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Optimising clonidine dosage for sedation in mechanically ventilated children: a pharmacokinetic simulation study

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What is already known?

- Clonidine is in widespread use as a sedative in paediatric critical care despite a limited evidence base for efficacy
- A variety of dosage regimens have been employed in previous studies and in clinical practice

What does this article add?

- Clonidine dosage regimens used in practice and research studies are likely suboptimal
- Clonidine titrated infusions with a loading dose of 2 µg/kg followed by a continuous infusion of

up to 2 µg/kg/hr are recommended in haemodynamically stable PICU patients to achieve adequate sedation. Doses should be halved in neonates.

Summary

Background: Clonidine is in widespread off-label use as a sedative in mechanically ventilated children, despite limited evidence of efficacy. A variety of dosage regimens have been utilised in clinical practice and in research studies. Within these studies, clonidine has inconsistently shown useful sedation properties. One of the reasons attributed to the inconsistent signs of efficacy is suboptimal clonidine dosing.

Aim: This study aims to propose a target plasma concentration and simulate clonidine pharmacokinetics (PK) in a cohort of mechanically ventilated children to evaluate the adequacy of clonidine dosage regimens used in clinical practice and research studies.

Method: A literature search was undertaken to identify a clonidine PKPD model, from which a target concentration for sedation was defined. Using a previously published PK model the projected plasma concentrations of 692 mechanically ventilated children (demographics taken from a recent study) were generated. Doses from recently published clinical studies were investigated. Adequacy of each regimen to attain therapeutic clonidine plasma concentrations was assessed.

Results: A target plasma concentration of above 2 µg/L was proposed. Nine dosage regimens (four intravenous boluses, four intravenous infusions and one nasogastric route boluses) were evaluated ranging from 1µg/kg 8 hourly intravenous boluses to a regimen up to 3µg/kg/hr continuous intravenous infusion. Regimens with a loading dose of 2µg/kg followed by variable continuous infusion of up to 2µg/kg/hr titrated according to sedation score appear most suitable.

Conclusions: The variety of dosage regimens in previous studies of clonidine along with difficulties in the conduct of interventional studies may have contributed to the lack of efficacy data to support its use. Simulations of clonidine plasma concentrations based on known population pharmacokinetic parameters suggest a loading dose followed by higher than current practice maintenance dose infusion is required to achieve adequate steady-state concentrations early in treatment. Further PKPD

studies will aid in the determination of the optimal clonidine dosage regimen.

Keywords: Clonidine, pharmacokinetics, conscious sedation, child, computer simulation, adrenergic alpha-agonists

Background:

The α_2 agonists have been of intense interest in the paediatric critical care literature as sedative agents.[1,2] An alternative mechanism of action to opioids and benzodiazepines makes them attractive to clinicians. Some of this interest has been extrapolated from the robust evidence base to support the use of the short-acting α_2 agonist dexmedetomidine in adults.[3,4] The older α_2 agonist clonidine has been in off-label use in the Paediatric Intensive Care Unit (PICU) for decades.[5] Less is known about clonidine's efficacy despite it being an older agent. Paradoxically, increased prescribing rates of dexmedetomidine has evoked interest in optimising the role of clonidine.[6,7] Of particular importance for paediatric use is that clonidine displays age-related changes in pharmacokinetics attributable to the maturation of clearance during infancy.[8] It has a long elimination half-life (16.9 hours in neonates, 11.4 hours in infants and 7.4 hours in children).[9] Additionally, intravenous formulations of clonidine are currently not marketed in North America although an oral formulation is available. Both oral and intravenous formulations are however commercially available in Europe. Bioavailability of orally administered clonidine formulations has been estimated to be approximately 55% in children.[10] Paediatric-derived information to date, on both α_2 agonists, has been scarce with limited evidence of efficacy on sedation outcomes.[1,2]

Evidence to support a particular dosage regimen of clonidine has also been limited. Of the RCTs previously performed, one previous study [Duffet et al.][11] was a pilot study and not powered for efficacy outcomes, and two studies [SLEEPS and CloSed][12,13] encountered recruitment difficulties prohibiting analysis of pre-planned outcomes. A final study [Hunseler et al.][14] reported efficacy as an opioid-sparing agent, though this was only observed in one age stratum, that of neonates. It has been proposed the isolated signs of efficacy (reduced fentanyl administration) in this RCT was due to higher plasma clonidine levels in neonates versus older infants due to the underdeveloped clearance in neonates.[9]

Recruitment difficulties within the multisite European CloSed trial suggest evidence from RCTs of dosage regimen efficacy might remain elusive for the near future.[13] A recent comparative effectiveness observational study included 692 children in Ireland who received clonidine while mechanically ventilated.[15] While an increased time at the target sedation score was observed, a concomitant decrease in opioid and benzodiazepine use was not found. Of note, clonidine intravenous bolus dosages in this study were in the range of 1-2 µg/kg six to eight hourly. Continuous intravenous infusions were not used in this study. There appears to be a shift; however, within the literature, towards higher clonidine dosage regimens than the dosages which are in current clinical practice in Ireland.[16] While the optimal clonidine dosage regimen remains undefined, it is reasonable to consider many children may be sub-optimally dosed within the current practice, although this has not been formally tested. Population pharmacokinetic parameters for clonidine have previously been published[8], although comparing these is sometimes difficult unless the standardised maturation parameters are used.[17] These parameters provide for formal clonidine dosage simulations to predict plasma concentrations achieved by various dosing strategies.

The aim of this study was first to provide some rationale for a proposed target concentration for sedation in PICU, and second to assess whether clonidine dosage regimens used in previous clinical studies and in routine practice are likely to achieve this therapeutic concentration. Patient demographics of the 692 included children from the recent comparative effectiveness study of clonidine in Ireland are used in the simulation replicating a real-life clinical population. This study will inform both current off-label clinical practice and provide evidence for dosage regimen design in future clonidine RCT attempts.

Methods:

Method for pharmacodynamic analysis for the proposal of a clonidine target plasma concentration

A comprehensive literature review was undertaken in order to identify pharmacokinetic-pharmacodynamic (PKPD) studies on clonidine and sedation. The search terms clonidine AND pharmacodynamics were used in PUBMED with limits to clinical trials and human subjects. The

search was carried out in January 2019. Titles and abstracts were screened to identify studies detailing clonidine use alone as a sedative.

Only one PKPD study was identified.[18] The single study found which used clonidine in the absence of other sedative agents was a study by Hall et al.[18] This study was conducted in healthy adults volunteers, who received doses of 0, 1, 2 and 4 μg/kg over 15 min followed by 45 min of continuous infusion. Sedation was measured by bispectral index (BIS) which analyse the EEG signal by providing a value between 0 and 100 inversely correlated with the level of hypnosis.

For our present study, we extracted data from the study by Hall et al.[18] Experimental data (BIS scores with time under different clonidine dose schemes) from this study were extracted. No PK data were reported by Hall et al[18], and hence we used typical PK parameters from a previous study by Larsson et al.[10] An effect compartment model was then used to estimate the delay between predicted plasma concentration and effect.

This effect compartment concentration was then used to derive a sigmoidal E_{max} model of the BIS score with time. As follows:

$$BIS(t) = BIS_{max} - BIS_{max}\, Ce^{Hill}/(BIS_{50}{}^{Hill} + Ce^{Hill})$$

where BIS_{max} is the maximum BIS score (the baseline), Ce is the effect compartment concentration, BIS_{50} the concentration to decrease BIS score by half, and Hill is the Hill coefficient (shape parameter). The target was assumed to be a BIS score of approximately 60-70.[19]

Method for Dosage Regimen Identification

Eligible studies were identified from a recent systematic review which included three clonidine RCTs.[1] In addition, the ongoing CloSed trial was included.[13] Dosage regimens used in local clinical practice in Ireland were also included.[16]

Clinical and Pharmacokinetic Parameters used in the PK simulation

Demographic details from the 692 children who received clonidine while mechanically ventilated in a

recent comparative effectiveness observational study were extracted (Table 1)[16] These children represent a 30 month admission period in the PICUs of Our Lady's Children's Hospital, Crumlin, Dublin, Ireland, and Children's University Hospital, Temple Street, Dublin. Gestational and postnatal age alongside body weight at admission were detailed for each child who received clonidine.

Clonidine pharmacokinetic data were obtained from the model of Larsson and al.(Table 2).[10] This model used a sigmoidal postmenstrual age function.[17]

$$CL_i = CL_T.\left(\frac{WT_i}{70}\right)^{0.75}.\frac{PMA_i{}^{Hill}}{PMA_{50}^{Hill} + PMA_i{}^{Hill}}$$

where CL is drug clearance in an individual, CL_T is the typical CL for a 70 kg adult, WT is body weight, PMA_{50} is the PMA (usually in weeks) for CL to reach 50% mature, and Hill is the shape parameter describing the steepness of the clearance maturation curve. Volume and inter compartmental clearance (Q) were scaled with standard allometric scaling (exponents of 1 for central and peripheral volume, 0.75 for Q) centred on 70kg

Pharmacokinetic model and simulations detail

Using this model and the dataset including the demographic data of the 692 children, simulations were performed with NONMEM (version 7.4) to predict plasma concentrations of clonidine for the nominated dosage regimens in 24 hours of treatment. Variable dosage range infusions were permitted in two studies. These were the SLEEPS RCT [0-3 µg/kg/hr], and the CloSed RCT [dosage for neonates was 1 µg/kg over 15 mins followed by 0.5-1 µg/kg/hr, and the dosage for older children was 2 µg/kg over 15 mins followed by 1-2 µg/kg/hr]. For the purposes of the simulation, the mid-way point of each infusion range was chosen. For the SLEEPS RCT this was 1.5 µg/kg/hr. For the CloSed neonatal dosage this was 0.75 µg/kg/hr and 1.5 µg/kg/hr for older children. The CloSed study also permits additional rescue boluses if insufficient sedation is not achieved. These were not included in the simulation in this study. Plasma concentration profiles for 24 hours were plotted using R (Version 3.4.4) to determine if therapeutic levels are likely to be achieved. Median plasma concentrations of clonidine attained by each child at each time point along with 95th percentiles were plotted.

Results

Results of the pharmacodynamic analysis for the proposal of a clonidine target plasma concentration

Pharmacokinetic data were modelled for the four dose levels [0, 1, 2 and 4 µg/kg] given by Hall et al.[18] using fixed parameters updated from Larsson et al. (Table 2).[10] The observed/population predicted plasma concentrations versus time are given in Supplementary Figure 1.

A sigmoid E_{max} model was then used to describe the pharmacodynamic relationship between concentration and BIS score. No improvement in fit was observed with Hill estimated or fixed equal to one. The BIS_{50} was estimated at 5.29 µg/L, the effect compartment equilibration coefficient at 5.74 h^{-1} and the baseline (BIS_{max}) was estimated at 97.5. Figure 1 shows the experimental data, along with the population model predictions of BIS measurements versus time.

Figure 2 shows that target concentrations of 2, 3 or 4 µg/L correspond to a BIS score of 71, 62 and 56 respectively

Results for Target Plasma Clonidine Concentration

The BIS derived target suggests adequate sedation at concentrations of 3 µg/L, but in most cases patients will require analgesia using agents with sedative effects. A study conducted by Arena-Lopez et al.[20] in children showed adequate sedation once steady state has reached an average clonidine concentration around 1.4 µg/L. In this study, sedation was measured by COMFORT score after administration of clonidine and morphine. Clonidine was administered via the nasogastric tube at 1 µg/kg followed one hour later by 3 µg/kg every eight hours and, depending on sedation requirements, this dose could be adjusted up to 5 µg/kg. In addition, lorazepam bolus doses (50–100 mg/kg) were used prior to invasive procedures and to provide appropriate sedation. Current clinical practice favours use of clonidine as an adjunct agent alongside an opioid infusion to minimise further opioid and benzodiazepine requirements. Hence, based on the results from the Hall study[18] and taking into consideration the adequate sedation obtained in the study by Arenas Lopez et al.[20], a minimum target concentration above 2 µg/L was chosen to evaluate the adequacy of clonidine dosage regimens. This target level of 2 µg/L has also been proposed in a study of clonidine PK-PD during paediatric extracorporeal membrane oxygenation.[21]

Results of Dosage Regimen Identification

A summary of the included studies is included in Table 3. Three large-scale clonidine RCTs have been attempted to date or are on-going[12-14], in addition to one pilot RCT[11]. Within these four RCTs, one study used a fixed bolus of 5 µg/kg six hourly via the nasogastric route[11], one study used a fixed infusion of 1 µg/kg/hr [14], and two studies used a loading bolus followed by a variable infusion rate up to 2 µg/kg/hr in the CloSed study[13] and 3 µg/kg/hr in the SLEEPs study[12]. The final observational study reflects local practice in PICUs in Ireland with a bolus dosage of 1-2 µg/kg six to eight hourly. Additional studies have described similar intravenous clonidine bolus dosages within the lower range of 1- 2.5 µg/kg[8]. For the CloSed study dosages were halved in neonates and a series of additional boluses were permitted if insufficient sedation was achieved. All efficacy studies included were based on the use of clonidine in combination with an opioid. This is likely due to the need for sufficient analgesia alongside the use of sedatives.

Plasma profiles obtained following PK simulation

The results for the simulated plasma clonidine concentrations for the first 24 hours of treatment are shown in Figure 3. The intravenous bolus dosages of 1-2 µg/kg 6-8 hourly studied did not achieve the target plasma concentration. The higher nasogastric dosage of Duffett et al. was associated with significant time above the target concentration although high variability was observed with this route of administration.[11] The intravenous infusion regimens attained the target levels for many children. The study by Hunseler et al. of a fixed dosage of 1 µg/kg/hr without a loading dose was associated with a longer time to steady-state concentrations than the other infusion regimens. The SLEEPs study regimen of a 3 µg/kg/hr loading dose followed by a variable infusion rate of 0-3 µg/kg/hr achieved the highest median plasma concentrations with most patients above the target level after five to ten hours.[12] The CloSed study neonatal regimen achieved below target plasma concentrations while a majority of the children older than 28 days achieved target concentrations after twenty hours.[13]

Discussion

Uncertainty relating to optimal clonidine dosage may have contributed to inconsistent reports of efficacy in previous studies. This simulation study was conducted to evaluate the adequacy of previously reported clonidine dosage regimens. Firstly a target plasma clonidine concentration of above 2 µg/L was proposed using a combination of a pharmacodynamic analysis of a bispectral index

study in healthy adult volunteers[18] along with empirical data from a paediatric critical care study[20]. Updated pharmacokinetic parameters incorporating a maturation function are then presented. A literature review showed a range of clonidine dosages from 1 µg/kg boluses every 8 hours up to infusion rates of 3 µg/kg/hr had been used in previous studies. Simulation of plasma concentrations using the demographics of a large cohort of children who received clonidine highlight many of these dosage regimens are unlikely to achieve the target plasma concentration. Clinicians should be mindful of clonidine pharmacokinetics when selecting a dosage strategy. In particular, the long half-life of clonidine in children delays the achievement of steady-state concentrations. Administration by continuous infusion is required to achieve concentrations above a minimum threshold of 2 µg/L at steady state. Without a loading dose, concentrations above 2 µg/L are not achieved in the first 24 hours of treatment for many children. Fixed bolus dosages of clonidine via the intravenous or nasogastric route produce relatively low plasma concentrations. •Clonidine titrated infusions with a loading dose of 2 µg/kg followed by a continuous infusion of up to 2 µg/kg/hr are recommended in haemodynamically stable PICU patients to achieve adequate sedation. Doses should be halved in neonates.

Clonidine dosage regimens and target plasma concentrations have evolved in recent years. In 2003, a lower concentration range of 0.3 - 0.8 µg/L was estimated as satisfactory for preoperative sedation in children 1 - 11 years.[22] This was consistent with an earlier study in 1998, which found postoperative sedation was unsatisfactory in children of 1 - 9 years at concentrations below 0.3 µg/L.[23] Studies in adults report therapeutic analgesia and sedation in the range of 1.5 -2 µg/L.[8] The paediatric study by Arenas-Lopez et al. suggests a similar range is adequate in children. Their study of twenty-four mechanically ventilated children who received clonidine and morphine had 82% of sedation assessments at the target range and showed a majority of steady-state plasma concentrations in the range 0.9 – 2.5 µg/L.[20] Of note, the largest paediatric RCT of clonidine by Hunseler et al. did not report plasma clonidine concentrations.[14] Efficacy was evaluated in three different age strata: [Strata One from 0 days to 28 days, Strata Two from 29 days to 120 days and Strata Three from 121 days to 2 years]. A significant reduction in fentanyl co-administration was reported only in the neonate cohort of Strata One. Subsequently, plasma clonidine concentration profiles for each of the three age strata were predicted[9] based on the dosage regimen employed and literature pharmacokinetic parameters by Potts et al.[8] Steady-state concentrations were predicted at

approximate means of 6 µg/L, 5 µg/L and 3 µg/L respectively for each stratum. Given efficacy was observed in the youngest cohort only; this would imply that higher plasma concentrations than previously anticipated are required. While the optimal clonidine plasma concentration remains undefined, concentrations at least above 2 µg/L are warranted, and concentrations up to a median of 6 µg/L are attained in mechanically ventilated children. Potts et al. previously proposed a dosage regimen for clonidine infusions aimed at maintaining plasma concentration above 0.3 µg/L with a median concentration target of 1 µg/L.[8] A loading dose of 1 µg/kg followed by an infusion of 2 µg/kg/hr for 30 minutes, 1 µg/kg/hr for 30 minutes to 1 hour, then 0.5 µg/kg/hr for 1 to 3 hours and 0.3 µg/kg/hr thereafter. To our knowledge, this regimen has not been incorporated into subsequent clinical studies. The relative complexity of this regimen or a preference to reproduce existing clinical practice in research studies may have contributed to this. The variety of dosage regimens of clonidine described in the literature reflects a research gap that should be addressed before future efficacy studies are attempted.

When contemplating loading doses and increasing target plasma concentrations of clonidine, dose-related adverse effects must be considered. The use of α_2 agonists may induce hypotension and bradycardia by inhibiting cardiac and vascular sympathetic activities.[1] An important consideration is thus, how well tolerated clonidine infusions are in the general PICU population, especially at higher dosages. Fear of cardiovascular instability was attributed as a barrier to recruitment in the SLEEPS trial evaluating clonidine versus midazolam.[12] Recently, a cohort study of 168 critically ill children evaluated haemodynamic safety in children who received a clonidine infusion as part of their sedation regimen.[24] The study aimed to determine the prevalence of bradycardia and hypotension in a mixed population of PICU patients with high disease severity during a clonidine infusion of up to 2 µg/kg/hr. Control patients were not included in the study and clonidine plasma concentrations were not measured. Clonidine infusions were administered at a median (IQR) maximal infusion rate of 0.7 (0.3 - 1.5) for 2 days (1 - 6 days) with most (69%) patients receiving a loading bolus of 1- 2 µg/kg at the start of the infusion. Severe bradycardia and systolic hypotension occurred in 40% and more than 50% of included children, respectively. Younger age was the only significant risk factor for bradycardia. Despite these high prevalence rates of bradycardia and hypotension, haemodynamic stability did not appear to be compromised. Severe bradycardia was unrelated to hypotension, and vasoactive drug use decreased in parallel with increasing clonidine infusion rates. Compensatory

mechanisms such as increased stroke volume with decreased heart rate and reduced afterload from decreased blood pressure are hypothesised to explain this maintenance of stability. Good haemodynamic tolerance was also reported in three previous studies of clonidine infusions in children under one year after heart surgery[5,7,25] and a study of clonidine 3 µg/kg nasogastric boluses in children under two with respiratory failure[20]. These findings suggest, unless patients are haemodynamically unstable, clonidine loading doses and infusions up to 2 µg/kg/hr are tolerated in the general PICU population. The results of the simulations of this study support the dosage regimens of the SLEEPs study [3 µg/kg loading dose followed by a continuous titrated infusion of 0-3 µg/kg/hr] and CloSed study for children older than a month [2 µg/kg loading dose followed by a continuous titrated infusion 1-2 µg/kg/hr]. Of note, in this study, the continuous infusion was fixed at the midway point of the infusion range and not titrated according to clinical response. Furthermore, the additionally permitted rescue boluses for insufficient sedation at the start of the CloSed regimen were not included in the simulation. Combining these predicted concentrations with the observed haemodynamic safety data of the study by Kleiber et al.[24] supports an initial loading dose of 2 µg/kg (with intermittent rescue doses if insufficient sedation achieved) followed by a continuous infusion of 0-2 µg/kg/hr titrated according to sedation scores. Doses should be halved in neonates.

Despite being an older drug in widespread clinical use, there is limited knowledge on optimal dosage regimens. This is the first study in the literature to simulate the various dosage regimens employed in previous randomised controlled trials alongside in clinical practice. A strength of this study is the inclusion of the demographics of children who received clonidine for the indication of sedation. The large population of almost seven hundred children should increase the generalisability of the study findings. A further strength of the study is the updated pharmacokinetic parameters incorporating maturation function, and this adds to the literature for clonidine in children. A potential limitation of the study is uncertainty of the target plasma concentration for clonidine to provide sedation alongside opioids in mechanically ventilated children. The target proposed in this study is partly informed by a study using the BIS in adults. The extrapolation of BIS data to paediatrics where it is less well validated is a limitation of this study. The BIS was developed from adult EEG data and paediatric EEGs may differ markedly. Despite these differences, studies suggest that the performance of BIS in children older than six months is similar to that in adults.[26 27] BIS has been found to correlate with sedation measured with the Ramsay sedation scale[28] , the University of Michigan Sedation

Scale[29]] and the COMFORT Behaviour scale[30]. BIS is however less useful at identifying undersedation than it is oversedation and evidence is limited in younger infants, particularly in neonates. with low BIS values seen even with only light sedation[31] . Given this limitation, we also incorporated paediatric efficacy data from a study of oral clonidine in infants. This study cohort included neonates and supported clonidine concentrations averaging 1.4 µg/L. The proposed target of above 2 µg/L represents a compromise between the available data. Further pharmacokinetic-pharmacodynamic data from cohorts of adequately sedated children receiving clonidine (such as that which should arise from the data available from the CloSed study) may aid clarification of target plasma concentrations and further confirm an optimal dosage regimen. Trials of efficacy have encountered recruitment difficulties and have employed heterogeneous dosing strategies. An evidence-based dosing regimen is a pre-requisite for further trial attempts. Even outside of research studies, clonidine dosage in practice should reflect an evidence-based foundation.

Conclusions:

Off-label use of older drugs in paediatrics, such as clonidine, has meant a bypassing of traditional dose-determining clinical studies during drug development. This has led to clinicians employing heterogeneous dosage regimens without a supporting evidence-base. This is likely to contribute to the lack of efficacy data available from clinical studies to support the use of clonidine as a sedative in critically ill children. Simulations of clonidine plasma concentrations based on known population pharmacokinetic parameters suggest a loading dose followed by a continuous infusion is required to achieve adequate steady-state concentrations early in treatment. A limitation of this method, however, is the lack of clarity of the therapeutic clonidine plasma concentration. Further pharmacokinetic-pharmacodynamic studies will further aid in the determination of the optimal clonidine dosage regimen.

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Ethical approval:

This project was a secondary analysis of anonymised data obtained from a previously published study, for which ethical approval was obtained.

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Table 1: Characteristics of children included in the simulation

Characteristic		N	%
Number of Patients		692	
Gender	Male	387	56
	Female	305	44
Corrected Age Category (at admission)	Neonate	234	34
	1 month - 6 months	242	35
	6 months - 12 months	76	11
	12 months - 3 years	57	8
	> 3 years	83	12
Weight (at admission)	<5kg	325	47
	5kg-10kg	246	36
	10kg -20kg	80	12
	>20kg	41	6
Reason for admission	Post-cardiac surgery	346	50
	Post non-cardiac surgery	44	6
	Cardiac Disorder (non-surgical)	118	17
	Respiratory Disorder	77	11
	Gastrointestinal Disorder	35	5
	Sepsis	25	4
	Congenital Diaphragmatic Hernia	18	3
	Seizure	3	0
	Other	26	4
Baseline Paediatric Logistic Organ Dysfunction (PELOD) score Mean (SD)		6.4 (2.1)	
Paediatric Index of Mortality (PIM2r) score Mean (SD)		0.04 (0.06)	
Neurodevelopmental Disorder N (%)		163	24

Table 2: Pharmacokinetic Parameters derived after updating the model of data by Larsson et al.

Parameter	Estimate	%BSV
Cl_{std} (l h^{-1} 70kg $^{-1}$)	17.9	30.3
$V1_{std}$ (l 70 kg^{-1})	81.2	71.5
Q_{std} (l h^{-1} 70 kg^{-1})	121	44.3
$V2_{std}$ (l 70 kg^{-1})	113	33.9
T_{abs} (h)	0.454	85.1
Tl_{ag}	0.148	91.2
PMA_{50} (weeks)	61.6	
Hill	2.42	

Table 3: Characteristics of studies from which clonidine dosage information was derived

Study	Route of administration	Regimen	Number of patients	Patient characteristics
Hayden at al.[15]	Intravenous	1-2 µg/kg 6- 8 hourly	692	Mechanically ventilated children 0 days -18 years
Duffett et al.[11]	Nasogastric	5 µg/kg 6 hourly	50	Mechanically ventilated children 30 days - 18 years
Hunseler at al.[14]	Intravenous	1 µg/kg/hr	219	Mechanically ventilated children under 2 years
Wolf at al.[12] (SLEEPS)	Intravenous	3 µg/kg loading over 1 hour followed by 0-3 µg/kg/hr titrated infusion	120	Mechanically ventilated children 30 days - 15 years
Neubert at al.[13] CloSed)	Intravenous	2 µg/kg loading over 15 mins followed by 1-2 µg/kg/hr titrated infusion	200 planned	Mechanically ventilated children 28 days - 18 years
Neubert at al.[13] (CloSed)	Intravenous	1 µg/kg loading over 15 mins followed by 0.5-1 µg/kg/hr titrated infusion	100 planned	Mechanically ventilated children 0 days - 28 days

Supplementary Figure 1: Plot of the observed and population predicted plasma concentrations versus time for the four dosage levels given by Hall et al.[0, 1, 2 and 4 µg/kg over 15 min followed by 45 min of continuous infusion].The circles/black line is the observed data, and the dotted line is the model prediction.

Figure 1: Plot of the observed and population predicted BIS score versus time for the 4 dose levels given by Hall et al. [0, 1, 2 and 4 µg/kg over 15 min followed by 45 min of continuous infusion]. Circles are observed BIS data from Hall et al. and the dashed line is the model prediction

Figure 2: The Model predicted change in BIS index with clonidine concentration

Figure 3: Simulated plasma clonidine concentrations. A= 1µg/kg/8h IV bolus, B= 1µg/kg/6h IV bolus, C= 2µg/kg/8h IV bolus, D= 2µg/kg/6h IV bolus, E = 5µg/kg/6h NG bolus (Duffett at al), F= 3µg/kg/h loading then 1.5µg/kg/h IV infusion (Wolf et al/SLEEPS), G= 1µg/kg/h IV infusion (Hunseler et al), H= 1µg/kg/h then 0.75µg/kg/h IV infusion (Neubert et al/CloSed neonates), I= 2µg/kg/h then 1.5µg/kg/h IV infusion (Neubert et al/CloSed > age 28 days). The dotted line represents the minimum target concentration. The black line is the predicted median concentration, and the dashed line represents the 95% Confidence Interval.