British Journal of Anaesthesia **113** (6): 964–9 (2014)
Advance Access publication 30 July 2014 · doi:10.1093/bja/aeu258

BJA

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

S. Arenas-Lopez[1], H. Mulla[3], S. Manna[2], A. Durward[2], I. A. Murdoch[2] and S. M. Tibby[2]*

[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
[3] 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 C_{max} ranging from 0.15 to 1.55 ng ml^{-1} (median 0.73), and T_{max} 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 T_{max} (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 V_d 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

Accepted for publication: 22 May 2014

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;[2–4] 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

© The Author 2014. Published by Oxford University Press on behalf of the British Journal of Anaesthesia. All rights reserved.
For Permissions, please email: journals.permissions@oup.com

Downloaded from http://bja.oxfordjournals.org/ at Rudolph Matas Medical Library on January 20, 2015

and efficacy in a group of mechanically ventilated infants with respiratory failure.[14] 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 $\mu g\ kg^{-1}$ 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 $\mu g\ ml^{-1}$ 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.[15 16] 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 $\mu g\ kg^{-1}\ min^{-1}$); no other inotropes were used during the study period. The median (IQR) dose of morphine at each time point was 30 $\mu g\ kg^{-1}\ h^{-1}$ (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 (T_{max}) 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}.[14] 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 T_{max} (Fig. 2). There was a positive association between cumulative morphine dose and T_{max} among patients who did not receive milrinone (coefficient

Downloaded from http://bja.oxfordjournals.org/ at Rudolph Matas Medical Library on January 20, 2015

Download English Version:

https://daneshyari.com/en/article/8932285

Download Persian Version:

https://daneshyari.com/article/8932285

Daneshyari.com