

## **Pharmacokinetics and sedative effects of dexmedetomidine in dairy calves**

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### **Abstract**

**AIMS:** To evaluate the pharmacokinetics of dexmedetomidine (DEX) administered I/V at a dose of 5 µg/kg bodyweight in dairy calves and to compare the sedative effects of anaesthetic protocols involving DEX and xylazine.

**METHODS:** Nine dairy calves, aged 17–20 days, were treated with 5 µg/kg bodyweight I/V dexmedetomidine. For pharmacokinetic evaluation, blood samples were collected over 12 hours and serum samples were analysed by high performance liquid chromatography-mass spectrometry. Another nine dairy calves, aged 16–20 days, were treated with 0.2 mg/kg bodyweight I/V xylazine. After both treatments, heart rate, respiratory rate and rectal temperature were measured for 20 minutes. Sedation quality and recovery times were also assessed.

**RESULTS:** The kinetics of DEX was best described by a two compartment model. The distribution and elimination half-lives were 8.7 (SD 5.0) and 83.5 (SD 67.5) minutes, respectively. Mean maximum concentration and body clearance were 12.5 (SD 8.6) ng/mL and 27.9 (SD 13.1) mL/minute/kg, respectively; the mean volume of distribution at steady state was 2,170.8 (SD 1657.5) mL/kg. A decrease in heart rate was observed after treatments with both DEX and xylazine. No differences in heart or respiration rate, or rectal temperature were observed between the two treatment groups. The onset of sedation occurred after 2.7 (SD 0.67) minutes for calves treated with DEX and 2.8 (SD 0.78) minutes for calves treated with xylazine, and was characterised by a similar degree of deep sedation and ease of handling of the calves. All recoveries were eventless, and no adverse reactions were noted.

CONCLUSIONS AND CLINICAL RELEVANCE: Dexmedetomidine treatment resulted in a reliable and long lasting sedation in calves, a transient decrease in heart rate and no modification in respiratory rate or rectal temperature. The results were comparable to xylazine, the most popular alpha-2-agonist among bovine practitioners. The use of DEX in dairy calves for rapid procedures such as dehorning or castration could be suggested.

KEY WORDS: *Dexmedetomidine, pharmacokinetics, sedative effects, xylazine, dairy calf*

DEX Dexmedetomidine

HPLC High performance liquid chromatography

LOD Limit of detection

LOQ Limit of quantification

## Introduction

The sedative effects of xylazine in horses and cattle were first reported in the late 1960s (Clarke and Hall 1969). Since then other alpha-2-adrenoreceptor agonists, such as detomidine, romifidine, medetomidine and dexmedetomidine (DEX) have been introduced in small and large animal practice, gaining wide acceptance. Alpha-2-agonists are dose-dependent sedative agents, used for premedication prior to general anaesthesia, to reduce the required amount of injectable anaesthesia (Bühner *et al.* 1994) and decrease minimum alveolar concentration of inhaled anaesthetic agents (Ewing *et al.* 1993). Further positive activities that influence alpha-2 agonists use are their synergistic action with opioids and analgesic properties (Short 1992). In addition, alpha-2-agonists are relatively safe substances and their effects are reversible by antagonists such as yohimbine and atipamezole (Schwartz and Clark 1998).

Xylazine was the first alpha-2-agonist to be licensed in veterinary medicine. It is commonly used in bovine practice to sedate calves undergoing clinical or surgical practices thanks to its rapid onset, relatively short duration of action, analgesic properties and quality of sedation (Rioja *et al.* 2008). DEX is structurally related to detomidine and is the pharmacologically active d-enantiomer of the racemic mixture medetomidine. DEX is authorised for use in small animal practice and is one of the most potent alpha-2-agonists commercially available (Marcilla *et al.* 2012). Compared to medetomidine, DEX has sedative and analgesic effects at equivalent doses, but is twice as potent and has various cardiovascular and analgesic advantages (Kuusela *et al.* 2000).

Pharmaceutical products authorised for pain management in cattle are quite limited (Hewson *et al.* 2007). The concern regarding pain management in food animals is increasing and research on this issue in cattle is needed. Calf dehorning and castration are common practices in cattle husbandry and are perceived as painful, though pain management is not always deemed necessary (Stafford and Mellor 2005ab; Hewson *et al.* 2007). The need for pain relief during these procedures and the use of analgesia and anaesthesia for castration and dehorning have been proposed. The administration of DEX in dairy calves during dehorning or castration could represent a significant improvement in pain management. Thus, the aims of this study were to evaluate the pharmacokinetics of DEX administered I/V at a dose of 5 µg/kg bodyweight in dairy calves, and to compare the sedative effects of anaesthetic protocols involving DEX and xylazine. The dose of DEX administered was derived from the authorised dose in dogs and cats, and from the dose used in sheep and horses (Raekallio *et al.* 2010; Rezende *et al.* 2014).

## **Materials and methods**

### **Animals**

The protocol for this study was approved by the Institutional Ethical Committee for Animal Care at University of Milan (Milan, Italy; protocol No. 28/2011).

Eighteen (seven male and 11 female), Italian Holstein Friesian calves, aged 17.7 (SD 1.3) days, weighing 42.7 (SD 6.3) kg, were included in the study. All animals were admitted to the Clinic for Ruminants and Swine of the Veterinary Teaching Hospital of Lodi (University of Milan, Italy) and were judged to be healthy on the basis of physical examinations and haematological and biochemical blood tests.

At arrival at the facility, the calves were weighed and housed separately in 1.8 x 1.2 m single indoor pens with a controlled temperature of 20°C. Pens were separated by solid walls and had straw bedding. During an acclimatisation period of 7 days, each calf had unlimited access to water, grass, hay and pellets, and was fed three times/day with 2 L milk replacer, at 7:00, 13:00 and 19:00.

Calves were randomly assigned to two groups. Group 1 was aged 17–20 days, weighed 32–50 kg and comprised five females and four males, and Group 2 was aged 16–20 days, weighed 30–52 kg and comprised six females and three males. For the comparison of sedation, calves in Group 1 were treated with 5 µg/kg bodyweight I/V dexmedetomidine (Dexdomitor, Orion Corporation, Espoo, Finland) diluted in 0.9 % NaCl saline solution to a volume of 5 mL, and calves in Group 2 were treated with 0.2 mg/kg bodyweight I/V xylazine (Rompun, Bayer AG, Leverkusen, Germany)

diluted in 0.9 % NaCl saline solution to a volume of 5 mL. Both groups were injected using the right jugular vein.

### **Sample collection**

The left jugular vein of calves from Group 1 was catheterised aseptically approximately 48 hours before the study start. Catheter patency was maintained using 5 mL heparinised saline flush solution (5 IU of heparin sodium/mL of 0.9% NaCl saline solution) administered three times/day.

Blood samples for the pharmacokinetic analysis were collected from catheter, starting 30 minutes prior to DEX administration (0 minutes) and then at 5, 15, 30, 45, 60, 90 minutes and at 2, 3, 4, 6, 8 and 12 hours after DEX administration. Blood was immediately centrifuged for 15 minutes at 1,500g, serum was harvested and divided into aliquots which were immediately stored at  $-80^{\circ}\text{C}$  until analysis.

### **Liquid chromatography-mass spectrometry analysis**

Dexmedetomidine was extracted from the serum samples according to the method described by Li *et al.* (2009) which was modified and validated in our laboratory. Liquid-liquid extraction was chosen for the sample preparation. The serum sample (500  $\mu\text{L}$ ) was extracted with 5 mL of acetonitrile after addition of 10  $\mu\text{L}$  internal standard solution (6  $\mu\text{g}/\text{mL}$  tolazolin in methanol) and 50  $\mu\text{L}$  saturated  $\text{Na}_2\text{CO}_3$  solution. The mixture was vortexed for 10 minutes, and then centrifuged at 3000g for 10 minutes. The upper organic layer was transferred and evaporated to dryness under an air stream at  $50^{\circ}\text{C}$  using a TurboVap evaporator (Zymarck, Hopkinton, MA, USA). The dry residue was re-dissolved in 200  $\mu\text{L}$  mobile phase and filtered on Phenex-RC (Regenerated Cellulose) 0.22  $\mu\text{m}$  syringe filters (Phenomenex, Torrance, CA, USA) and 20  $\mu\text{L}$  was used for high performance liquid chromatography (HPLC)-mass spectrometry.

An Accela 600 HPLC pump with a CTC automatic injector was used (Thermo Fischer Scientific, San Jose, CA, USA). Chromatographic separation was achieved using a C-18 Kinetex column (100x2.1 mm, 2.6  $\mu\text{m}$ , Phenomenex, Torrance, CA, USA) with guard column. Samples were eluted with a mobile phase consisting of 5 mM ammonium acetate solution with 0.1% formic acid (A) and methanol/acetonitrile (50:50, v:v) with 0.1 % formic acid (B). The flow rate was set at 200  $\mu\text{L}/\text{minute}$  and the sample tray was maintained at  $4^{\circ}\text{C}$ .

Mass spectrometric analysis was performed using an LTQ XL ion trap (Thermo Fisher Scientific) equipped with a heated electrospray ionisation probe operating in the positive-ion mode. The mass transitions were: DEX,  $m/z$  201  $\rightarrow$  95 and internal standard  $m/z$  161  $\rightarrow$  77 (Ji *et al.* 2004). The Xcalibur (version 2.1) data acquisition software from Thermo Fisher Scientific was used.

Calibration curves were constructed using pooled calf serum obtained from untreated animals. The blank serum was spiked with 10  $\mu$ L of internal standard (6  $\mu$ g/mL tolazolin in methanol) and with DEX to obtain a concentration range of 0.025–20 ng/mL. DEX (>99% pure) was purchased from Tocris (Milan, Italy) and tolazoline (>99% pure) from Sigma-Aldrich (St. Louis, MO, USA). Other reagents and solvents were purchased from Carlo Erba–Reagenti (Milan, Italy).

The linearity of the method was evaluated through the preparation of six different calibration curves on six different days by spiking serum samples with different DEX concentrations in the range 0.025–20 ng/mL. To verify the specificity of the method, 20 blank serum samples were analysed to check for the absence of potential interfering peaks from the matrix at the retention times of the DEX.

The within-day precision and accuracy were determined by analysing blank samples (six for each concentration) spiked with DEX at 0.05, 0.5 or 5 ng/mL on the same day. The between-day precision and accuracy were calculated using replicate determinations (n=9) of each concentration (0.05, 0.5, 5 ng/mL) made on three separate days. The precision was determined using the CV (%) and the accuracies were expressed as the percentage difference between the measured concentration and the nominal concentration. The extraction efficiency of DEX (recovery) from serum was determined by comparing the peak areas of DEX added into blank serum before the extraction procedure with those obtained for un-extracted standard added with the same concentrations to the blank extracts. The limit of detection (LOD) and limit of quantification (LOQ) were estimated as the concentration corresponding to the mean signal-to-noise ratio plus three times (LOD), and 10 times (LOQ) its SD in 20 blank samples, respectively.

### **Pharmacokinetic analysis**

Pharmacokinetic parameters of DEX were determined from serum concentration data using the WinNonLin 6.3 Prof software (Pharsight Corporation, Mountain View, California, USA) which enables compartmental and non-compartmental analyses of the experimental data. Visual inspection of the curve, residual analysis and minimum Akaike's information criterion estimation (Yamaoka *et al.* 1978) were used to choose the model best fitting the data. All data points were weighted by the inverse square of the fitted value. The disposition of DEX following I/V administration was described by a standard two-compartment model (Gibaldi and Perrier 1982).

### **Comparison of sedation**

Heart rate and respiratory rate respiration rate of calves in both treatment groups were measured using a Mindray PM5000 (Shenzhen, China) multiparametric monitor 30 minutes before treatment then at 5 10, 15 and 20 minutes after treatment. Rectal temperature was also recorded at the same

time points. The quality of sedation was evaluated in all calves 10 minutes after drug administrations using the classification shown in Table 1, by an evaluator unaware of the drug administered to the groups.

The induction time of sedation was identified for each animal as the time between drug administration, reduction in reactivity to environmental stimuli, and acquisition of sternal recumbency. Recovery time was defined as the time between drug administration and the return to the quadrupedal position.

### **Statistical analysis**

Pharmacokinetic parameters and intra-operative variables were reported as means and SD; harmonic means with pseudo-standard deviations were calculated for half-lives using a jack-knife technique (Lam *et al.* 1985).

Repeated measures ANOVA with the Bonferroni post-test were used to compare clinical variables between treatment groups. The differences in sedation quality scores between groups were compared using a U-Mann Whitney test. All analyses were carried out using GraphPad InStat Software version 3.10 (La Jolla, California, USA).

## **Results**

### **Dexmedetomidine concentrations and pharmacokinetic analysis**

The HPLC method was shown to be linear with the correlation coefficient being  $>0.99$ , for each of the calibration curves from the six different days. At the retention times of the DEX peak, no significant endogenous interfering molecules were observed in the blank samples tested. Results for within-day and inter-day precision gave  $CV\% < 15\%$ , and accuracies were within  $\pm 15\%$  of the theoretical value. The mean extraction recovery of DEX from serum was 83.2 (SD 11.8)%. An LOQ of 0.023 ng/mL and an LOD of 0.006 ng/mL were obtained.

The change in mean concentrations of DEX in serum of nine calves is shown in Figure 1. The mean concentration at 5 minutes after administration was 9.01 (SD 5.78) ng/mL. There was then a rapid decrease in serum concentration and at 45 minutes the mean value was 0.78 (SD 0.29) ng/mL. Subsequently, concentrations decreased progressively and DEX was detectable in all calves up to 120 minutes, when the mean concentration was 0.3 (SD 0.26) ng/mL. At 180 and 240 minutes the concentration of DEX was below the LOQ (0.023 ng/mL) in two calves, and at 360 and 480 minutes was below the LOQ in five calves. At 720 minutes DEX was detected in only one calf, with a value of 0.027 ng/mL, close to the LOQ.

Results from all subjects were best fitted by a bi-compartmental model and the results of the pharmacokinetic analysis are presented in Table 2.

### **Comparison of sedation**

The changes in mean heart rate and respiration rate in calves treated with DEX or xylazine are shown in Figures 2 and 3, respectively. A decrease in heart rate was observed after treatment with both DEX and xylazine ( $p < 0.05$ ). Temperature did not differ among the time point measurements in either group. There were no differences in heart rate, respiration rate or temperature between the two groups ( $p > 0.05$ ).

The quality of sedation, and intervals to induction and recovery did not differ between the two groups ( $p > 0.05$ ; Table 3). All recoveries were eventless, and no adverse reactions were noted in any of the animals. All calves were able to stand up and walk at the end of the observation period.

### **Discussion**

The welfare of livestock and the limited number of drugs available for pain relief in calves have instigated this study to determine the pharmacokinetic parameters of DEX administered I/V in dairy calves and to evaluate its sedative effect compared to xylazine. The pharmacokinetic profile of DEX in calves was characterised by a fast distribution half life (8.7 (SD 5.0) minutes) and relatively short elimination half life (83.5 (SD 67.5) minutes). Despite the young age of the calves (approximately 20 days) in the present study, and the presumable immature metabolic pool, the volume of distribution at steady state and body clearance values were reasonably homogenous among individuals, with values of 2,170.79 (SD 1,657.51) mL/kg and 27.9 (SD 13.1) mL/kg/minute, respectively.

~~In horses after I/V bolus of DEX, Rezende *et al.* (2014) reported a more rapid elimination (8.03 (SD 0.84) minutes) and higher Cl 78.62 (SD 59.97) (mL/kg/min). Besides species, differences in elimination could also be attributed to the higher LOQ values in horses (0.1 ng/mL) which could have limited the complete characterisation of the elimination phase in this species.~~ The mean clearance value reported in this study is comparable to the hepatic blood flow calculated for calves (26.5 mL/kg/minute; Toutain and Bousquet-Melou 2004), which suggests that hepatic metabolism plays a primary role in the DEX metabolic pathway in young calves. The distribution volume at steady state (2170.8 (SD 1657.5) mL/kg) was approximately 42% of the volume of distribution based on the terminal phase (5954.6 (SD 4236.4) mL/kg). Therefore, in our calves limited amounts of DEX were eliminated during the distribution phase.

No data on the pharmacokinetics of DEX have been published in bovine species to date, thus only tentative comparisons can be carried out with medetomidine and detomidine in cows. After I/V treatment with medetomidine in lactating cows, Ranheim *et al.* (1999) reported comparable values for Cl (24.2 (SD 6.5) mL/min/kg), but lower values for elimination half-life (52.7 (SD 25.3) minutes) and Vdss (1210 (SD 320) mL/kg). Data on detomidine in milking cows reported comparable values for distribution and elimination half-lives (14.4 (SD 7.8) and 79.2 (SD 27) minutes, respectively), but lower values for Cl (9.5 (SD 1.9) mL/min/kg) and Vdz (730 (SD 170) mL/kg) (Salonen *et al.* 1989). The differences could be attributed, not only to the different molecules (detomidine or medetomidine vs DEX) and age-correlated metabolic capacity of the subjects (cows vs calves), but also to the sensitivity of the analytical techniques used (radioimmune assay or HPLC vs HPLC/MS).

The two groups of calves treated with DEX or xylazine were very similar in terms of age, bodyweight and gender. DEX is a more potent and selective alpha-2-agonist than xylazine (Rioja *et al.* 2008), but surprisingly no differences were observed in respiration or heart rate between the two groups after treatment. The typical bradycardia induced by alpha-2-agonist developed soon after DEX and xylazine administration and lasted for the whole observation period of 20 minutes. This is due to the development of peripheral vasoconstriction and probable reflex and centrally mediated decrease in heart rate (Rezende *et al.* 2014). In calves treated with xylazine, similar cardiovascular effects were detected and the decrease in heart rate lasted for 35 minutes (Rioja *et al.* 2008). In our calves heart rate measurements were carried out for 20 minutes and the time course of bradycardia could not be monitored for longer periods.

The development of hypoxaemia has been shown with xylazine, detomidine, romifidine, and medetomidine in sheep (Celly *et al.* 1997). In our study, respiration rate was highly variable and not influenced by the treatments, however respiratory rate alone is probably not a reliable clinical indicator to detect and explain hypoxaemia in ruminants injected with an alpha-2-agonist.

The effect of alpha-2-agonists on the body temperature of ruminants is variable. We did not observe any influence of DEX or xylazine administration on the rectal temperature of our calves. Some alpha-2-agonists have been reported to cause hypothermia or hyperthermia in cattle, but the mechanism by which this is produced seems to be drug- and species-specific (Young 1979; Hall and Clarke 1991; Ranheim *et al.* 1999).

Induction and recovery times were comparable between the two groups. The onset of sedation was very rapid with both drugs and the clinical effects associated with DEX and xylazine were characterised by a similar degree of deep sedation and ease of handling of the animals. The long and



comparable duration of the sedative effect was not completely expected. Ruminants are considered to be extremely sensitive to xylazine compared to horses or dogs and cats (Plumb 2011). The young age of our calves could have influenced the metabolism and elimination of both DEX and xylazine and could explain the long sedative effect of both drugs. The recovery time (return to quadrupedal position) for calves administered medetomidine I/V at a dose of 0.03 mg/kg was reported as 242.11 (SD 108.67) minutes (Rioja *et al.* 2008), which was longer than we observed after I/V injection of DEX (80.5 (SD 30.7) minutes). For xylazine, the recovery time of 88 (SD 28.7) minutes in this study was comparable to 128.12 (SD 84.83) minutes that was reported previously (Rioja *et al.* 2008).

Induction quality was evaluated with a specific scale developed for this study. We observed a good quality of sedation with both drugs. In our opinion the scale was easy to use, specific and appropriate to determine induction quality in calves, therefore we propose its use in future studies on sedation quality in this species.

In order to obtain concentrations of DEX at the recovery time (approximately 80 minutes), these were extrapolated from the curve of the predicted concentrations and ranged from 0.16–1.09 ng/mL. However, for high lipophilic drugs, such as alpha-2-agonists, concentrations of drugs in serum do not necessarily represent concentrations at the effector site. A remote agonist-receptor interaction may occur with a serum concentration below the limit of detection (Kästner *et al.* 2003).

In conclusion, DEX induced a safe, reliable and long lasting sedation in our calves, leading to a transient decrease in heart rate and no modification in respiration rate or temperature. The results were comparable to xylazine, the most popular alpha-2-agonist among bovine practitioners. The lack of specific maximum residue levels for DEX limits its use in animals destined for human consumption, but the low dose administered and the short tissue and milk withdrawal times of all alpha-2-agonists are positive aspects which should stimulate further residual studies in cattle. In addition, the higher selectivity and potency of DEX compared to other alpha-2-agonists are further positive pharmacological aspects which could indicate the selection of this drug in the therapeutic armamentarium of calves. It should be underlined that pain management is still underestimated in calves and that there is an increasing need for new and safe analgesic molecules for this species. Thus, DEX could be used in calves for rapid procedures such as dehorning or castration, as it possesses a specific antagonist and was shown to be safe for young healthy calves.

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**Table 1. Classification of the quality of sedation used in dairy calves following treatment with dexmedetomidine or xylazine .**

<b>Degree/Level</b>	<b>Quality of sedation</b>
0	The animal is slightly sedated, quadrupedal standing.
1	The animal is uncoordinated in lying down, falling to the ground
2	The animal shows ataxia and in the act of lying down tries to stand up
3	The animal lies down in a coordinated way, pushing on the carpus and lowering the back, taking a sternal position with the head turned toward the flank

**Table 2. Mean ( $\pm$  SD) and range of pharmacokinetic parameters determined using a two-compartment model following I/V administration of 5  $\mu$ g/kg dexmedetomidine to nine dairy calves.**

Parameter	Mean $\pm$ SD	Min, Max
C0 (ng/mL)	12.1 $\pm$ 8.6	3.1, 29.9
Distribution half life (minutes)	8.7 $\pm$ 5.0 <sup>a</sup>	3.6, 18.3
Elimination half life (minutes)	83.5 $\pm$ 67.5 <sup>a</sup>	31, 317.3
Mean residence time (minutes)	87.9 $\pm$ 69.5	30.5, 242.9
Body clearance (mL/minute/kg)	27.9 $\pm$ 13.1	8.56, 42.5
AUC <sub>(0-<math>\infty</math>)</sub> (minute*ng/mL)	238.0 $\pm$ 56.2	117.6, 584.4
AUMC <sub>(0-<math>\infty</math>)</sub> (minute*minute*ng/mL)	23,494.3 $\pm$ 25,747.8	3,680.4, 73,593.6
K <sub>10</sub> (per minute)	0.05 $\pm$ 0.02	0.03, 0.08
K <sub>12</sub> (per minute)	0.03 $\pm$ 0.02	0.01, 0.08
K <sub>21</sub> (per minute)	0.02 $\pm$ 0.02	0.004, 0.05
t <sub>1/2 K10</sub> (minutes)	15.0 $\pm$ 7.4 <sup>a</sup>	7.1, 26.3
V <sub>1</sub> (mL/kg)	643.3 $\pm$ 454.0	167.6, 1615.1
V <sub>dss</sub> (mL/kg)	2,170.8 $\pm$ 1,657.5	287.6, 4,468.1
V <sub>2</sub> (mL/kg)	1,527.5 $\pm$ 1,426.0	119.9, 2,853.1
V <sub>dZ</sub> (mL/minute/kg)	5,954.6 $\pm$ 4,236.4	881.9, 9,121.2

<sup>a</sup> Harmonic mean $\pm$ pseudo-SD

C0=serum concentration extrapolated at time 0

AUC=area under serum concentration-time curve ; AUMC=area under moment curve; K<sub>10</sub>=the rate at which the drug leaves the system from the central compartment; K<sub>12</sub>=the rate at which the drug passes from central to peripheral compartment; K<sub>21</sub>=the rate at which the drug passes from peripheral to central compartment; t<sub>1/2 K10</sub>=the half-life associated with the rate constant K<sub>10</sub> ; V<sub>1</sub>=volume of distribution in the central compartment; V<sub>dss</sub>=volume of distribution at steady-state curve; V<sub>2</sub>=volume of distribution in the peripheral compartment; V<sub>dZ</sub>=volume of distribution based on the terminal phase

**Table 3. Median (min, max) quality of sedation, and mean ( $\pm$ SD) interval to induction of and recovery from sedation in dairy calves treated I/V with 5  $\mu$ g/kg dexmedetomidine (n=9) or 0.2 mg/kg xylazine (n=9) .**

	<b>Dexmedetomidine</b>	<b>Xylazine</b>
Sedation quality	3 (2–3)	3 (2–3)
Induction time (minutes)	2.7 $\pm$ 0.67	2.8 $\pm$ 0.78
Recovery time (minutes)	80.5 $\pm$ 30.7	88 $\pm$ 28.7

**Figure 1. Mean ( $\pm$ SD) concentration of dexmedetomidine in serum of nine dairy calves following I/V administration of 5  $\mu$ g/kg dexmedetomidine. Note logarithmic scale on y-axis.**

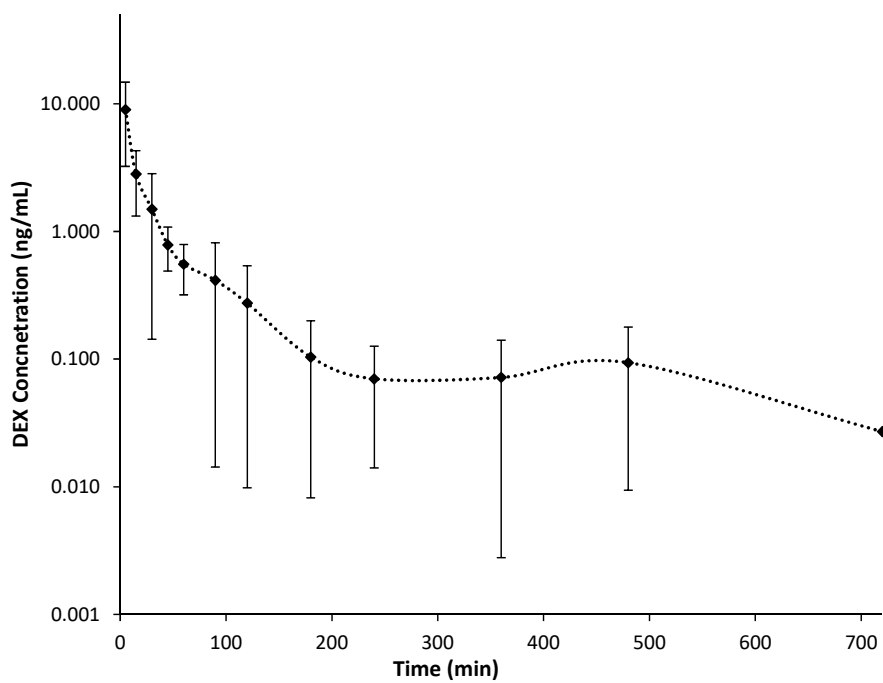




Figure 2. Mean±SD heart rate of dairy calves from 30 minutes before and 20 minutes after I/V treatment with 5 µg/kg dexmedetomidine (●; n=9) or 0.2 mg/kg xylazine (▲; n=9). \*indicates mean differs from value at 0 minutes (p<0.05).

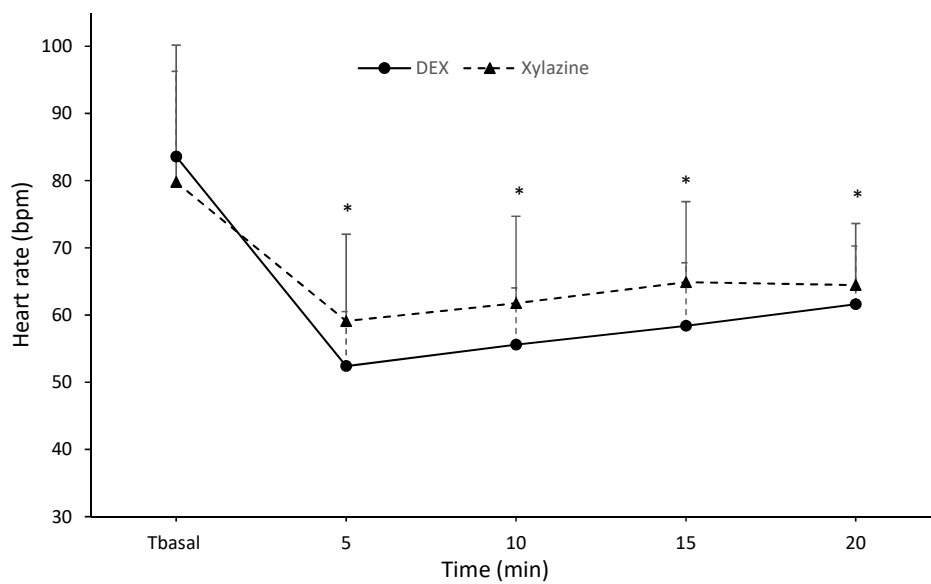


Figure 3. Mean $\pm$ SD respiratory rate of dairy calves from 30 minutes before and 20 minutes after I/V treatment with 5  $\mu$ g/kg dexmedetomidine (●; n=9) or 0.2 mg/kg xylazine (▲; n=9).

