

Medetomidine- and Medetomidine-Ketamine-induced Immobilization in Blue Foxes (*Alopex lagopus*) and its Reversal by Atipamezole

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Jalanka, H.: Medetomidine- and medetomidine-ketamine-induced immobilization in blue foxes (*Alopex lagopus*) and its reversal by atipamezole. Acta vet. scand. 1990, 31, 63-71. – The sedative and immobilizing effects of the α_2 -adrenoceptor agonist medetomidine alone or combined with the dissociative anesthetic ketamine, were studied in blue foxes. Medetomidine at doses of 25 and 50 $\mu\text{g}/\text{kg}$ induced moderate to deep sedation, but only with the highest medetomidine dose tested, 100 $\mu\text{g}/\text{kg}$, was the immobilization complete. Medetomidine 50 $\mu\text{g}/\text{kg}$ combined with ketamine 2.5 mg/kg rapidly induced complete immobilization, characterized by good myorelaxation, and no clinically significant alterations in serially determined hematologic and serum chemistry parameters.

The α_2 -adrenoceptor antagonist atipamezole effectively reversed the medetomidine- or medetomidine-ketamine-induced immobilizations. A transient increase in heart rates was noted after each atipamezole injection.

anesthesia; α_2 -adrenoceptor agonist, antagonist; hematology; serum chemistry.

Introduction

Complete and reliable immobilization is frequently needed to enable veterinary medical and research procedures in canid species other than the dog. The method for immobilization should be easy to use even under field conditions, have no significant adverse effects with clinical doses, and be reversible. The potent and selective α_2 -adrenoceptor agonist medetomidine¹ (4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole hydrochloride) (Savola *et al.* 1986) has dose-dependent sedative, analgesic and muscle-relaxing properties in dogs (Vainio *et al.* 1987, Vainio & Palmu 1989). When medetomidine is combined with the dissociative anesthetic ketami-

ne², a more complete and reliable immobilization is achieved (Jalanka *et al.* 1989). Medetomidine-ketamine combinations have also been used in immobilization of a variety of nondomestic animal species (Jalanka 1987, 1988, 1989, Röken 1987).

Atipamezole, (MPV-1248; 4-[2-ethyl-2,3-dihydro-1H-inden-2-yl]-1H-imidazole hydrochloride) is a potent and selective α_2 -adrenoceptor antagonist (Virtanen *et al.* 1989, Virtanen & MacDonald 1987). Atipamezole has been used in nondomestic animals to reverse the chemical immobilization induced by medetomidine, medetomidine-ketamine and xylazine (Jalanka 1987, 1988, 1989, Röken 1987).

The objectives of this study were to establish clinically useful doses for medetomidine or medetomidine-ketamine combinations in

1. Medetomidine 1 mg/ml Farnos Group Ltd., P. O. Box 425, 20101 Turku, Finland.

2. Ketalar[®] 50 mg/ml Parke-Davis & Co., Pontypool, Gwent, United Kingdom.

blue foxes (*Alopex lagopus*), to assess the induced immobilizations using clinical, hematologic, and serum chemistry parameters, and to determine the usefulness of atipamezole as a reversal agent.

Materials and methods

In November and December 1986 and in December 1987, medetomidine, alone or combined with ketamine, was administered to 43 blue foxes at the Research Farm of the Finnish Fur Breeders' Association, Veikkola, Finland. The blue foxes [26 males and 17 females, mean±SD (range) values for age and weight were 1.7±1.5 years (0.5-5.5 years) and 6.6±0.7 kg (3.8-9.0 kg), respectively] that were managed in standard outdoor cages, were fasted overnight, but had free access to drinking water. All animals were brought indoors (ambient temperature 16-20°C) in transfer cages and preweighed to enable accurate dose-planning. Medetomidine (1 mg/ml) and ketamine (50 mg/ml) were administered in separate syringes im into the triceps muscle. The administered doses, and the number of animals in each dose group, are presented in Fig. 1.

This study was divided into a phase of clinical orientation and into more detailed stu-

dies. During each phase, the animals were monitored and the degree of immobilization was determined clinically by recording mucous membrane color, palpebral reflex, relaxation of the jaws and tongue, and by turning the animals. Possible adverse effects were recorded. During the immobilizations, no painful stimuli were used to determine the analgesic effects of the agents used.

During the initial trials, medetomidine was administered at doses of 25 µg/kg (n=2), 50 µg/kg (n=2) and 100 µg/kg (n=2), and medetomidine + ketamine at doses of 50 µg/kg + 2.5 mg/kg (n=2), µg/kg + 5.0 mg/kg (n=2) and 100 µg/kg + 2.5 mg/kg (n=1) to determine clinical dose-responses. Atipamezole (5 mg/ml) was administered at doses 5 times (w/w) the initial medetomidine dose to 4 medetomidine-treated and to 3 medetomidine-ketamine-treated animals. Immobilizations and reversals were evaluated clinically. After these initial trials, medetomidine 100 µg/kg and a combination of medetomidine 50 µg/kg and ketamine 2.5 mg/kg were chosen for more detailed studies.

Medetomidine 100 µg/kg was then administered to 7 blue foxes. The resulting immobilization was assessed clinically and by periodic ECG recordings (Cardiostat 1⁴) Atipamezole was administered either at 20 or 60 min after the initial medetomidine injection at doses and by routes indicated in Figs. 3 and 4. ECG's were recorded prior to the atipamezole injections, and continuously until the animals started to move and made recordings impossible. Time until arousal and type of recovery were recorded.

The combination of medetomidine 50 µg/kg and ketamine 2.5 mg/kg was administered by simultaneous injections to 24 blue foxes.

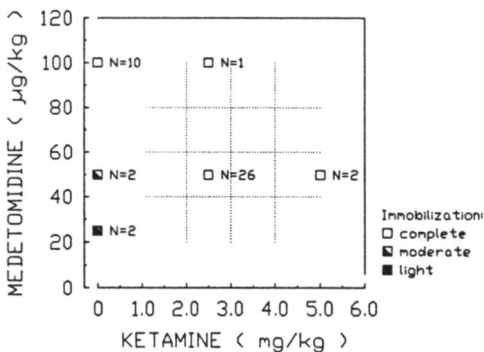


Figure 1. Medetomidine and ketamine doses (im) used and respective degree of immobilization in 43 blue foxes.

³. Atipamezole 5 mg/ml Farnos Group Ltd., P. O. Box 425, 20101 Turku, Finland.

⁴. Cardiostat 1, Siemens-Elema AB, Sweden.

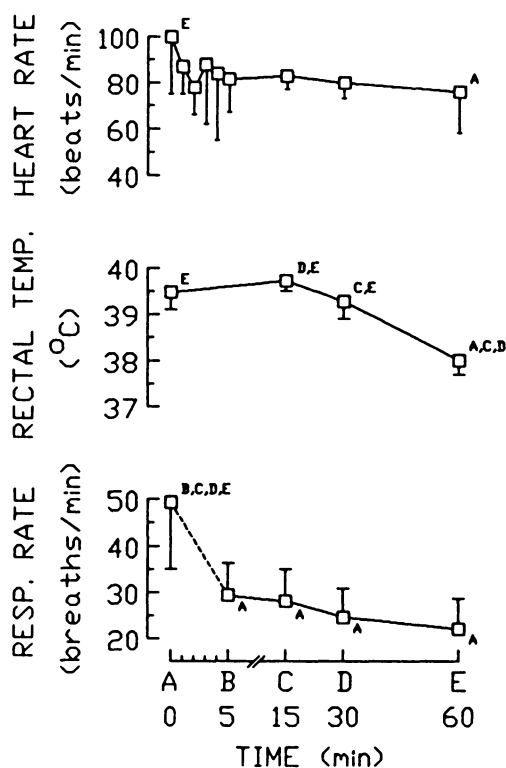


Figure 2. Mean and SD values for serially recorded heart rates, respiratory rates, and rectal temperatures in 6 blue foxes, immobilized with medetomidine 50 µg/kg and ketamine 2.5 mg/kg by simultaneous im injections. Baseline respiratory rates recorded before animals were physically restrained. A, B, C, D, E = value statistically different ($P < 0.05$) from that in indicated column.

Serial determinations and recordings were performed in 6 of these animals (Fig. 2 and Table 2) and 18 animals were used for antagonist evaluation. The 6 blue foxes used for serial recordings were physically restrained prior to the anesthetic injections for baseline recordings, and were gradually released as the immobilization developed, usually within 3 to 4 min. Heart rates were recorded by ECG monitoring prior to the anesthetic injections, continuously during the first 5 min, and at time points indicated in Fig. 2. Respiratory rates were determined before restraint (animals in cages) and as indicated in Fig. 2. Time points when rectal temperatures were recorded, and blood samples for hematology and serum chemistry were obtained, are presented in Fig. 2 and Table 2. Blood samples were stored at 1-3°C until hematology was completed or serum separated (less than 8 h). Serum samples were stored at -20°C until analyzed. Methods and instrumentation were according to Scandinavian standards and have been reported previously (Jalanka 1988). No antagonists were used. The recovery was observed periodically for 3-4 h.

Atipamezole was administered to 18 blue foxes 15 min after treatments with medetomidine 50 µg/kg and ketamine 2.5 mg/kg. Atipamezole was used at doses of 250 µg/kg im (n = 6), 125 µg/kg im (n = 6) and 125 µg/kg iv (n = 6; one injection perivascularly,

Table 1. Data and characteristics on medetomidine and medetomidine-ketamine-induced immobilizations in blue foxes. Values expressed as mean ± SD (range).

	Medetomidine	Medetomidine + Ketamine
n	7	24
Dose(s)	100 µg/kg	50 µg/kg + 2.5 mg/kg
Induction time (min)	6.6 ± 2.5 (3.5-10)	2.5*** ± 0.7 (1.8-4.5)
Duration (min)	≥ 60	≤ 60
Total recovery time	not determined	2-3 hours

***Respective values significantly different ($P < 0.001$).

Table 2. Results of serial determinations of hematological, and serum chemistry parameters in 6 blue foxes, immobilized with medetomidine 50 µg/kg and ketamine 2.5 mg/kg by simultaneous im injections. Values expressed as mean ±SD (range).

	A	B	C
Time (min after injection)	Before	15	60
HEMATOLOGY			
PCV (%)	51.2 ^{b,c} ±4.4 (45-58)	45.8 ^{a,c} ±4.4 (40-51)	42.7 ^{a,b} ±2.0 (37-48)
Leukocytes (E9/liter)	6.8±1.5 (5.8-8.5)	6.1±1.3 (4.7-7.2)	5.9±0.6 (5.2-6.4)
SERUM CHEMISTRY			
ALT (U/liter)	55.8±28.1 (26-104)	54.5±23.7 (29-94)	57.3±25.7 (34-104)
AST (U/liter)	25.5±3.6 (21-32)	30.8±6.2 (24-42)	32.5±6.8 (22-44)
Alkaline phosphatase (U/liter)	61.3±17.8 (46-84)	57.5±20.2 (39-92)	56.8±14.6 (44-80)
Protein (g/liter)	71.6 ^b ±4.7 (66.6-79.4)	67.7 ^a ±4.5 (63.9-75.8)	68.5±5.7 (61.9-75.5)
Glucose (mmol/liter)	8.4 ^c ±1.3 (6.8-10.3)	9.9±1.7 (8.0-12.4)	12.0 ^a ±2.6 (8.9-16.9)
Creatinine (mmol/liter)	60.3 ^b ±2.9 (57-64)	64.7 ^a ±4.5 (60-72)	64.7±5.6 (58-73)
Na (mmol/liter)	149.2 ^c ±2.9 (145-153)	151.0±4.9 (144-158)	146.7 ^a ±3.3 (142-150)
K (mmol/liter)	4.9±0.3 (4.5-5.2)	4.8±0.3 (4.5-5.2)	5.2±0.8 (4.5-6.8)
Cl (mmol/liter)	114.0 ^c ±3.2 (110-118)	115.8±4.0 (110-120)	112.3 ^a ±2.3 (110-115)
Ca (mmol/liter)	2.28±0.17 (2.1-2.5)	2.25±0.10 (2.1-2.4)	2.23±0.14 (2.1-2.4)
P-inorg. (mmol/liter)	1.00 ^{b,c} ±0.23 (0.72-1.31)	1.72 ^a ±0.44 (0.92-2.07)	1.79 ^a ±0.28 (1.42-2.27)

[3 males and 3 females; age and weights 1.7±0.4 years (1.5-2.5 years) and 5.4±0.8 kg (6.6-9.0 kg)].

^{a,b,c} Value significantly different ($p < 0.05$) from that in columns A, B, and C.

results based on 5 recordings). ECG's were recorded prior to the atipamezole injection, and continuously for 5 min or until movements of the animals made recordings impossible. Time until arousal and type of recovery were recorded.

All statistical calculations and comparisons were performed using a computer program⁵ (Statgraphics®). The Student's *t*-test for paired data was used to compare results of the

serial recordings and determinations at different time points. The Student's *t*-test for unpaired data was used to compare induction and arousal times with different treatment.

Results

The clinical dose-response with the medetomidine and ketamine doses used is presented in Fig. 1. Medetomidine 25 µg/kg sedated

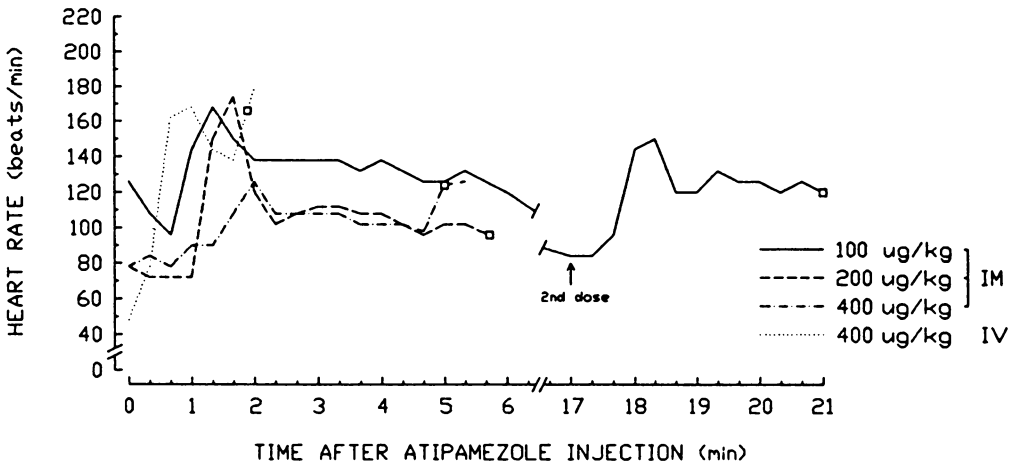


Figure 3. Continuously recorded heart rates in 4 blue foxes, treated with atipamezole at doses and by routes indicated, 20 min after an initial im injection of medetomidine 100 µg/kg. 2nd dose = additional dose of atipamezole 213 µg/kg im was administered. □ = arousal time.

the animals but they were easily aroused by approach or manipulation and able to run, with only slightly impaired coordination. Medetomidine 50 µg/kg induced deep sedation. However, apparently unconscious animals were aroused if turned over, showing increased muscle tone or movements, but were unable to move in a directed manner. Medetomidine 100 µg/kg immobilized the blue foxes completely (Table 1). With this dose, myorelaxation was good, and the jaws and tongue were relaxed. Mucous membrane color was mildly cyanotic. During 3 of 7 immobilizations, second degree atrioventricular blocks were noted in the ECG recordings. Duration of immobilization was not determined as most animals received atipamezole. The immobilization was still complete in 1 animal 2 hours after the initial medetomidine injection, and in the 3 animals that received atipamezole at 60 min (Fig. 4).

Medetomidine 50 µg/kg and ketamine 2.5 mg/kg induced complete and reliable immo-

bilization (Table 1). Results of the serial recordings and determinations in 6 blue foxes immobilized with this combination are presented, and statistically significant alterations indicated, in Fig. 2 and Table 2. During the immobilization, myorelaxation and mucous membrane color were good, jaws and tongue relaxed, and capillary refill times approximately to 1 sec. No second degree atrioventricular blocks were noted in the medetomidine-ketamine-treated animals. At the end of the 60 min monitoring period, 2 animals were still completely and 4 moderately immobilized. All recoveries were uneventful.

Atipamezole effectively reversed the medetomidine- or medetomidine-ketamine-induced immobilizations. Heart rates and arousal times in 7 blue foxes, treated with different doses of atipamezole at 20 or 60 min after the initial injection of medetomidine 100 µg/kg, are presented in Figs. 3 and 4. On one occasion, when atipamezole (100 µg/kg im) was administered 20 min after medetomidine, no reversal effect was noted for 17 min. A second dose of atipamezole

⁵ Statgraphics®, STSC, Inc., Rockville, Maryland 20852, USA.

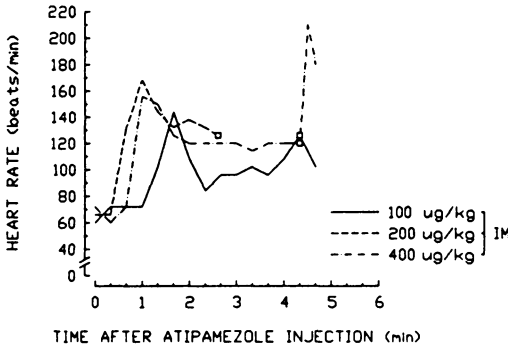


Figure 4. Continuously recorded heart rates in 3 blue foxes, treated with atipamezole im at doses indicated, 60 min after an initial im injection of medetomidine 100 µg/kg. □ = arousal time.

213 µg/kg im reversed the immobilization in 4 min (Fig. 3). A comparison of the reversal effects of atipamezole at different doses and routes of administration in blue foxes, immobilized with medetomidine and ketamine, is presented in Table 3. Relative changes in the heart rates after atipamezole injections in these animals are presented in Fig. 5. An obvious, transient increase in heart rates of medetomidine- and medetomidine-ketamine-treated animals were noted within 1.5 min after each atipamezole injection, well before the animals showed any signs of arousal. The maximum individual heart rate

recorded was 222 beats/min. The second degree atrioventricular blocks noted in some animals treated with medetomidine 100 µg/kg, disappeared as the heart rate increased.

Clinically, no adverse effects were noted with medetomidine or medetomidine-ketamine. No animals vomited. During the initial trials, 3 blue foxes experienced an excitatory period 6 to 8 min after atipamezole treatments. The animals first became nervous and overalert, then muscle fascicula-

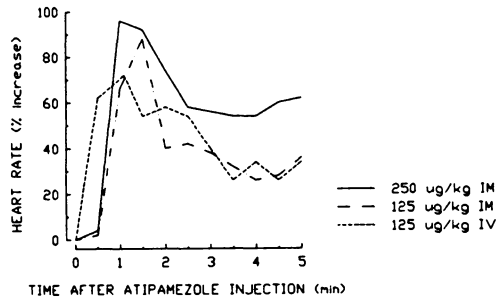


Figure 5. Mean values for relative changes in continuously recorded heart rates in blue foxes, treated with atipamezole at doses and by routes indicated, 15 min after initial im injection of medetomidine 50 µg/kg and ketamine 2.5 mg/kg. N = 6 in 250 µg/kg im; N = 5 in 125 µg/kg im; N = 5 in 125 µg/kg, but reduced after 3 min as movements made recordings impossible.

Table 3. Data and characteristics on the use of atipamezole as a reversal agent in blue foxes. Atipamezole was administered 15 min after initial im injections of medetomidine 50 µg/kg and ketamine 2.5 mg/kg. Values expressed as mean±SD.

	Dose and administrative route		
	250 µg/kg im A	125 µg/kg im B	125 µg/kg iv C
n	6	6	5
Degree of immobilization at reversal	complete	complete	complete
Atipamezole: medetomidine ratio (w/w)	5:1	2.5:1	2.5:1
Arousal time (min)	4.1 ^{b,c} ±0.9 (3.6-6.0)	6.4 ^{a,c} ±1.7 (4.5-8.9)	2.4 ^{a,b} ±1.0 (1.5-4.0)
Type of recovery	most animals nervous and overalert	calm	calm

a,b,c Value significantly different (p < 0.05) from that in columns A, B, and C.

tions and extreme muscle tension developed for 30 to 40 sec, which gradually relaxed without treatment. One fox had been treated with medetomidine 100 µg/kg and given atipamezole 500 µg/kg iv 2 h later. One had been treated with medetomidine 50 µg/kg and ketamine 2.5 mg/kg and given atipamezole 250 µg/kg im 60 min later. One was treated with medetomidine 50 µg/kg and ketamine 5 mg/kg and given atipamezole 250 µg/kg im 50 min later. No similar effects were seen in later studies.

Discussion

In blue foxes, the response to different medetomidine doses resembled that in dogs with equivalent doses, although medetomidine 100 µg/kg is infrequently used in this species (Vainio *et al.* 1987). The 8 lower doses tested (25 and 50 µg/kg) immobilized the animals incompletely and they were aroused by manipulations. Incompletely immobilized animals may be hazardous to handlers by being able to inflict trauma. Xylazine⁶ at doses of 2.7 to 3.9 mg/kg (together with atropine) has been used to sedate arctic wolves (*Canis lupus*) (Philo 1978). Gauze muzzles were applied to these wolves as they were able to bite extremely quickly if aroused by manipulations. In blue foxes, this is unlikely to happen if the highest tested dose (100 µg/kg) is used.

Medetomidine induces bradycardia, bradyarrhythmias, and an increase in the blood pressure, which is later followed by a decrease (Järvensivu *et al.* 1989). Bradycardia and sinus arrhythmia, related to changes in blood pressure, have been reported in xylazine-treated dogs (Hsu *et al.* 1985). Simultaneous decreases in heart rates and increases in mean arterial pressures were recorded in dogs after a combination of medetomidine 50 µg/kg and ketamine 2.5 mg/kg im (Jalan-

ka *et al.* 1989). The second degree atrioventricular blocks noted in blue foxes treated with medetomidine 100 µg/kg were probably similarly related to changes in blood pressure.

Medetomidine 50 µg/kg and ketamine 2.5 mg/kg immobilized the blue foxes completely. If ketamine is used alone in nondomestic canids, doses of 20 to 35 mg/kg have been recommended, as have been doses of 10 mg/kg when ketamine is combined with xylazine 2 mg/kg (Wallach & Boever 1983). Much smaller ketamine doses (in medetomidine combinations) were used in this study, but they were equivalent to those reported to induce complete immobilization in snow leopards (*Panthera uncia*) (Jalanka 1989). Induction times in this study were only 2.5±0.7 min, indicating rapid distribution of the agents. The injections were administered into the triceps muscle as a standard. This was probably of significance as, in dogs, times to recumbency after xylazine-ketamine injections were markedly shorter when injections were given into the triceps muscle instead of the quadriceps muscle (McWade 1982).

No clinically significant alterations occurred in the serially recorded heart rates, respiratory rates, rectal temperatures, or in the hematologic or serum chemical parameters. The animals were physically restrained for baseline recordings. This probably caused some stress to the animals, increased the heart rates at the time and immediately after the anesthetic injections, and caused the slight elevation in the rectal temperatures noted in 15 min (Fig. 2).

Atipamezole effectively reversed the medetomidine or medetomidine-ketamine-induced immobilizations. Reversal was probably enhanced by the low ketamine doses used. The alpha₂-adrenoceptor antagonist yohimbine has been reported to shorten the arousal

⁶ Rompun® Bayer, Leverkusen, West Germany.

times in ketamine-treated wolves but times until animals were able to walk in a directed manner were not different from controls (Kreeger & Seal 1986). Even if arousal times could be recorded reliably, keeping of the blue foxes in small transfer cages did not permit to determine the time until the animals had fully recovered and e.g. would have been fit to be released in field conditions.

A transient increase in the heart rates was noted after each atipamezole injection, both in medetomidine- and medetomidine-ketamine-treated blue foxes. In horses, sedated with detomidine⁷, atipamezole induces a decrease in the blood pressure, which is compensated by an increase in the heart rate (Nilsfors & Kwart 1986). In xylazine-ketamine-treated wolves, yohimbine decreases the mean arterial blood pressure and increases the heart rate to a maximum of 369 beats/min within 3 min after iv doses of more than 0.2 mg/kg (Kreeger *et al.* 1987). After im atipamezole injections, the heart rates remained very stable in markhors (*Capra falconeri megaceros*) and increased only by 19% in snow leopards (Jalanka 1988, 1989). The much greater changes in heart rates noted in this study may suggest that atipamezole induces more pronounced alterations in blood pressure in blue foxes than it does in markhors or in snow leopards, or that there may be other species-related differences in regulatory mechanisms mediated via α_2 -adrenoceptors.

The excitatory periods noted in 3 blue foxes during the initial trials seemed to be related to the administration of atipamezole when the effects of medetomidine or medetomidine-ketamine were already wearing off. The doses *per se* were not exceptionally high. The reversals in blue foxes immobilized with

medetomidine 50 $\mu\text{g}/\text{kg}$ and ketamine 2.5 mg/kg were calm after atipamezole 125 $\mu\text{g}/\text{kg}$ im, and after 125 $\mu\text{g}/\text{kg}$ iv, but most animals became nervous and overalert when the dose of 250 $\mu\text{g}/\text{kg}$ im was used (Table 3). In blue foxes, immobilized with medetomidine 100 $\mu\text{g}/\text{kg}$, only the highest atipamezole dose, 400 $\mu\text{g}/\text{kg}$, especially when administered iv, induced some overalertness after reversal. These findings suggest that the atipamezole dose should be adjusted according to the medetomidine dose used, and according to the time interval between anesthetic and antagonist injections.

Acknowledgements

This work was supported by grants from the Finnish Veterinary Research Foundation and the Research and Science Foundation of Farnos. I wish to thank Mr. Pertti Muuronen and Ms. Mary-Ann Vane-Tempest for their technical assistance, and Jaakko Mäkelä, Manager of Research Department, Finnish Fur Breeders' Association, for letting us use the facilities of the Veikkola Research Farm. Medetomidine and atipamezole were generously provided by Tapani Vähä-Vahe, DVM, Research Center, Farnos Group Ltd.

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⁷ Domosedan® Farnos Group Ltd., P. O. Box 425, 20101 Turku, Finland.

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Sammandrag

Medetomidin- och medetomidin-ketamin inducerad immobilisation hos blåräv (Alopex lagopus) samt dess upphävande med atipamezol.

Medetomidin allena eller i kombination med ketamin användes för immobilisering av blåräv. Med en dos på 20 och 50 µg/kg medetomidin, uppnåddes sedation. En fullständig immobilisation och god muskelrelaxering uppnåddes med en dos på 100 µg/kg medetomidin och med 50 µg/kg medetomidin i kombination med 2.5 mg/kg ketamin. Atipamezol upphävde effektivt sedationen framkallad av medetomidin och medetomidin-ketamin.

(Accepted April 3, 1989).

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