inter-quartile range 111).

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**Table 1** Study population. aRemifentanil sedation maintained overnight. bWithdrawn from study due to hypotension. cHypotension on commencement of remifentanil. Volume given with good effect. dHypotension after onset of remifentanil. Settled spontaneously.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age</th>
<th>Weight (kg)</th>
<th>Sex</th>
<th>Procedure</th>
<th>Bypass/cross-clamp time (min)</th>
<th>Remifentanil infusion duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 yr 9 months</td>
<td>12.5</td>
<td>Male</td>
<td>Left pulmonary artery patch for stenosis</td>
<td>33/0</td>
<td>286</td>
</tr>
<tr>
<td>2*</td>
<td>1 month</td>
<td>3.1</td>
<td>Male</td>
<td>Left BT shunt</td>
<td>No bypass</td>
<td>1238</td>
</tr>
<tr>
<td>3*</td>
<td>3 months</td>
<td>4.52</td>
<td>Female</td>
<td>BT shunt</td>
<td>No bypass</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>6 yr 2 months</td>
<td>19.3</td>
<td>Female</td>
<td>ASD closure</td>
<td>37/27</td>
<td>190</td>
</tr>
<tr>
<td>5</td>
<td>1 yr 4 months</td>
<td>6.2</td>
<td>Male</td>
<td>VSD closure</td>
<td>83/54</td>
<td>185</td>
</tr>
<tr>
<td>6</td>
<td>9 months</td>
<td>6.1</td>
<td>Female</td>
<td>Closure of large ASD and small VSD</td>
<td>58/33</td>
<td>210</td>
</tr>
<tr>
<td>7</td>
<td>3 months</td>
<td>4.6</td>
<td>Male</td>
<td>Atrial septectomy</td>
<td>25/7</td>
<td>206</td>
</tr>
<tr>
<td>8*</td>
<td>1 yr 11 months</td>
<td>10.4</td>
<td>Male</td>
<td>Dysplastic pulmonary valve stenosis</td>
<td>42/26</td>
<td>197</td>
</tr>
<tr>
<td>9</td>
<td>3 months</td>
<td>3.5</td>
<td>Female</td>
<td>Closure of large VSD</td>
<td>52/34</td>
<td>254</td>
</tr>
<tr>
<td>10</td>
<td>6 yr 11 months</td>
<td>20.4</td>
<td>Male</td>
<td>Subaortic stenosis repair</td>
<td>32/16</td>
<td>177</td>
</tr>
<tr>
<td>11</td>
<td>4 yr 1 month</td>
<td>15</td>
<td>Female</td>
<td>ASD closure</td>
<td>43/25</td>
<td>225</td>
</tr>
<tr>
<td>12</td>
<td>4 yr 7 months</td>
<td>26.6</td>
<td>Female</td>
<td>Repair of ASD</td>
<td>59/20</td>
<td>133</td>
</tr>
<tr>
<td>13</td>
<td>1 yr 6 months</td>
<td>11.6</td>
<td>Male</td>
<td>Glenn shunt</td>
<td>58/0</td>
<td>237</td>
</tr>
<tr>
<td>14</td>
<td>9 months</td>
<td>8</td>
<td>Male</td>
<td>L modified BT shunt</td>
<td>No bypass</td>
<td>219</td>
</tr>
<tr>
<td>15</td>
<td>7 yr 10 months</td>
<td>39.8</td>
<td>Female</td>
<td>ASD repair</td>
<td>19/28</td>
<td>212</td>
</tr>
<tr>
<td>16</td>
<td>1 yr 11 months</td>
<td>17.7</td>
<td>Male</td>
<td>VSD closure and pulmonary stenosis repair  (subvalvular)</td>
<td>58/39</td>
<td>231</td>
</tr>
<tr>
<td>17</td>
<td>1 yr 4 months</td>
<td>10.5</td>
<td>Female</td>
<td>Multiple VSD repair</td>
<td>29/15</td>
<td>189</td>
</tr>
<tr>
<td>18*</td>
<td>1 yr 5 months</td>
<td>8.74</td>
<td>Female</td>
<td>Pericardial patch</td>
<td>33/18</td>
<td>132</td>
</tr>
<tr>
<td>19</td>
<td>1 yr 10 months</td>
<td>11.7</td>
<td>Female</td>
<td>ASD closure</td>
<td>49/27</td>
<td>154</td>
</tr>
<tr>
<td>20</td>
<td>1 yr 9 months</td>
<td>9.83</td>
<td>Female</td>
<td>Closure of sinous venous ASD</td>
<td>50/31</td>
<td>183</td>
</tr>
<tr>
<td>21</td>
<td>5 months</td>
<td>3.65</td>
<td>Female</td>
<td>VSD and pulmonary valvotomy and PDA ligation</td>
<td>51/28</td>
<td>202</td>
</tr>
<tr>
<td>22</td>
<td>2 yr 18 months</td>
<td>18.8</td>
<td>Male</td>
<td>Coarctation of the aorta and PDA ligation</td>
<td>No bypass/24</td>
<td>150</td>
</tr>
<tr>
<td>23</td>
<td>6 yr</td>
<td>21.8</td>
<td>Female</td>
<td>Coarctation repair</td>
<td>No bypass/14</td>
<td>248</td>
</tr>
<tr>
<td>24</td>
<td>3 yr 3 months</td>
<td>13.3</td>
<td>Male</td>
<td>Repair of TAPVD</td>
<td>45/30</td>
<td>190</td>
</tr>
<tr>
<td>25</td>
<td>7.5 months</td>
<td>7.51</td>
<td>Male</td>
<td>VSD and PFO closure</td>
<td>53/36</td>
<td>108</td>
</tr>
<tr>
<td>26</td>
<td>9 yr 3 months</td>
<td>30.7</td>
<td>Male</td>
<td>MV Re-do</td>
<td>49/29</td>
<td>160</td>
</tr>
</tbody>
</table>
The arousal blood sample from patient 19 did not contain detectable quantities of remifentanil. The point of arousal blood samples from patient 1, in which the remifentanil concentration was 600% higher than in the previous sample, and from patient 23, who awoke after stimulation from nursing staff, were not included in the summary statistics. Fentanyl concentrations in the arousal samples ranged from 0 (undetectable, \( n = 6 \)) to 7.2 ng ml\(^{-1} \) (median 1.7, inter-quartile range 2.15). Midazolam concentrations in the arousal samples ranged from 14 to 133 ng ml\(^{-1} \) (median 59, inter-quartile range 37).

**Pharmacokinetics**

Remifentanil pharmacokinetics were best described using a two-compartment model with all structural parameters allometrically scaled to body weight. Age and CPB were not supported as model covariates. Interindividual variance was modelled in all structural parameters with the exception of \( Q \) (distributional clearance). The typical parameter values for the final model are given in Table 2. Table 3 shows the parameter estimates and the 95% confidence intervals for a standard individual weighing 10.5 kg. Figure 4 shows the model structure and the rate constants, clearances, and volume for children representing the minimum, maximum, and median body weights in our study population.

**Model evaluation**

Figure 5 shows the best and worst model fits. Figure 6 shows the goodness-of-fit plots. The model predicted remifentanil blood concentrations, based on the typical pharmacokinetic parameter values, demonstrated a median prediction error (reflecting model bias) of −6.6% and a median absolute prediction error (a measure of model precision) of 19.2%. The leverage analysis demonstrated that no one patient had undue influence on the parameter estimates. Particular attention was paid to the data sets excluding patients 2 and 3, who received significantly longer and shorter duration remifentanil infusions, respectively, which may have skewed the population parameter estimates. However, excluding these patients resulted in a <10% change in the structural model parameter values. The mean values and the 95% confidence intervals resulting from the bootstrap procedure (\( n = 712 \) successful runs) were comparable with the NONMEM estimates from the original data set. The mean bootstrap values for the structural model parameters differed from the final NONMEM model values by less than 8%.

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Typical value</th>
</tr>
</thead>
</table>
| CL (ml min\(^{-1} \))     | 716*(weight/10.5)
| \( Q \) (ml min\(^{-1} \)) | 840*(weight/10.5)
| V1 (ml)                   | 963*(weight/10.5) |
| V2 (ml)                   | 1480*(weight/10.5) |

**Table 3** Typical parameter estimates for a standard individual weighing 10.5 kg. The 95% confidence intervals are symmetric approximations and were determined as the final parameter estimate ±1.96×standard error of the estimate. The coefficient of variation (CV%) was determined, where possible, as the typical magnitude of the ETA parameter associated with the pharmacokinetic parameter. NA, not applicable.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical value</th>
<th>95% confidence interval</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (ml min(^{-1} ))</td>
<td>716</td>
<td>663–769</td>
<td>18.4</td>
</tr>
<tr>
<td>( Q ) (ml min(^{-1} ))</td>
<td>840</td>
<td>26.6–1650</td>
<td>NA</td>
</tr>
<tr>
<td>V1 (ml)</td>
<td>963</td>
<td>489–1440</td>
<td>35.4</td>
</tr>
<tr>
<td>V2 (ml)</td>
<td>1480</td>
<td>639–2320</td>
<td>63.1</td>
</tr>
<tr>
<td>Residual error (( e )) (ng ml(^{-1} ))</td>
<td>1.4</td>
<td>1.36–2.50</td>
<td></td>
</tr>
</tbody>
</table>
Simulation

Our model was used to calculate typical pharmacokinetic parameter values for children of different body weights. For comparison, parameter values were also calculated using the pharmacokinetic models developed by Davis and colleagues\textsuperscript{11} and Minto and colleagues\textsuperscript{21} (Table 4). The parameter values for all three models were used to simulate remifentanil blood concentration vs time profiles (Fig. 7). Compared with our data, the Minto model overpredicts the remifentanil blood concentration. When adjusted for bodyweight, the concentration predicted by the Davis model is similar to that predicted by our model.

Discussion

We have carefully evaluated remifentanil as an adjunct sedative in paediatric patients after cardiac surgery and demonstrated that it is effective. Our study population was small; hence, general comments about the safety of this technique would be inappropriate. However, the adverse event profile we observed is similar to that reported by others.\textsuperscript{11}

As our data are entirely derived from cardiac surgery patients, their applicability to other paediatric populations cannot be assumed. In addition, our patients were non-stationary in various regards; drugs given for anaesthesia and CPB are only gradually eliminated and although we allowed a reasonable ‘washout’ period with at least 1 h at the initial remifentanil infusion rate, residual effects of anaesthesia cannot be excluded. Residual fentanyl blood concentrations were probably sufficiently high in some patients to be
Remifentanil sedation in paediatric intensive care

Figs 7  Predicted arterial blood concentrations for remifentanil using three pharmacokinetic models. Simulations of a 60-min infusion of remifentanil at 0.8 μg kg⁻¹ min⁻¹ were made using our model and that developed by Davis and colleagues¹¹ and Minto and colleagues.²¹

contributing to the sedative effect provided by remifentanil and midazolam.²⁴ In addition, despite a fixed scheme for midazolam administration, measured midazolam concentrations demonstrated substantial interpatient variability.

The degree of sedation achieved by a particular infusion rate may also be different from other paediatric groups, both for pharmacokinetic reasons (lower blood concentrations achieved in smaller patients) and possibly for pharmacodynamic reasons.

Several groups have evaluated remifentanil as a sedative agent in children. Bauman and colleagues²⁵ studied six sedative-hypnotic and analgesic combinations in spontaneously breathing children aged 1–12 undergoing brief painful procedures. Bolus doses between 0.53 and 1.1 μg kg⁻¹ and infusion rates between 0.1 and 0.2 μg kg⁻¹ min⁻¹ were administered with the smallest doses proving most satisfactory. When remifentanil was administered alone or in combination with midazolam to children aged 5–16, undergoing bone marrow aspiration, clinical conditions were satisfactory without adverse events. However, the patients only received a single bolus of remifentanil 0.5 or 1 μg kg⁻¹ and no infusion.⁸ When used as a sole agent for sedation during cardiac catheterization, remifentanil 0.1 μg kg⁻¹ min⁻¹ was satisfactory in 23/55 children aged 2 months to 12 yr with the remainder requiring supplemental midazolam or midazolam and ketamine.²⁶ Thus, small doses of remifentanil are capable of producing useful sedation and analgesia in a paediatric population, although almost all clinical experience is with children older than those in our investigation.

Experience with remifentanil in ventilated children is more recent and less extensive. Stoppa and colleagues studied 18 newborns undergoing mechanical ventilation who received remifentanil for a mean of 70 h with a mean remifentanil infusion rate of 0.15 μg kg⁻¹ min⁻¹. No other sedative or hypnotic drugs were administered. No adverse events were observed, and the authors concluded that remifentanil may be a useful analgesic in neonates.²⁷

When remifentanil was compared with fentanyl in children aged 3–16 who required mechanical ventilation after spinal surgery, analgesia was clinically comparable with faster recovery in those patients receiving remifentanil. Remifentanil infusion was commenced at 0.1 μg kg⁻¹ min⁻¹ and titrated, but average doses are not reported. Three of 11 children received supplementary propofol with the remainder receiving remifentanil alone.⁸ The majority of our patients had undergone CPB and were likely significantly ‘sicker’ than those described earlier. In addition, they were receiving their remifentanil infusions after a substantial dose of fentanyl which may have altered subsequent opioid sensitivity.

Remifentanil pharmacokinetics after bolus administration have been previously described by Davis and colleagues¹¹ in cardiac surgery paediatric patients and by Ross and colleagues²⁸ in children undergoing elective surgery (including cardiac) and diagnostic procedures. Our study is the first description of remifentanil pharmacokinetics during infusion for paediatric sedation.

The allometric relationship between clearance and body weight in our model results in clearance values that are proportionally higher in smaller children. The nature of this relationship, and the range of parameter values, is in good agreement with the study conducted by Ross and colleagues, in which children of similar ages and body weights are compared. In contrast to Ross’s study of children from birth to 18 yr, our data did not support a pharmacokinetic model in which the distribution volume per kg was larger in smaller children. This may be due to the smaller age range in our study. We found that although models including age and body weight as covariates did result in a reduction in the −2 log-likelihood value (a model diagnostic in which a smaller value is generally indicative of an improved model fit), the standard errors of the estimates of the pharmacokinetic parameters increased substantially resulting in model instability. This was likely due to the collinearity of age and weight in our study population.

When adjusted for body weight, our typical values for metabolic clearance, volume of the central compartment (V1) and the volume of distribution at steady state (VSS) are within 15% of those reported by Davis and colleagues¹¹ and hence, produce similar predicted remifentanil blood concentration vs time profiles (Fig. 7). The combination of enhanced metabolic clearance and a larger central compartment volume explains the low remifentanil blood concentrations predicted by our paediatric model when compared with Minto’s adult model.

Davis and colleagues¹¹ found that remifentanil clearance increased by 20% after CPB in children but found no significant difference in estimates of distribution volume or half-life. We evaluated CPB as a potential model covariate based on this finding, and on our previous experience with propofol, where CPB was found to substantially reduce postoperative metabolic clearance.²² In addition, differences in volume loading, capillary leakage, and the use of ultrafiltration could feasibly have resulted in differences in
the estimates of distribution volume between bypass and non-bypass patients. However, we were unable to justify the incorporation of CPB as a pharmacokinetic model covariate. Our study was not designed to investigate the influence of CPB and as such, our data were unbalanced (5 of 26 children did not undergo CPB). Our study was most likely underpowered to detect small kinetic differences between children who underwent CPB and those who did not.

In agreement with previous studies,11,28 our data indicate low interpatient variability in the remifentanil pharmacokinetic parameter values, particularly for clearance and the volume of the central compartment (<35%). However, the interpatient variability in the estimates of the peripheral volume of distribution (V2) was larger at 63.1%. This may be a result of cardiac surgery and CPB. Cardiac surgery has profound systemic effects and cardiac function changes, generally improving, during the first few hours after surgery. This may influence drug disposition and elimination as accumulated fluid is cleared. Koren and colleagues29 have shown that estimates of distribution volume for fentanyl in children undergoing cardiac surgery can depend on the severity of the haemodynamic disturbance.

Although midazolam and fentanyl blood concentrations were quantified, the absence of a full dosing history for these drugs prevented pharmacokinetic modelling. However, had a full dose history been available, it is unlikely that the blood-sampling scheme (designed solely to characterize remifentanil kinetics) would have produced reliable parameter estimates for fentanyl or midazolam.

Ethical restrictions in the volume of blood that could be withdrawn for kinetic sampling prohibited quantification of remifentanil acid, the major remifentanil metabolite, as this would have required a second assay. Remifentanil acid is, however, markedly less potent (1/4600th) than the parent drug.30 Breen and colleagues31 found no correlation between remifentanil acid blood concentrations and the time of offset of analgesic and sedative effects after remifentanil infusion in adults with renal impairment.

In conclusion, remifentanil can provide effective sedation for children requiring ventilation after cardiac surgery. Dose requirements are higher than those reported for adults with significant weight-dependency in the smallest patients.

Acknowledgements

Appendix
Sample preparation
Analytical standards of remifentanil and GR92 559, the assay internal standard, were provided by GlaxoWellcome (Stevenage, UK). A midazolam analytical standard was provided by Roche (Basel, Switzerland). Remifentanil, fentanyl, and midazolam were extracted from whole blood using a modified liquid–liquid extraction technique.13 The blood sample (0.9 ml) was aspirated into a pre-cooled glass tube containing 20 µl of the internal standard solution (GR92 559, 2 µg ml⁻¹ in 0.01 M HCl), followed by 1 ml of sodium phosphate buffer (1 M, pH 7.4). After brief mixing by agitation, 5 ml 1-chlorobutane was added. The sample was then mixed (rotary mixer, 50 rpm) for 15 min before centrifugation (3150g) for 15 min at 4°C. The upper organic layer was transferred to a second pre-cooled glass tube containing 0.2 ml 0.01 M HCl. The tube was vortex-mixed for 2 min and then centrifuged as above. The upper organic layer was aspirated and discarded, and the lower aqueous phase transferred to a glass autosampler vial. Aliquots (20 µl) of the concentrated sample extract were analysed in duplicate using a novel high performance liquid chromatography method.

High performance liquid chromatography
The separation of remifentanil, fentanyl, GR92 559, and midazolam was achieved at room temperature using a Kya HiQSil C18 3 µ [150×1.0 mm (i.d.)] column (Kromatex, Essex, UK) and an AS950 autosampler, 2×PU2085 micro-pumps, a 50 µl mixing tee, and a UV2075 detector, all supplied by Jasco (UK) Ltd (Essex, UK). The mobile phases consisted of: A: 0.06 M sodium dihydrogen orthophosphate pH 3.60, containing 20% methanol:acetoniitrile (2.5:1, v/v), and B: mobile phase A containing 20% methanol:acetoniitrile (2.5:1, v/v). Mobile phase A (100%) ran for the first 45 min after sample injection during which time remifentanil eluted from the column, then mobile phase B (100%) was used to elute fentanyl, GR92 559, and midazolam. The flow rate was 0.05 ml min⁻¹ and the detection wavelength was 208 nm.

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