British Journal of Anaesthesia **84 (6)**: 794–6 (2000)

BJA

SHORT COMMUNICATION

Intravenous clonidine infusion in critically ill children: dose-dependent sedative effects and cardiovascular stability

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Clonidine is used for analgesia and sedation in paediatric anaesthesia, but there are no data on its sedative properties and side effects in critically ill children. We studied 30 ventilated children aged 10 yr and under to determine an effective i.v. dosing range and to assess its cardiovascular effects. Twenty non-paralysed, ventilated children were given a background infusion of midazolam 50 μg kg^{-1} h^{-1} combined with a variable clonidine infusion (0.1–2 μg kg^{-1} h^{-1}) to maintain optimal sedation. The effects of clonidine 1 μg kg^{-1} h^{-1} on cardiac index were measured in 10 postoperative cardiac patients using a reverse Fick method. Dose-dependent sedation was achievable (713 out of 861 h) without cardiovascular side effects, but an infusion limit of clonidine 1 μg kg^{-1} h^{-1} was inadequate in two patients. An increased dose limit of 2 μg kg^{-1} h^{-1} combined with midazolam 50 μg kg^{-1} h^{-1} achieved satisfactory sedation scores for 602 out of a total of 672 h studied with no failures. Clonidine in combination with midazolam at 1 μg kg^{-1} h^{-1} was not associated with significant changes in heart rate arterial pressure or cardiac index.

Br J Anaesth 2000; **84**: 794–6

Keywords: anaesthesia, paediatrics; hypnotics; measurement techniques, cardiac output

Accepted for publication: January 7, 2000

Clonidine is a lipid-soluble, partial α-2 adrenoreceptor agonist with antihypertensive, analgesic and sedative properties. Recently there has been much interest in the paediatric literature on the use of clonidine as an oral premedicant and as an adjunct to epidural blockade to provide long-lasting analgesia without ventilatory depression.[1] Data from the adult intensive care has suggested that clonidine can provide dose-dependent sedation with cardiovascular stability and a noticeable lack of drug tolerance and withdrawal.[2 3] These attributes suggest that clonidine might be a useful continuous i.v. sedative in the critically ill child, but we are not aware of any data defining a dose range or describing its use in this population. In this open dose ranging study, we set out to determine whether clonidine is an effective sedative agent in the ventilated child, to establish a clinical dose range for sedation, and to assess cardiovascular side effects.

Methods and results

With appropriate ethical approval and informed parental consent, 30 children, aged 10 yr and under were enrolled in a three-part study. Ten ventilated, unparalysed critically ill children (group 1) were sedated with a variable i.v. infusion of clonidine (0.2–1.0 μg kg^{-1} h^{-1}) together with a fixed background dose of midazolam 50 μg kg^{-1} h^{-1}. The clonidine infusion was started at 0.6 μg kg^{-1} h^{-1} in neonates and 0.8 μg kg^{-1} h^{-1} in children older than 6 months. The infusion was increased or decreased by 0.2 μg kg^{-1} h^{-1} according to the level of sedation which was measured hourly by the nursing staff using a sedation score[4] derived from the observational pain score (OPS).[5] The score ranges from 0 to 10 with optimal sedation between 2 and 7, and the clonidine infusion was adjusted to try to maintain sedation within this band. Children with a sedation score of greater than 7, despite maximal clonidine, were given an increased infusion of midazolam (100 μg kg^{-1} h^{-1}) for up to 2 h and, if sedation remained inadequate after this time, the technique was deemed to have failed. Heart rate and blood pressure were recorded as part of the routine paediatric intensive care unit (PICU) practice.

A further 10 postoperative cardiac surgical patients were

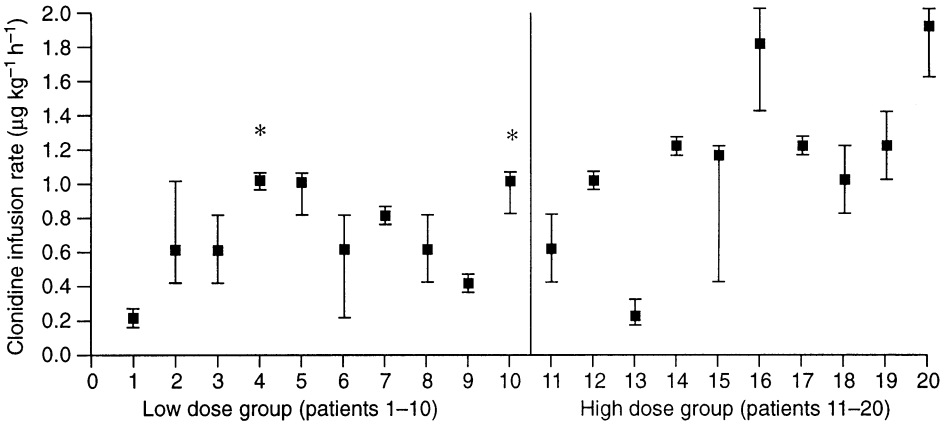

Fig 1 Median and interquartile infusion rates of clonidine needed to achieve adequate sedation using a maximum infusion of 1 (patients 1–10) or 2 μg kg^{-1} h^{-1} (patients 11–20). Asterisks denote the failure of sedation in patients 4 and 10 in the low-dose clonidine infusion rates.

assessed for the haemodynamic effects of a fixed clonidine infusion at a rate of 1.0 μg kg^{-1} h^{-1} specifically to determine if there were effects on cardiac index, heart rate and arterial pressure at this dose. Core and peripheral temperature were measured routinely but were not documented for the purpose of this study. These patients had central venous, pulmonary arterial and systemic arterial catheters in place which allowed trends in cardiac index to be measured using the reversed Fick method (cardiac output = oxygen demand/ arteriovenous oxygen difference). Oxygen uptake was not measured, but an assumption was made that oxygen demand would be relatively fixed in these anaesthetized, paralysed but stable patients. An oxygen uptake[6] of 160 ml min^{-1} m^{-2} was taken as a representative value in order to calculate trends in cardiac index. Most patients were receiving low-dose ionotropic support on return from theatre, but these infusions either remained at the same rate or were reduced during the 8-h study period. High-dose morphine (0.5 mg kg^{-1}) was given in a standardized fashion to all patients after separation from cardiopulmonary bypass, and a rectal dose of chloral hydrate (25 mg kg^{-1}) was given to all patients on arrival on the intensive care unit. This allowed patients to maintain adequate levels of analgesia and sedation prior to starting the clonidine infusion. Heart rate, arterial pressure and cardiac index parameters were measured immediately on returning to the intensive care unit from theatre and at 30-min intervals for 2 h before starting the clonidine infusion, and thereafter at 1-h intervals for 6 h.

Having assessed the cardiovascular safety aspects using a clonidine infusion of 1 μg kg^{-1} h^{-1}, we studied a further group of unparalysed, ventilated patients (group 2), using an identical study design to that used in the initial part of the study, but with a new maximum infusion dose of clonidine 2 μg kg^{-1} h^{-1}.

The first group of patients, in whom sedation was assessed, ranged from 7 to 38 months old (median 12.5 months). The study duration ranged from 21 to 222 h (total study time 861 h). There was large variability in the infusion rates required to achieve acceptable sedation (patients 1–10 in Fig. 1). Two patients failed to maintain adequate sedation at the maximum infusion of clonidine 1 μg kg^{-1} h^{-1}, but the other eight patients were adequately sedated (score of 2–7) for the entire study period. Using the data from the eight patients that successfully completed the study, and the data up to withdrawal for the other two patients, sedation was judged adequate for 713 of the 861 study hours (89% of the total study time). Children in group 2 receiving up to 2 μg kg^{-1} h^{-1} clonidine were significantly younger than patients in group 1. Ages varied from 1 day to 15 months (median 2.0 months) and the individual study duration ranged from 25 to 181 h (total study 672 h). Median clonidine infusion rates for group 2 are shown as patients 11–20 in Figure 1. Adequate sedation was recorded in 602 of the 672 hourly assessments (89.5%), and there were no failures. It was clear from both groups that increasing the clonidine infusion increased the levels of sedation in a dose-dependent fashion. Bradycardia and hypotension were not recorded in any patient.

The group receiving a fixed infusion of 1 μg kg^{-1} h^{-1} had no significant change in trends over 6 h in heart rate (166 (SD 17.9) to 154 (20.2) beat min^{-1}), blood pressure (60 (9.8) to 64 (11.1) mm Hg) or derived cardiac index (5.7 (2.2) to 6.0 (1.51) ml m^{-2} min^{-1}).

Comments

These data suggest that a variable i.v. infusion of clonidine at 0.2–2.0 μg kg^{-1} h^{-1} in combination with a fixed low-dose infusion of midazolam, can provide dose-dependent sedation in ventilated critically ill children without adverse effects on cardiovascular performance. It is unclear whether doses greater than 2.0 μg kg^{-1} h^{-1} of clonidine can increase sedation without significant haemodynamic effects. Morphine and midazolam are commonly used for sedation in PICU but prolonged use results in tolerance and withdrawal phenomena. In adults, clonidine is commonly used to aid opioid withdrawal and has been used as an effective alternative sedative to opioids.[3] We have now used this

drug routinely in our PICU for 3 yr, as a replacement for morphine in those patients who have become tolerant to opioids or who are difficult to sedate. Ventilatory side effects, tolerance and withdrawal have not been significant features of this drug in our clinical practice even after long-term use of 7 days or more, but there are no published data to confirm this. Further substantive studies are needed to define its role within PICU and determine its side effect profile in the paediatric population.

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