









Enantiospecific pharmacokinetics of intravenous dexmedetomidine in beagles

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Abstract

The goal of this study was to investigate the pharmacokinetic (PK) behaviour of dexmedetomidine in dogs administered as a pure enantiomer versus as part of a racemic mixture. Eight unmedicated intact purpose-bred beagles were included. Two intravenous treatments of either medetomidine or dexmedetomidine were administered at 10- to 14-day intervals. Atipamezole or saline solution was administered intramuscularly 45 min later. Venous blood samples were collected into EDTA collection tubes, and the quantification of dexmedetomidine and levomedetomidine was performed by chiral LC-MS/MS. All dogs appeared sedated after each treatment without complication. Plasma concentrations of levomedetomidine were measured only in the racemic group and were 51.4% (51.4%–56.1%) lower than dexmedetomidine. Non-compartmental analysis (NCA) was performed for both drugs, while dexmedetomidine data were further described using a population pharmacokinetic approach. A standard two-compartment mammillary model with linear elimination with combined additive and multiplicative error model for residual unexplained variability was established for dexmedetomidine. An exponential model was finally retained to describe inter-individual variability on parameters of clearance (Cl_1) and central and peripheral volumes of distribution (V_1 , V_2). No effect of occurrence, levomedetomidine or atipamezole could be observed on dexmedetomidine PK parameters. Dexmedetomidine did not undergo significantly different PK when administered alone or as part of the racemic mixture in otherwise unmedicated dogs.

KEYWORDS

dexmedetomidine, dog, medetomidine, pharmacokinetic, stereoselective

1 | INTRODUCTION

Dexmedetomidine [(R)-(+)-medetomidine] is commonly administered to sedate dogs (Murrell & Hellebrekers, 2005; Truchetti et al., 2020) and also has analgesic properties (Siegenthaler et al., 2020). It can

be administered as a single enantiomer, or as a racemic mixture together with levomedetomidine [(S)-(-)-medetomidine] (“medetomidine”). Clear clinical advantages of using the single enantiomer over the racemate are under debate. Although some studies found the effects of the two products similar (Gómez-Villamandos et al., 2006;

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Granholm et al., 2007), others documented clinical differences. The same dose of dexmedetomidine provided stronger (Raszplewicz et al., 2013) or more prolonged (Siegenthaler et al., 2020) sedation when administered within the racemate than when administered alone. However, the subjective reaction to pinching was reduced for a slightly longer duration when dexmedetomidine was administered alone rather than with the racemate (Kuusela et al., 2000).

Differences may be the result of pharmacodynamic (PD) or pharmacokinetic (PK) interactions between enantiomers. In dogs, Kuusela et al. reported no relevant sedative effect of levomedetomidine alone (Kuusela et al., 2001). However, interactions at a receptor level when the enantiomers are administered together cannot simply be excluded (Brocks, 2006). Variations in plasma concentrations of dexmedetomidine when administered alone or together with levomedetomidine (Kuusela et al., 2001) may also explain some of the differences. Dexmedetomidine and levomedetomidine undergo a significantly different metabolic pathway (Kuusela, 2004). It is unknown whether dexmedetomidine exhibits a similar behaviour in the presence or absence of the other enantiomer. Such a significant PK interaction between enantiomers is rather seldom (Brocks, 2006), but has been reported with, for example, S-ketamine in ponies (Larenza et al., 2007, 2008).

The goal of this study was to investigate the PK behaviour of dexmedetomidine in dogs, administered as a pure enantiomer or within the racemic compound medetomidine. It was hypothesized that plasma concentrations of dexmedetomidine administered alone or in the racemate would not differ strongly.

2 | MATERIALS AND METHODS

The experiment was approved by the local Committee for Animal Experimentation (approval number 30356). The primary aim of the present report was to investigate the differences in the PK of dexmedetomidine when administered alone or as part of a racemate. However, the experiment was part of a larger study published elsewhere where the primary aims were to investigate the differences between medetomidine and dexmedetomidine on antinociception (Siegenthaler et al., 2020) as well as on the non-invasive monitoring of selected cardiopulmonary variables (Pleyers et al., 2020). Therefore, the study design was oriented towards these goals.

2.1 | Sample size, design

The median peak nociceptive withdrawal reflex (NWR) values from a previous publication were used to calculate the sample size; the details of the sample size calculation are presented elsewhere (Siegenthaler et al., 2020). Eight dogs were included in this randomized crossover study.

For the purposes of the pharmacological analysis, a 20% difference in plasma concentrations between the two formulations was

arbitrarily considered a relevant endpoint. Assuming a within-group data variance of 15%, the inclusion of eight dogs was considered appropriate (Wilcoxon signed-rank test, paired, two-tailed, effect size = 1.4, $\alpha = .05$, $1-\beta = .9$, GPower 3.1).

2.2 | Animals

The eight dogs included in this study were intact beagles (two females and six males), bred for research purposes. They were housed in small groups, in a dedicated enriched kennel, with access to an outdoor course. Physical examinations were regularly performed. Selected haematology and blood chemistry were analysed before the experiment. Dogs were considered healthy and were not involved in any other study. No drug (other than anthelmintics) was administered for at least two months before the trial. Dogs had body condition scores of 5 or 6 on a scale of 9 (Laflamme, 1997). They were weighed before each session.

Additional details on dogs housing and husbandry, randomization, blinding process and other variables assessed (nociceptive tests and non-invasive cardiopulmonary monitoring) can be found elsewhere (Pleyers et al., 2020; Siegenthaler et al., 2020).

2.3 | Treatment

Two intravenous (IV) treatments consisting of medetomidine (group RAC, Domitor, 1 mg/mL; Orion Corporation; 0.02 mg/kg) or dexmedetomidine (group DEX, Dexdomitor, 0.5 mg/mL; Orion Corporation; 0.01 mg/kg) were administered both to each dog with a wash-out period of 10–14 days. The first treatment was randomly assigned (see above); the other drug was administered in the second experimental session (Table 1). Approximately 1 h before the start of the session, EMLA cream (Aspen Pharma Schweiz GmbH) was applied over the cephalic veins, covered with a plastic film and wrapped in an occlusive bandage. A 20- or 22-gauge catheter (Optiva2 IV Catheter radiopaque, Smiths Medical International Ltd) was placed in each cephalic vein, one for drug administration and the contralateral for blood sampling. The treatment was diluted in saline solution (NaCl 0.9%; Dr G Bichsel AG) up to 2 mL and administered by hand over 60 s through the right cephalic catheter. A bolus of either saline solution (Group SAL, NaCl 0.9%) or atipamezole

TABLE 1 Number (*n*) of dogs receiving dexmedetomidine (DEX) or medetomidine (MED) followed 45 min later by atipamezole (ATI) or saline solution (SAL)

| <i>n</i> | First treatment (randomized order) | Second treatment |
|----------|------------------------------------|------------------|
| 2 | DEX/ATI | MED/SAL |
| 2 | DEX/SAL | MED/ATI |
| 2 | MED/ATI | DEX/SAL |
| 2 | MED/SAL | DEX/ATI |

(Group ATI, Antisedan, 5 mg/mL; Orion Corporation; 0.1 mg/kg) was administered intramuscularly 45 min after the medetomidine or dexmedetomidine injection (Siegenthaler et al., 2020) (Table 1).

2.4 | Blood sampling and quantification assay

Blood samples (2 mL) were collected from the left cephalic IV catheter into EDTA collection tubes (Monovette). One "blank" blood sample was always collected before drug administration, and further sampling times were 2, 4, 8, 16, 30, 60, 80, 90 and 120 min after the start of the IV infusion (T_0). Samples were kept on ice just after collection and until processing. Blood was then centrifuged for 10 min at 1500 g at 10°C, the plasma extracted and then stored frozen at -80°C until analysis. The quantification of dexmedetomidine and levomedetomidine was performed by chiral LC-MS/MS as described previously (Bardhi et al., 2021). The analytical method was validated in accordance with EMEA/CHMP/EWP/192217/2009 guidelines at the beginning of the experiment (EMA, 2011). The details of the quantification methodology are provided elsewhere (Bardhi et al., 2021). The calculated limit of detection (LOD) was 0.01 ng/mL, and the lower limit of quantification (LLOQ) was 0.1 ng/mL. The intraday accuracy and precision were 4.8 [3.1–5.8]% and 6.2 [4.4–7.0]% for dexmedetomidine, and 2.2 [2.0–3.6]% and 6.7 [6.1–7.0]% for levomedetomidine, respectively (Bardhi et al., 2021).

2.5 | Pharmacokinetic analysis

Each step of the PK modelling was performed with a commercially available software (Phoenix 64® v.8.3 WinNonlin® NLME®, Pharsight Inc.). The details of the PK analyses and modelling are presented in Appendix S1. Non-compartmental analysis (NCA) was performed on both levomedetomidine and dexmedetomidine plasma concentrations. In addition, a population PK approach was applied to describe dexmedetomidine concentration–time course by comparing increasingly complex models and sequentially testing inter-individual variability (IIV) on basic PK parameters (i.e. volumes (V_i) and clearances (Cl_i)), as well as potential effects of occasion (first-second), group (medetomidine-dexmedetomidine) or atipamezole administration (saline-atipamezole). The Quasi-random Parametric Expectation Maximization (QRPEM) algorithm implemented in Phoenix NLME initialized by the NCA estimates was used for the popPK analysis. Standard validation methods in popPK were used to assess model adequacy (see Appendix S1). Proportional prediction correction was applied for the visual predictive check (VPC). Secondary parameters were derived from the final popPK estimates in order to compare with NCA results (see Appendix S1).

2.6 | Statistical analysis

In addition to the PK analyses, the differences in dexmedetomidine plasma concentrations between groups were tested using two-way

ANOVA for repeated measures followed by Holm–Sidak pairwise multiple comparisons. Differences between NCA PK parameters including volume, clearance and area under the curve (AUC) were tested with a Wilcoxon signed-rank test (paired samples). Statistical evaluation was performed with the SigmaStat 3.5 software package, and significance was set at $p = .05$. Due to the small number of samples, the data are presented as median [IQR 25%–75%], regardless of its distribution.

3 | RESULTS

All dogs appeared sedated after each treatment. There was no complication observed at any stage. A total of 14/160 blood samples were discarded (inadequate sampling) or missing.

3.1 | Concentration time course of dexmedetomidine with and without atipamezole

Analysis of differences for pooled plasma concentrations of dexmedetomidine (Figure 1) between group ATI ($n = 8$) and group SAL ($n = 8$) revealed no significant difference neither during the first 30 min after T_0 ($p = .89$), nor afterwards ($p > .18$).

3.2 | Concentration time course of dex- and levomedetomidine

After administration of racemic medetomidine (0.02 mg/kg, IV), both enantiomers dex- and levomedetomidine were measurable. Plasma concentration of levomedetomidine was 51.4 [51.4–56.1]% lower than the concentration of dexmedetomidine (Figure 2). As expected, no levomedetomidine was measured at any time point after administration of the pure enantiomer dexmedetomidine.

The dexmedetomidine plasma concentrations from the dogs receiving the pure dexmedetomidine enantiomer (DEX) at 0.01 mg/kg IV were 18.5 [3.2–26.8]% lower than from the dogs receiving it as part of the racemic mixture (medetomidine, RAC) (Figure 3). This difference was neither statistically significant ($p = .071$) nor considered clinically relevant (<20%).

3.3 | Pharmacokinetic analysis

The results of both NCA and popPK modelling are presented in Appendix S1. Table 2 shows the final estimates for levo- and dexmedetomidine NCA as well as the NLME analysis for dexmedetomidine. Volumes and clearances obtained from NCA were significantly different ($p = .016$ in both cases) between levomedetomidine and dexmedetomidine. There was no significant difference between the AUCs for dexmedetomidine after administration as a racemic mixture or as a single enantiomer ($p = .69$).

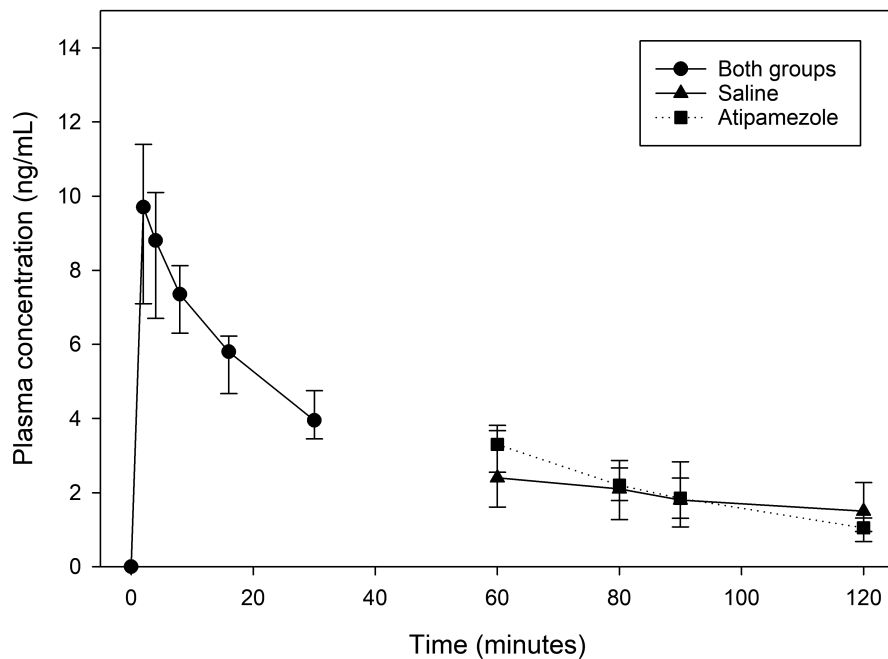


FIGURE 1 Dexmedetomidine plasma concentrations over time in eight beagles (crossover design) after administration of dexmedetomidine (0.01 mg/kg, IV, $n = 16$, pooled data from both groups receiving either dexmedetomidine alone or within the racemate), additionally receiving either atipamezole (0.1 mg/kg) or saline (NaCl 0.9%) intramuscularly at 45 min. Data are presented as median [IQR 25%–75%]

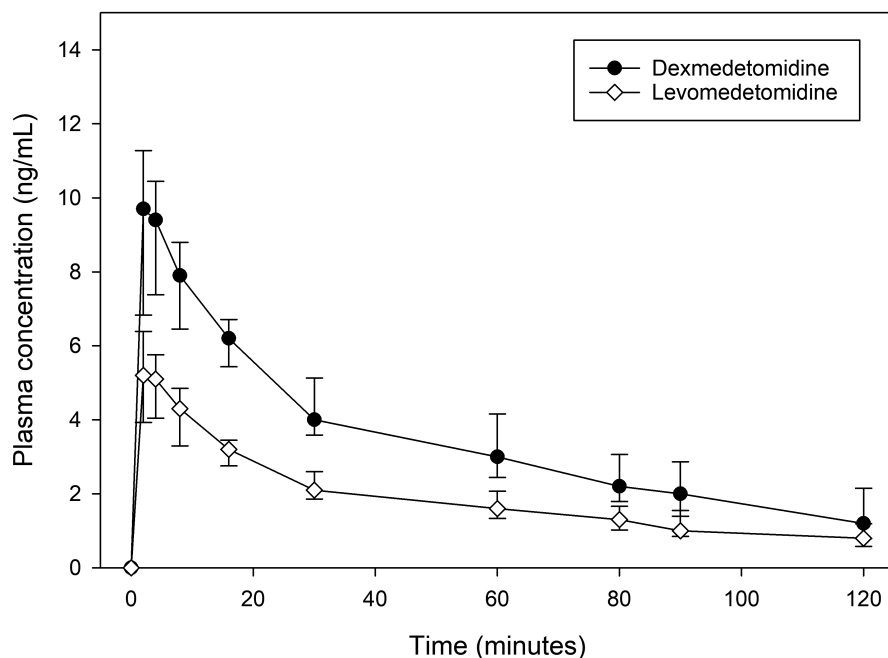


FIGURE 2 Plasma concentrations over time for dex- and levomedetomidine after administration of racemic medetomidine (0.02 mg/kg, IV) in eight beagles. Data are presented as median [IQR 25%–75%]

The final NLME model was a standard two-compartment mammillary model with combined additive and multiplicative residual error model. An exponential model was finally retained to describe the IIVs on clearance (Cl_1) and central and peripheral volumes of distribution (V_1 and V_2 , respectively). No effect of occurrence, levomedetomidine or atipamezole could be observed on dexmedetomidine PK parameters. Standard validation methods, shown in Figure 4, support the good predictive performances of the model.

4 | DISCUSSION

This study supports previous observations that medetomidine undergoes stereoselective metabolism with markedly lower plasma

concentrations of levomedetomidine compared to dexmedetomidine. Dexmedetomidine did not appear to convert to levomedetomidine. Dexmedetomidine plasma concentrations were similar after administration of dexmedetomidine as a pure enantiomer or as a racemic mixture that included levomedetomidine. Atipamezole did not seem to interact with the PK of dexmedetomidine.

The PK parameters obtained here from modelling the plasma concentration of intravenous dexmedetomidine were close to previously reported values in the same animal species (Bennett et al., 2016; Honkavaara et al., 2012; Kuusela et al., 2000). Enantioselective PK of dex- and levo- medetomidine observed here confirmed former reports. As in previous studies, the plasma concentration of levomedetomidine was significantly lower than dexmedetomidine after administration of the racemic mixture (Bennett et al., 2016). The

FIGURE 3 Dexmedetomidine plasma concentrations over time after administration of racemic medetomidine (0.02 mg/kg, IV, RAC) or the pure enantiomer dexmedetomidine (0.01 mg/kg, IV, DEX) in eight beagles (crossover design). Data are presented as median [IQR 25%–75%]

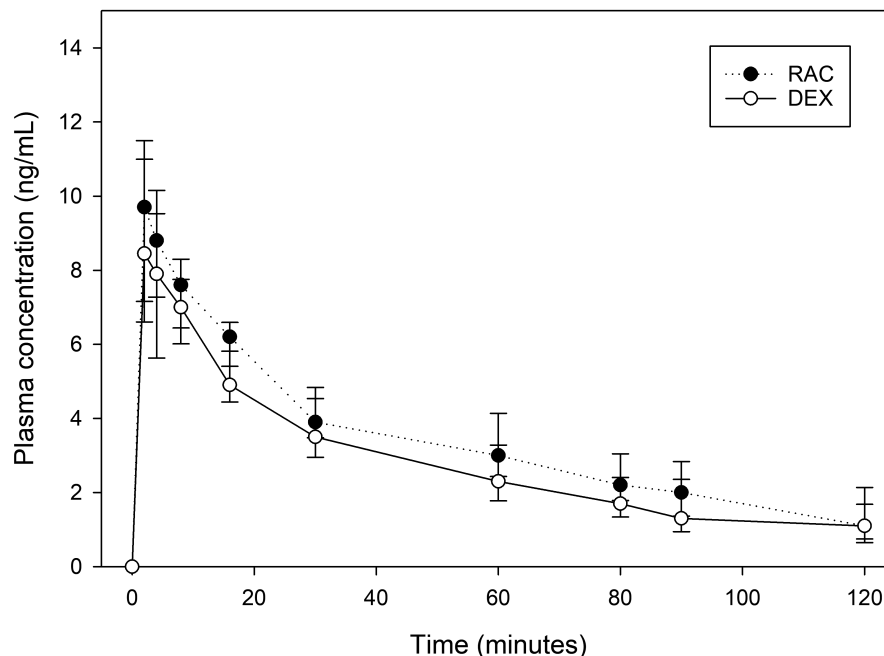


TABLE 2 Pharmacokinetic parameters of levo- and dexmedetomidine (0.01 mg/kg, IV) in eight beagles

| | C _{max} ng/mL | t _{1/2} h | V L/kg | V ₂ L/kg | V _{ss} L/kg | Cl L/h/kg | Cl ₂ L/h/kg | AUC h ng/mL | MRT h |
|---|---------------------------|-----------------------|-----------|------------------------|-------------------------|--------------|---------------------------|----------------|-----------|
| Levomedetomidine (Non-compartmental analysis) | | | | | | | | | |
| Median | 5.7 | 0.93 | 2.80 | - | 2.56 | 1.96 | - | 5.11 | 1.22 |
| IQR 25%–75% | 4.7–6.3 | 0.83–1.32 | 2.58–2.97 | - | 2.55–2.74 | 1.79–2.15 | - | 4.66–5.58 | 1.18–1.79 |
| Dexmedetomidine (non-compartmental analysis) | | | | | | | | | |
| Median | 9.7 | 0.80 | 1.47 | - | 1.40 | 1.24 | - | 8.09 | 1.14 |
| IQR 25%–75% | 7.2–10.4 | 0.75–0.93 | 1.31–1.83 | - | 1.28–1.63 | 1.05–1.59 | - | 6.29–9.50 | 0.99–1.28 |
| Dexmedetomidine (final population compartmental analysis) | | | | | | | | | |
| Estimates | - | 0.92 | 1.03 | 0.41 | 1.45 | 1.16 | 1.87 | 8.65 | 1.25 |
| CI 2.5%–97.5% | - | 0.68–1.06 | 0.92–1.15 | 0.13–0.70 | 1.31–1.62 | 0.95–1.37 | 1.35–2.38 | 6.52–9.70 | 0.95–1.42 |

Note: Data for dexmedetomidine are pooled from crossover administration either as pure enantiomer or as part of a racemic mixture (medetomidine). Abbreviations: C_{max}, maximal measured concentration; V, volume of distribution; V_{ss}, volume of distribution at steady state; cl, clearance; AUC, area under the curve; MRT, mean residence time; t_{1/2}, terminal half-life.

peak concentration of levomedetomidine was less than 60% that of dexmedetomidine. There was a marked difference in the volume of distribution while elimination half-life was quite similar between the enantiomers. Potential reasons for these discrepancies are not reported and cannot be further discussed here.

A previous study observed that atipamezole increased the clearance of medetomidine in dogs when administered at 30 min interval (Salonen et al., 1995). In the present study, the PK parameters were not significantly different with or without atipamezole administered 45 min after dexmedetomidine. A similar observation has been reported for dairy cows that had been administered atipamezole intravenously 60 min after medetomidine (Ranheim et al., 1999). The effect of IM atipamezole on dexmedetomidine PK was not the primary objective of the present investigation and both study design and number of animals restrict validity of these results. The analysis was performed to distinguish between the potential effects

of atipamezole and racemic administration on dexmedetomidine disposition. It was not expected to show an effect of intramuscular atipamezole on dexmedetomidine concentrations that had been measured only four times during 75 min. Such an extrapolation should be taken with caution.

The main limitation of this study is the small number of observations. The conclusions presented require further confirmation. However, the crossover design and the population PK approach employed in this study allow a report of the variability of dexmedetomidine concentrations at the same dose and in the same subjects with or without concomitant administration of levomedetomidine. A certain degree of intra-individual PK variability is expected even in a crossover design (Chang & Wong, 1997). The IIV should be accounted for in the population model.

The sedative and analgesic effects of dexmedetomidine observed during the present study were reported previously (Siegenthaler

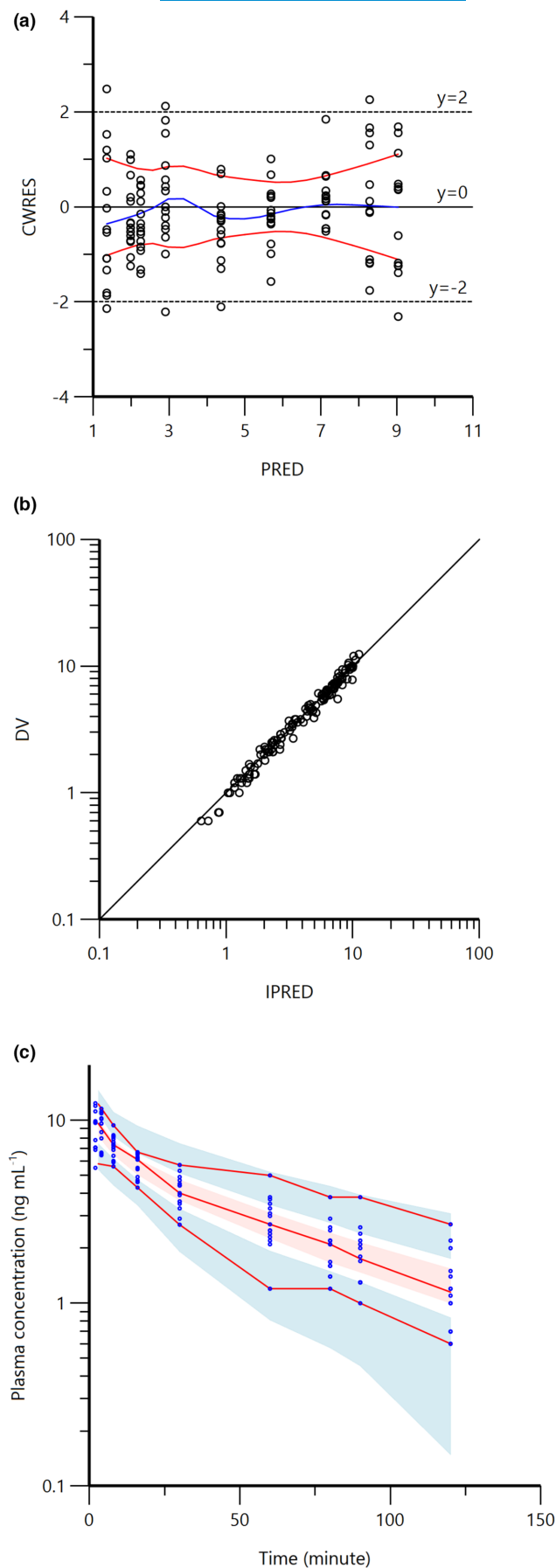


FIGURE 4 Goodness-of-fit plots of the final population PK model for dexmedetomidine after single bolus administration (0.01 mg/kg, IV) in eight beagles (crossover design either with the pure enantiomer or as a racemic mixture). (a) Distribution of the conditional weighted residuals (CWRES) against population model prediction (PRED). (b) Observed data (DV) against individual-predicted concentrations (IPRED). (c) Prediction corrected visual predictive check (VPC); observed concentrations are depicted by dots and their 95th, 50th, and 5th percentiles by continuous lines; the 95th, 50th and 5th percentiles of the model predicted concentrations and their 95% confidence intervals are represented the shaded areas

et al., 2020). A longer lasting sedative effect of medetomidine was observed compared to dexmedetomidine. It was hypothesized that this could have been the result of different plasma concentrations of dexmedetomidine but PK analyses had not been performed at the time of the first manuscript preparation. The present analysis proved this hypothesis to be wrong. A reinforcing effect of levomedetomidine on sedation from dexmedetomidine remains controversial as levomedetomidine did not elicit relevant behavioural effects when administered alone (Kuusela et al., 2001). High doses of levomedetomidine even decreased the sedation quality from dexmedetomidine (Kuusela et al., 2001). Now that the PK has been characterized and is in agreement with former results, further investigation of the observed effect is required to demonstrate whether there may be a clinically relevant advantage of using either medetomidine or dexmedetomidine.

5 | CONCLUSION

Based on the present study, dexmedetomidine does not seem to undergo significantly different PK when administered either alone or as part of the racemic mixture in otherwise unmedicated dogs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. The funders had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

AUTHOR CONTRIBUTION

All the authors contributed to writing the paper. MG contributed to PK analysis. A. Barbarossa and A. Bardhi contributed to the PK assay. JS, TFP and CS contributed to study design and data collection. OL and MR were involved in all steps of the study (conceived and designed the analysis, collected the data, contributed data analysis, wrote the paper).

DATA AVAILABILITY STATEMENT

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

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