Effects of medetomidine and atipamezole on serum glucose and cortisol levels in captive reindeer (*Rangifer tarandus tarandus*)

Jon M. Arnemo[1] **& Birgit Ranheim**[2]

[1] Department of Arctic Veterinary Medicine, The Norwegian School of Veterinary Science, N-9292 Tromsø, Norway (jon.m.arnemo@veths.no).

[2] Department of Pharmacology, Microbiology and Food Hygiene, The Norwegian School of Veterinary Science, P.O. Box 8146 Dep., N-0033 Oslo, Norway.

Abstract: Serum concentrations of glucose and cortisol were measured in five adult captive reindeer (*Rangifer tarandus tarandus*) at 24 h and 10 min before, and at 0.5, 1, 2, 4, 8, 12 and 24 h after, treatment with 60 µg/kg of medetomidine i.v. followed by 300 µg/kg of atipamezole i.v. 60 min later. The experiments were performed in January and repeated in July-August. The animals were used as their own controls and treated with saline in July-August. The wash-out period between experiments in summer was 2 weeks or more. No obvious seasonal differences were observed. Mederomidine induced a 2.5-fold increase in glucose (mean ± standard error of the mean being 15.4 ± 0.6 mmol/l at 1 h) and a 3.5-fold increase cortisol (349 ± 28 nmol/l at 0.5 h). Serum glucose reached control levels within 12 h, and cortisol declined to baseline levels within 4 h after injection og medetomidine. The use of blood concentrations of glucose and cortisol to assess nutritonal status, body condition and stress may be significantly biased in animals chemically immobilized with medetomidine or other alpha-2 adrenoceptor agonists.

Key **words:** alpha-2 adrenoceptor, drug, immobilization, serum biochemistry, wildlife.

Rangifer, 19 (2): 85–89

Introduction

In wild animals, chemical restraint is often required for handling and sampling procedures. The alpha-2 adrenoceptor agonists medetomidine and xylazine have been widely used for wildlife capture and immobilization, either alone or in combination with other drugs (Kreeger, 1996; Nielsen, 1999). However, the physiological effects of sedative and immobilizing drugs may significantly bias the outcome of scientific experiments and clinical biochemistry. Alpha-2 agonists are known to induce hypoinsulinaemia, with subsequent hyperglycaemia, and to modify the stress response measured as the plasma concentration of cortisol (Brearley *et al.,* 1990; Maze & Tranquilli, 1991; MacDonald & Virtanen, 1992; Raekallio *et al.,* 1992; Sanhouri *et al.,* 1992).

Serum glucose and cortisol levels may serve as useful indicators of capture and handling stress in both free-ranging and captive wildlife (Franzmann *et al.,* 1975; Rehbinder & Edqvist, 1981; Rehbinder *et al.,* 1982; Kock *et al.,* 1987; Rehbinder, 1990; Morton *et al.,* 1995; Sire *et al.,* 1995). Serum glucose has also been used to assess nutritional status and body condition in wild animal species

(Franzmann & LeResche, 1978; Neminen, 1980; Nieminen & Timisjärvi, 1983; Soveri, 1995).

In the present study, we report the effects of medetomidine-induced sedation, with subsequent reversal by atipamezole, on serum glucose and cortisol levels in captive reindeer (*Rangifer t. tarandus*).

Materials and methods

Blood samples for the present study were collected from five female reindeer during a pharmacokinetic study on medetomidine and atipamezole (Ranheim *et al.*, 1997). The animals were sedated with 60 µg/kg of medetomidine (Zalopine® 10 mg/ml, Orion Corporation Animal Health, Turku, Finland) i.v. in January and July-August 1994. Atipamezole, 300 µg/kg, (Antisedan® 5 mg/ml, Orion Corporation Animal Health) was administered i.v. for reversal 60 min after injection of medetomidine. Ten ml of blood were collected into sterile, evacuated tubes with no anticoagulant (Venoject®, Terumo Europe NV, Leuven, Belgium) from each animal 24 h and 10 min before and then at 0.5, 1, 1.5, 2, 4, 8, 12 and 24 h after injection of medetomidine. As a control, blood was sampled at the same intervals from each animal in July-August after treatment with corresponding volumes of saline i.v. instead of medetomidine and atipamezole. Treatment with drugs or saline in the summer was separated by at least two weeks and the sequence of treatment was randomized. Serum was separated by centrifugation at 1500 g for 10 min, and was assayed for glucose and cortisol the following day at the Central Laboratory, the Norwegian School of Veterinary Science, Oslo. Serum glucose was measured using an enzymatic method that involves the conversion of glucose to 6-phosphogluconate and NADH. The amount of NADH produced is directly proportional to the concentration of glucose present in the sample and is measured by its absorbance at 340 nm (Technicon Axon® Systems, Miles Inc., Tarrytown, NY, USA). Serum cortisol was analyzed using a competitive immunoassay technique. Cortisol in serum competes with horseradish peroxidase (HRP)-labelled cortisol for a limited number of binding sites on a sheep anti-cortisol antibody presented in the liquid phase. The HRP activity of the bound conjugate is measured by an enhanced luminiscence reaction (Amerlite Cortisol Assay, Ortho-Clinical Diagnostics, Amersham, UK).

Results and discussion

As no obvious seasonal differences were observed, and because of the small number of experimental animals, data from winter and summer treatments were combined (Figs. 1 and 2).

In the present study, serum glucose levels in pretreated and control animals are comparable to reported values in Norwegian reindeer. Larsen *et al.* (1985) found that the mean plasma glucose level in captive reindeer was slightly higher during the fat mobilization phase (November-January) than during the fat deposition phase (July-September). This seasonal difference, 5.27 versus 6.13 mmol/l, is not clinically relevant. In free-ranging reindeer, Hoff *et al.* (1993) reported mean serum glucose values of

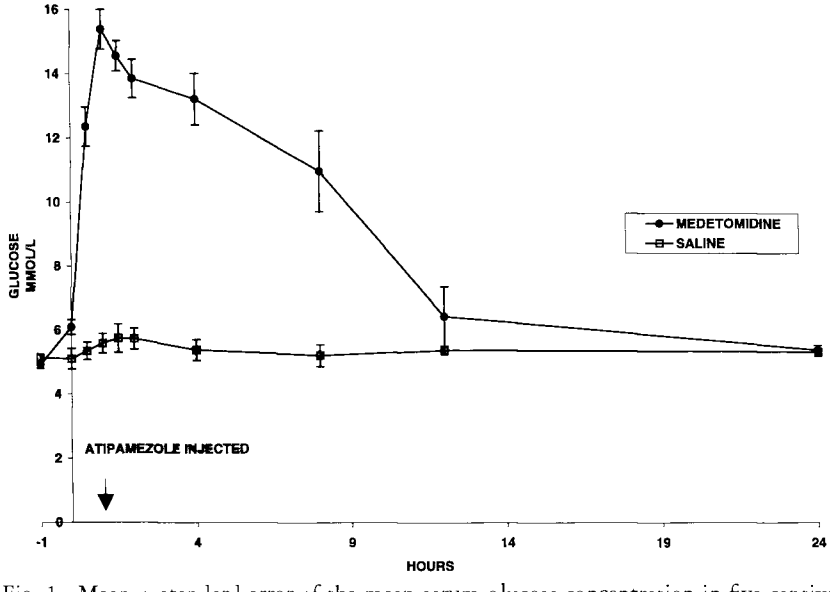

Fig. 1. Mean ± standard error of the mean serum glucose concentration in five captive reindeer (*Rangifer tarandus tarandus*). Medetomidine (60 µg/kg i.v.) was followed by atipamezole (300 µg/kg i.v.) after 1 h (arrow). The experiments were conducted in January and repeated in July-August. The same animals injected with saline in summer were used as controls.

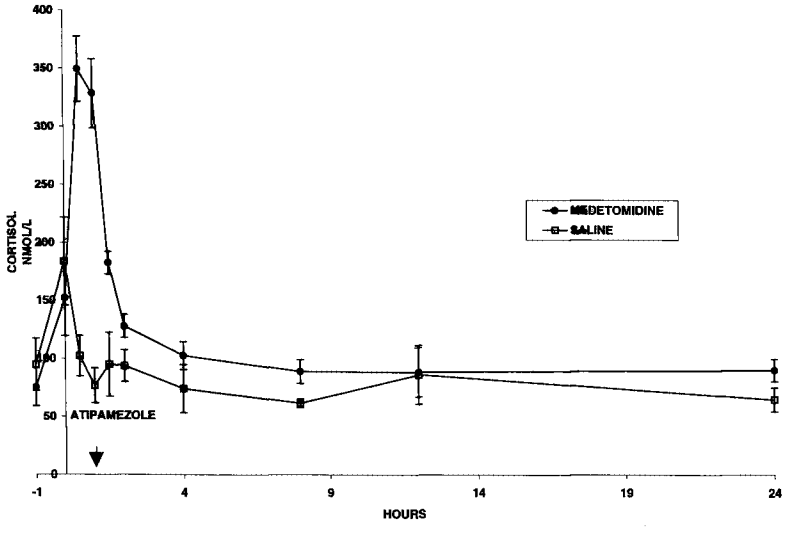

Fig. 2. Mean ± standard error of the mean serum cortisol concentration in five caprive reindeer (*Rangifer tarandus tarandus*). Medetomidine (60 µg/kg i.v.) was followed by atipamezole (300 µg/kg i.v.) after 1 h (arrow). The experiments were conducted in January and repeated in July-Augusr. The same animals injected with saline in summer were used as controls.

5.6 and 7.6 mmol/l, respectively, in two groups of adult animals. Blood levels of glucose in reindeer are highly variable and are influenced by nutritional status and stress (Rehbinder & Edqvist, 1981; Rehbinder *et al.*, 1982; Rehbinder, 1990; Soveri, 1995).

After injection of medetomidine, the serum glucose increased and 0.5 and 1 h postinjection, the mean levels were approximately two to three times higher than in untreated controls. A similar rise in serum glucose has been found in other studies on alpha-2 agonists in ruminants (Eichner *et al.*, 1979; Brockman, 1980; Mautz *et al.*, 1980; Hsu & Hummel, 1981; Kasuya *et al.*, 1996a; Kasuya *et al.*, 1996b).

Following administration of atipamezole, serum glucose concentrations decreased but 8 h after injection of medetomidine, the mean glucose level was still approximately two times higher compared to the controls. In studies on domestic ruminants (Ranheim *et al.*, unpubl.), atipamezole effectively antagonized the medetomidine-induced hyperglycaemia in dairy cows and calves. In sheep, the hyperglycaemic response to medetomidine was biphasic and atipamezole appeared to counteract the second rise in plasma glucose concentrations (Ranheim *et al.*, unpubl.). There are few published reports on the effect of an antagonist on the hyperglycaemic response induced by alpha-2 agonists in ruminants. Hsu & Hummel (1981) found that xylazine-induced hyperglycaemia in cattle was greatly reduced by pretreatment with yohimbine, while Kasuya *et al.* (1996b) reported that atipamezole inhibited xylazine-induced hyperglycemia when the two agents were administered in combination. Alpha-2 adrenoceptor antagonists have no effect on serum glucose when used alone (Hsu & Hummel, 1981; Kasuya *et al.*, 1996b).

In reindeer, a circadian rhythm or an obvious seasonal variation in blood levels of cortisol have not been described (Lund-Larsen *et al.*, 1978; Ringberg, 1979; Nilssen *et al.*, 1985; Sire *et al.*, 1995; Bubenik *et al.*, 1998). Baseline values of plasma cortisol are probably below 30 nmol/l (Rehbinder & Edqvist, 1981; Sire *et al.*, 1995), while values of 30-170 nmol/l have been reported in reindeer being handled or subjected to other forms of stress (Rehbinder & Edqvist, 1981; Rehbinder *et al.*, 1982; Rehbinder, 1990; Sire *et al.*, 1995).

As our reindeer were accustomed to handling and blood sampling, the increase in cortisol concentrations at -10 min in both groups was unexpected. After injection of medetomidine, there was a substantial increase in cortisol and at 0.5 h, the mean concentration was more than three times higher than in the controls. Apparently, a decline in serum cortisol started before administration of atipamezole, and pretreatment levels of serum cortisol were reached 4 h after administration of medetomidine.

Alpha-2 agonists are known to reduce the stress response measured as plasma levels of cortisol in several species, and the increase in cortisol concentrations seen in our reindeer after treatment with medetomidine was not expected. Kallio *et al.* (1988) reported a dose dependent decrease in cortisol concentrations in humans treated with medetomidine, while Raekallio *et al.* (1992) described a decrease in cortisol levels after detomidine administration in horses. In ruminants, xylazine was found to suppress resting cortisol concentrations in goats

(Sanhouri *et al.*, 1992) and to prevent a stress-induced increase in blood levels of cortisol in cattle and goats (Brearley *et al.*, 1990; Sanhouri *et al.*, 1992). In contrast, an increase in plasma cortisol was observed in dairy cows and sheep, but not in dairy calves, after injection of medetomidine (Ranheim *et al.*, unpubl.). The mechanisms of action of alpha-2 andrenoceptor agonists are clearly complex and may be both species and age dependent.

In a previous paper (Ranheim *et al.*, 1997), we showed that medetomidine and atipamezole were rapidly eliminated in reindeer, the median elimination half-lives being 76.1 and 59.9 min, respectively. The decline in serum cortisol levels seemed to parallel the reported fall in plasma concentration of the drugs, while the duration of the serum glucose response lasted several hours after the drugs were detectable in plasma (Ranheim *et al.*, 1997). Obviously, the plasma concentration of medetomidine and atipamezole does not necessarily reflect the concentration of these drugs at the receptors in various tissues. According to Salonen & Eloranta (1990), the metabolites of medetomidine are devoid of any pharmacological effect on the alpha-2 adrenoceptors.

In conclusion, sedation of reindeer with medetomidine caused a substantial increase in serum concentrations of glucose and cortisol. Possible drug-induced effects on these biological parameters should therefore be taken into account in animals which are chemically restrained by alpha-2 adrenoceptor agonists.

Acknowledgements

We thank Hege Osen for valuable cooperation during the experiments. The study was partly funded by the Norwegian Reindeer Husbandry Research Council (Grant no. 10/94) and the Norwegian Research Council (Grant no. 103097/100). Generous supplies of Zalopine® was provided by Orion Corporation Animal Health.

References

Brearley, J. C., Dobson, H. & Jones R. S. 1990. Investgations into the effect of two sedatives on the stress response in cattle. – *J. Vet. Pharmacol. Therap.* 13: 367–377.

Brockman, R. P. 1980. Effects of xylazine on plasma glucose, glucagon and insulin concentrations in sheep. – *Res. Vet. Sci.* 30: 383–384.

Bubenik, G. A., Schams, D., White, R. G., Rowell, J., Blake J. & Bartos, L. 1998. Seasonal levels of metabolic hormones and substrate in male and female reindeer (*Rangifer tarandus*). – *Comp. Biochem. Physiol.* 120C: 307–315.

Eichner, R. D., Prior, R. L. & Kvasnicka, W. G. 1979. Xylazine-induced hyperglycemia in beef cattle. – *Am. J. Vet. Res.* 40: 127–129.

Franzmann, A. W., Flynn, A. & Arneson, P. D. 1975. Serum corticoid levels relative to handling stress in Alaskan moose. – *Can. J. Zool.* 53: 1424–1426.

Franzmann, A. W. & LeResche, R. E. 1978. Alaskan moose blood studies with emphasis on condition evaluation. – *J. Wildl. Manage.* 42: 334–351.

Hoff, B., Rognmo, A., Havre, G. & Morberg, H. 1993. Seasonal hypomagnesemia in reindeer on Kaurokeino winrer pasture in Finnmark County, Norway. – *Rangifer* 13: 133–136.

Hsu, W. H. & Hummel, S. K. 1981. Xylazine-induced hyperglycemia in cattle: a possible involvement of α_2-adrenergic receptors regulating insulin release. – *Endocrinology* 109: 825–829.

Kallio, A., Koulu, M., Scheinin, H., Viikari, J. & Scheinin, M. 1988. Acute effects of medetomidine, a selective α_2-adrenoceptor agonist, on anterior pituitary hormone and cortisol in man. – *Acta Endocrinol.* 119: 11–15.

Kasuya, E., Hodate, K., Matsumoto, M, Sakaguchi, M., Hashzume T. & Kanemats, S. 1996a. The effects of xylazine on plasma concentrations of growth hormone, insulin-like growth facror-I, glucose and insulin in calves. – *Endocr. J.* 43: 145–149.

Kasuya, E., Hodate, K., Matsumoto, M, Sakaguchi, M., Hashzume T. & Kanemats, S. 1996b. Effects of atipamezole, an α_2-adrenergic antagonist, and somatostatin on xylazine-induced growth hormone release in calves. – *Endocr. J.* 43: 551–556.

Kock, M. D., Jessup, D. A., Clark, R. K. & Franti, C. E. 1987. Effects of capture on biological parameters in free-ranging bighorn sheep (*Ovis canadensis*): evaluation of drop-net, drive-net, chemical immobilization and the net-gun. – *J. Wildl. Dis.* 23: 641–651.

Kreeger, T. J. 1996. – *Handbook of Wildlife Chemical Immobilization.* International Wildlife Veterinary Services Inc., Laramie, Wyoming, USA.

Larsen, T. S., Lagercrantz. H., Riemersma, R. A. & Blix, A. R. 1985. Seasonal changes in blood lipids, adrenaline, noradrenaline, glucose and insulin in Norwegian reindeer. – *Acta Physiol. Scand.* 124: 53–59.

Lund-Larsen, T. R., Kofstad, J. & Aakvaag, A. 1978. Seasonal changes in serum levels of aldosterone, cortisol and inorganic ions in rhe reindeer (*Rangifer tarandus*). – *Comp. Biochem. Physiol.* 60A: 383–386.

MacDonald, E. & Virtanen, R. 1992. Chemistry and pharmacology of medetomidine and detomidine: two chemically similar α_2-adrenoceptor agonists used as

veterinary sedatives. – *In:* Short, C. E. & Van Poznak, A. (eds.). *Animal Pain.* New York: Churchill Livingstone Inc., pp. 181–191.

Mautz, W. W., Seal, U. S. & Boardman, C. B. 1980. Blood serum analyses of chemically and physically restrained whire-railed deer. – *J. Wildl. Manage.* 44: 343–351.

Maze, M, & Tranquilli, W. 1991. Alpha-2 adrenoceptor agonists: defining the role in clincal anesthesia. – *Anesthesiology* 74: 581–605.

Morton, D. J., Anderson, E. Foggin, C. M., Kock, M. D. & Tiran, E. P. 1995. Plasma cortisol as an indicator of stress due to capture and translocation in wildlife species. – *Vet. Rec.* 136: 60–63.

Nielsen, L. 1999. *Chemical Immobilization of Wild. and. Exotic Animals.* Iowa State University Press, Ames, Iowa, USA.

Nieminen, M. 1980. Nutritional and seasonal effects on the haematology and blood chemistry in reindeer (*Rangifer tarandus tarandus* L.). – *Comp. Biochem. Physiol.* 66A: 399–413.

Nieminen, M. & Timisjärvi, J. 1983. Blood composition of reindeer. II. Blood chemistry. – *Rangifer* 3: 16–32.

Nilssen, K., Bye, K., Sundsfjord, J. A. & Blix A. S. 1985. Seasonal changes in T_3, FT_4 and cortisol in free-ranging Svalbard reindeer (*Rangifer tarandus platyrhynchus*). – *Gen. Comp. Endocrinol.* 59: 210–213.

Raekallio, M., Leini, A., Vainio, O. & Scheinin, M. 1992. Sympatho-adrenal acrivity and the clinical sedative effect of detomidine in horses. – *Eq. Vet. J.,* Suppl. 11: 66–68.

Ranheim, B., Horsberg, T. E., Nymoen, U., Søli, N. E., Tyler, N. J. C. & Arnemo, J. M. 1997. Reversal of medetomidine-induced sedation in reindeer (*Rangifer tarandus tarandus*) wirh atipamezole increases the medetomidine concentration in plasma. – *J. Vet. Pharmacol. Therap.* 20: 350–354.

Rehbinder, C. 1990. Management stress in reindeer. – *Rangifer* Special Issue No. 3: 267–288.

Rehbinder, C. & Edqvist, L. E. 1981. Influences of stress on some blood consrituents in reindeer (*Rangiferi tarandus* L). – *Acta. Vet. Scand.* 22: 480–492.

Rehbinder, C., Edqvist, L. E. Lundström, K. & Villafane, F. 1982. A field study of management stress in reindeer (*Rangifer tarandus* L). – *Rangifer* 2 (2): 2–21.

Ringberg, T. 1979. The Spirzbergen reindeer – a winrer-dormant ungulate? – *Acta Physiol. Scand.* 105: 268–273.

Salonen, J. S. & Eloranta, M. 1990. Biotransformation of mederomidine. – *Xenobiotica* 20: 471–480.

Sanhouri, A. A., Jones, R. S. & Dobson, H. 1992. Effects of xylazine on the stress response to transporr in male goats. – *Br. Vet. J.* 148: 119–128.

Sire, J. E., Blom, A., Sjaastad, Ø. V., Ropstad, E., Bergdahl Nilsen, T. A., Pedersen, Ø. & Forsberg, M. 1995. The effect of blood sampling on plasma cortisol in female reindeer (*Rangifer tarandus tarandus* L). – *Acta Vet. Scand.* 36: 583–587.

Soveri, T. 1995. *Liver and. rumen microstructure and. blood. values of reindeer calves* (*Rangifer tarandus tarandus* L.) *in winter.* Dissertation, College of Veterinary Medicine, Helsinki, Finland.

Manuscript received. 10 August, 1999
accepted. 24 September, 1999