Enteral absorption and haemodynamic response of clonidine in infants post-cardiac surgery

S. Arenas-Lopez1, H. Mulla3, S. Manna2, A. Durward2, I. A. Murdoch2 and S. M. Tibby2*

1 Department of Pharmacy and 2 Department of Paediatric Intensive Care, Evelina London Children’s Hospital, Guy’s & St Thomas’ NHS Foundation Trust, King’s Health Partners, Westminster Bridge Road, London SE1 7EH, UK
2 Department of Pharmacy, University Hospitals of Leicester, Groby Road, Leicester, UK
* Corresponding author. E-mail: shane.tibby@gstt.nhs.uk

Editor’s key points

- This study investigated the absorption profiles and pharmacokinetic parameters for enterally administered clonidine in post-cardiac, critically ill infants, with a secondary aim of assessing haemodynamic stability.
- The pharmacokinetics were best described by a three-transit compartment absorption model coupled with a one-compartment disposition model, scaled to weight.
- Clonidine absorption after enteral administration was slow.
- Haemodynamic stability was maintained.
- Enteral clonidine is a safe sedative agent in the postoperative cardiac surgery period; however, if rapid analgo-sedative effects are needed, parenteral administration may be preferable.

Background. Clonidine is a useful analgesic-sedative agent; however, few data exist regarding its use in infants after congenital heart disease surgery. We thus aimed to assess the absorption and safety of enterally administered clonidine in this setting.

Methods. Sixteen infants (median age 6.7 months) received a single nasogastric dose of 3 μg kg⁻¹ clonidine 2–6 h after surgery. Blood samples were obtained at seven time intervals (up to 480 min). Plasma concentration profiles were obtained, and then pooled with a previous study (137 samples, 30 infants) for estimation of population pharmacokinetic parameters (NONMEM version 7.2).

Results. Enteral absorption showed considerable inter-individual variability, with clonidine Cmax ranging from 0.15 to 1.55 ng ml⁻¹ (median 0.73), and Tmax from 12 to 478 min (median 190). Although therapeutic sedative plasma concentrations were achieved in 94% of patients, only half had attained this by 70 min post-dose. Patients who did not receive inotropes exhibited a positive association between cumulative morphine dose and Tmax (interaction effect P=0.03); this was not seen among those receiving inotropes. The haemodynamic profile was favourable; few patients required fluid boluses, and this bore no relationship to plasma clonidine concentration. Population pharmacokinetic parameter estimation yielded results similar to previous paediatric studies: clearance 13.7 litre h⁻¹ 70 kg⁻¹ and Vd 181 litre 70 kg⁻¹.

Conclusions. Early postoperative enteral clonidine produces favourable haemodynamic profiles and therapeutic plasma concentrations in the majority of cardiac surgical infants; however, the time to achieve this can be erratic. Thus, parenteral administration may be preferable if rapid analgo-sedative effects are needed.

Keywords: cardiac surgical procedures; clonidine; infants

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The importance of optimizing the balance between oxygen delivery and consumption after surgery for congenital heart disease is widely acknowledged.1 Several studies have evaluated strategies for optimizing oxygen delivery;2–6 however, comparatively little attention has been devoted to exploring therapies that minimize oxygen consumption. A major component of oxygen consumption in the immediate postoperative period is the degree of sedation/analgesia. Surprisingly, there is lack of consensus regarding the optimal sedative regime in critically ill children; as a result, a wide variety of agents are used.

Clonidine has several properties which make this drug a potentially useful agent in the cardiac postoperative period. It is a partial agonist of central and peripheral α–2 receptors with analgesic, sedative, and antihypertensive effects.5 Thus, it may both reduce oxygen consumption and prevent deterioration in oxygen delivery secondary to sustained increases in afterload. The majority of paediatric reports have evaluated clonidine use in the general perioperative or paediatric intensive care settings,6 7 with only two reports assessing clonidine administration after cardiac surgery.8 9 In addition, reports have primarily assessed clonidine when administered via i.v., intrathecal, and/or rectal routes.10–12 Recently, a team from Karolinska University Hospital has published an observational study investigating oral bioavailability of clonidine in children when used as a premedication for adenotonsillectomy.13

We have been using an oral preparation of this agent in critically ill patients since 2000, and demonstrated its safety
and efficacy in a group of mechanically ventilated infants with respiratory failure. However, as the beneficial effects of early use of the gastrointestinal tract in cardiac patients are increasingly recognized, we wished to evaluate the enteral absorption of clonidine when used in the immediate postoperative period after congenital heart disease surgery. Our primary aim was to characterize absorption profiles for clonidine after enteral administration, with a secondary aim of assessing haemodynamic stability. In addition, these data could be used to refine previously estimated pharmacokinetic parameters of oral clonidine when used in critically ill infants.

Methods

The study was conducted over a 6 month period (March–August 2006) and approved by the Guy’s local research ethics committee (ref: 2004/02/12), with informed consent obtained from patients’ parents or legal guardians.

Inclusion criteria were any infant (>28 days to 1 yr of age) undergoing surgery for congenital heart disease that required postoperative monitoring with central venous and arterial lines. Exclusion criteria included: pre-existing renal or hepatic impairment, or clinically significant haemodynamic instability.

Conduct of the study

Patients who were haemodynamically stable (defined as not requiring an increasing inotropic dose or more than 15 ml kg⁻¹ fluid boluses in the previous hour) received a single, nasogastric dose of 3 μg kg⁻¹ clonidine at between 2 and 6 h after surgery. Clinical observations were as per routine care. Clonidine solution was manufactured by Guy’s & St Thomas’ manufacturing unit under a special manufacturing licence (10 μg ml⁻¹ solution).

Arterial blood samples (2 ml) for plasma clonidine assay were obtained immediately before clonidine administration (t₀), and at the following post-administration time intervals: 5–20 min (t₁), 25–40 min (t₂), 50–70 min (t₃), 110–130 min (t₄), 180–300 min (t₅), and 420–480 min (t₆). Time points were chosen using information derived from two prior studies. Designation of sampling time intervals, rather than single points, allows for greater accuracy in estimation of pharmacokinetic profiles using population-based pharmacokinetic software (provided the time of sampling was recorded accurately).

Blood specimens were immediately centrifuged for separation of plasma and stored at –70°C. Plasma clonidine concentration was assayed using high performance liquid chromatography mass spectrometry at the Advanced Bioanalytical Service Laboratories Ltd, Hertfordshire. Sample preparation included addition of the internal standard (d₄-clonidine), basification with ammonium hydroxide, extraction into dichloroethane/isopropanol (90:10), drying, and then reconstitution in 1% (v/v) formic acid solution for quantitative determination using high performance liquid chromatography tandem mass spectrometry with selected reaction monitoring of the protonated molecular ions using a CTC autosampler (CTC Analytics, Zwingen, Switzerland), Agilent 1100 liquid chromatograph (Agilent Technologies, Wokingham, UK), interfaced to an API4000 tandem mass spectrometer (AB SCIEX, Framingham, MA, USA). The samples were analysed with duplicate calibration standards containing clonidine in control human plasma prepared at 0 (blank), 0.1, 0.2, 0.5, 1, 2, 5, 10, and 20 ng ml⁻¹ and duplicate quality control samples (QCs) at 0.3, 2.5, and 15 ng ml⁻¹. The limit of quantification of this method is 0.1 ng ml⁻¹, with the range of linearity 0.1–20 ng ml⁻¹, and intra- and inter-assay coefficients of variation of <10 and <15%, respectively. We were unable to detect metabolites of clonidine, as the above method is highly specific, and no reference standards for metabolites were available at the time of analysis.

Pharmacokinetic methodology and statistics

Plasma concentration profiles after the single oral dose of clonidine were first examined for the post-cardiac surgical patients in the current study. These data were then pooled with trough plasma concentrations from our previous study in infants with respiratory failure, and pharmacokinetic parameters recalculated. The population pharmacokinetic model was developed using the mixed effects non-linear regression modelling programme, NONMEM (version 7.2; Icon) and a gfortran compiler. Post-processing of NONMEM output was conducted using the software Perl-speaks-NONMEM (v 3.4.1), R (v2.13.0), and Xpose (v4.3.2). A detailed description of the modelling method including model selection, development, and validation is provided in the Supplementary material.

Results

Sixteen infants post-cardiac surgery were studied, with a median (IQR) age of 6.7 months (5.9–8.6) and weight 6.9 kg (5.4–7.8). Diagnoses included: tetralogy of Fallot repair (n=8), ventricular septal defect (n=4), ventricular and atrial septal defect (n=2), and atrioventricular septal defect (n=2). Eleven of 16 patients were receiving the phosphodiesterase inhibitor milrinone (dose range 0.3–0.7 μg kg⁻¹ min⁻¹); no other inotropes were used during the study period. The median (IQR) dose of morphine at each time point was 30 μg kg⁻¹ h⁻¹ (20–40).

Enteral absorption

Enteral absorption profiles showed considerable variability (Fig. 1), with the maximum measured plasma clonidine concentration ranging from 0.15 to 1.55 ng ml⁻¹ (median 0.73), and the time to maximum measured concentration (Tₘₐₓ) ranging from 12 to 478 min (median 190). Of note, 94% of patients (15/16) achieved the minimum therapeutic sedative plasma concentration of >0.3 ng ml⁻¹. However, this was achieved relatively slowly, in that only half of the patients had attained this concentration by 50–70 min (t₃), and three-quarters by 110–130 min (t₄). Multiple linear regression revealed an interaction effect between cumulative morphine dose (over the first 8 postoperative hours) and milrinone use in terms of their relationship with Tₘₐₓ (Fig. 2). There was a positive association between cumulative morphine dose and Tₘₐₓ among patients who did not receive milrinone (coefficient
1.68, \( P=0.009 \)); with no such relationship for patients receiving milrinone (coefficient \(-0.09, P=0.86\), interaction \( P=0.03\)).

**Haemodynamic effects**

Haemodynamic profiles are shown in Figure 3. Five patients required a total of seven fluid boluses for hypotension; four of these occurred at t1. Timing of fluid bolus bore no relationship to the plasma clonidine concentrations; five boluses were given when plasma clonidine was below the limit of quantification; for the remaining two, the plasma clonidine concentrations were 0.15 and 0.63 ng ml\(^{-1}\).

**Pharmacokinetic parameters**

Estimation utilized data pooled from this and our previous study.\(^{14}\) A total of 137 samples from 30 children were available.
for analysis (97 from the current study, the remaining 40 coming from 14 respiratory patients).

A three-transit compartment absorption model coupled with a one-compartment disposition model was found to be the most appropriate structural model. Estimation of the between-subject variability in the absorption model parameters was not possible as it resulted in model convergence difficulties. The mean (SD) of individual subjects absorption half-life was 3.3 (1.2) h.

Significant improvement in model fit was achieved when weight (standardized to 70 kg) was associated linearly with both clearance and volume. In the case of clearance, weight was allometrically transformed by setting weight to a power of 0.75. No other covariate was found to have significant influence in the model. The population estimates (and associated between-subject variability) of clearance and volume of distribution were 13.7 (56.3% CV) litre h\(^{-1}\) 70 kg\(^{-1}\) and 181 (37.8% CV) litre kg\(^{-1}\), respectively.

The parameter estimates from the final model along with their associated 95% confidence intervals are shown in Table 1. Both the absorption and disposition parameters were estimated with reasonable precision. The bootstrapped values show no real bias in comparison with the final model suggesting model stability. Plots of the observed vs the final model-predicted plasma clonidine concentrations indicated excellent correlation (see Supplementary Fig. S1). Plots of weighted residuals vs both time and predicted serum clonidine concentrations revealed no systematic error (data not shown). The ability of the final model to simulate (and hence describe) the observed data is illustrated by the visual predictive check (Fig. 4). Overall, the median and 5th and 95th percentile ‘capture and envelope’ the observed data reasonably well, suggesting model appropriateness.

### Discussion

The value of clonidine and other \(\alpha-2\) agonists as sedatives in the intensive care unit are increasingly recognized.\(^{14,17}\) Over the last decade, enteral and i.v. clonidine have been used in our unit as first-line sedative agents, including patients post-cardiac surgery. Limited pharmacological data exist on clonidine use in paediatric intensive care, with the majority of reports detailing i.v. use. However, there are several reasons why enteral administration may be preferable in the intensive care setting (e.g. reduced infection risk, drug compatibility, fluid restriction), which provided the impetus for our study.

Our results show that although the majority (94%) of patients achieved therapeutic plasma clonidine concentrations, the absorption was often slow, with half of the patients requiring longer than 1 h to reach these values. Compared with healthy children in the study by Larsson and colleagues,\(^{13}\) our \(T\_{\text{max}}\) was approximately three times longer (190 vs 63 min), with a longer absorption half-life (3.3 vs 0.45 h) and more

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**Table 1** Pharmacokinetic parameter estimates from the final model. *Bias % calculated using the following equation: % bias = (final model estimate/bootstrap estimate)/final model estimate *\(100.\) \(^{1}\)Absorption rate constant, \(K_a=K_{a1}+K_e\), where \(K_e=\text{CL}/V\). Parameterized in this way to avoid ‘flip-flop’. \(^{2}\)Absorption half-life = 0.693/\(K_a\), presented as mean (so). This was determined using post hoc individual subject’s Bayesian estimate of \(K_a\). \(^{3}\)Study 1, postoperative cardiac children (current study); Study 2, ventilated respiratory children.\(^{14}\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study data set Estimate</th>
<th>95% CI</th>
<th>Bootstrap (500 replicates) Estimate</th>
<th>95% CI</th>
<th>Difference (bias %)*</th>
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<tr>
<td>CL (litre h(^{-1}) 70 kg(^{-1}))</td>
<td>13.7</td>
<td>10.1–17.3</td>
<td>14.1</td>
<td>9.9–21.8</td>
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<td>V (litre 70 kg(^{-1}))</td>
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<td>143–219</td>
<td>182</td>
<td>138–235</td>
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<td>(K_e) (h(^{-1}))</td>
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<tr>
<td>(K_{a1}) (h(^{-1}))(^{†})</td>
<td>0.07</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Absorption half-life (h)(^{‡}), mean (so)</td>
<td>3.32 (1.16)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BSV in CL (%CV)</td>
<td>56.3</td>
<td>22.9–76.7</td>
<td>61.2</td>
<td>31.9–113</td>
<td>1.6</td>
</tr>
<tr>
<td>BSV in V (%CV)</td>
<td>37.8</td>
<td>24.9–47.3</td>
<td>36.7</td>
<td>20.9–50.8</td>
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<td>Residual error, additive (so) ng ml(^{-1})</td>
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<tr>
<td>Study 1(^{§})</td>
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<td>0.21</td>
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<tr>
<td>Study 2(^{¶})</td>
<td>0.26</td>
<td>0.16–0.33</td>
<td>0.26</td>
<td>0.15–0.33</td>
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</table>
variable peak plasma concentrations. Simulated plasma concentrations illustrating the difference in typical absorption profiles between our and Larsson and colleagues' studies are shown in Figure 5. The reduced rate of absorption in our population may be due to reduced splanchnic blood supply post-cardiac surgery, which can be exacerbated by pharmacological effects of drugs such as opioids which delay gut transit time. This is consistent with our findings, whereby increasing morphine doses were associated with higher \( T_{\text{max}} \) only in patients who were not receiving inotropic support (Fig. 2); it is possible that these patients had an unappreciated lower cardiac output state. Conversely, this relationship was not seen for patients who were receiving inotropes. An additional difference is the administration method; unlike the study by Larsson and colleagues, our patients received the clonidine solution nasogastrically without further dilution in water or juices.

The population estimates of oral clearance and volume of distribution in our postoperative cardiac children are very similar to those reported by Potts and colleagues in their pooled population pharmacokinetic analysis of i.v., epidural, and rectal clonidine data, 13.7 vs 14.6 litre h\(^{-1}\) 70 kg\(^{-1}\) and 181 vs 182 litre 70 kg\(^{-1}\), respectively, and also similar to values reported in adults. However, whereas Potts and colleagues identified an effect of age on the clearance parameter, no such effect of age or any other covariate was found during model development, perhaps a reflection of our limited sample size and restricted age limit.

Our data also add to previous work documenting the safe haemodynamic profile with this drug when used after cardiac surgery. Ambrose and colleagues studied the use of i.v. clonidine infusion in a cohort of 10 post-cardiac surgery patients. They specifically investigated the effects on cardiac index, heart rate, and arterial pressure after a dose of 1 \( \mu g \) kg\(^{-1}\) h\(^{-1}\). Most of the patients received concomitant low-dose inotropic support which either stayed the same or was reduced during the 8 h study period. They found no significant change in trends over 6 h in heart rate [166 (so 17.9) to 154 (20.2) beats min\(^{-1}\)], arterial pressure [60 (so 9.8) to 64 (11.1) mm Hg], or derived cardiac index [5.7 (so 2.2) to 6.0 (1.51) ml m\(^{-2}\) min\(^{-1}\)]. These results are consistent with our haemodynamic findings (Fig. 3). In addition, we found no relationship between need for treatment with fluid boluses and neither timing of clonidine administration nor plasma clonidine concentrations. This was also shown in our previous study in children with respiratory failure, where the arterial pressure did not decrease over time, and although heart rate exhibited a small temporal reduction, this could have been explained by disease resolution, and never fell outside the normal limits for patients' age. In summary, the findings from these three studies suggest that clonidine has a safe haemodynamic profile in critically ill children.

The slow and erratic absorption profiles for enteral clonidine shown in our study patients are somewhat countered by two potentially beneficial effects. First, this appears to largely avoid the biphasic arterial pressure changes associated with i.v. bolus administration. Secondly, once the potentially sedative plasma concentration of 0.3 ng ml\(^{-1}\) is achieved, this appears to be sustained. These findings suggest that there may be some advantage to early enteral administration in this patient group.

**Limitations**

Several limitations of this study require acknowledgement and elaboration. First, we did not attempt to measure the primary desired pharmacodynamic effect of clonidine, sedation, but rather chose to target achieving a pre-defined minimum plasma concentration of \( >0.3 \) ng ml\(^{-1}\). However, we feel that this was a reasonable assumption, as it was based upon pharmacodynamic assessment (via the COMFORT score) in our previous study, conducted on infants of a similar age. Furthermore, accurate assessment of sedation in this patient group is confounded by many factors, such as cardiovascular status, cerebrovascular status, and recent emergence from prolonged general anaesthesia. The study design could have been strengthened by concurrent measurement of oxygen consumption, of which level of sedation is a major contributor.

Secondly, we could not estimate bioavailability, as patients did not receive i.v. clonidine. However, we feel this is a minor limitation. Furthermore, as our \( C_{\text{max}} \) was similar to Larsson and colleagues, it is possible that bioavailability is broadly comparable.

Finally, as this was a single-dose study, it is thus difficult to extrapolate to steady state. In addition, the erratic and occasionally reduced rate of enteral absorption for clonidine may become less important after multiple dosing.

**Conclusion**

Clonidine is a safe sedative agent in the postoperative cardiac surgery period. However, enteral administration between 2 and 6 h after surgery in haemodynamically stable patients may be associated with a delayed absorption profile, with the majority of patients eventually achieving therapeutic plasma
concentrations. Thus, we would recommend early enteral administration, or, if rapid analgo-sedative effects are needed, parenteral administration may be preferable.

Supplementary material
Supplementary material is available at British Journal of Anaesthesia online.

Author’s contributions
S.A.-L.: idea for the project, study design, data collection, preliminary analyses, and co-wrote first draft. H.M.: study design, pharmacokinetic modelling, and data interpretation. S.M.: patient recruitment, data collection, and preliminary analyses. A.D.: patient recruitment, data collection, data cleaning, preliminary analyses, and advanced data interpretation. I.A.M.: study design, advised on data collection, and data interpretation. S.M.T.: idea for the project, study design, data collection, preliminary analyses, and co-wrote first draft. All authors have contributed to revision of the initial drafts and have seen and approve the final draft of the manuscript.

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Declaration of interest
None declared.

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