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Use of oral clonidine for sedation in ventilated paediatric intensive care patients

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Abstract *Objectives:* We aimed to document our experience with oral clonidine when used as a sedative in combination with intravenous morphine and lorazepam in a group of mechanically ventilated children with single-organ, respiratory failure. In particular, our objectives were to establish the relationship between oral dose, plasma concentration, and sedative effect, and second, to document the side-effect profile. *Design:* Prospective, cohort study over a 72-h period. *Setting:* Regional paediatric intensive care unit. *Patients and participants:* Twenty-four children were enrolled (median age 3 months) of whom ten were excluded (six due to extubation before 72 h, three sedation failures, one protocol violation). *Measurements and results:* Plasma clonidine was measured using gas chromatography mass spectrometry, and sedation assessed using the COMFORT score. Using a dose of 3–5 μg/kg every 8 h, plasma concentrations appeared to plateau at approximately 41 h giving a mean value of 1.38 ng/ml (95% confidence interval 1.0–1.8). Adequate sedation was achieved during 82% (837/1022 h) of the study period; however, this decreased to 70.3% when analysed on an intention-to-treat basis. There was a concomitant overall decrease in the average hourly requirements for both morphine ($P = 0.02$) and lorazepam ($P = 0.003$). There were no documented episodes of bradycardia, hypotension or hyperglycaemia. *Conclusions:* Oral clonidine may be a safe and effective sedative in combination with morphine and lorazepam for young children with single-organ, respiratory failure. This agent may also exhibit opioid and benzodiazepine sparing effects in this patient group. A full pharmacokinetic study is warranted.

Keywords Clonidine · Sedation · Paediatric · Intensive care

Introduction

Patients requiring mechanical ventilation in the Paediatric Intensive Care Unit (PICU) frequently need a combination of analgesic and sedative drugs to facilitate ventilator synchrony, reduce anxiety, and decrease oxygen consumption. This is commonly achieved with combination therapy, usually an opioid and a benzodiazepine [1]. Unfortunately, many benzodiazepines carry a significant side-effect profile, including tolerance, withdrawal, and respiratory/circulatory depression [2, 3].

Clonidine is an alpha-2 partial agonist with sedative properties offering advantages over other agents, as it does not produce respiratory depression, decreases the dose requirements of other sedatives, facilitates opiate withdrawal, and can be administered orally [4, 5, 6]. The majority of studies in children have examined the use of clonidine as a co-analgesic prior to surgery [7, 8, 9, 10, 11, 12, 13]; only one study has documented its use in the PICU as an intravenous sedative [14]. To date, no study has reported the use and pharmacokinetics of oral clonidine for routine sedation in PICU.

Since 2000, oral clonidine has been used with morphine as a first-line sedative agent in our 20-bed, tertiary PICU. Our annual admission rate is between 850 and 1,000 patients, and approximately 85% of patients receive clonidine at some stage during their admission. The aims of this study were thus to document our experience with oral clonidine in a group of children with single-organ (respiratory) failure. In particular, our objectives were to establish the relationship between oral dose, plasma concentration, and sedative effect, and second, to document the side-effect profile.

Methods

The study was conducted over 1 year (January 2002 to January 2003). Inclusion criteria included any child up to 5 years of age requiring intubation for primary respiratory failure who was likely to need mechanical ventilation for longer than 72 h. Exclusion criteria included renal impairment (serum creatinine >100 mmol/l), liver impairment (total bilirubin >85 mmol/l and serum ALT or AST >100 U/l) [15], gastric intolerance, administration of inotropes, arrhythmias, complex congenital heart disease, and severe neurological impairment. For the purpose of this study an arrhythmia was defined as any non-sinus tachycardia, junctional or idioventricular rhythm, or sinus bradycardia less than the lower limit of normal for age. The study was approved by the local research ethics committee, and informed consent obtained from patients' parents or guardians.

Study protocol

Sedation

All patients were treated using the standard PICU sedation protocol. This included bolus intravenous morphine (100 μg/kg), followed by infusion (20–40 μg·kg·h for children, 10–20 μg·kg·h for neonates). Clonidine was administered via the nasogastric tube at time 0 h as a test dose (1 μg/kg) to assess the blood pressure response, followed 1 h later by 3 μg/kg every 8 h. This could be adjusted up to 5 μg/kg, depending upon the patient's sedation requirement. Clonidine was administered as an oral solution, formulated as a 10 μg/ml preparation by the Pharmacy, St. Thomas' Hospital which holds an MHRA "specials" manufacturing license. The stability of the preparation was confirmed using a stability indicating assay. Lorazepam bolus doses (50–100 μg/kg) were used whilst determining the optimal clonidine dose, and prior to invasive procedures. Neuromuscular blockade was not routinely used. Adequacy of sedation was assessed objectively using the COMFORT score on an hourly basis. The COMFORT score is a validated numerical scale comprising eight physiological and psychological domains, each graded as 1–5, producing a range between 8 (comatose) and 40 (hyperalert) [16]. An adequate level of sedation was agreed a priori as 13 to 23. This range was chosen to target a level of sedation that would produce a patient who was under anlegesics, calm, with minimal risk of self-extubation, but able to maintain an appropriate cough reflex and spontaneous respiratory effort to achieve ventilator synchrony.

Sedation failure was defined as the need for greater than 400 μg/kg of lorazepam in a 24-h period while receiving the maximal morphine (40 μg·kg·h) and clonidine (5 μg/kg every 8 h) doses.

Clonidine sampling and analysis

Blood sampling was limited to four occasions due to ethical considerations. As a detailed pharmacokinetic profile was not possible, we elected to measure clonidine trough concentrations only. A baseline sample was taken at time 0 h, and subsequently at times 17 h, 41 h, and 65 h. These time points represented 16 h after the initial dose and thereafter at 24-h intervals, and were chosen to accommodate the likely range of time to achieve steady state (41 h and 65 h samples), with the inclusion of a mid point sample (17 h sample). Blood samples were collected in lithium/heparin tubes, centrifuged within 1 h at 13,000 rpm for 5 min, and the supernatant transferred to a clear tube and frozen at –20 °C until analysis.

Plasma samples were assayed via gas chromatography mass spectrometry (ABS laboratories, London). The limit of detection of this method is 0.1 ng/ml, and the limit of quantification is 0.5 ng/ml. Sample preparation included addition of the internal standard (d4-clonidine), basification with sodium hydroxide, extraction into dichloroethane, and then derivatisation to form a pentafluorobenzyl derivative. The derivative was then cleaned via an acid wash and hexane extraction performed.

Side-effect profile

Potential side effects of clonidine include bradycardia, hypotension, and hyperglycaemia. An electrocardiogram was performed prior to commencing clonidine. Blood pressure and heart rate were monitored as per routine PICU practice. Blood glucose was measured 4–6 hourly using the Advantage Blood Glucose Monitoring System (Boehringer-Mannheim).

Statistical analysis

Continuous, temporal data were analysed using one-way, repeated measures analysis of variance, with post hoc Bonferroni-corrected *t*-tests where appropriate (Instat, Graphpad Software, San Diego, Calif., USA).

Results

Twenty-four patients were enrolled (13 male) with a median (interquartile) age of 3 months (1.3–15.9 months), weight of 5.0 kg (4.5–5.6 kg) and PIM-derived mortality risk of 8.0% (5.3–9.8%). The commonest reasons for admission were acute viral bronchiolitis (n =13), pneumonia (n = 4), and croup (n = 3). Ten patients were excluded from final analysis, six because of extubation before 72 h, three secondary to sedation failure and one due to protocol violation. All three sedation failures occurred within 24 h and were subsequently managed successfully using intravenous clonidine infusions at 1 μg·kg·h.

The median length of ventilation among the remaining 14 patients was 81 h (78–111 h).

Clonidine dose and plasma concentration

All patients were commenced on clonidine as per protocol. There were no episodes of hypotension following the test dose. However, by 24 h 9/14 patients were receiving

Table 1 Temporal values for cumulative dose, plasma concentration and area under the curve (clonidine plasma concentration versus time) following oral clonidine administration. The area under the curve is evaluated on the trough (pre-dose) plasma concentrations only, as a full pharmacokinetic profile was not obtained. As such, it represents the minimum exposure to clonidine. Data are mean (95% confidence interval)

Time	Cumulative dose	Plasma concentration	Area under curve
(h)	(μg/kg)	(ng/ml)	(ng·ml·h)
0	0	0	0
17	8.1 (7.3–8.9)	0.9 (0.7–1.1)	7.9 (6.2–9.6)
41	20.3 (18.4–22.2)	1.38 (1.0–1.8)	34.9 (27.3–42.5)
65	32.7 (29.0–36.4)	1.4 (1.2–1.6)	68.6 (54.8–82.4)

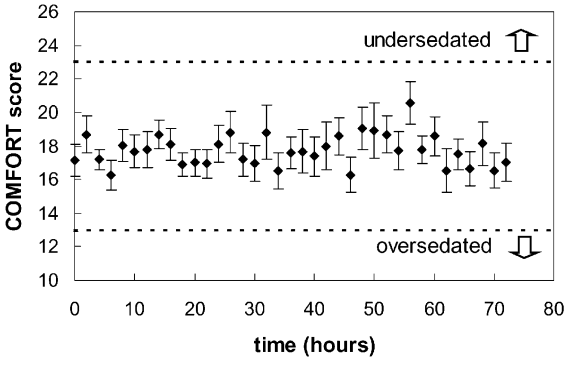

Fig. 1 Group sedation scores (COMFORT) over the study period. Data are mean, error bars SEM. Adequate sedation was defined as a COMFORT score of 13–23

the maximum dose (5 μg/kg). Table 1 shows the relationship between clonidine dose and plasma concentration. Although this increased with time (ANOVA P <0.001), the concentration appeared to reach a plateau by 41 h (P >0.05 compared to 65 h). The majority (23/28) of the plasma concentrations measured at time 41 h and 65 h were in the range 0.9–2.5 ng/ml.

Efficacy of sedation

The mean COMFORT score remained within the specified range throughout the study period (Fig. 1). Adequate sedation was achieved in 837/1,022 (81.9%) study h, while oversedation and undersedation occurred in 75/1,022 (7.3%) h, and 110/1,022 (10.8%) h respectively. However, the number of study hours where adequate sedation was achieved decreased to 70.3% (1023/1456) when analysed on an intention to treat basis. This figure incorporates the COMFORT scores for the six patients extubated before 72 h, and assumes a failure rate of 72 h for each of the three patients who required intravenous clonidine.

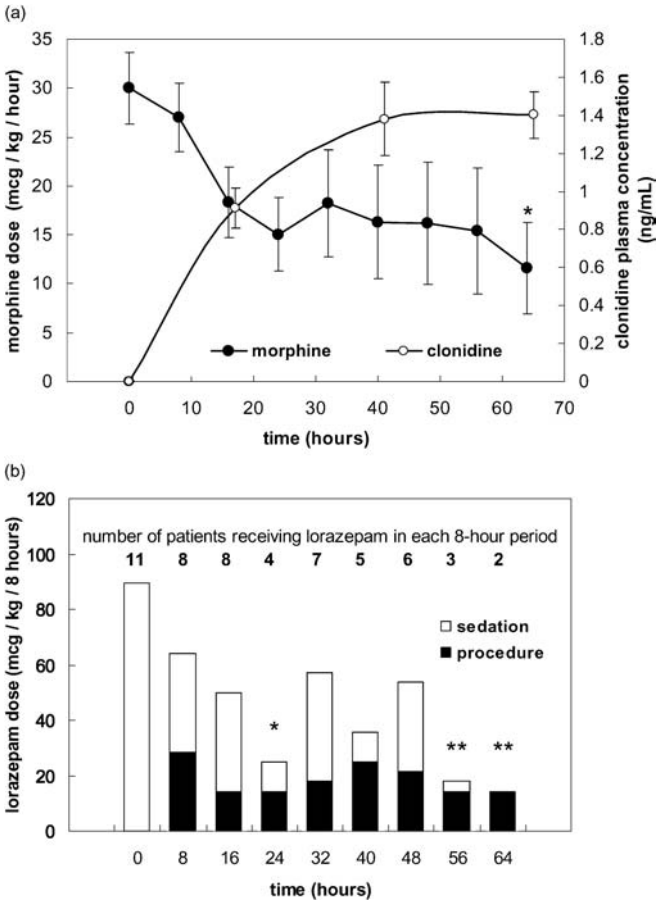

Fig. 2A,B **A** Average hourly morphine dose, plasma clonidine concentration; **B** average 8-h lorazepam dose with time. There was an overall decrease in both morphine (ANOVA P = 0.02) and lorazepam use (ANOVA P = 0.003). Bonferroni-corrected t-tests were performed, comparing time 0 with all subsequent time points (* P< 0.05, ** P< 0.01). Data are mean, error bars SEM

There was a concomitant overall decrease in the average hourly requirements for both morphine (ANOVA P = 0.02) and lorazepam (ANOVA P = 0.003) when analysed over the first 64 h for the fourteen patients who completed the study (Fig. 2). This time interval was chosen for statistical analysis (rather than the complete 72 h study period) as it excluded a period of at least 12 h prior to the first patient extubation and was thus unlikely to be confounded by planned sedative weaning to facilitate extubation. Figure 2b also shows that by 56 h, the majority of the lorazepam was administered prior to invasive procedures, rather than for sedation.

Side-effect profile

Table 2 shows the mean heart rate, blood pressure, and blood glucose profiles over the study period. Although the heart rate decreased significantly, this may have been

Table 2 Heart rate, mean blood pressure, and blood glucose values. The ANOVA *P* values were as follows: heart rate ($P < 0.001$), mean blood pressure ($P = 0.03$), blood glucose ($P = 0.54$). Data are mean (95% confidence interval)

Time	Heart rate	Mean blood pressure	Blood glucose
(h)	(beats per min)	(mmHg)	(mmol/l)
0	152 (143–160)	69 (62–76)	4.1 (3.8–4.4)
8	137 (129–146)	60 (54–66)	4.3 (3.9–4.7)
16	134 (126–142)	62 (56–68)	4.6 (4.2–5.0)
24	137 (129–146)	62 (55–69)	4.6 (4.2–5.0)
32	134 (122–146)	59 (53–66)	4.9 (4.2–5.6)
40	139 (131–46)	61 (56–65)	4.8 (4.5–5.2)
48	132 (122–143)	60 (55–65)	4.6 (4.3–4.9)
56	130 (118–142)	63 (56–70)	4.4 (4.3–4.5)
64	129 (119–139)	63 (58–68)	4.6 (4.4–4.8)
72	126 (117–135)	66 (61–70)	5.0 (4.5–5.5)

influenced by other factors such as disease resolution. Of note, there were no episodes of bradycardia requiring treatment, and the lowest recorded heart rate was 85 beats per minute. Similarly, there were no recorded episodes of hypotension or hyperglycaemia.

Discussion

Clonidine was introduced over 30 years ago as a centrally acting antihypertensive agent [17]. More recently, its role in analgesia, sedation, and opioid withdrawal has been highlighted in adult practice [5, 18, 19]. Over the last decade, many reports have examined its use in children primarily as a co-analgesic, usually prior to surgical procedures [7, 8, 9 ,10 ,11 ,12, 13, 20].

To date, one study has reported its use as an intravenous sedative in the PICU [14]. On the basis of this study, and its known excellent absorption profile in adults, we adopted the oral preparation of this agent into our sedation regime in 2000, replacing intravenous midazolam. Although our clinical impression was favourable, we felt it necessary to formally assess and document its clinical efficacy and safety in reference to plasma concentration.

The clonidine dose range used in this study was 3–5 μg/kg, which was extrapolated from previous paediatric premedicant studies [13, 20] and adult schedules on a dose/kg basis. This produced an initial temporal increase in plasma concentration, which appeared to plateau by 41 h, suggesting that steady state values were achieved by this time. However, this cannot be ascertained with certainty from our data as a full pharmacokinetic profile was not obtained, nor were identical clonidine doses given to each patient. Nonetheless, steady state approximating 41 h is conceivable if we assume the half-life of oral clonidine to be similar to that following intravenous and rectal administration in children (6–12 h) [7, 8], knowing that steady state is typically achieved at four to five times the drug half-life.

The plasma concentrations reported in our study represent 8-h trough values following oral administration, and are similar to previous paediatric reports. Lonqvist documented a median maximum plasma concentration of 0.7 ng/ml following rectal administration (2.5 μg/kg) [8], while Bergendhal reported median levels of 0.38 ng/ml and 0.76 ng/ml 15 min after single intravenous doses (0.625 μg/kg and 1.25 μg/kg, respectively) [9]. Although our study differs from these in regard to route of administration, patient age, and timing of samples, the comparable plasma concentrations suggest a favourable absorption profile with oral use. Again, a full pharmacokinetic study is warranted.

The sedation routine used in this study was the standard regime for our unit. Our sedation regime produced acceptable sedation in 82% of the study hours, remarkably similar to that reported by Ambrose [14]. However, direct comparison between these two studies is difficult because of differences in sedation scores used, endpoints, and adjunctive sedatives. We demonstrated a consistent and adequate level of sedation in the majority of cases at clonidine plasma concentrations of 0.9–2.5 ng/ml. This is comparable to that reported in adults, where maximal sedative effect is achieved at concentrations of 1.5–2.0 ng/ml [17]. Our data also suggest a benzodiazepine and morphine sparing effect when the plasma clonidine concentration approaches this range, although this cannot be proven without a randomised controlled study. However, the antinociceptive effects of clonidine have been well known for over 20 years [21], and the benzodiazepine sparing effects of this agent in healthy volunteers have been shown recently [22].

We found an acceptable side-effect profile using oral clonidine at doses of up to 5 μg/kg every 8 h. The safe upper limit in children remains unknown, although doses higher than this have been tolerated when used intravenously [14, 23]. However, high-dose clonidine can cause hypertension secondary to agonistic effects on alpha-1 receptors. This has been reported in adults achieving plasma concentrations of 3–4 ng/ml, typically receiving doses greater than 10 μg/kg [17].

There are several limitations to our study. As stated earlier, we did not perform a full pharmacokinetic profile because of the excessive volume of blood required relative to patient size. This means that detailed information on peak plasma concentration, half-life, and clearance are lacking. We cannot extrapolate our findings with confidence to the wider PICU population, particularly those with multiple organ failure for several reasons. First, hepatic and renal impairment are likely to alter clonidine pharmacokinetics, as approximately 40% of an administered dose undergoes oxidative metabolism in the liver leading to inactive metabolites, while the remaining 60% is excreted unchanged by the kidney. Second, the appar-

ent volume of distribution (0.96 l/kg) [7, 8] may change in critical illness. Third, although haemodynamic side effects have not been demonstrated following cardiac surgery [14], this may differ in patients with cardiac failure from other causes such as sepsis. Fourth, it is difficult to separate the sedative effects of clonidine from the other two agents used, namely morphine and lorazepam. We did not measure plasma concentrations of either of these compounds or their active metabolites; however the doses used were modest, as can be seen from Fig. 2.

In summary, we have shown that oral clonidine is a safe and effective sedative in combination with morphine and lorazepam for young children with single-organ, respiratory failure. Over time, this agent demonstrates morphine- and benzodiazepine-sparing effects. Using a dose of 3–5 μg/kg every 8 h, plasma concentrations appear to plateau at approximately 41 h, usually in the range of 0.9–2.5 ng/ml. Further studies are warranted to elucidate the full pharmacokinetic profile of clonidine and to explore its use in the wider PICU population.

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