A pharmacokinetic study including some relevant clinical effects of medetomidine and atipamezole in lactating dairy cows

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Medetomidine is the most potent and selective α_2-agonist used in veterinary medicine and its effects can be antagonized by the α_2-antagonist atipamezole. The pharmacokinetics of medetomidine and atipamezole were studied in a cross-over trial in eight lactating dairy cows. The animals were injected intravenously (i.v.) with medetomidine (40 μg/kg) followed by atipamezole i.v. (200 μg/kg) or saline i.v. after 60 min. Drug concentrations in plasma were measured by HPLC. After the injection of atipamezole, the concentration of medetomidine in plasma increased slightly, the mean increment being 2.7 ng/mL and the mean duration 12.1 min. However, atipamezole did not alter the pharmacokinetics of medetomidine. It is likely that the increase in medetomidine concentration is caused by displacement of medetomidine by atipamezole in highly perfused tissues. The volume of distribution at steady state (V_{ss}) for medetomidine followed by saline and medetomidine followed by atipamezole was 1.21 and 1.32 L/kg, respectively, whereas the total clearance (*Cl*) values were 24.2 and 25.8 mL/min·kg. V_{ss} and *Cl* values for atipamezole were 1.77 mL/kg and 48.1 mL/min·kg, respectively. Clinically, medetomidine significantly reduced heart rate and increased rectal temperature for 45 min. Atipamezole reversed the sedative effects of medetomidine. However, all the animals, except one, relapsed into sedation at an average of 80 min after injection of the antagonist.

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INTRODUCTION

The α_2-adrenoceptor agonists have been widely used as sedatives, immobilizing agents and analgesics in veterinary medicine for more than two decades. Medetomidine is the most potent and selective of these, and its clinical effects can be reversed by atipamezole, the most selective α_2-adrenoceptor antagonist currently known (Virtanen *et al.*, 1989). This agonist-antagonist combination has been successfully used for reversible immobilization of both domestic and wild animals, including ruminants (Jalanka, 1993). Recently, we described the pharmacokinetics and certain clinical effects of medetomidine and atipamezole in reindeer and dairy calves (Ranheim *et al.*, 1997; Ranheim *et al.*, 1998). The pharmacokinetics of medetomidine have also been determined in sheep (Muge *et al.*, 1996) and in dogs, cats and rats (Salonen, 1989) using tritium-labelled drug.

An interaction between medetomidine and atipamezole in dogs was first described by Salonen *et al.* (1995). In that study, the administration of atipamezole increased clearance of medetomidine from 21.2 to 30.5 mL/min·kg. We did not find evidence for such an interaction in dairy calves, where atipamezole injected intravenously (i.v.) increased the mean residence time for medetomidine due to an increase in the plasma concentration of medetomidine (Ranheim *et al.*, 1998). A similar increase in medetomidine concentration was also observed in reindeer when atipamezole was injected i.v. (Ranheim *et al.*, 1997). The aim of the present study was to describe the pharmacokinetics of medetomidine administered alone and medetomidine followed by atipamezole in lactating dairy cows. Clinical effects were recorded in order to determine if the drug combination could be suitable for use in cows.

MATERIALS AND METHODS

Experimental animals

Eight dairy cows with a mean (SD) weight of 590 (42) kg and a mean daily milk yield of 25.4 (5.4) kg were included in the

study. The animals were found to be healthy by clinical examination. They were not treated with any drugs for 2 weeks prior to the experiments. The animals were stalled in a conventional tie stall barn, and kept there for the duration of the experimental period. Food and water were not restricted during the study period, but the cows were not permitted to eat grain the same morning as the experiments took place. The study was approved by the Norwegian Animal Research Authority.

Drug treatments and study design

The design of the study was a cross-over trial in which each animal received the following treatments: medetomidine, 40 μg/kg i.v. (Domitor® 1 mg/mL, Orion Corporation Animal Health, Turku, Finland), followed by atipamezole, 200 μg/kg i.v. (Antisedan® 5 mg/mL, Orion Corporation) after 1 h, or medetomidine (40 μg/kg i.v.) followed by saline (i.v., volume equal to volume of atipamezole injected) after 1 h. The treatment order in each animal was randomized and the wash-out period between experiments was 2 weeks.

Blood sampling

One day prior to the experiments, a catheter (Secalon® T, gauge 16) with an extension tube was placed in the left jugular vein and flushed with heparinized saline. The catheters and extension tubes were used to sample blood and rinsed with 2.5 mL of heparinized saline after each sampling to keep blood from clotting in the catheter and tube. The same volume was discarded before blood was subsequently collected. Medetomidine, atipamezole and saline were injected into the right jugular vein.

Samples of blood (10 mL) were drawn into heparinized tubes before and at 5, 10, 15, 25, 35, 45, 55, 65, 70, 75, 85, 95, 105, 120, 135, 150, 180, 210, 240, 270, 300, 360, 420 and 480 min after the injection of medetomidine. Plasma was separated by centrifugation for 10 min at 1500 × ***g*** and stored at −70 °C until assayed.

Drug analysis

Medetomidine and atipamezole were detected using a high-performance liquid chromatography method (HPLC) as previously described by Ranheim *et al.* (1998). The limits of detection were ≈ 2.5 and 5 ng/mL for medetomidine and atipamezole, respectively. The analytical method has been validated and demonstrated to be linear within the detected concentration range. The coefficients for interassay repeatability were 13.5% for medetomidine and 7.1% for atipamezole. The intra-assay repeatability was 4.5% for medetomidine and 5.2% for atipamezole.

Clinical variables

Heart rate, respiratory rate and rectal temperature were recorded before and at 15 min intervals up to 125 min after the injection of medetomidine in the saline treated group. Sedative effects of medetomidine were evaluated by recording the time (min) from injection of medetomidine until the animals were deeply sedated, recumbent and apparently unable to lift their heads ('down'), and the time (min) until the animals spontaneously regained their feet ('on-feet'). The effects of atipamezole were evaluated by recording the time (min) from the injection until the animals were 'on-feet', the time (min) elapsing until resedation occurred and the total time (min) the animals remained resedated. Resedation was also evaluated in a more subjective manner by observing signs such as reduced alertness, head drooping and recumbency. Resedation ended when the cows were normal and alert, responding as an untreated animal would when approached and handled. The same two persons carried out all observations. The animals were supported so that they would remain in sternal recumbency. The cows were observed for 7 h after the injection of atipamezole or saline.

Pharmacokinetic analysis

Noncompartmental models were used in pharmacokinetic analysis. The pharmacokinetic parameters were calculated using the software WinNonlin® version 1.1 (Scientific Consulting Inc., Cary, NC, USA 1996).

Areas under the zero-moment plasma concentration–time curve (*AUC*) and the area under the first-moment plasma concentration–time curve (*AUMC*) were calculated using the linear trapezoidal method. The elimination half-life was determined using the equation $t_{½} = ln2/\lambda_z$, where λ_z is the elimination rate constant. Total clearance (*Cl*) was estimated by the formula $Cl = \text{Dose}/AUC$. Mean residence time (*MRT*) was calculated using the formula $MRT = AUMC/AUC$ and volume of distribution at steady state (V_{ss}) by $V_{ss} = \text{Dose}\ MRT/AUC$. The number of points used to calculate λ_z for medetomidine followed by atipamezole ranged from 3 to 10. The R^2 for the regression ranged from 0.78 to 0.99.

Statistical analyses

The pharmacokinetic parameters were compared using a Wilcoxon signed rank sum test, two-tailed. The ANOVA model used in the analysis of heart rate, respiratory rate and rectal temperature provided an overall test for differences in time. A Bonferroni correction factor was used to account for repeated measures in the study. Differences were considered significant when $P < 0.05$.

RESULTS

In all the cows there was an increase in the medetomidine concentration in plasma when atipamezole was injected. The mean increase was 2.7 (1.4) ng/mL and occurred at a maximum of 5 min after the injection of atipamezole, except in one animal in which the maximum increase occurred at 10 min. The mean length of time elapsing before medetomidine had returned to pre-atipamezole levels was 12.1 (6.4) min. The

disposition curves for medetomidine followed by atipamezole, medetomidine followed by saline and atipamezole are shown in Fig. 1.

The pharmacokinetic parameters of medetomidine and atipamezole are presented in Table 1. There were no significant differences between the pharmacokinetic parameters of medetomidine followed by saline, and medetomidine followed by atipamezole. The elimination half-life and mean residence time of atipamezole was slightly shorter than those of medetomidine when followed by atipamezole. However, there was considerable interindividual variation in these pharmacokinetic parameters. Unfortunately, one animal had to be excluded from the medetomidine-atipamezole data due to extravascular injection of atipamezole.

When medetomidine was injected i.v., the animals became maximally sedated within 1.7 (1.6) min. The average time until the animals were 'on-feet' when allowed to recover spontaneously, was 180 (60) min. The cows were considered normal and alert 433 (67) min after medetomidine was injected. When atipamezole was injected i.v. 60 min after medetomidine, the mean (SD) time until the animals were fully alert, was 1.8 (0.4) min. All the animals, except one, relapsed into sedation at an average of 80 (28) min after reversal. The resedation period lasted 151 (41) min. Three animals showed slight excitation for a few minutes when atipamezole was injected.

Heart rate fell significantly after the injection of medetomidine, for a period up to 125 min after the administration of the drug. Rectal temperature increased for 45 min. The change in respiratory rate was quite variable. The plots of heart rate, respiratory rate and rectal temperature vs. time after medetomidine injection are shown in Fig. 2.

DISCUSSION

In this study, the rise in medetomidine concentration was smaller and the duration of the increase shorter, than in a similar study in dairy calves in which the same doses and

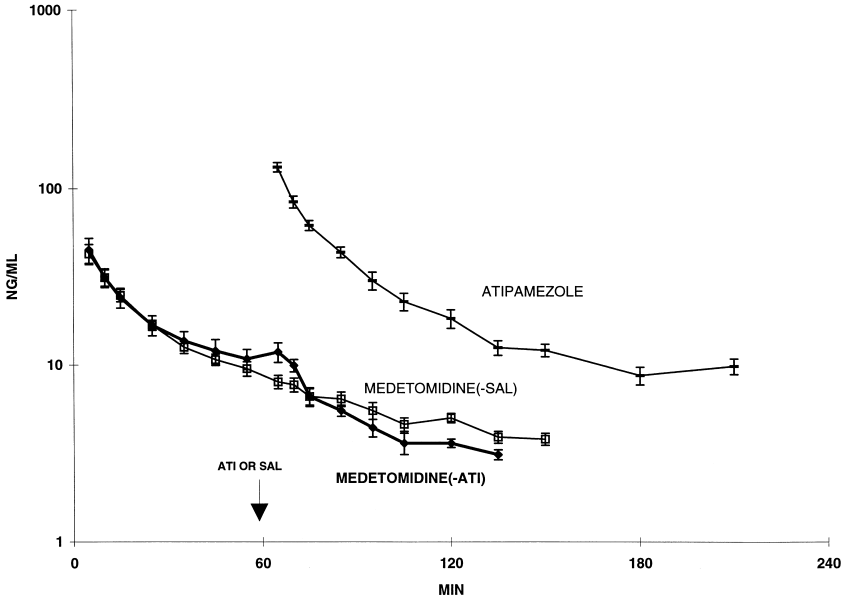

Fig. 1. Mean (± SEM) plasma medetomidine followed by saline or atipamezole and atipamezole concentrations vs. time after i.v. administration of 40 μg medetomidine/kg and 200 μg atipamezole/kg. Atipamezole or saline was injected after 60 min.

Table 1. Pharmacokinetic parameters of medetomidine and atipamezole in lactating dairy cows administered 40 μg medetomidine/kg i.v., followed by 200 μg atipamezole/kg or saline i.v. after 60 min. Mean (SD) values are given

	Medetomidine i.v. followed by saline after 1 h	Medetomidine i.v. followed by atipamezole i.v. after 1 h	
Parameter	medetomidine $n = 8$	medetomidine $n = 7$	atipamezole $n = 7$
λ_z (min^{-1})	0.0226 (0.0176)	0.0220 (0.0133)	0.0228 (0.0076)
$t_{½}$ λ_z (min)	52.7 (25.3)	41.6 (20.9)	35.2 (17.9)
AUC (ng·min/mL)	1759 (395)	1875 (777)	4363 (912)
AUMC (ng·min^2/mL)	131922 (69761)	109679 (71030)	172034 (84980)
MRT (min)	72.7 (30.7)	55.3 (17.0)	38.3 (15.7)
Vss (L/kg)	1.21 (0.32)	1.32 (0.49)	1.77 (0.64)
Cl (mL/min·kg)	24.2 (6.5)	25.8 (13.7)	48.1 (13.1)

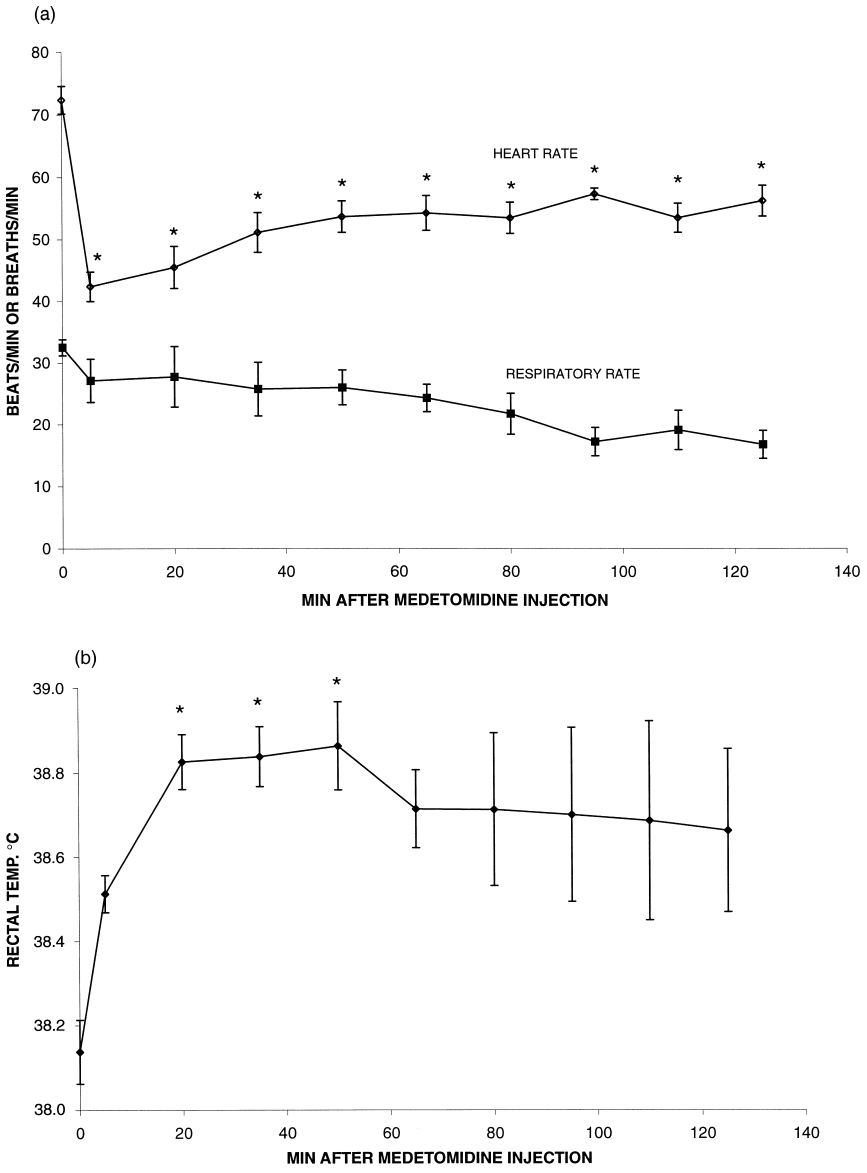

Fig. 2. Mean (± SEM) of eight animals. (a) Changes in heart rate and respiratory rate and (b) rectal temperature after i.v. administration of 40 μg medetomidine/kg to lactating dairy cows. Significant differences from baseline are indicated with *.

sampling schedules were used (Ranheim *et al.*, 1998). In a pharmacokinetic study in reindeer the plasma concentration of medetomidine increased after injection of atipamezole i.v. to the same extent as in the dairy calf study (Ranheim *et al.*, 1997). The *AUC* and the *AUMC* were larger in the lactating dairy cow than in the calf. This is reflected in the larger *MRT* values in cows when medetomidine was followed by saline, which was 40.2 min longer than the corresponding value in calves. The clearance of medetomidine followed by saline in cows (24.2 mL/min·kg) was also lower than the value reported in calves (33.1 mL/min·kg). Salonen *et al.* (1995) described an increase in clearance of medetomidine when atipamezole was subsequently injected in dogs from 21.2 to 30.5 mL/min·kg. No such interaction was observed in this study or in the previous pharmacokinetic study of medetomidine and atipamezole in dairy calves (Ranheim *et al.*, 1998).

Medetomidine is extensively distributed in highly perfused tissues such as brain, liver, kidney, adrenal glands and lungs. A large fraction of the dose is found in these tissues 0.3–0.5 h after the injection of medetomidine to rats (Salonen, 1992). Atipamezole most likely displaces medetomidine from these tissues, thereby increasing the concentration in plasma.

Medetomidine injected i.v. resulted in a maximum sedation level within 2 min. When subsequently injected with saline after 60 min, the animals showed residual sedative effects of medetomidine as long as 7.2 h, which was nearly 5 h past the time point where medetomidine could no longer be detected in plasma.

Atipamezole i.v. effectively reversed the sedation within 2 min. However, as in dairy calves and reindeer, all the animals relapsed into sedation at a time when medetomidine could no longer be detected in plasma. At this high dose of medetomidine there seems to be a lack of correlation between the plasma concentration of the agonist and the sedative effects in the bovine. When sheep were injected with 15 μg medetomidine/kg, the level of sedation was reported to decline in parallel with the

plasma concentration (Muge *et al.*, 1996). However, the duration of the effect seems to be dose-related. This dose dependent duration is also described in dogs injected with medetomidine (Vainio, 1989; Pypendop & Verstegen,1998).

As medetomidine and atipamezole are highly lipophilic drugs, they equilibrate rapidly across the blood–brain barrier and other well perfused tissues. Usually, the time delay in effect of lipophilic drugs is minimal in such tissues. A slow elimination from the brain is described in rats, in which the elimination of radiolabelled medetomidine paralleled that in plasma, but levelled off later (Salonen, 1989). It seems likely that the kinetics of the drug-receptor complex are poorly reflected in the plasma pharmacokinetics.

α_2-Agonists are known to reduce heart rate, an effect which is reported to be caused by both central and peripheral mechanisms (McGrath *et al.*, 1982; Bryant *et al.*, 1998). In the present study, heart rate fell significantly from the baseline value and was reduced during the entire observation period of 125 min. The duration of cardiovascular effects of α_2-adrenoceptor agonists are dose-dependent and are described by various researchers (Campbell *et al.*, 1979; Celly *et al.*, 1997b; Bryant *et al.*, 1998; Pypendop & Verstegen,1998). The magnitude of these effects is generally considered to be dose-dependent (Kallio *et al.*, 1989; Savola, 1989). However, this has recently been questioned by Pypendop & Verstegen (1998), who reduced the recommended dosage of medetomidine in dogs up to six times without significantly influencing the cardiovascular effects.

Different α_2-agonists are known to induce hypoxaemia in sheep and cattle and the mechanism by which this effect occurs has been investigated in sheep by Celly *et al.* (1997a), who found that both central and peripheral mechanisms were involved. After administration of the α_2-agonist clonidine to sheep they observed an initial period of apnoea, followed by increased respiratory rate. At the same time PaO_2 was significantly lowered. We found a variable respiratory rate. This was also described in a study in sheep administered medetomidine and ketamine, in which the animals also developed hypoxaemia (Tulamo *et al.*, 1995). The α_2-induced hypoxaemic response in ruminants is well documented (De Moor & Desmet, 1971; Eisenach, 1988; Celly *et al.*, 1997b). Celly *et al.* (1997b) found that the hypoxaemia observed in sheep was not caused by hypoventilation, as no increase in $PaCO_2$ was observed after the administration of medetomidine or other $\alpha_2$agonists. Respiratory rate alone is therefore probably of limited value as a clinical parameter in ruminants injected with an α_2-agonist.

Most α_2-agonists have been reported to cause hypothermia, but the mechanism by which this is produced seems to be drug and species-specific (Hall & Clarke, 1991). At high ambient temperatures, hyperthermia also develops (Jalanka & Röken,1990). In this study, the cows rectal temperature increased during the observation period. It is possible that the lactating dairy cow, which has a high metabolic activity and a small body surface relative to body mass, is more prone to develop hyperthermia than smaller species.

Atipamezole injected i.v. effectively reversed the sedative effects of medetomidine, but all the animals, except one, relapsed into sedation. It is possible that the dose of atipamezole relative to medetomidine (5 : 1) used in this study and in several others is too low for persistent reversal in the bovine. Arnemo & Søli (1993, 1995) used 2 mg atipamezole per mg medetomidine in free-ranging cattle and reported resedation after 1–2 h or 3–4 h following the injection of atipamezole by the i.v. or intramuscular (i.m.) route, respectively. It is also possible that the distribution of atipamezole is less effective when injected i.v. A relapse into sedation when atipamezole was injected i.v. has previously been reported (Jalanka, 1989; Ranheim *et al.*, 1997; Ranheim *et al.*, 1998). As three of the animals exhibited excitation for a few minutes after the injection of atipamezole, we would not recommend that a higher dose be used by the intravenous route. A sympathetic activation was also evident in human volunteers who received atipamezole i.v. after sedation with dexmedetomidine (Scheinin *et al.*, 1998), and in different animal species when atipamezole was injected i.v. (Jalanka & Röken,1990).

In this study, medetomidine induced a reliable and long-lasting sedation in cattle. The medetomidine dose of 40 μg/kg is in the upper dose range for cattle. A smaller dose would probably be sufficient to sedate an animal not experiencing stress or pain, but in a clinical situation, this is unusual (Lumb & Jones,1996). Also, for the chemical capture of free-ranging cattle, the dose of medetomidine is reported to be as high as 60–80 μg/kg (Arnemo & Søli, 1995). Although a high dose of medetomidine was used to facilitate drug analysis, side-effects, such as bradycardia and increased rectal temperature, did not represent clinical problems in these healthy cows. However, it is possible that such adverse effects could be clinically significant in sick animals.

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