# COMPARISON OF THE EFFECTS OF ATIPAMEZOLE AND TOLAZOLINE ON ANALGESIA, CARDIOPULMONARY AND RECTAL TEMPERATURE CHANGES INDUCED BY LUMBOSACRAL EPIDURAL INJECTION OF MEDETOMIDINE IN GOATS

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## ABSTRACT

*The present study was carried out in order to compare the reversing effects of $a_2$-adrenergic receptor blockers, atipamezole and tolazoline on analgesia, cardiopulmonary depression and rectal temperature changes induced by epidural administration of medetomidine in goats. Eight clinically healthy, Small East African goats of both sexes weighing between 12 to 17kg (mean 14.4±1.8kg) were used in this study. The animals were randomly divided into two groups of four animals. The first group was given 20mg/kg medetomidine followed by intravenous (IV) administration of 80mg/kg atipamezole, 30 minutes after the initial injection. The second group was given same treatment of medetomidine as group one but followed by IV administration of 2.2mg/kg tolazoline, 30 minutes after the initial injection. In both treatment groups, medetomidine was administered epidurally through the lumbosacral intersperse. Analgesia of the flank and perineum was evaluated at 10 minutes intervals up to 60 minutes. The cardiopulmonary and rectal temperature values were monitored and recorded after every 5 minutes up to 60 minutes. In both groups, lumbosacral epidural injection of medetomidine induced generalised analgesia, variable cardiopulmonary and rectal temperature depression. These changes developed as early as five minutes and continued until when $a_2$ /$a_1$ blockers were administered. Intravenous administration of a-adrenergic receptor blockers; atipamezole and tolazoline reversed the analgesia, cardiopulmonary and rectal temperature changes induced by lumbosacral epidural injection of medetomidine. However, atipamezole appeared to be superior ($P<0.05$) to tolazoline. It was concluded that IV administration of 80mg/kg atipamezole was better than 2.2mg/kg tolazoline in reversing analgesia, cardiopulmonary depression effects and rectal temperature changes induced by lumbosacral epidural injection of medetomidine. This indicates the superiority of atipamezole to tolazoline as an antidote for medetomidine induced effects in goats.*

Key words: Lumbosacral epidural; Medetomidine; Atipamezole; Tolazoline; Goats

## INTRODUCTION

Medetomidine, a 4 (5)-[ 1-(2,3-dimethyl phenyl) - ethyl] imidazole is a $\alpha_2$-adrenergic receptor agonist. It has analgesic, sedative, and muscle relaxation properties similar to that of xylazine and detomidine. The $\alpha_2$ /$\alpha_1$ receptor binding selectivity of medetomidine is 1620 whereas that of xylazine is 160, detomidine 260 and clonidine 220 (Virtanen et al., 1988; Virtanen, 1989). Medetomidine is also reported to be more lipophilic than xylazine, detomidine or clonidine (Savola et al., 1986).

Several $\alpha_2$-adrenergic receptor blockers such as yohimbine, tolazoline, piperoxan, idazoxan and atipamezole are known to reverse the effects of various $\alpha_2$-adrenergic receptor agonist drugs after intramuscular (IM) or IV administrations in different animal species (Brondke and Kowollik, 1988; Komulainen and Olson, 1991; Ko and McGrath, 1995). Studies in horses (Skarda, 1991) and buffaloes (Tiwari et al., 1998) have shown that both atipamezole and yohimbine can effectively reverse the analgesic, sedative and cardiopulmonary depression effects attributed to caudal epidural injection of detomidine or xylazine. Recently, medetomidine at 10µg, 20µg and 30µg/kg body weight have been reported to induce sedation, variable changes on cardiopulmonary functions, and rectal temperature values, and adequate surgical analgesia after lumbosacral epidural administration in goats (Mpanduji, 1998). The purpose of the present study was to compare the reversing effects of two $\alpha_2$-adrenergic receptor blockers, atipamezole and tolazoline on analgesia, cardiopulmonary and rectal temperature changes induced by medetomidine administered through the lumbosacral epidural space in goats.

## MATERIAL AND METHODS

Eight clinically healthy adult Small East African goats of both sexes weighing from 12 to 17kg (14.4±1.8kg) were used in this study. Of these, 5 were females and 3 were males. Twelve hours prior to experimentation, feeding was withheld but each animal was allowed to drink water adlibitum. The eight animals were randomly assigned to two groups of four goats and subjected to the following treatments: The first group was given 20µg/kg medetomidine epidurally followed by IV administration of 80µg/kg atipamezole, 30 minutes after the initial injection. The second group was given same treatment as group one for medetomidine but followed by IV administration of 2.2mg/kg tolazoline, 30 minutes after the initial injection. In both groups, medetomidine was administered epidurally through the lumbosacral intersperse as described by Gray and MacDonell (1986) with the injection taking over 20 seconds. The preinjection (base line) cardiopulmonary, rectal temperature and analgesia values were determined and recorded.

### Analgesia; Heart and Respiration rates and Rectal Temperatures

Analgesia of the flank and perineum was evaluated at 10 minutes intervals up to 60 minutes. The levels of analgesia for the flank and perineum was determined using a scoring system of 0 to 3 as described by Skarda and Muir (1996). A score of 0 (no analgesia) was given if there was an avoidance response to pricking the surface of the skin. A score 1 (mild analgesia) was given if there was no avoidance response to superficial skin pricks by the needle. A score of 2 (moderate analgesia) was given if there was no avoidance response to the insertion of half the needle length and a score of 3 (adequate analgesia) was given if there was no avoidance response to inserting the needle through the skin and the underlying tissues (deep muscle pricks). During each test period, superficial skin prick and deep muscular pricks were performed using a 2.54cm, 23-gauge needle. The spread of analgesia to the thorax, head and forelimbs were also determined and noted. Heart and respiration rates were measured by thoracic auscultation using stethoscope at 5 minutes intervals up to 60 minutes. Rectal temperature (RT) was monitored continuously and recorded at every 5 minutes up to 60 minutes, using digital thermometer (Exacon$^R$, Exacon Scientific, Rosklide Denmark) with a rectal thermocouple probe placed deep into rectum.

### Data Analysis

The cardiopulmonary and rectal temperature values were handled in accordance with the SAS (1988). The cardiopulmonary and rectal temperature values of the two treatment groups were subjected to analysis of variance and the least square mean (LSM) was used for the multiple comparisons of means. The wilcoxon's rank test was used to compare the levels of analgesia of the two treatment groups as described by Sykes et al. (1981). Differences of the data were significant when P was less than 0.05. All data are expressed as mean±SE.

## RESULTS

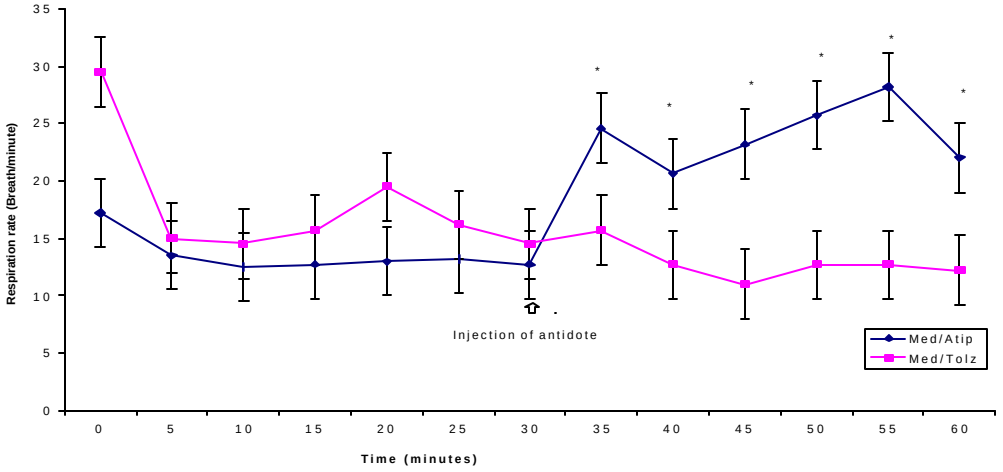
Epidural injection of 20μg/kg medetomidine induced profound analgesia that extended to the thorax, forelimbs, neck and head. Variable depression effects on the mean respiration rates (MRR), mean heart rates (MHR), and non- significant changes on rectal temperatures within 5 minutes. Between 0 to 30 minutes post medetomidine injection, no significant difference ($P>0.05$) was noted on the levels of analgesia for the flank and perineum between the two treatment groups as the antagonist were administered 30 minutes post medetomidine injection. However, the difference was obvious 10 minutes after IV administration of the $\alpha_2$-adrenergic receptor blockers (atipamezole and tolazoline) and continued to the end of observation period ($P<0.05$) (Table 1).

Table 1: Comparison of the reversing effects of 80μg/kg atipamezole (n=4) and 2.2mg/kg tolazoline (n=4) on the mean analgesic scores of the flank and perineum induced by epidural injection of20μg/kg medetomidine in goats

| Region | Drug | Dose (μg/kg) | Time after treatment (Minutes) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 0# | 10 | 20 | 30Ψ | 40 | 50 | 60 |
| Flank | Atipamezole | 80 | 0 | 3.0± 0.2$^{a*}$ | 3.0± 0.2$^{a*}$ | 3.0± 0.2$^{a*}$ | 0.25± 0.2$^{a}$ | 0.0± 0.2$^{a}$ | 0.0± 0.2$^{a}$ |
| | Tolazoline | 2200 | 0 | 3.0± 0.2$^{a*}$ | 3.0± 0.2$^{a*}$ | 3.0± 0.2$^{a*}$ | 2.25± 0.2$^{b*}$ | 2.25± 0.2$^{b*}$ | 1.75± 0.2$^{b*}$ |
| Perineum | Atipamezole | 80 | 0 | 3.0± 0.3$^{a*}$ | 3.0± 0.3$^{a*}$ | 3.0± 0.3$^{a*}$ | 1.25± 0.3$^{a*}$ | 1.0± 0.3$^{a*}$ | 0.75± 0.3$^{a}$ |
| | Tolazoline | 2200 | 0 | 3.0± 0.3$^{a*}$ | 3.0± 0.3$^{a*}$ | 3.0± 0.3$^{a*}$ | 2.5± 0.3$^{a*}$ | 2.25± 0.3$^{a*}$ | 2.0± 0.3$^{a*}$ |

Note Data are expressed as Mean±SE adjusted to one decimal place. Means in the same column same regions that have same superscripts are not significantly different ($P\geq0.05$). *Significantly different from the pre-injection values are indicated. # and Ψ indicates the injection time for the agonist (Medetomidine) and antagonists (atipamezole and tolazoline) respectively.

Intravenous administration of atipamezole showed a tendency of increasing the MRR, MHR and RT values as compared to tolazoline. Atipamezole also caused shivering and piloerection to all treated goats. The dose-time effects of medetomidine/atipamezole and medetomidine/tolazoline on the MRR, MHR and RT values are shown in Figures 1 to 3.




**F ig 1: Respiration rate response after epidural injection of 20µg/kg medetomidine followed by intravenous injection of 80µg/kg atipamezole (n=4) and 2.2mg/kg tolazoline (n=4) in goats. *Significant differences between groups are indicated.**

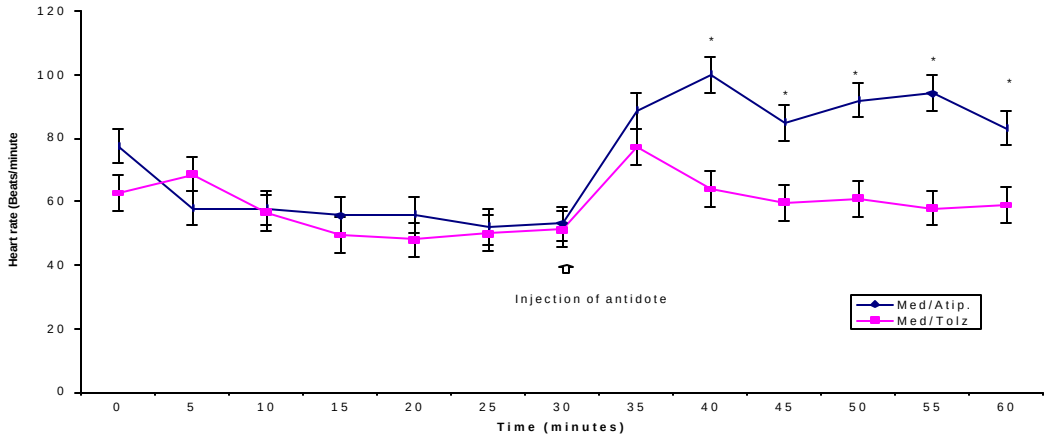



**Fig 2: Heart rate response after epidural injection of 20 µg/kg medetomidine followed by intravenous injection of 80µg/kg atipamezole (n=4) and 2.2mg/kg tolazoline (n=4) in goats. *Significant differeces between groups are indicated.**

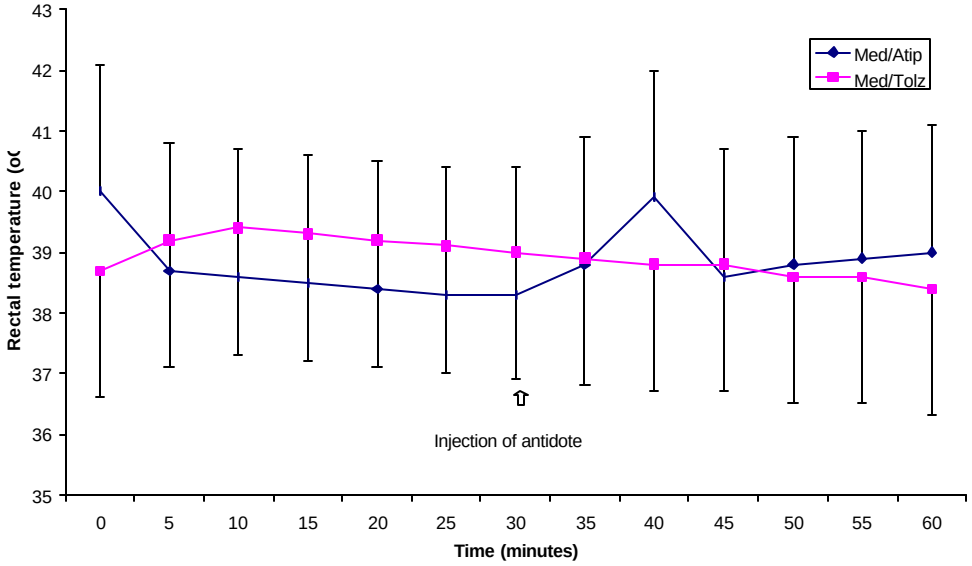



**Fig 3: Rectal temperature response after epidural injection of 20µg/kg medetomidine followed by intravenous injection of 80µg/kg atipamezole (n=4) and 2.2mg/kg tolazoline (n=4) in goats.**

## DISCUSSION

Profound and generalised analgesia, variable cardiopulmonary depression and rectal temperature changes were observed within 5-10 minutes after lumbosacral epidural injection of 20µg/kg medetomidine in goats. Similar observations have been reported after lumbosacral epidural administration of 10µg, 20µg and 30µg/kg medetomidine in goats by Mpanduji (1998). These effects are typical characteristics of the $\alpha_2$-adrenergic receptor agonists (Short, 1992).

Atipamezole, tolazoline, idazoxan and yohimbine are $\alpha_2$-adrenergic receptor blockers commonly used to reverse both sedative and analgesic effects attributed to $\alpha_2$-adrenergic receptor agonists in various animal species (Brondke and Kowollik, 1988; Komulainen and Olson, 1991; Tiwari et al, 1998). The reason for the reversal of the systemic effects of $\alpha_2$-adrenergic receptor agonists in ruminants includes occasional cessation of forestomach motility with the associated tympany and lack of supervision of animals after treatments (Brondke and Kowollik, 1988). Extensive studies with $\alpha_2$-adrenergic receptor antagonist tolazoline by Roming (1984) and Roming et al. (1987) at dose of 1.5mg/kg body weight showed that within few minutes after IV injection, the principal reaction was an increase in respiration and heart rates with a tendency to revert to initial values in cattle. In sheep, Zingoni et al (1982) using 2.0mg/kg tolazoline reversed both cardiopulmonary and ruminal atony attributable to xylazine treatments. In another comparative study, Tiwari et al (1998) using intravenous administration of yohimbine (0.125µg/kg) and atipamezole (10µg/kg) completely reversed the clinicophysiological effects of either xylazine (0.1mg/kg) or detomidine (50µg/kg) administerd epidurally in buffaloes (Bubalus bubalis). In that study, atipamezole reversed the effects of xylazine or detomidine more rapidly than yohimbine. In

the present study, the MRR, MHR and RT depression effects, and analgesia induced by lumbosacral epidural injection of medetomidine were reversed by both IV administrations of 2.2mg/kg tolazoline and 80µg/kg atipamezole. However, atipamezole was superior to tolazoline. In addition, atipamezole caused mild shivering and piroerection in goats. These effects are probably caused by blockade of the α-adrenergic receptors on the skin (Short, 1992).

The regression of analgesia attributed by lumbosacral epidural injection of medetomidine in goats concurred with the previous report by Skarda (1991), where analgesia attributed to caudal epidural injection of 80µg/kg detomidine were completely reversed by intravenous administration of 120µg/kg atipamezole in horse. However, this study differed in part with a study by Ko et al (1992) where intravenous administration of 200µg/kg atipamezole failed to reverse analgesia attributed by lumbosacral epidural injection of xylazine in pigs, but reversed both analgesia and cardiopulmonary depression effects induced by detomidine in the same specie. The differences seen may probably be caused by specie differences on the densities of the $\alpha_2/\alpha_1$ adrenergic receptor on the brain and/or spinal cord and by the various possibilities by which epidurally administered $\alpha_2$-adrenergic receptor agonists induces analgesia.

In pigs, it has been postulated that lumbosacral epidural injection of xylazine do induce analgesia most likely by the local analgesic action and/or through $\alpha_1$-adrenergic receptors (Ko et al., 1992). Same mechanism have earlier been proposed for xylazine mediated analgesia after caudal epidural administration in cattle (Skarda et al., 1990). In goats however, analgesia and cardiopulmonary depression effects induced by lumbosacral epidural injection of medetomidine seems to be mediated by more of $\alpha_2$-adrenergic action than the $\alpha_1$-adrenergic receptors stimulation and/or the locally mediated effects. The reason is, goats which were treated with 80µg/kg atipamezole, a specific $\alpha_2$–adrenergic receptor antagonist reversed completely analgesia of the flank and to greater extent that of perineum and cardiopulmonary effects induced by medetomidine (a specific $\alpha_2$–adrenergic receptor agonist) as compared to tolazoline (a competitive $\alpha_2$ /$\alpha_1$ blocker).

## CONCLUSION

From this study, it can therefore be concluded that, both analgesia and cardio-pulmonary depression effects induced by lumbosacral epidural injection of medetomidine in goats can be reversed by intravenous administration of tolazoline or atipamezole. However, atipamezole proved to be more superior to tolazoline.

## ACKNOWLEDGEMENT

The authors are grateful to the Farmos Group LTD of Turku Finland for the generous supply of Medetomidine (Domitor$^R$) and Atipamezole (Antisedan$^R$) and to Prof. Arnbjerg, J. of the Royal Veterinary and Agricultural University (RVAU) Denmark for the supply of Tolazoline and to the Norwegian Agency for International Development (NORAD) for sponsoring the study. Also thanks are due to the Department of Veterinary Surgery and Theriogenology, Faculty of Veterinary Medicine, Sokoine University of Agriculture for provision of facilities used in this study.

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