Sedative Effect of Medetomidine and its Reversal by Atipamezole in House Musk Shrews (Suncus murinus)

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Abstract: This study was undertaken to evaluate the sedative effect of medetomidine, an α₂-adrenoceptor agonist, and the counteractive effect of atipamezole, an antagonist to medetomidine, in house musk shrews (Suncus murinus). Two hundred, 300, 400, or 600 μg/kg of medetomidine was intraperitoneal injected into 89 house musk shrews. A sedative effect was produced in one to two minutes after injection. The dose-dependent prolongation of the sedative duration and the dose-dependent appearance of a hypothermic effect were demonstrated. With 200 μg/kg of medetomidine, the sedative effect obtained was not adequate in some of the animals. With 300 μg/kg and above, a stable sedative state was induced in all the animals. The duration of sedation in the house musk shrews was much longer (p<0.01) in males than in females. This suggested the higher susceptibility of male house musk shrews to this drug. The sedative effect and hypothermia obtained with 400 μg/kg of medetomidine were completely counteracted by more than 2.0 mg/kg of atipamezole. With 0.5 and 1.0 mg/kg of atipamezole, only a partial antagonistic action was produced. Transient vomiting appeared in 4.5% of the house musk shrews at approximately one minute after injection of medetomidine. This side-effect had occurred before the sedative effect was obtained, and was not serious enough to be a problem. None of the 89 house musk shrews died in this experiment. The above results show that the combination of medetomidine and atipamezole is a highly effective and safe anesthetic treatment which permits easy handling of house musk shrews.

Key words: α₂-adrenoceptor agonist, atipamezole, medetomidine, sedation, Suncus murinus.

Introduction

The house musk shrew (Suncus murinus) is an insectivore and has a variety of characteristic feature not seen in rodents such as rats and mice [8]. It is therefore expected to be very useful as an experimental animal. The house musk shrew is ferocious in nature. Since no safe method for restraint has been established,
great caution is required in the handling of this animal species. Harmless sedation is therefore needed in experiments with this animal.

Medetomidine is an $\alpha_2$-adrenoceptor agonistic sedative/analgesic drug with high selectivity of the $\alpha_2$-receptor [5, 14, 19]. This drug is recognized for its usefulness as a sedative for dogs [1, 17], cats [15, 17] and horses [2, 3], and as a premedication for general anesthesia [11, 12, 16]. It is also used for ruminants [10] and rodents [5, 6, 7, 16]. Since the effect of medetomidine is antagonized specifically by atipamezole, an $\alpha_2$-antagonist, these drugs have gained general acceptance as highly useful [6, 5, 10].

The effects and side-effects of medetomidine and the effects of atipamezole in house musk shrews were evaluated in this study. The practical utility of these drugs for this animal was examined. In addition, the optimum dosage of these drugs was determined. The sex difference in the susceptibility of house musk shrews to medetomidine was also studied.

Materials and Methods

Test animals: The test animals used were 89 Jic:SUN strain house musk shrews reproduced and reared in closed colonies at the Central Research Laboratory for Experimental Animals. They consisted of 45 males and 44 females, and ranged in age from 2 to 8 months (mean 4 months) and in weight from 30 to 71 g (mean 44 g). These animals had been reared at a room temperature of 20–25 °C and 40–60 % humidity, with lighting for 12 hours/day. The males and females had been reared separately. They had been maintained on standard laboratory pellets for house musk shrews (CLEA Japan Inc., Tokyo, Japan) and water. They were continuously allowed free access to the pellets and water until just before the experiments.

Drugs and experimental groups: Medetomidine (Domitor; Farmos Group, Ltd., Turku, Finland) was tested at doses of 200, 300, and 400 $\mu$g/kg. In addition, a higher dose (600 $\mu$g/kg) group was prepared for comparison. Atipamezole (Antisedan; Farmos Group, Ltd., Turku, Finland) was tested at doses of 0.5, 1.0, 2.0, and 4.0 mg/kg. Both drugs were diluted fiftyfold in physiological saline immediately before use. The drugs were administrated by intraperitoneal injection with a disposable 1-ml tuberculisation syringe and a 25G subdermal needle.

The following three kinds of experiment were performed in this study. The 89 house musk shrews were divided into 11 groups according to the type of drug and the dose. In Experiment 1 (Groups 1–4), medetomidine was singly used at each of the doses described to determine the dose which produced an adequate sedative effect in the house musk shrews. To determine the sex difference in the susceptibility of house musk shrews to medetomidine, 6 males and 6 females were used for the 400 $\mu$g/kg dose group in Experiment 1. In Experiment 2 (Groups 5–8), atipamezole was used at different doses at 15 minutes after injection of 400 $\mu$g/kg of medetomidine. In Experiment 3 (Groups 9–11), medetomidine was used at 400 $\mu$g/kg at 15 minutes after injection of atipamezole at different doses. In Experiment 3, the antagonistic effect of atipamezole at 4 mg/kg was not examined. Experiments 2 and 3 were carried out to assess the antagonistic action of atipamezole on medetomidine. Controls in Experiments 2 and 3 were treated with physiological saline instead of an antagonist. In the preparation of groups for these experiments, the animals were distributed at random, but all groups were so prepared as to consist of equal numbers of males and females, in consideration of a possible sex difference in the susceptibility of these animals to the drug.

Evaluation of the sedative effect: After administration of the drugs, the house musk shrews were placed in an acrylic resin chamber measuring 40 cm in length, 30 cm in width and 20 cm in height to observe their behavior. Animals that ceased to move were removed from the chamber and placed in a supine position on a flat table. The nonappearance of righting reflex for 30 seconds was judged as a manifestation of the sedative effect [5]. When the animals resumed a normal walking movement, they were judged as having recovered from the sedative state.

Measurement of rectal temperature: The rectal temperature was measured with an electron thermometer (MC-3BW, Omron Matsuzaka Co., Ltd., Mie, Japan). Its probe was inserted 2 cm into the rectum. Measurement of the rectal temperature was carried out every time the sedative state was examined, namely, before and at intervals of 10 minutes after administration of medetomidine.

Statistical analysis: The data obtained were expressed
as the mean ± standard deviation. Statistical analysis was carried out between groups by analysis of variance with one-way classification and Duncan's multiple range test, and p<0.05 was defined as statistically significant.

Results

Sedative effect of medetomidine (Experiment 1): The duration of the sedative effect of medetomidine in the house musk shrews was examined at each dose. Almost all the house musk shrews lost the righting reflex within 2 min after medetomidine administration except one of the 6 house musk shrews in the 200 µg/kg medetomidine group. In all groups treated with 300 µg/kg and more of this drug, an adequate sedative effect was obtained. The duration of the sedative state, as shown in Fig. 1, was 45.8 ± 10.9 minutes in the 200 µg/kg group, 43.7 ± 9.9 minutes in the 300 µg/kg group, 105.6 ± 31.0 minutes in the 400 µg/kg group and 217.3 ± 73.9 minutes in the 600 µg/kg group, and thus medetomidine tended to prolong the sedative effect dose-dependently. Significant differences were found between the 400 and 200 µg/kg groups and between the 400 and 300 µg/kg groups (p<0.01).

A sex difference in the duration of the sedative effect with 400 µg/kg of medetomidine was examined in 6 male and 6 female house musk shrews: as shown on the right side of Fig. 1, the duration in the males was 127.2 ± 29.4 minutes and that in the females 84 ± 11.5 minutes, which was a significant difference (p<0.01).

Changes in rectal temperature (Experiment 1): The changes in rectal temperature after administration of medetomidine are shown in Fig. 2. After administration of medetomidine, the rectal temperature decreased dose-dependently. The higher the dose was, the more the temperature recovery time tended to be prolonged.

Antagonistic action of atipamezole on the sedative effect of medetomidine (Experiments 2 and 3): The house musk shrews were treated with atipamezole at 0.5, 1.0, 2.0, and 4.0 mg/kg at 15 minutes after injection of 400 µg/kg of medetomidine. The sedative effect of the latter drug lasted for 31.1 ± 8.2, 21.6 ± 7.1, 20.1 ± 7.1 and 21.2 ± 5.5 minutes respectively. With any dose of atipamezole, the duration of sedation was significantly (p<0.01) shortened compared to the duration of 105.6 ± 31.0 minutes in the group not treated with the antagonist (Fig. 3).

When the house musk shrews were given 400 µg/kg of medetomidine at 15 minutes after pretreatment with

![Fig. 1. Sedation time following administration of different doses of medetomidine. Sex difference represented on the right side of the figure. Data are represented as the mean ± SD (n=3–12). *Significant difference at p<0.01.](image)
Fig. 2. Hypothermic properties following administration of different doses of medetomidine. Data are represented as the mean ± SD (n=3-12). MED: medetomidine. *Significant difference at p<0.01.

Fig. 3. Antagonistic effect of different doses of atipamezole to 400 µg/kg of medetomidine-induced sedation. Data are represented as the mean ± SD (n=6-8). *Significant difference at p<0.01, and **at p<0.05, respectively.

Fig. 4. Antagonistic effect of pretreatment (15 min before) with different doses of atipamezole on 400 µg/kg as the mean ± SD (n=6-8). *Significant difference at p<0.01, and **at p<0.05, respectively.
0.5–2.0 mg/kg of atipamezole, the duration of sedation was significantly (p<0.01) decreased compared to the animals not pretreated with the antagonist, as shown in Fig. 4. In 2 (33.3%) of the 6 animals treated with 2.0 mg/kg of atipamezole, the sedative effect completely failed to appear.

Effect of atipamezole on the hypothermal effect of medetomidine (Experiments 2 and 3): The hypothermal effect produced by medetomidine was antagonized by atipamezole. With 0.5–4.0 mg/kg of atipamezole, the decreased body temperature returned almost to a baseline level (level before administration of medetomidine) at 10–20 minutes after atipamezole treatment. The body temperature drop therefore tended to recover apparently more rapidly than in the animals not treated with the antagonist (Fig. 5).

Fig. 6 shows the changes in rectal temperature in the house musk shrews pretreated with 0.5–2.0 mg/kg of atipamezole before administration of medetomidine. Measurement at 15 minutes after atipamezole treatment (just before administration of medetomidine) disclosed a transient increase in the rectal temperature, and even after administration of medetomidine, the increased rectal temperature never failed to fall below the

![Graph](image-url)

**Fig. 5.** Antagonistic effect of different doses of atipamezole on 400 μg/kg medetomidine-induced hypothermia. MEDI: medetomidine, ATI: atipamezole, *Significant difference at p<0.01 (n=6–8).

![Graph](image-url)

**Fig. 6.** Effect of pretreatment (15 min before) with different doses of atipamezole on 400 μg/kg of medetomidine-induced hypothermia. Data are represented as the mean ± SD (n=6–8). MEDI: medetomidine, ATI: atipamezole, *Significant difference at p<0.05.
pretreatment level. The hypothermal effect of medetomidine (400 µg/kg) could therefore be inhibited by pretreatment with 0.5–2.0 mg/kg of atipamezole.

Side-effect: Vomiting appeared at approximately one minute after administration of medetomidine in 4 (4.5%) of the 89 house musk shrews. This side-effect was transient and was not found after the onset of the sedative effect. None of the house musk shrews used in the experiment died.

Discussion

This study was designed to assess the applicability of medetomidine, a new α₂-adrenoceptor agonist, as a sedative for house musk shrews, and to evaluate the counteractive properties of atipamezole, an antagonist to medetomidine.

Medetomidine is very potent, selective and specific full agonist at both pre- and postsynaptic α₂-adrenoceptors, compared with other α₂-adrenoceptor agonists such as xylazine and detomidine [5, 14, 19].

Atipamezole has been shown to be a highly potent, selective and specific antagonist of centrally and peripherally located α₂-adrenoceptors. In receptor binding experiments, the α₂/α₁ selectivity ratio of atipamezole is 8500 compared to 27 for idazoxan and yohimbine [19]. Other models have strengthened the profile of atipamezole as one of the most selective and potent α₂ antagonist known today. Besides behavioral effects, atipamezole is able to antagonize also the cardiovascular, gastrointestinal, neurochemical and hypothermic effects of medetomidine in laboratory models [15, 19].

This is one of the reasons why a combination of medetomidine and atipamezole has been found more useful than combinations of other existing α₂-agonists and antagonists. One of the reasons why medetomidine has been found useful is that the antagonist is thus available when it is needed for the management of overdosage or for quickening the awakening or recovery from sedation. This provides a considerable benefit to medetomidine not only in clinical veterinary medicine but also in animal experiments. Furthermore, medetomidine is a sedative/analgic which is more rapidly metabolized and excreted from the body than diazepam and fenothiazine [13].

This experiment showed that the dose of medetomidine required to produce an adequate sedative effect in house musk shrews is more than 300 µg/kg. The effect of medetomidine was evaluated at an increased dose of 600 µg/kg in 3 house musk shrews. The increased dose only prolonged the duration of sedation, compared to the dose of 400 µg/kg. Compared to the other dose group, no remarkable findings were obtained at this dose with respect to its side-effect. The duration of the sedative effect was dose-dependent. The duration of sedation tended to be longer in males than females. Susceptibility was therefore found to be different in males from that in females. The difference in susceptibility between the sexes disagreed with the results of an earlier study in rodents which showed higher susceptibility in females than in males [7]. This and possible differences due to animal species in general may be an important theme to be studied in future.

In animals treated singly with medetomidine, sedative and muscle relaxant effects can be obtained to some degree due to its properties. But since its anxiolytic and analgesic effects are insufficient [11], treatments that do not inflict pain (e.g., restrain) are possible, but the use of general anesthesia is needed when pain is involved in treatments such as surgery [1, 7, 12, 16].

The inhibition of sympathetic tone in the CNS and stimulation of the chemotactic trigger zone (CTZ) by medetomidine leads to a characteristic pattern of pharmacodynamic responses as side effects, including e.g. hypotension, bradycardia, emesis, and hypothermia. Especially a hypothermic effect and emesis as side effects following medetomidine administration were observed in this study. Dose-dependent hypothermia appeared after administration of medetomidine [4, 19]. The rectal temperature is decreased by approximately 5°C in rats given 300 µg/kg of medetomidine, but this rectal temperature drop can be prevented by administration of 1 mg/kg of atipamezole [4]. In this experiment, sedation and hypothermia, which reflect the effects of medetomidine recovered rapidly following treatment with atipamezole. Pretreatment with 0.5–2.0 mg/kg of atipamezole prior to administration of 400 µg/kg of medetomidine resulted in complete prevention of hypothermia, regardless of the dose of atipamezole. This suggests that the effect of medetomidine is partially counteracted by even a low dose of atipamezole. But the dose of atipamezole needs to be increased to more than five times that of medetomidine to obtain an adequate antagonistic action.
by atipamezole.

Transient vomiting was induced at approximately one minute after administration of medetomidine in 4 (4.5%) of the 89 medetomidine-administered house musk shrews. This incidence was extremely low compared to those found in dogs and cats [17, 18]. Since vomiting occurred while the pharyngolaryngeal reflex of the house musk shrew was still present, it seemed that even animals that had not been kept fasting were not at risk of developing aspiration pneumonia.

In addition, none of the house musk shrews died after administration of medetomidine at doses ranging from 200 to 600 µg/kg. This suggests the safety of this drug at these dose levels.

References