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ORIGINAL ARTICLE

Optimising the dose of clonidine to achieve sedation in intensive care unit patients with population pharmacokinetics

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Aims: The aim of this study was to investigate the population pharmacokinetics (PK) of clonidine in intensive care unit (ICU) patients in order to develop a dosing regimen for sedation.

Methods: We included 24 adult mechanically ventilated, sedated patients from a mixed medical and surgical ICU. Intravenous clonidine was added to standard sedation in doses of 600, 1200 or 1800 μg/d. Within each treatment group, 4 patients received a loading dose of half the daily dose administered in 4 hours. Patients gave an average of 12 samples per individual. In total, 286 samples were available for analysis. Model development was conducted with NONMEM and various covariates were tested. After modelling, doses to achieve a target steady-state plasma concentration of >1.5 μg/L were explored using stochastic Monte Carlo simulations for 1000 virtual patients.

Results: A 2-compartment model was the best fit for the concentration-time data. Clearance (CL) increased linearly with 0.213%/h; using allometric scaling, body weight was a significant covariate on the central volume of distribution (V1). Population PK parameters were: CL 17.1 (L/h), V1 124 (L/70 kg), intercompartmental CL 83.7 (L/h), and peripheral volume of distribution 178 (L), with 33.3% CV interindividual variability on CL and 66.8% CV interindividual variability on V1. Simulations revealed that a maintenance dose of 1200 μg/d provides target sedation concentrations of >1.5 μg/L in 95% of the patients.

Conclusion: A population PK model for clonidine was developed in an adult ICU. A dosing regimen of 1200 μg/d provided a target sedation concentration of >1.5 μg/L.

KEYWORDS

clonidine, population pharmacokinetics, sedation

Michael E. Cloesmeijer and Huub L.A. van den Oever, contributed equally.

The authors confirm that the PI for this paper is Huub L.A. van den Oever and that he had direct clinical responsibility for patients.

1 | INTRODUCTION

Adequate sedation and analgesia are crucial for patients in intensive care units (ICUs) to tolerate tracheal tube, artificial ventilation and other ICU procedures. Ideally, sedative agents should have minimal adverse effects and preferably no interactions with other drugs. Current sedation medication consisting of **propofol**, **midazolam** and **lorazepam** have potential adverse effects such as increased morbidity and prolonged ICU duration, and they may provoke delirium.[1,2] The presence of delirium may result in an increased hospital and ICU length of stay.[3]

In recent years, α-2 adrenergic agonists have been used as an additive treatment to the standard sedation regimen.[4] **Alpha-2 adrenergic** agonists produce both sedative and analgesic effects with minimal respiratory depression.[5] **Clonidine** is a potent α-2 adrenergic agonist and its sedative and analgesic effects have been investigated in clinical studies.[5–7]

The optimal therapeutic range of clonidine for the purpose of sedation has not been determined. The sedative effects of clonidine were illustrated in an experiment by Hall *et al*. who administered different doses of IV clonidine to healthy volunteers. Significant reduction in observer-assessed sedation was measured at plasma concentrations of 1.96 (± 0.5) μg/L.[5] Dose dependent sedation was observed in all subjects. The authors remarked that subjects remained rousable throughout the experiment, even at higher doses of clonidine. A condition in which patients are comfortably asleep, but can easily be roused, is often desired in ventilated critically ill patients. This may explain why clonidine has found use as a sole sedative or as an adjunct to sedation in many ICUs. We found only 1 study in which serum levels of clonidine in adult patients during intensive care sedation were measured, reporting levels from 1.5 to 6.0 μg/L.[8] Although some self-reported sedation has been described at serum levels below 1.5 μg/L,[9,10] higher degrees of sedation may be required to treat discomfort in the ICU. Another study, in healthy volunteers, showed significant reduction in observer-assessed sedation at serum levels of 1.5–5.0 μg/L.[6] For the purpose of the present pharmacokinetic study, we defined an optimal level for ICU sedation ranging from 1.5 to 4.0 μg/L.

Clonidine is known to produce haemodynamic effects, which are mediated through both the heart and the peripheral vascular system. Clonidine reduces the heart rate, although severe bradycardia is uncommon,[11] and it decreases the blood pressure.[6] It exerts these effects through the activation of presynaptic α_2-adrenoceptors in the central nervous system and through activation of α_2-adrenoceptors in vascular endothelial cells.[12,13]

In many ICUs in Europe, Asia and Canada, the use of intravenous clonidine as an off-label additive sedative is common practice. However, hospitals have reported a wide range of dosing regimens, which may vary up to 10-fold.[7] Dosing regimens are presented in Tables S1–4. Currently, adult population pharmacokinetics (PK) of clonidine have not been investigated in the ICU setting.

The aims of this study were to investigate the PK of clonidine in critically ill patients in the ICU and to develop a population PK model to suggest a dosing regimen for the usage of clonidine as sedative.

What is already known about this subject

- Clonidine is used as a sedative agent in intensive care unit patients, although clinical studies have been sparse.
- The use of clonidine as an off-label additive sedative is common practice; however, hospitals have reported a wide range of dosing regimens.
- Levels of sedation adequate for tolerating invasive or uncomfortable procedures seem to be in the range of 1.5–4.0 μg/L of clonidine.

What this study adds

- A population pharmacokinetic model for clonidine was developed in adult intensive care patients and can be used to simulate and explore dosing regimens.
- Simulations revealed a dosing regimen of 1200 μg/d (50 μg/h) results in 95% of the virtual population attain clonidine concentrations >1.5 μg/L at steady state.
- A loading dose of 150 μg, which is common practice, reduces the time to reach steady state only minimally. An effective loading dose, that avoids peaks in serum concentration, is to double the infusion rate for 6 hours.

2 | METHODS

2.1 | Study design and drug regimen

This study was approved by the medical ethics review committee (METC Isala Zwolle) and was registered in the ClinicalTrials.gov database (NCT02466373).

Intubated and sedated patients admitted to the ICU of the Deventer Hospital with an expected stay of 3 days or more were included, after written proxy consent. The following criteria were used to exclude patients: age < 18 years, neurotrauma, postanoxic coma, use of clonidine 96 hours before start of the study, bradycardia, severe hypotension, hypertensive emergency, pregnancy and lactation, epilepsy, clonidine intolerance, liver cirrhosis, recent and acute myocardial infarction, severe heart failure, and second or third degree AV-block without a permanent pacemaker or renal failure.

Patients received clonidine after standard sedation with morphine, combined with midazolam or propofol was initiated. A total of 24 patients were divided into 3 treatment groups of 8 subjects receiving continuous IV infusions of clonidine of 600, 1200 or 1800 μg/d (infusion rate of 25, 50 or 75 per hour, respectively). Four patients in each treatment group, received a loading dose of 50% of the daily dose in 4 hours. This was an open label trial and randomisation was not applied.

2.2 | PK measurements

Blood samples were taken from arterial catheters at 2, 4, 8 and 12 hours after the start of clonidine infusion. Subsequently, a sample was taken once daily until the termination of treatment. After stopping the infusion, blood samples were taken at 0, 8, 16, 24 and 48 h. Blood samples were stored at −20°C and transferred to Amsterdam University Medical Centre AUMC for analysis. Plasma concentrations were measured using a validated high-perfomance liquid chromatography–mass spectrometry system (liquid chromatography: LC30 UPLC, Shimadzu, Kyoto, Japan; mass spectrometry: QTRAP 5500 system, Sciex, Framingham, MA, USA), as described previously by Kleiber *et al.*[14] The lower limit of quantification (LLOQ) was 0.1 μg/L and the upper limit of quantification was 20 μg/L. The accuracy of the assay was between 99–114%.

2.3 | Population PK model development

A population PK analysis was performed using nonlinear mixed effects modelling (NONMEM 7.3 ICON Development Solutions, Hanover, MD, USA), using the first-order estimation method with the interaction option and subroutine ADVAN13, TOL6 Pirana (version 2.9.8), R (version 3.4.1) and PsN version (version 4.6.0). The population PK model was developed in a stepwise sequence, first developing a structural model, followed by attributing interindividual variability (IIV) to the PK parameters, again followed by refining the appropriate residual error model. Lastly, covariate relationships were established with PK parameters, to potentially reduce the unexplained IIV. Model selection criteria were based on change in the objective function value (OFV), goodness-of-fit plots, precision of parameter estimates, decreases in IIV and residual variability, condition number, shrinkage and successful convergence step, with at least 3 significant digits in parameter estimates.[15]

2.3.1 | Structural and statistical model

One-, 2- and 3-compartment models were evaluated to describe the PK of clonidine. For structural model selection, a decrease in OFV of 3.84 units or greater between nested models was considered statistically significant, which corresponds to $P < .05$ assuming a χ^2 distribution. IIV in model parameters was estimated using an exponential model, assuming a log-normal distribution, as shown in equation (1),

$$\theta_i = \theta_{pop} \times \exp(\eta_i) \quad (1)$$

where θ_i is the individual parameter value, θ_{pop} is the population mean parameter value and η_i is a random variable from normal distribution with a mean of zero and estimated variance of ω^2. For the residual error model, additive (equation 2), proportional (equation 3), and combined error models (combination of equation 2 and 3) were tested, in which Y_{ij} was the individual concentration prediction at time j, and ε is the residual error originating from a normal distribution with a mean of zero and estimated variance of σ^2.

$$Y_{ij} = f(\theta, \eta i, x_{ij}) + \varepsilon_{ij} \quad (2)$$

$$Y_{ij} = f(\theta, \eta_i, x_{ij}) \times (1 + \varepsilon_{ij}) \quad (3)$$

2.3.2 | Covariate model

The influence of body weight, body surface area (BSA), body mass index, height, age, sex, creatinine clearance (CLcr), albumin, bilirubin, time after infusion and continuous veno-venous haemofiltration (CVVH) status of the patient was evaluated on the PK parameters using a forward selection–backward elimination procedure. Allometric scaling based on body weight was applied to the PK parameters (equation 4).

$$\theta_{pop} = \theta_{pk} \times \left(\frac{Bodyweight}{70}\right)^{\theta_{exp}} \quad (4)$$

In which, θ_{pop} is the population mean value, θ_{pk} is the mean PK value, and θ_{exp} is the allometric scaling exponent for clearance (CL) with an allometric exponent of 0.75. While the power exponent was fixed at 1 for central volume of distribution (V1).

For other covariates, a power function was utilised and centred around the median value of the covariate (equation 5) or a linear function was utilised (equation 6), using the following equation:

$$\theta_{pop} = \theta_{pk} \times \left(\frac{Cov}{Cov_{median}}\right)^{\theta_{exp}} \quad (5)$$

$$\theta_{pop} = \theta_{pk} \times (1 + Cov) \times \theta_{slope} \quad (6)$$

Equation 6 was also used for time after start of clonidine infusion on CL, in which $\theta_{pk}$was the CL, Cov was time in hours and θ_{slope} represented the slope of the CL. The categorical covariate CVVH was incorporated using indicator variables. The coding was illustrated using an indicator variable 0 for non-CVVH patients and 1 for CVVH patients. CLcr was calculated by using the Cockcroft–Gault formula,[16] Chronic Kidney Disease Epidemiology Collaboration[17] or using 24-hour urine creatinine clearance.[18] BSA was calculated by the Du Bois formula,[19] and the CLcr estimations were converted to mL/min to adjust for the patient's individual BSA. All CLcr equations were tested separately in the model and compared regarding their significance in OFV decrease. The CLcr equation with the largest significant decrease in OFV will be retained in the model.

A priori, graphical plots of *posthoc* Bayesian estimates *vs the* covariates were generated to explore possible covariate relationships. For forward selection, an OFV decrease by 3.84 units or greater (corresponding to $P < .05$) indicated that the covariate had a significant effect on the model fitting. The full covariate model was obtained when all significant covariates were introduced into the model. In

backward elimination, covariates were eliminated 1 by 1 from the full covariate model and an increase in OFV of 6.63 units ($P < .01$) or greater was required to retain the covariate in the final model.

2.3.3 | Handling data below the LLOQ

During model development, LLOQ data values were replaced by LLOQ/2 as described by Beal.[20] In the final PK model 3 different methods used for handling data below LLOQ were evaluated[21]: (i) below LLOQ data were replaced by LLOQ/2, (ii) below LLOQ data were discarded; (iii) below LLOQ data were treated as categorical data and the likelihood of the below LLOQ data assume that the value is less than the LLOQ. The method with the highest precision of parameter estimates was chosen as the final PK model.

2.4 | Internal model validation

A bootstrap was performed to estimate the uncertainty of the population PK and parameters and to evaluate the stability of the model. Five hundred bootstraps were performed and the median, 2.5th and 97.5th (denoting the 95% confidence interval) of the population parameters were determined and compared with the estimates of the final model. A visual predictive check was conducted by simulating 500 individuals using the final PK model in NONMEM. The median and 2.5th and 97.5th percentiles of the simulated data were calculated and compared with observations to evaluate the predictive performance of the final PK model.

2.5 | Monte Carlo simulations

Using the PK parameter estimations, IIV and residual variability from the final population PK model, stochastic Monte Carlo simulations were performed for 1000 virtual patients to design a dosing regimen for sedation. The bodyweight of the simulated patients followed a normal distribution from 53 to 113 kg with a mean of 84 kg, representing the patient population in the original study. Dosing regimens were considered clinically relevant if 90% of the patients reached concentrations >1.5 μg/L at steady-state loading doses were evaluated to reduce the time to achieve steady state. Practical considerations, such as easy preparation (clonidine comes in 150 μg/mL ampoules) and unambiguous prescription, also played a role in choosing the final dosing schedule.

3 | RESULTS

3.1 | Population PK modelling

3.1.1 | Structural model development

The study population consisted of 24 adult patients, 16 men, 8 women. At the start of treatment, the median age was 67 (range 25–83) years and body weight 84 (range 53–113) kg. Further characteristics of participants are presented in Table 1. Continuous infusion was briefly terminated for 2 hours in 1 patient due to short hypotension.

TABLE 1 Summary of subject demographics

	Median (range)
Patients (*n*)	24
Continuous veno-venous haemofiltration patients (*n*)	3
Total duration of treatment, h	96 (25–171)
Sex (male/female)	16/8
Age, y	67 (25–83)
Bodyweight, kg	84 (53–113)
Height, cm	173 (155–189)
Body mass index, kg/m^2	27 (20–44)
Body surface area, m^2	2.0 (1.5–2.4)
Urine creatinine, μmol/L	6.5 (0.8–17.6)
Serum creatinine, μmol/L	74 (32–441)
Albumin, g/L	20 (12–32)
Bilirubin, μmol/L	7 (<3–59)

In total, 275 plasma concentrations were included in the dataset. Patients gave an average of 12 [range 5–16] samples per individual. Individual concentration–time profiles were explored prior to population PK modelling (Figure 1). A 2-compartment structural model adequately described the concentration–time profiles of clonidine. The residual variability was described using a combined additive and proportional error model. The IIV was estimated on only CL and V1. IIV was omitted on Q and V2 due to large IIV (>125%) and these parameters proved relatively unstable from run to run.

3.1.2 | CVVH patients

Three patients were treated with CVVH. The CL and V1 of CVVH patients were estimated separately as well together with the non-CVVH patients. The OFV difference between these models was >3.84 units, indicating that the CL and V1 values of CVVH patients were not significantly different compared to non-CVVH patients.

3.1.3 | Covariate model development

Univariate analysis showed a significant effect ($P < .05$) of time after start of clonidine infusion on CL, and of body weight, CLcr, albumin and bilirubin on V1. Table 2 displays the covariate model development. Allometric scaling based on body weight was applied to V1 with an exponent of 1, in which the exponent was not significantly different from unity. For the remaining covariates a linear model was used. Afterwards, all significant covariates were added into a full covariate model. After backward deletion, only time after start of clonidine

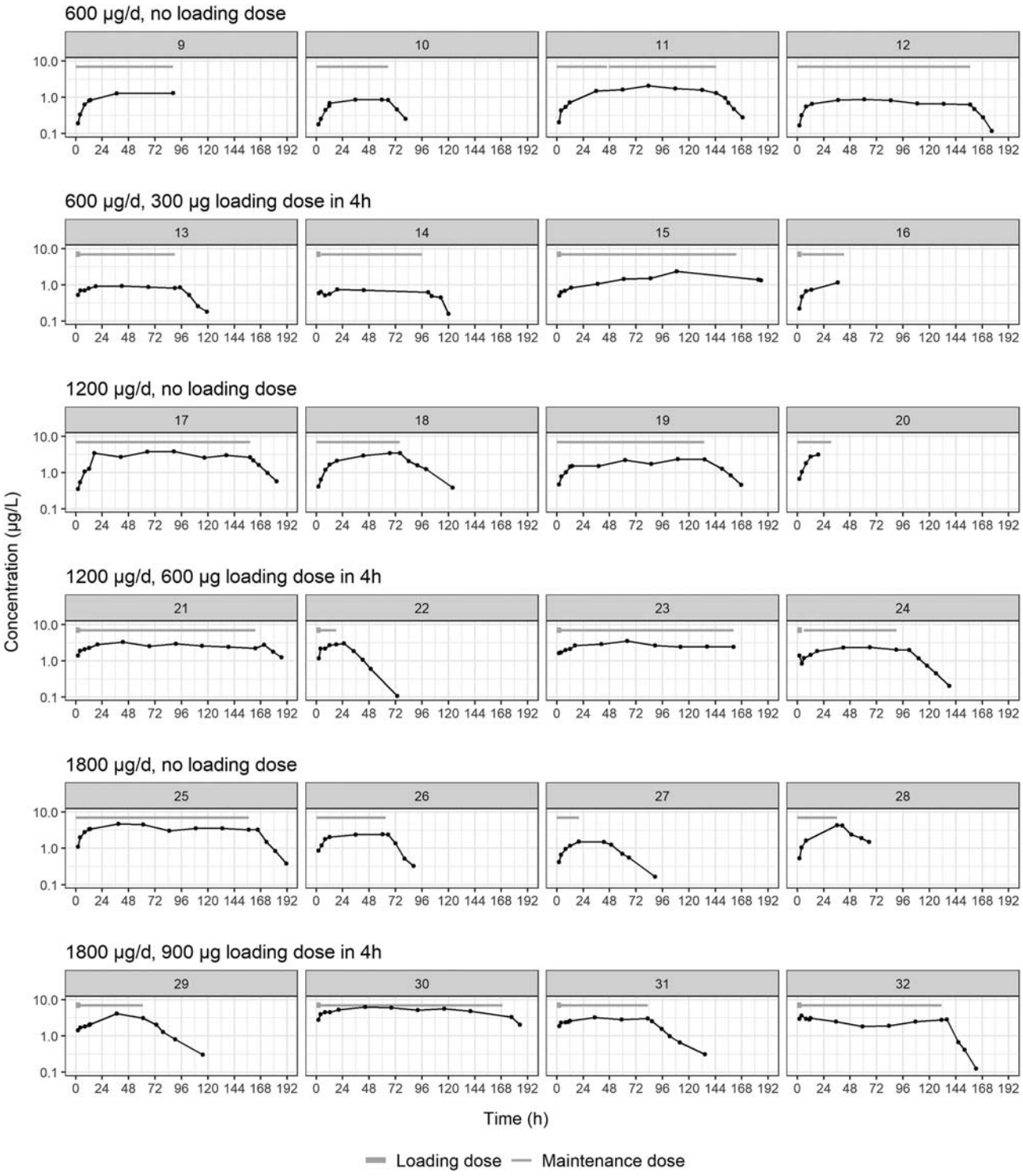

FIGURE 1 Individual clonidine concentration: time profiles on semi-logarithmic scale. Numbers 9–32 indicate the ID numbers of the patients. Patients 9–12 received clonidine 600 µg/d; patients 13–16 received 600 µg/d with a loading dose of 300 µg in 4 hours; patients 17–20 received 1200 µg/d; patients 21–24 received 1200 µg/d with a loading dose of 600 µg in 4 hours; patients 25–28 received 1800 µg/d; and patients 29–32 received 1800 µg/d with a loading dose of 900 µg in 4 h. The horizontal grey solid line denotes the total infusion duration. The thick horizontal grey solid line represents the duration of the loading dose, while the thin horizontal grey solid line represents the duration of the maintenance dose. In patient 11, continuous infusion was terminated for 2 hours due to hypotension

TABLE 2 Covariate model development

Model no.	Model	Covariate function	OFV
0	2-compartment model base	-	−499.57
Forward addition			
1	Model 0 + time after start infusion on CL	Linear	−516.05
2	Model 0 + body weight on V1	Allometric	−503.35
3	Model 0 + creatinine CL on V1	Linear	−504.81
4	Model 0 + albumin on V1	Linear	−508.00
5	Model 0 + bilirubin on V1	Linear	−503.51
6	Full covariate model, covariates of model 1–5 combined		−531.69
Backward deletion			
7	Model 6 – Time after infusion on CL	Linear	−515.87
8	Model 6 – Bodyweight on V1	Allometric	−507.84
Final model			
9	Model 0 + time after start infusion on CL + bodyweight on V1	Linear and allometric	−519.63

CL, clearance.

TABLE 3 Population pharmacokinetic parameters of the final model and the results of the bootstrap analysis

Parameter	Final parameter values (RSE%) [shrinkage %]	Bootstrap median [95% CI] of parameter value
CL (L/h)	17.0 (10)	16.9 [14.1–20.3]
V1 (L/70 kg)	124 (36)	119 [66.2–186]
Q (L/h)	83.7 (35)	89.9 [25.1–175]
V2 (L)	178 (35)	181 [128–269]
Increase CL per hour	0.213 (19)	0.220 [0.0544–0.441]
Interindividual variability		
CL (%CV)	33.3 (23) [1]	33.1 [23.9–44.6]
V1 (%CV)	66.8 (39) [4]	64.7 [34.8–121]
Residual variability		
Proportional error (%)	0.141 (4)	0.139 [0.111–0.167]
Additive error (μg/L)	0.0532 (14)	0.0496 [0.00651–0.0829]

V_1, central volume of distribution; V_2, peripheral volume of distribution; CL, clearance; Q, intercompartmental clearance of peripheral compartment; CV, coefficient of variation; RSE, relative standard error; CI, confidence interval. RSE was calculated as: RSE = 100 × standard error/parameter estimate.

infusion on CL and body weight on V1 were significant covariates ($P < .01$).

Eleven samples (2.8% of total amount of samples) were below the LLOQ. Of all the evaluated methods for handling data below LLOQ, discarding these data resulted in the highest precision of PK parameter estimates. The PK parameter estimates of the final model are presented in Table 3.

3.1.4 | Model evaluation

Goodness-of-fit plots showed good agreement between predicted and observed clonidine concentrations with no apparent bias in residuals (Figure 2). The visual predictive check for the final model is presented in Figure 3. Overall, the 2.5th, 50th and 97.5th percentiles of observed concentrations were within the predicted 95% confidence interval (CI) of these percentiles, demonstrating good predictability of the final population PK model. The median values of the parameter estimations of the bootstraps were approximately equal to the final model's respective values, thus indicating that the PK parameter estimates from the final model were precise and the model was robust (Table 3).

3.2 | Simulations to optimise dosing regimens

We examined the possibility of using the same dose for every patient. Simulations with daily clonidine doses of 1200 μg for 4 days showed that the target clonidine level of 1.5 μg/L or higher would be achieved at steady state in 95% of the simulated patients (Figure 4A).

Lower doses were simulated but resulted in <90% of the simulated patients reached 1.5 μg/L at steady state (data not shown). Thus, a dosing regimen 1200 μg/d was recommended.

When we simulated the administration of 1200 μg/d as a continuous infusion without a bolus, it took 14.5 hours for 50% of the population to reach the target concentration. We tested 2 strategies that are used in ICU practice to reduce the time to achieve steady state.

The strategy encountered most is to give an IV bolus of 150 μg at the start of infusion.[7] In Figure 4B we simulated the administration of 150 μg in 30 minutes. It resulted in a sharp rise in plasma concentration, followed by a steep drop, and the time to achieve the target concentration is reduced from 14.5 to 11 hours.

Another strategy, which is popular among clinicians because it is easy to prescribe, is to double the infusion rate for several hours at the beginning of infusion. Figure 4C depicts the predicted plasma concentrations when the clonidine infusion of 1200 μg/d (50 μg/h) is preceded by 6 hours of infusion at a rate of 100 μg/h. There is no peak in plasma concentration, and the time to achieve target is reduced from 14.5 to 5 hours. Therefore, a loading dose of 600 μg in 6 hours would seem optimal.

Since body weight was a covariate on V1, clonidine concentrations during the loading dose would be dependent on the patient's body weight. To investigate the body weight effect on clonidine concentrations, the loading doses were stratified in body weight <80 and >80 kg. Simulations showed that differences in clonidine concentrations were

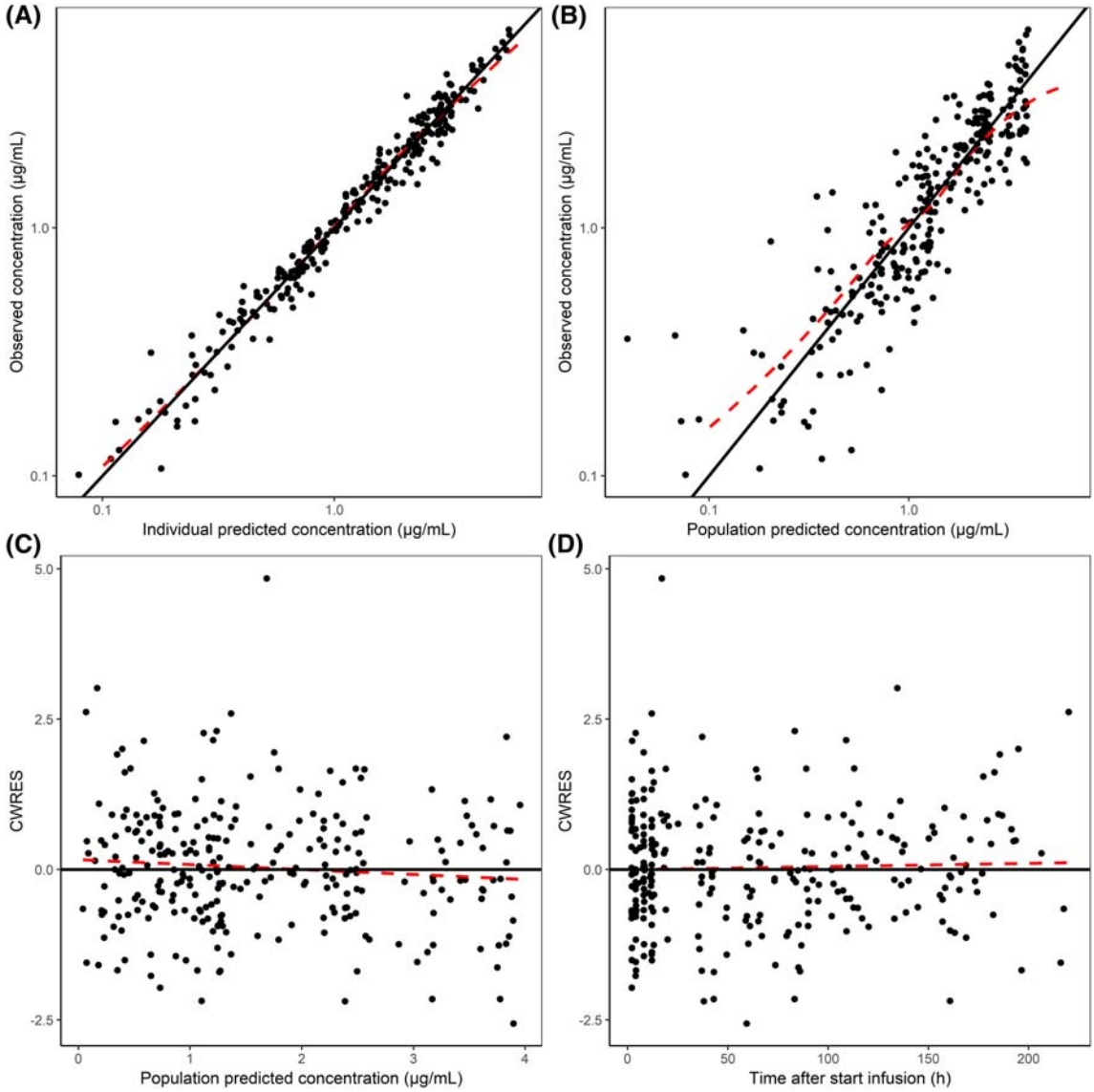

FIGURE 2 Goodness-of-fit plots of the final population pharmacokinetic model of clonidine. A, Individual predicted *vs* observed concentrations; B, population predicted *vs* observed concentrations; C, conditional weighted residuals (CWRES) *vs* population predicted; D, time after start infusion *vs* CWRES. The solid line is the line of identity. The red dashed line represents the local regression smooth line (loess smooth)

small (25%) after 4 h, when stratifying on body weight (data not shown). Therefore, we suggest a loading dose independent of body weight.

4 | DISCUSSION

The present study describes the population PK of clonidine in critically ill adult patients that provides a basis for dose optimisation for sedation.

In our population PK model, time after infusion was the only covariate to have a significant influence on the CL of clonidine. CL increased linearly with 0.213%/h from baseline. The population CL was 17 L/h at the start of the treatment and increased to 20.4 L/h after 4 days on continuous infusion, which was the median treatment duration in this study. The reason for the increase in clonidine clearance over time is unknown, but it might reflect the recovery of organ function during stabilisation of critical illness. The increased clearance might have an effect on steady-state concentrations, and it would seem rational to adjust the dose after several days of infusion. However, the Monte Carlo simulations showed that this effect was modest in the first few days of treatment.

The population V1 was 124 L/70 kg in our study. A central volume larger than the actual volume of body water suggests distribution to tissues. Body weight, introduced into the equation by allometric scaling was a significant covariate on V1. One would expect this to have an influence on the loading dose required.

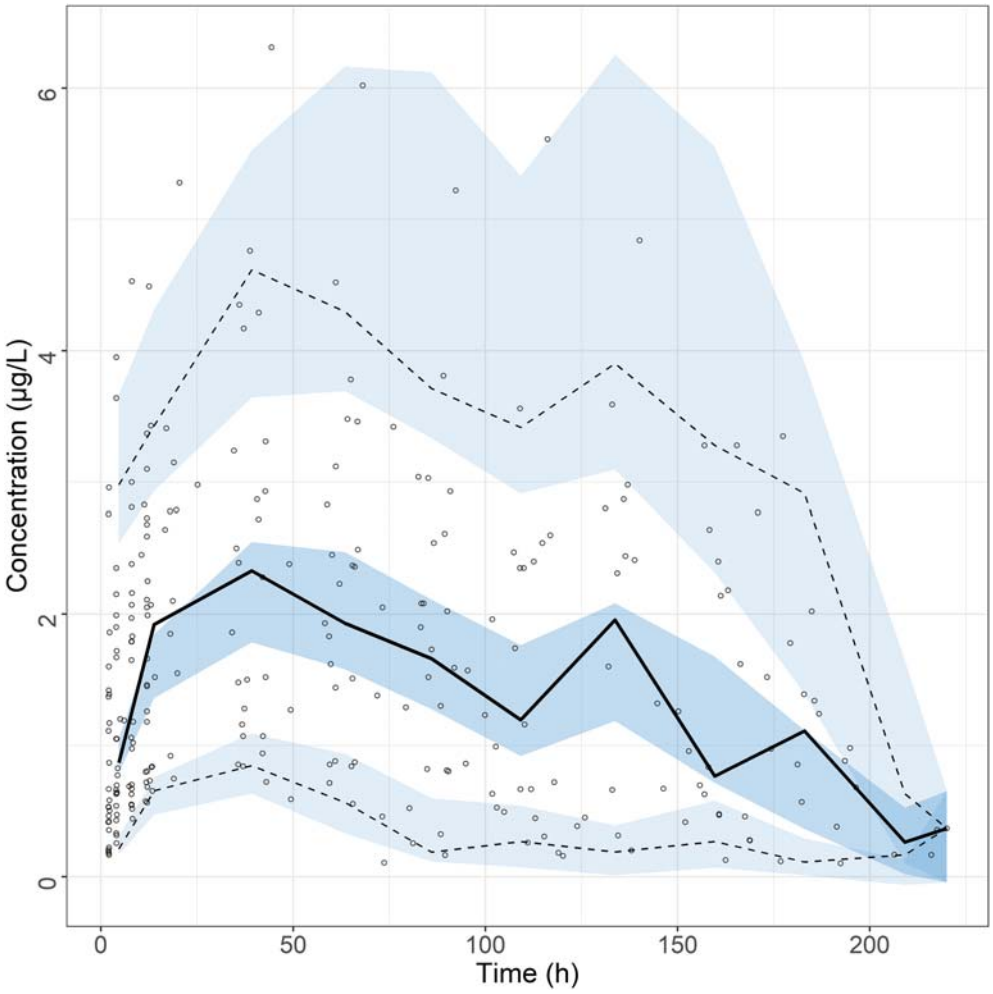

FIGURE 3 Visual predictive check of the final population pharmacokinetic model of clonidine. Dots represent observed data points; the solid black line represents the 50th percentile of observed data; the dashed black lines represent the 5th and 95th percentiles of the population pharmacokinetic model. Shaded areas depict the model predicted 95% confidence intervals of the simulated percentiles

Our PK parameter estimates correspond with previously published studies. Keranen *et al*. reported a CL of 8–18 L/h/70 kg and V1 of 119–175 L/70 kg,[9] which lends credibility to our results.

Although 3 patients received CVVH, our analysis did not show any significant difference in CL between patients who received CVVH and patients who did not received CVVH. Clonidine may potentially be removed by CVVH because of its low molecular weight (230 g/mol) and low protein binding (20–40%).[22] Another effect that may mask the significant effect of renal function and renal replacement therapy on CL is that almost 50% of clonidine is cleared by the liver.[6,23] The small number of patients in our study may have reduced the power to identify liver and kidney function as covariates. The CL in both CVVH and non-CVVH patients were similar in our study, However, our study only included 3 CVVH patients and thus of relatively low power.

Many ICUs in the Netherlands are using clonidine for additional sedation. A survey showed that continuous infusion rates varied from 240 to 2400 µg/d.[7] The optimal target range or clonidine for sedative purposes has not been established, but previous literature suggest that it might be in the order of 1.5–4.0 µg/L. Accepting that, a fixed dose of 1200 µg/d by continuous infusion would maintain that level for several days in 95% of patients, irrespective of body weight, as is shown in Figure 4. The simulations also illustrate that the effect of time on steady state concentration is limited, obviating the need for dose adjustments after several days of infusion. Dosing by body weight, as has been used in several studies, would not improve steady state levels by much, and therefore seems unnecessary.

Our simulation suggested that a loading dose of 150 µg had little effect on the time to reach steady state. When loading doses were simulated stratified to body weight <80 and >80 kg, differences in clonidine concentrations after 4 hours were small (<25%, data not shown). Therefore, despite a significant effect of body weight on V1 in our model, we recommend a standardised loading dose independent of body weight.

When clonidine is added to other sedatives that are titrated down while the sedating effect of clonidine effect is building up, the time to reach steady state may not be considered clinically important. When clonidine infusion is started without a loading dose, 50% of patients will reach serum concentrations in the target range after 14.5 hours. However, when a more rapid effect is desired, our population PK model for clonidine in ICU patients suggests a loading dose of 600 µg in 6 hours to attain target sedation concentrations of >1.5 µg/L within 5 hours in 50% of the simulated patients.

This study had some limitations. A potential limitation of our study is the small sample size. This might have caused potentially important covariates to be not significant. IIV on CL and V1 were estimated as

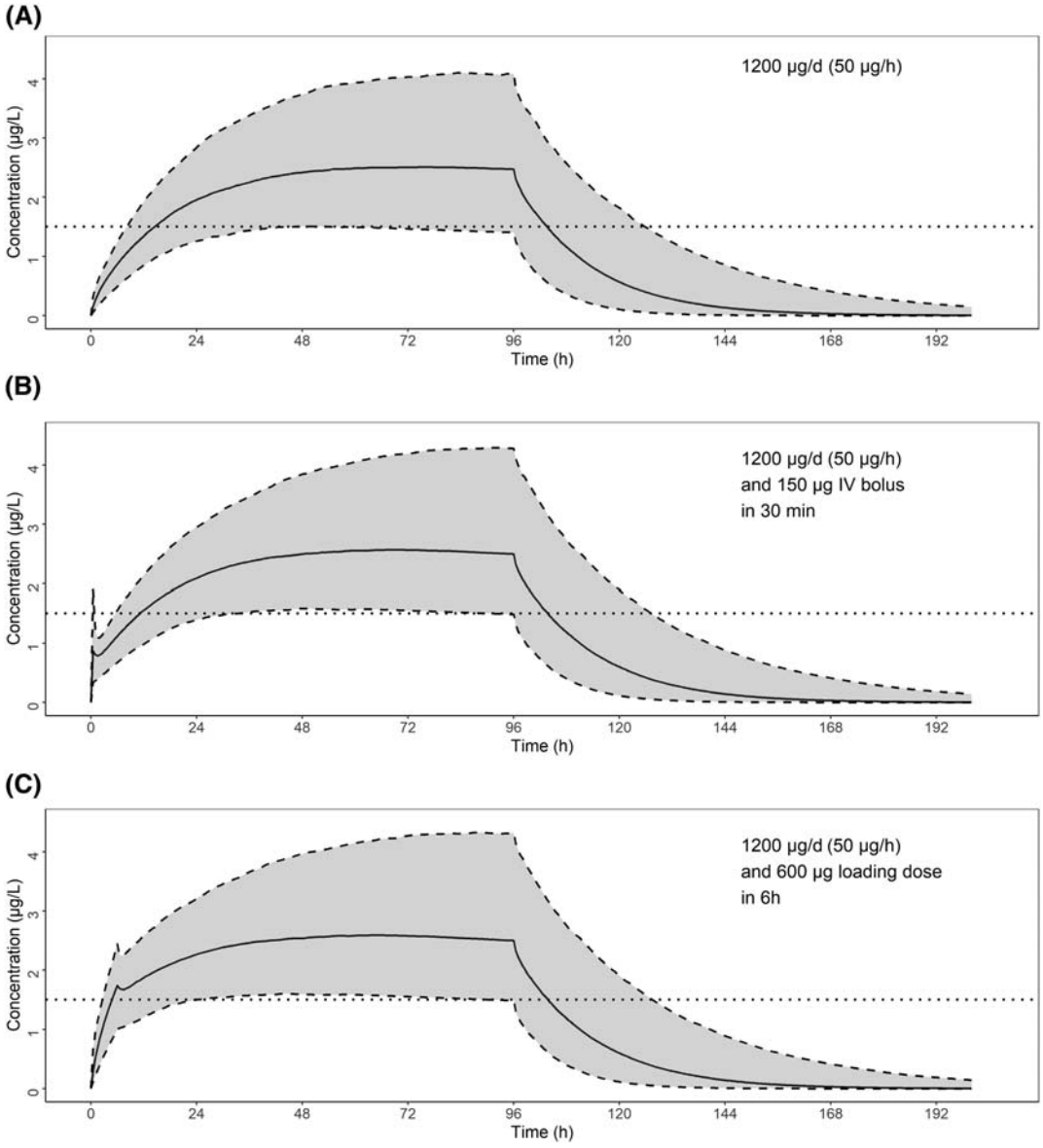

FIGURE 4 Simulations of 1000 individuals using continuous intravenous (IV) clonidine for 4 days in patients 53–113 kg, mean 84 kg. A, Continuous IV clonidine of 1200 µg/d (50 µg/h); B, continuous IV clonidine of 1200 µg/d (50 µg/h) and 150 µg IV bolus in 30 minutes; C, continuous IV clonidine of 1200 µg/d (50 µg/h) and 600 µg loading dose in 6 hours. The solid lines represent the median value, while the dashed lines represent the 5th and 95th percentile, respectively. The shaded grey areas depict the 90% prediction interval

33.3 and 66.8%, respectively. This relatively high variability in PK estimations could be explained by heterogeneity in critically ill population, with large differences in organ function and drug metabolism.

Another limitation is the target concentration range for sedation is not well defined in current literature. The safety and efficacy profiles are crucial to limit the risk of procedural failure, discomfort, extension of sedation, and deeper sedation levels than intended for the procedure. Therefore, the range of target concentrations for achieving optimal sedation need further investigations.

In conclusion, our data provide the description of population PK of clonidine in critically ill ICU patients. Our results suggest that a dosing regimen of 1200 µg/d would provide clonidine concentrations adequate for sedation in a wide range of patients.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

Wrote, provided critical revisions and approved manuscript: M.E.C., H.L.A.O., R.A.A.M., M.Z., M.E.L.A. Designed research: M.E.C., H.L.A.O., R.A.A.M., M.Z., A.K.G., C.B., P.N., A.R.M., A.L.S., M.E.L.A. Collected data: H.L.A.O., M.Z., A.K.G., C.B., P.N., A.R.M., A.L.S., M.E.L.A. Data analysed: M.E.C., R.A.A.M.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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REFERENCES

1. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*. 2006;104(1):21-26.
2. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. 2009;301(5):489-499. https://doi.org/10.1001/jama.2009.56
3. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med*. 2007;33 (1):66-73. https://doi.org/10.1007/s00134-006-0399-8
4. Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. *Br J Anaesth*. 2001;87(5):684-690.
5. Hall JE, Uhrich TD, Ebert TJ. Sedative, analgesic and cognitive effects of clonidine infusions in humans. *Br J Anaesth*. 2001;86(1):5-11.
6. Davies DS, Wing AM, Reid JL, Neill DM, Tippett P, Dollery CT. Pharmacokinetics and concentration-effect relationships of intervenous and oral clonidine. *Clin Pharmacol Ther*. 1977;21(5):593-601.
7. Zeeman M, Van Den Oever HLA, Arbouw M, Van Der Valk J, Kramers C. Prolonged use of intravenous clonidine for sedation and analgesia in critically ill adult patients. *Netherlands J Crit Care*. 2015; 21(3):6-13.
8. Fauler J, Verner L. The pharmacokinetics of clonidine in high dosage. *Eur J Clin Pharmacol*. 1993;45(2):165-167. https://doi.org/10.1007/bf00315500
9. Keranen A, Nykanen S, Taskinen J. Pharmacokinetics and side-effects of clonidine. *Eur J Clin Pharmacol*. 1978;13(2):97-101.
10. Hogan MJ, Wallin JD, Chu LC. Plasma clonidine concentration and pharmacologic effect. *Clin Pharmacol Ther*. 1981;30(6):729-734. https://doi.org/10.1038/clpt.1981.230
11. Brest AN. Hemodynamic and cardiac effects of clonidine. *J Cardiovasc Pharmacol*. 1980;2(Suppl 1):S39-S46.
12. Figueroa XF, Poblete MI, Boric MP, Mendizábal VE, Adler-Graschinsky E, Huidobro-Toro JP. Clonidine-induced nitric oxide-dependent vasorelaxation mediated by endothelial alpha(2)-adrenoceptor activation. *Br J Pharmacol*. 2001;134(5):957-968. https://doi.org/10.1038/sj.bjp.0704320
13. Talke P, Lobo E, Brown R. Systemically administered alpha2-agonist-induced peripheral vasoconstriction in humans. *Anesthesiology*. 2003; 99(1):65-70.
14. Kleiber N, Mathot RAA, Ahsman MJ, Wildschut ED, Tibboel D, de Wildt SN. Population pharmacokinetics of intravenous clonidine for sedation during paediatric extracorporeal membrane oxygenation and continuous venovenous hemofiltration. *Br J Clin Pharmacol*. 2017;83 (6):1227-1239. https://doi.org/10.1111/bcp.13235
15. Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. *CPT Pharmacometrics Syst Pharmacol*. 2013;2(4):e38-e38. https://doi.org/10.1038/psp.2013.14
16. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41. https://doi.org/10.1159/000180580
17. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.
18. Jia LJ, Jiang L. A comparative study of 2- and 24-hour creatinine clearance in patients in intensive care unit. *Zhonghua Yi Xue Za Zhi*. 2018;98(47):3878-3882. https://doi.org/10.3760/cma.j.issn.0376-2491.2018.47.013
19. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition*. 1989;5(5): 303-313.
20. Beal SL. Ways to fit a PK model with some data below the quantification limit. *J Pharmacokinet Pharmacodyn*. 2001;28(5):481-504.
21. Keizer RJ, Jansen RS, Rosing H, et al. Incorporation of concentration data below the limit of quantification in population pharmacokinetic analyses. *Pharmacol Res Perspect*. 2015;3(2):e00131-e00131. https://doi.org/10.1002/prp2.131
22. Clonidine. Clonidine - Drugbank. https://www.drugbank.ca/drugs/DB00575. Accessed April 24, 2019.
23. Arndts D, Doevendans J, Kirsten R, Heintz B. New aspects of the pharmacokinetics and pharmacodynamics of clonidine in man. *Eur J Clin Pharmacol*. 1983;24(1):21-30. https://doi.org/10.1007/bf00613922
24. Rubino AS, Onorati F, Caroleo S, et al. Impact of clonidine administration on delirium and related respiratory weaning after surgical correction of acute type-A aortic dissection: results of a pilot study. *Interact Cardiovasc Thorac Surg*. 2010;10(1):58-62. https://doi.org/10.1510/icvts.2009.217562
25. Liatsi D,Tsapas B, Pampori S, Tsagourias M, Pneumatikos I, Matamis D. Respiratory, metabolic and hemodynamic effects of clonidine in ventilated patientspresenting with withdrawal syndrome. *Intensive Care Med*. 2009;35(2):275-281. https://doi.org/10.1007/s00134-008-1251-0
26. Bernard JM, Hommeril JL, Passuti N, Pinaud M. Postoperative analgesia by intravenousclonidine. *Anesthesiology*. 1991;75(4):577-582. https://doi.org/10.1097/00000542-199110000-00006
27. De Kock MF, Pichon G, Scholtes JL. Intraoperative clonidine enhancespostoperative morphine patient-controlled analgesia. *Can J Anaesth*. 1992;39(6):537-544. https://doi.org/10.1007/BF03008314
28. Striebel WH, Koenigs DI, Kramer JA. Intravenous clonidine fails to reduce postoperative meperidine requirements. *J Clin Anesth*. 1993;5 (3):221-225. https://doi.org/10.1016/0952-8180(93)90019-b
29. Jeffs SA, Hall JE, Morris S.Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia. *Br J Anaesth*. 2002;89(3):424-427. https://doi.org/10.1093/bja/89.3.424
30. Marinangeli F, Ciccozzi A, Donatelli F, et al. Clonidine for treatment of postoperativepain: a dose-finding study. *Eur J Pain*. 2002;6(1):35-42. https://doi.org/10.1053/eujp.2001.0270
31. Spies CD, Dubisz N, Funk W, et al. Prophylaxis of alcohol withdrawal syndrome in alcohol-dependent patients admitted to the intensive care unit after tumour resection. *Br J Anaesth*. 1995;75(6):734-739. https://doi.org/10.1093/bja/75.6.734
32. Spies CD, Dubisz N, Neumann T, et al. Therapy of alcohol withdrawalsyndrome in intensive care unit patients following trauma: results of aprospective, randomized trial. *Crit Care Med*.1996;24(3): 414-422. https://doi.org/10.1097/00003246-199603000-00009
33. Spies CD, Otter HE, Huske B, et al. Alcohol withdrawal severity is decreased by symptom-orientated adjusted bolus therapy in the ICU. *Intensive Care Med*. 2003;29(12):2230-2238. https://doi.org/10.1007/s00134-003-2033-3

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APPENDIX A

TABLE A1 Clonidine use in Dutch intensive care units[7]

IC level	Clonidine use	Indication	Loading dose (μg)	Continuous infusion dose (μg/70 kg/24 h)
3	Often	Hypertension; sedation	Unknown	Unknown
3	Often	Substance withdrawal; hypertension; delirium; sedation	40–120	240–1920
3	Often	Substance withdrawal; sedation	150	1200
3	Often	Substance withdrawal	75–150	1200
3	Often	Substance withdrawal; hypertension; delirium	10	960–2400
3	Sometimes	Delirium	No loading dose	720–2400
3	Sometimes	Hypertension; delirium	150	
3	Sometimes	Substance withdrawal; delirium		960
2	Sometimes	Substance withdrawal; delirium		480–1200
2	Sometimes	Hypertension; sedation	150	960
2	Sometimes	Substance withdrawal; hypertension; delirium	150	450–1000
1	Sometimes	Hypertension; delirium	150	No continuous infusion
1	Sometimes	Delirium	50	1200–2400
1	Sometimes	Delirium	Unknown	Unknown

TABLE A2 Summary of studies of intravenous clonidine for treatment of critically ill patients[7]

Study (*n*)	Intervention/clonidine dose	Outcome	Main findings	Study design
Rubino[24] 2010 (30)	Bolus 0.5 μg/kg followed by 1–2 μg/kg/h continuous, or placebo 1680–3360 μg/70 kg/24 h	Neurological outcome and respiratory function	Lower DDS, shorter weaning and shorter period of ICU stay in clonidine group	RCT, blinded pilot study
Liatsi[25] 2009 (30)	900–1800 μg in 2 doses of 10 min interval, when effective: 1800–2500 μg/24 h continuous infusion *vs* remifentanyl-propofol	Respiratory, metabolic and haemodynamic effects	25/30 pts responded to clonidine. Mild sedation, better ventilation weaning. No severe hypotension or bradycardia	Prospective intervention study, not blinded
Fauler[8] 1993 (11)	Bolus 150 μg. Mean dose 720 (290–2370) μg/24 h	Kinetic parameters, side effects	Lowering MAP and heart rate not clinically significant	Pharmacokinetic study

ns, not significant; DDS, delirium detection scale; RCT, randomised controlled trial

TABLE A3 Literature on clonidine in perioperative situations[7]

Study (*n*)	Intervention/clonidine dose/max daily dose	Outcome	Main findings	Study design
Bernard[26] 1991 (50)	Load 5 μg/kg/60 min 0.3 μg/kg/h during 11 h *vs* placebo 231 μg/70 kg/11 h	Pain	Clonidine delayed onset of pain lower pain score with clonidine 42 ± 5 to 26 ± 3 (scale 0 to 100)	Double blind RCT
De Kock[27] 1992 (187)	Load 4 μg/kg/30 min 2 μg/kg/h with Anaesthesia *vs* *Anaes*thesia alone 3360 μg/70 kg/24 h	Number of analgesic demands sedation scores	Reduction of analgesic demands 45 ± 27 *vs* 81 ± 60 (P = .0001) no difference in sedation scores	RCT, observer blinded
Striebel[28] 1993 (60)	300 μg/2 h *vs* placebo	Pain	No pain reduction	Double blind RCT
Jeffs[29] 2002 (60)	Load 4 μg/kg/20 min PCA clonidine 20 μg + morphine 1 mg vs placebo iv + morphine 1 mg	Pain, nausea	Clonidine: Lower pain score in the first 12 h 1 (0–3) *vs* 3 (1–4; P < .05) no reduction in morphine use reduction in nausea	Double blind RCT
Marinangeli[30] 2002 (80)	Load 2,3,5 μg/kg/30 min 0.3 μg/kg/h during 12 h *vs* placebo 252 μg/70 kg/12 h	Optimal dose when sedation and analgesia is required	3 μg/kg followed by 0.3 μg/kg/h during 12 h is optimal dose for sedation 2 μg/kg: 5 ± 2 dose morphine 3 μg/kg: 11 ± 3 dose morphine 5 μg/kg: 19 ± 4 dose morphine placebo: 29 ± 8 dose morphine	Double blind RCT dose finding

RCT, randomised controlled trial

TABLE A4 Literature on clonidine in alcohol withdrawal related agitation and delirium[7]

Study (*n*)	Intervention/clonidine dose	Outcome	Main findings	Study design
Spies[31] 1995 (197)	Load 150 (75–300) μg max 0.83 (0.07–3.39) μg/kg/h iv flunitrazepam/clonidine 1394 (118–5695) μg/70 kg/24 h or chlormethiazole/haloperidol or flunitrazepam/haloperidol or ethanol	Duration of ICU stay prevention of AWS rate of major intercurrent complications	No difference between the groups	RCT, blinded
Spies[32] 1996 (159)	Flunitr/clonidine max dose 0.88 (0.14–4.69) μg/kg/h 1478 (235–7879) μg/70 kg/24 h chlormethiazole/haloperidol or flunitrazepam/haloperidol or ethanol	Duration of ventilation major intercurrent complications	Some advantage (pneumonia)	RCT, partially blinded (AWS score blinded)
Spies[33] 2003 (44)	Bolus 150–300 μg max infusion rate 5.5 (2.2–7.4) μg/kg/h 9240 (3696–12432) μg/70 kg/24 h clonidine or flunitrazepam bolus or haloperidol bolus or continuous infusion clonidine/flunitrazepam/haloperidol	Effect of bolus *vs* *contin*uous infusion adjustment on severity and duration of AWS	Decreased severity of AWS with the bolus approach	RCT, blinded

AWS, alcohol withdrawal syndrome