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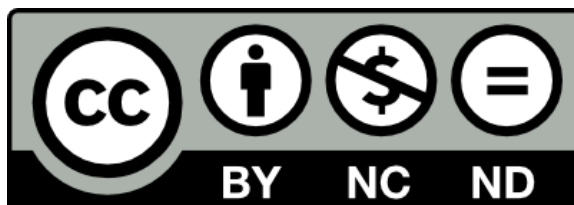
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Abstract

There is sound evidence that medetomidine is an effective analgesic for acute pain in sheep. In this study, 15 µg kg^{-1} of medetomidine was administered intravenously, and into the oesophagus, in a cross-over study, using eight sheep. Following intravenous administration, medetomidine could be detected in the plasma of these sheep for 120-180 minutes but following oesophageal administration, medetomidine could not be detected in the plasma of any sheep at any of 17 time points over four days. It is suspected that this is due to high first pass metabolism in the liver. Consequently, we conclude that future studies investigating the use of analgesics in orally-administered osmotic pumps in sheep should consider higher doses of medetomidine (e.g. > 100 µg kg^{-1}), further investigations into the barriers of medetomidine bioavailability from the sheep gut, liver-bypass drug delivery systems, or other α_2-adrenergic agonists (e.g. clonidine or xylazine).

Keywords

Sheep, analgesia, pain, oral administration, medetomidine, osmotic pump

Abbreviations

C_{max} – maximum plasma concentration

EDTA – ethylenediaminetetraacetic acid

HPLC – high performance liquid chromatography

IU – international units

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Introduction

Medetomidine is an α_2-selective adrenergic agonist that has been used in veterinary medicine as a sedative, analgesic and skeletal muscle relaxant (Posner and Burns, 2009). It is registered only for use in dogs (and cats in some countries) but it has also been investigated in horses (England and Clarke, 1996), donkeys (Lizarraga and Janovyak, 2013), cattle (Ranheim et al., 1999), pigs (Sakaguchi et al., 1992), sheep (Kästner, 2006) and a wide range of non-domestic species (Jalanka, 1989).

In sheep, medetomidine has been shown to be an effective analgesic, especially for acute pain (Lizarraga and Chambers, 2012). In 1992, Chambers demonstrated that 5 µg kg^{-1} IV of medetomidine provided a similar level of analgesia to 15 µg kg^{-1} IV of fentanyl in sheep, as assessed by nociceptive threshold testing using mechanical stimulation. These sheep were apparently healthy and were not exposed to any noxious stimuli (besides the mechanical stimulation itself) at any time during this experiment. Later, Muge et al. (1994) showed that 2-7 µg kg^{-1} IV of medetomidine raised the nociceptive threshold of similarly non-painful sheep in a dose-dependent manner. Depending on dose, this analgesic effect was detected for up to 60 minutes. In a more recent study, Murdoch et al. (2013) used osmotic pumps to demonstrate that an intraperitoneal infusion of medetomidine in sheep at 3 µg kg^{-1} h^{-1} significantly decreased pain scores for 10 hours. Moreover, this analgesia was detected independent of sedation.

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The studies by Muge et al. (1994) and Murdoch et al. (2013) show the inextricable association between the method and route of drug administration, and its duration of effect. There are a number of commercially-available orally-administered drugs for ruminants that utilise various drug delivery mechanisms to provide sustained effects. As two examples, Ivomec Maximizer® Controlled Release Capsules (Merial) and Rumensin Capsules (Elanco) are able to deliver ivermectin and monensin, respectively, into the reticulorumen for 100 days using plastic-bodied "winged" capsules with tableted cores. Methods of drug administration like these offer attractive options for the sustained-administration of analgesic drugs (e.g. α_2-agonists) to sheep.

There have been a number of studies that have reported on the pharmacokinetics and pharmacodynamics of α_2-agonists following administration into the alimentary tract in animals but the majority of these have focussed on the buccal transmucosal route of administration (Malone and Clarke, 1993; Sleeman et al., 1997; Ansah et al., 1998; Freeman and England, 1999; Ramsay et al., 2002; Slingsby et al., 2009; Gardner et al., 2010; Naples et al., 2010; DiMaio Knych and Stanley, 2011; Kaukinen et al., 2011; Vermunt et al., 2012; Hopfensperger et al., 2013). Furthermore, a commercially-available preparation of buccal transmucosal detomidine gel suitable for horses is manufactured by Orion Pharma (Orion Corporation, Finland) and is distributed by Elanco (Domosedan Gel®) in Europe and Zoetis (Dormosedan Gel®) in USA and Australia.

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In contrast to these reports on the *buccal transmucosal* absorption of α_2-agonists, other publications exist that have investigated the *gastrointestinal* absorption of four α_2-agonists: dexmedetomidine (Proctor et al., 1991; Anttila et al., 2003), detomidine (Devitt, 1989), medetomidine (Vainio, 1988) and clonidine (Davies et al., 1977; Larsson et al., 2011). We were unable to find any studies that report on the gastrointestinal bioavailability of medetomidine in sheep but the limited data available suggests that the bioavailability of α_2-agonists from the gastrointestinal system varies depending on species, α_2-agonist and the methodology of the study.

Combining all of these findings, the intriguing question can be raised as to whether an analgesic that is effective in sheep, such as medetomidine, can be delivered to sheep in a way that provides a sustained effect and is easy to administer, and additionally, is without a prohibitive suite of adverse side effects, such as excessive sedation. Our theory was that osmotic pumps containing medetomidine, administered orally to sheep, might be able to achieve these aims. Consequently, the aim of this preliminary investigation was to quantify the bioavailability of medetomidine in sheep following administration into the oesophagus.

Materials and Methods

Approval of our experimental protocol was provided by the Murdoch University Animal Ethics Committee which adheres to the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (2004).

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Eight adult merino sheep (seven ewes and one wether) of similar weight were randomly selected and purchased from a sales yard for inclusion in this study. Their ages were unknown but based on their dentition were estimated to be 2-6 years of age. Sheep were transported to Murdoch University and placed onto pasture for one week. During the study, the sheep were held in individual raised pens (1.5 x 1 m). The pens were adjacent to each other and allowed eye contact between animals. Oaten hay and water were provided *ad libitum*, and each sheep was also given approximately one kilogram of lupins at the end of each day.

A catheter (16 G, 83 mm, Becton Dickinson Angiocath, North Ryde, Australia) was placed into a jugular vein (secured with tissue glue) of each sheep at the commencement of the study. Extension sets (75 cm, priming volume 1.6 mL, BMDi TUTA Healthcare, Sydney, Australia) were then attached to the catheters and secured to the neck of each animal with an adhesive bandage. Approximately 2 mL of blood was collected from each sheep for baseline analyses. All blood samples were transferred to EDTA blood collection tubes. Collected blood was centrifuged at 2,000 x *g* for 10 min at 4 ^{o}C within 1 h of sampling. Plasma was frozen at -80 ^{o}C until analysis.

Four of the eight sheep were randomly selected and administered 15 µg kg^{-1} of medetomidine (Sedamed™, Ceva Animal Health, Australia, 1mg mL^{-1}) IV in the opposite jugular vein at zero minutes. At 1, 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 90, 120, 240 and 360 minutes, approximately 5 mL of blood was collected from the jugular catheter

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and held in a syringe. A separate syringe was then used to collect an additional 2 mL of blood. The initial aspirate of blood, which was being held in the first syringe, was then injected back into the jugular vein. Withdrawn blood was always auto-transfused within 15 seconds of collection. The catheter was then flushed with 5 mL of heparinised saline (5 IU mL^{-1}).

The remaining four sheep were administered 15 µg kg^{-1} of medetomidine (Zalopine®, Orion Corporation Animal Health, Turku, Finland, 5 mg mL^{-1}, diluted to 0.3 mg mL^{-1} with isotonic saline) into an 8 FG 500 mm sterile canine urinary catheter (Henry Schein, New York, USA) which in turn was in the lumen of the tube from a Magrath calf feeder (Springer Magrath, Minnesota, USA) that had been positioned into the oesophagus (see Figure 1). Drug was administered at zero minutes and urinary catheters were then immediately flushed with 20 mL of isotonic saline before the urinary catheter and Magrath calf feeder tube were removed from each animal's oesophagus. Blood was collected using the same method previously described for the IV group. Blood samples were collected at 0, 30, 60 and 90 min, then at 2, 3, 4, 5, 6, 12 and 24 h, and at 2, 3, 4 and 5 d. On day 8, following a one week washout period, the two groups of four sheep were crossed over and the experiment was repeated. To calculate bioavailability, the area under the plasma drug concentration-time curve (AUC) following oesophageal administration was divided by AUC following intravenous administration.

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To confirm the presence of medetomidine in the preparation we used, and to determine if the urinary catheter altered the concentration of medetomidine that passed through it, diluted medetomidine (Zalopine®, diluted to 0.3 mg mL^{-1} using isotonic saline) was flushed through two urinary catheters into two plain glass tubes (0 h). Two more urinary catheters were filled with diluted medetomidine but samples were not collected from these catheters until 24 h later (24 h). The concentrations of medetomidine were then compared to diluted medetomidine that had not been exposed to a urinary catheter (pre-catheter).

Samples were prepared and analysed using a method of medetomidine detection that has been validated for selectivity, recovery, precision, linearity and limits of detection (Netto et al., 2011). Briefly, samples were extracted by solid phase extraction (SPE) using 30 mg Bond Elut Plexa (Varian Inc., Palo Alto, USA) 1 mL cartridges. Standards and samples were injected individually in 1 µL volumes into an Agilent 1100 HPLC (Agilent Technologies, Santa Clara, CA, USA). The analytical column used was a Pursuit XRs Ultra diphenyl (Varian Inc.) with dimensions of 30 mm x 2.0 mm x 3 µm. The HPLC was coupled to an Agilent Classic series ion trap mass spectrometer with an electrospray ionization source (Agilent Technologies) in positive ionization mode. Tandem mass spectrometry (MS/MS) of medetomidine was carried out using the transition *m/z* 201 → 95.

The heart rate, respiratory rate, rectal temperature, frequency of rumen contractions, recumbency and demeanour of the sheep were also recorded. Demeanour was assessed subjectively by three veterinarians experienced in large animal medicine (THH, GCM & FRM) as being alert and responsive, quiet and responsive, mildly sedated, moderately sedated or heavily sedated. To investigate the effect that medetomidine had on heart rate and respiratory rate, data were tested for normality using a Shapiro-Wilk test and statistically significant differences between the time = 0 data points and subsequent data points were analysed using a Kruskal-Wallis One Way Analysis of Variance (ANOVA) on Ranks.

To investigate the possibility that a low bioavailability following oesophageal administration might not be determined because the 15 µg kg^{-1} dose was too low, one sheep was chosen at random and was administered 50 µg kg^{-1} into its oesophagus as described earlier (Figure 1). The sheep was closely monitored for any clinical effects and then one hour later, the sheep was administered 100 µg kg^{-1} by the same route. Blood samples were not collected following these additional doses.

Results

The mean (SD) bodyweight of the sheep was 59 (5.9) kg and none of the sheep showed any overt signs of ill health at any stage of the study.

Plasma concentrations of medetomidine following intravenous administration of 15 µg kg^{-1} of medetomidine are shown in Figure

2A. The drug could not be detected in the plasma of more than two of the eight sheep after 120 minutes. Following oesophageal administration, plasma medetomidine could not be detected in any sheep at any of the 17 post-administration sampling time points (Figure 2B). The calculated bioavailability following the oesophageal administration of medetomidine was equal to zero.

The lower limits of quantification and detection of our assay for medetomidine were both 0.2 ng mL^{-1}. The urinary catheter did not appear to adsorb medetomidine as the concentrations of drug in the pre-catheter, 0 h and 24 h catheter samples were all 0.3 mg mL^{-1}.

Both heart rate and respiratory rate data were non-normally distributed. Following intravenous administration of medetomidine, the heart rate was significantly lower ($P < 0.05$) than baseline (t=0) values at 4, 10, 15, 20 and 30 min (Table 1). Respiratory rate was not significantly lower than baseline (t=0) values at any measured time point (Table 1). Moderate sedation and associated recumbency were seen in all eight sheep. Following drug administration, the median (interquartile range) times to recumbency and then standing were 1.75 min (1.0-3.8) and 59 min (39.8-97.5) respectively. Rectal temperature did not change by more than 0.7 °C in any sheep (median change = 0.35 °C increase) in the six hours following drug administration and the lowest and highest temperatures recorded in any sheep were 38.5 °C (median = 39.05 °C) and 39.9 °C (median = 39.2 °C), respectively. Ruminal contractions occurred at frequencies of zero, one or two per minute in the six hours following drug

administration. Only in one sheep were no ruminal contractions detected on more than one occasion but this was for less than 3.5 h.

Following oesophageal administration of medetomidine, both the heart rate and respiratory rate were not significantly different ($P > 0.05$) to baseline (t=0) values (Table 2). Neither sedation, nor associated recumbency, was observed in any sheep. Rectal temperature did not change by more than 1.4 °C in any sheep (median change = 0.5 °C increase) in the four days following drug administration and the lowest and highest temperatures recorded in the sheep were 38.3 °C (median = 38.6 °C) and 39.7 °C (median = 39.2 °C), respectively. Ruminal contractions occurred at frequencies of zero, one or two per minute in the four days following drug administration. The absence of ruminal contractions was not detected in any sheep on more than one occasion during this time.

Following the administration of two higher doses of medetomidine into the oesophagus of a single sheep, 50 µg kg^{-1} and then one hour later, 100 µg kg^{-1}, no observable signs of sedation were seen at any time.

Discussion

The aim of this study was to investigate the bioavailability of medetomidine in sheep after oesophageal administration. Our results did not demonstrate any bioavailability in eight sheep following the administration of 15 µg kg^{-1} by this route. The pharmacokinetics of medetomidine following intravenous administration to sheep has been reported by others (Muge et al.,

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1996; Ranheim et al., 2000), so detailed pharmacokinetic analysis was not performed in this study. This analysis could not be performed following oesophageal administration due to the lack of any detectable plasma concentrations.

To ensure our study was able to meet its objective of assessing the bioavailability of medetomidine following oesophageal administration in sheep, we chose a drug administration method that would prevent any medetomidine from contacting the buccal mucosa. Arguably, direct administration into the reticulorumen by a longer feeding tube may have been more appropriate as this would remove any possibility of oesophageal transmucosal absorption. It is theoretically possible that the medetomidine and saline placed into the oesophagus did not rapidly move distally (aborally) into the rumen. If this occurred, then this would provide longer contact time between the drug and the oesophageal mucosa. It is unknown what impact this had on our results. To accommodate for the possibility of flip-flop kinetics (where drug half-life is limited by absorption and not elimination rate), we sampled blood for five days after medetomidine was administered into the oesophagus. This decision was based on previous work with clonidine in humans. Clonidine has reliable gastrointestinal bioavailability in humans and it has been demonstrated that blood sampling over 48 hours was necessary to accurately measure the area under the plasma drug concentration-time curve (AUC) for this drug (Anavekar et al., 1982). For this reason, we settled on five days as a conservative length of time for our study.

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In our study, medetomidine was diluted to 0.3 mg mL^{-1} such that a higher volume could be administered into the oesophagus of each sheep. However, it was necessary to use a preparation of medetomidine (Zalopine®, 5 mg mL^{-1}) that, when undiluted, would be suitable for a low-volume osmotic pump which itself would be needed for subsequent studies if evidence of bioavailability was shown from this route of administration.

This study is the only work we are aware of that has investigated the bioavailability of medetomidine administered into the oesophagi of sheep. Vainio (1988) described unpublished work by Virtanen that investigated the oral administration of medetomidine in dogs. It was concluded that only doses that were at least 100-fold higher than parenteral doses produced a pharmacological effect. It was speculated for this species that this poor oral bioavailability was due to first pass metabolism in the liver and the presence of intestinal contents. Other studies have analysed the gastrointestinal bioavailability of the D-isomer of medetomidine, dexmedetomidine. Proctor et al. (1991) dissolved 10 or 20 µg kg^{-1} (concentration not defined) of dexmedetomidine into saline and then orally administered this to dogs in gelatin capsules. A number of haemodynamic parameters, including heart rate and cardiac output, were significantly reduced for up to four hours. Although blood concentrations of dexmedetomidine were not measured in this study, this work provides evidence of the gastrointestinal bioavailability of dexmedetomidine in dogs. In humans, it has been reported that dexmedetomidine has an oral bioavailability of 16%

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but in this study, the injectable preparation was swallowed in 150 mL of water and so the possibility that some (or most) of the drug was absorbed transmucosally in the mouth cannot be excluded. It is problematic to compare the present study to the previous work performed in dogs and humans. Not only would differences be expected between species but these differences would likely be even greater when comparing omnivorous species with simple alimentary tracts (e.g. dogs and humans) to herbivorous species with alimentary tracts containing complex populations of microbiota (e.g. sheep).

The impact that ruminal contents (e.g. ingesta and microbes) had on the bioavailability of medetomidine cannot be determined from this study. Future studies should consider catheterisation of the portal and hepatic veins and collection of faecal samples. If medetomidine concentrations were measured in these sampling spaces, then information explaining the low (nil) bioavailability may be obtained. High concentrations of faecal medetomidine with low venous (hepatic and portal) concentrations might suggest that absorption from the alimentary tract, between the oesophagus and the rectum, was not occurring. If high portal vein concentrations of medetomidine were detected in concert with low concentrations in the hepatic vein, then this would indicate that pre-systemic hepatic metabolism was causing the low hepatic vein drug concentrations. Experiments using these methods have been performed for some time in sheep, mainly in biochemistry studies (Annison et al., 1957; Lewis et al., 1957; Bergman and Wolff, 1971). For a more detailed

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discussion on the factors that affect oral bioavailability, the interested reader is referred to the review by Kwan (1997).

An *in vitro* study could also be considered to estimate the intrinsic hepatic clearance of medetomidine in sheep. Studies like these have been performed in herbivorous species before (Kimble et al., 2014) but results from such studies may not be clinically relevant as other factors, only seen *in vivo*, also influence hepatic metabolism (Iwatsubo et al., 1997).

Our study has shown that 15 μg kg^{-1} of medetomidine administered into the oesophagus of sheep is inadequate to achieve detectable (above 0.2 ng mL^{-1} in this study) plasma concentrations. Moreover, medetomidine doses, by this route of administration of up to 100 μg kg^{-1} were insufficient to cause observable signs of sedation in one sheep. To further develop the concept of a slow release device/osmotic pump in the reticulorumen, we have three recommendations for future work into this area.

Firstly, higher doses of the existing preparations of medetomidine could be considered. For this, animals should be closely supervised, and supplementary oxygen and an α_2-adrengeric antagonist (atipamezole) should be available. Increasing doses could then be carefully administered to sheep to estimate the dose range required to achieve sedation by this route of administration. Sedating doses could then provide the basis for a starting dose that would be appropriate for a pharmacokinetic study.

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Secondly, further work could be performed to better define the reason behind the poor bioavailability of medetomidine delivered into the oesophagus of sheep. To investigate the possibility that it was due to pre-systemic hepatic metabolism, an altered drug formulation could be considered. Two liver-bypass drug delivery systems were developed and then validated for propranolol, which has a high first-pass effect (Barnwell et al., 1992). In this study, a 6-fold increase in the AUC and a 4-fold increase in C_{max} were demonstrated using a mixture of unsaturated fatty acids (mainly oleic acid) and surfactants in enteric-coated liquid-filled hard gelatin capsules. Medetomidine and propranolol are both alkaline lipophilic drugs, and so the bioavailability of medetomidine by the oesophageal route may be improved using this strategy.

Thirdly, a different drug could be used. Xylazine is an α_2-agonist that is already registered for sheep (but only by injection) and may have better bioavailability than medetomidine following administration into the oesophagus. Clonidine is another α_2-agonist that could be considered. Although its pharmacokinetics, analgesic efficacy and safety have not been investigated in sheep, its reliable oral bioavailability in humans (Davies et al., 1977) makes it an intriguing option.

Conclusions

Our goal was to investigate the possibility that a recognised analgesic of sheep, medetomidine, could be administered in a way that would not require injection and could provide effects that were

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sustained over several days. The bioavailability of 15 μg kg^{-1} of

medetomidine administered into the oesophagus of sheep was zero.

Further investigation is needed to find a broadly-applicable

sustained-effect analgesic suitable for sheep.

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Figure Captions

Figure 1 Oesophageal administration of medetomidine in a sheep. A Magrath calf feeder was positioned into the oesophagus of the sheep and a 500 mm canine urinary catheter was then advanced through the lumen of the Magrath calf feeder. Drug was then administered into the urinary catheter. The catheter was then flushed with isotonic saline.

Figure 2A Mean (±SD, where applicable) plasma medetomidine concentration following the intravenous (IV) administration of 15 µg kg^{-1} to eight adult sheep. Plasma medetomidine could only be detected in two sheep at 150 and 180 minutes and no sheep at 240, 300 and 360 minutes.

Figure 2B Plasma medetomidine concentration following the oesophageal administration of 15 µg kg^{-1} to eight adult sheep. The lower limit of detection of

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medetomidine was 0.2 ng mL^{-1} but plasma concentrations that could not be

detected are displayed as 0 ng mL^{-1}.

Tables

Time (min)	Heart Rate (beats min^{-1})	Respiratory Rate (breaths min^{-1})
0	72 (59-86)	43 (32-59)
4	42 (36-47)*	29 (21-57)
10	40 (37-47)*	36 (25-59)
15	44 (36-47)*	26 (21-39)
20	44 (36-47)*	20 (20-38)
30	41 (40-51)*	27 (20-44)
45	48 (41-54)	28 (24-42)
60	44 (44-51)	24 (21-31)
90	48 (45-57)	24 (21-30)
120	49 (48-55)	24 (20-26)
150	48 (48-54)	26 (21-30)
180	50 (48-60)	24 (20-27)
240	56 (52-60)	24 (22-30)
300	60 (57-60)	23 (20-37)
360	56 (52-60)	26 (20-35)

Table 1 Median (interquartile range) heart rate and respiratory rate following the intravenous (IV) administration of 15 µg kg^{-1} of medetomidine to eight sheep.

*Significantly ($P < 0.05$) different from baseline values.

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Time	Heart Rate (beats min⁻¹)	Respiratory Rate (breaths min⁻¹)
0	76 (69-84)	44 (25-69)
60 min	60 (48-72)	48 (28-66)
120 min	60 (53-66)	44 (32-84)
4 h	62 (57-70)	33 (25-48)
6 h	61 (59-66)	38 (34-45)
12 h	61 (60-68)	38 (30-44)
24 h	66 (64-69)	37 (31-60)
2 d	64 (64-67)	37 (29-52)
3 d	70 (60-76)	39 (36-47)
4 d	70 (58-72)	43 (37-51)

Table 2 Median (interquartile range) heart rate and respiratory rate following the oesophageal administration of 15 µg kg⁻¹ of medetomidine to eight sheep.
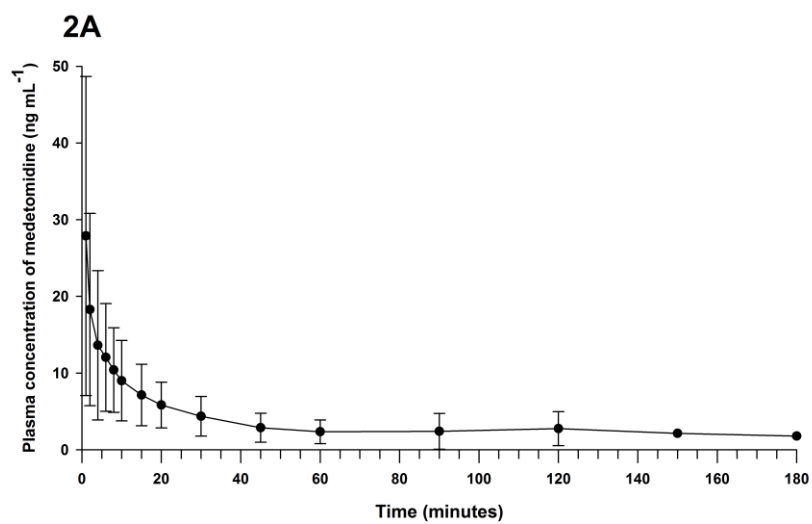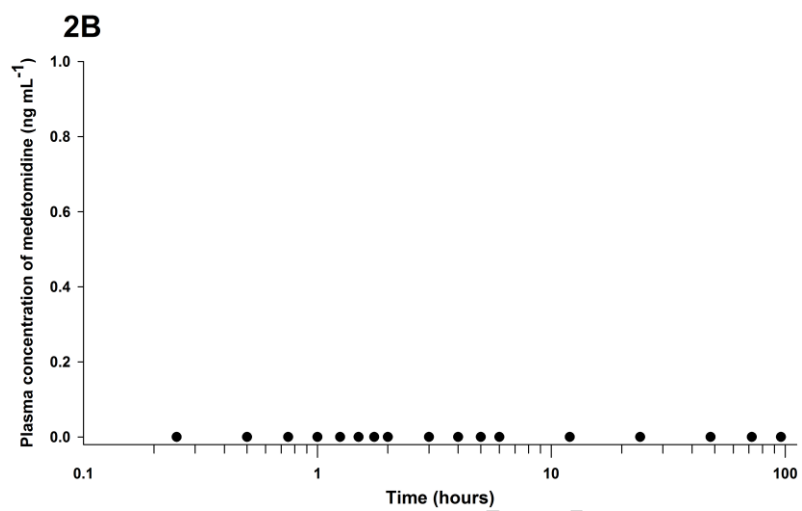
Figure 1

2A

Figure 2A

Figure 2B

Highlights

- $15~\mu g~kg^{-1}$ of medetomidine was administered into the oesophagus of eight sheep
- Bioavailability could not be demonstrated following this route of administration
- Ruminal contents (microbes and ingesta) and/or the first pass effect may have contributed to this
- Future research should consider alternative α_2-agonists for this route of administration
- Higher doses of medetomidine, administered cautiously, could also be considered