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

Michael E. Cloesmeijer1 | Huub L.A. van den Oever2 | Ron A.A. Mathôt4 | Marieke Zeeman3 | Arriette Kruisdijk-Gerritsen2 | Carmen M.A. Bles2 | Polina Nassikovker2 | Arthur R. de Meijer2 | Fred L. van Steveninck2 | Maurits E.L. Arbouw4

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
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. The presence of delirium may result in an increased hospital and ICU length of stay.

In recent years, α2 adrenergic agonists have been used as an additive treatment to the standard sedation regimen. Alpha-2 adrenergic agonists produce both sedative and analgesic effects with minimal respiratory depression. Clonidine is a potent α2 adrenergic agonist and its sedative and analgesic effects have been investigated in clinical studies.

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. 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. Although some self-reported sedation has been described at serum levels below 1.5 μg/L, 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. 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, and it decreases the blood pressure. It exerts these effects through the activation of presynaptic α2-adrenoceptors in the central nervous system and through activation of α2-adrenoceptors in vascular endothelial cells.

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. 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-performance 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. 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 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 criteria were based on change in the objective function value (OFV), parameters, to potentially reduce the unexplained IIV. Model selection was utilised (equation 6), using the following equation:

\[ \theta_{pop} = \theta_{pk} \times \left( \frac{\text{Bodyweight}}{70} \right)^{\theta_{exp}} \]  

(4)

In which, \( \theta_{pop} \) is the population mean value, \( \theta_{pk} \) is the mean PK value, and \( \theta_{exp} \) 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:

\[ \theta_{pop} = \theta_{pk} \times \left( \frac{\text{Cov}}{\text{Cov}_{\text{median}}} \right)^{\theta_{exp}} \]  

(5)

\[ \theta_{pop} = \theta_{pk} \times (1 + \text{Cov}) \times \theta_{slope} \]  

(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 \( \theta_{slope} \) 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, or using 24-hour urine creatinine clearance. BSA was calculated by the Du Bois formula 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 evaluated21: (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 \(\mu\)g/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 \(\mu\)g/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.

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 infusion on CL, and of body weight, CLcr, albumin and bilirubin on V1.
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.
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

---

**TABLE 2** Covariate model development

| Model no. | Model | Covariate function | OFV |
|-----------|-------|--------------------|-----|
| 0         | 2-compartment model base | - | -499.57 |
| 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**

| Model no. | Model | Covariate function | OFV |
|-----------|-------|--------------------|-----|
| 7         | Model 6 - Time after infusion on CL | Linear | -515.87 |
| 8         | Model 6 - Bodyweight on V1 | Allometric | -507.84 |
| 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) [1.41–20.3]                      | 16.9 [14.1–20.3]                            |
| V1 (L/70 kg) | 124 (36) [66.2–186]                  | 119 [66.2–186]                             |
| Q (L/h)   | 83.7 (35) [25.1–175]                    | 89.9 [25.1–175]                            |
| V2 (L)    | 178 (35) [128–269]                     | 181 [128–269]                              |
| Increase CL per hour | 0.213 (19) | 0.220 [0.0544–0.441] |

**Interindividual variability**

| V1 (%CV) | 33.3 (23) [1] | 33.1 [23.9–44.6] |
| V2 (%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] |

V1, central volume of distribution; V2, 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.
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.
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, 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 receive CVVH. Clonidine may potentially be removed by CVVH because of its low molecular weight (230 g/mol) and low protein binding (20–40%). 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. 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. 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...
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.

**ACKNOWLEDGEMENTS**

This project was supported by the Deventer Hospital Research Fund. There were no other funds for this study.

**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.
### Table A1  
Clonidine use in Dutch intensive care units

| 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

| Study (n) | Intervention/clonidine dose | Outcome                                               | Main findings                                                                 | Study design                      |
|-----------|-----------------------------|-------------------------------------------------------|-------------------------------------------------------------------------------|-----------------------------------|
| Rubino²⁴  | 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         |
| Liatsi²⁵  | 900–1800 μg in 2 doses of 10 min interval, when effective: 1800–2500 μg/24 h continuous infusion vs remifentanil-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 |
| Fauler⁸    | 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

| Study (n) | Intervention/clonidine dose/max daily dose | Outcome | Main findings | Study design |
|-----------|------------------------------------------|---------|---------------|--------------|
| Bernard²⁶ 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 Kock²⁷ 1992 (187) | Load 4 μg/kg/30 min 2 μg/kg/h with Anaesthesia vs Anaesthesia 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 |
| Striebel²⁸ 1993 (60) | 300 μg/2 h vs placebo | Pain | No pain reduction | Double blind RCT |
| Jeffs²⁹ 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 |
| Marinangeli³⁰ 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

| Study (n) | Intervention/clonidine dose | Outcome | Main findings | Study design |
|-----------|-----------------------------|---------|---------------|--------------|
| Spies³¹ 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 |
| Spies³² 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) |
| Spies³³ 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 continuous infusion adjustment on severity and duration of AWS | Decreased severity of AWS with the bolus approach | RCT, blinded |

AWS, alcohol withdrawal syndrome