Haloperidol and Azaperone in Drive-net Captured Southern Chamois (*Rupicapra pyrenaica*)

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ABSTRACT: We investigated the effect of haloperidol and azaperone in drive-net captured Southern chamois (*Rupicapra pyrenaica*). Both tranquilizers have been successfully used in a wide range of wild species for reducing postcapture stress response. During 2005, 39 free-ranging chamois were captured, randomly injected intramuscularly with haloperidol (0.29 ± 0.12 mg/kg; $n=24$), azaperone (1.1 ± 0.82 mg/kg; $n=6$), or saline (0.5 ml; $n=9$), and restrained for 3 hr. Heart rate was higher in the treated chamois; erythrocyte parameters and total protein concentration decreased over time owing to splenic sequestration, hemodilution, vasodilation, and reflex tachycardia. Creatinine, sodium, and chloride remained stable only in the haloperidol-treated group, suggesting an improvement in renal perfusion. Nevertheless, the azaperone-treated chamois displayed higher body temperature, and both treated groups had higher serum muscular enzymes than the control group, suggesting higher muscle stress. These results lead us not to recommend the use of these tranquilizers—especially azaperone—as first-choice neuroleptics in chamois.

Key words: Acute stress, azaperone, chamois, drive-net capture, haloperidol.

The Southern chamois (*Rupicapra pyrenaica*) is a medium-sized mountain ungulate at "low risk of extinction" (Herrero et al., 2008). This elusive species inhabits wild, steep mountain environments making capture by teleanesthesia difficult and risky; this has been described for other mountain species (Abderhalden et al., 1998). Drive-nets have been reported to be safe (2.1% mortality rate) and efficient for capturing chamois (Meneguz et al., 1994; López-Olvera et al., 2009) but stress must be kept to a minimum in order to prevent capture myopathy and improve animal welfare (Spraker, 1993).

The stress response resulting from capture varies depending on species and capture method (Kock et al., 1987). Cate-cholamines and corticosteroids released during stress, together with prolonged exertion, induce changes in hematologic, serum biochemical, and physiologic parameters that are proposed stress indicators (Guyton and Hall, 2006). Physical capture increases heart rate, body temperature, erythrocyte (RBC) count, packed-cell volume (PCV), and serum concentrations of hemoglobin (HGB), lactate, creatinine, urea, bilirubin, chloride, potassium, and muscular enzymes (López-Olvera et al., 2007). Hyperthermia and lactic acidosis may end in capture myopathy, one of the most common complications of wild animal capture (Williams and Thorne, 1996).

The appropriate use of tranquilizers may improve chamois welfare (López-Olvera et al., 2007). Both haloperidol and azaperone are short-acting neuroleptics belonging to the butyrophenones, whose tranquilizing effect is achieved through central dopaminergic and peripheral adrenergic blockade. They may induce hypotension because of their α-adrenergic blockade action (Plumb, 2002). Haloperidol has been stated to be effective as a sedative in small and medium-sized antelope species using doses ranging from 0.06 to 0.45 mg/kg. Azaperone has been used in a wide range of wild herbivores, doses ranging from 0.5 mg/kg to 2.5 mg/kg (Arnemo et al., 1993; Swan, 1993; Ebedes and Raath, 1999). The most common side-effects of butyrophenones are extrapyramidal signs, restlessness, hypertonia, catalepsy, stiffness, tremors, ataxia, allotriophagia, and severe hypotension, normally associated with overdosage (Booth, 1988). The objective of this study was to determine the effects of haloperidol and azaperone in drive-net captured Southern chamois. This study was ap-

proved by the Animal Welfare Committee of the Universitat Autònoma de Barcelona.

Fifty-one free-ranging adult Pyrenean chamois (*Rupicapra pyrenaica pyrenaica*), a subspecies of Southern chamois, were captured in eight capture events using 10×10-cm mesh drive-nets (Ziboni Ornitecnica, Bergamo, Italy) in the national hunting reserves of Cadí (42°18′N, 1°54′E) and Freser-Setcases (42°22′N, 2°09′E), Spain, in the spring and fall of 2005. Captures were performed in early morning to avoid the heat, under similar environmental conditions. Twelve (eight azaperone-treated, three haloperidol-treated, and one control) out of the 51 (24%) captured chamois died at the initial capture resulting from a combination of exhaustion and drug overdose (Mentaberre et al., unpubl. data). These animals are not included in the study. All released chamois that were included were identified with plastic collars, and no additional mortality was detected after the capture events.

Once trapped, 39 of the captured chamois (25 males and 14 females, aged 2–11 yr) were immediately physically restrained, blindfolded, placed in sack nets made of 4×4-cm mesh (Ziboni Ornitecnica) and randomly selected to receive intramuscularly one of three treatments: Six animals received 1.1±0.82 mg/kg (mean±standard deviation) of azaperone (Stressnil, 40 mg/ml; Janssen-Esteve Laboratories, Barcelona, Spain), 24 animals received 0.29±0.12 mg/kg of haloperidol (5 mg/ml; Kern Pharma-Esteve Laboratories, Barcelona, Spain), and nine animals acting as controls received 0.5 ml of saline. Random application of treatment produced disparity in the size of the groups.

Both heart rate and rectal temperature were measured and recorded at 60-sec intervals for at least 2 hr using recording devices (Polar Vantage NV and Polar S710i, Polar Electro Oy, Kempele, Finland and Mätman datalogger, Eltex of Sweden AB, Almut, Sweden), as previously described (López-Olvera et al., 2007). The mean value for every 5-min period was calculated for statistical analysis.

Blood samples were collected from the jugular vein at the moment of capture and each hour thereafter for 3 hr (1, 2, and 3 hr posttreatment). Hematology was performed by means of an automated laser analyzer (Advia 120 hematology system, Bayer, Fernwald, Germany), except white blood cell differential count, which was estimated by identifying 200 leukocytes in blood smears stained with a three-stage commercial rapid stain (Diff-Quick®, Química Clínica Aplicada, Amposta, Spain), and PCV, which was measured using the standard microhematocrit method (Hawksley, Lancing, England). Blood samples were centrifuged at 1200 × G for 15 min and serum was stored at −20 C until analyzed by means of an automated analyzer (Olympus AU400, Olympus, Tokyo, Japan).

Repeated-measures analyses of variance were performed to detect significant differences ($P<0.05$) between groups and within groups over time, using the PROC MIXED procedure of SAS System for Windows, V9.1 (SAS Institute, Cary, North Carolina, USA). The main factor was treatment (azaperone, haloperidol, or saline), and the repeated factor was time. Least-square means were used owing to the unbalanced distribution of animals in the groups.

Heart rate and rectal temperature decreased from the beginning of the monitoring in all groups (Fig. 1). Heart rate was significantly higher in the azaperone-treated group (at 15 min) and in the haloperidol-treated group (at 5–20 min) than in the control group, and stabilized (i.e., no significant differences were found between two consecutive means) at 35 min (haloperidol) or 45 min (azaperone). Heart rate did not stabilize throughout the study period in the control group, which displayed a higher interindividual coefficient of variation (27.25±8.04% [mean±SD]) than the treated groups (azaperone: 24.16±12.47%; hal-
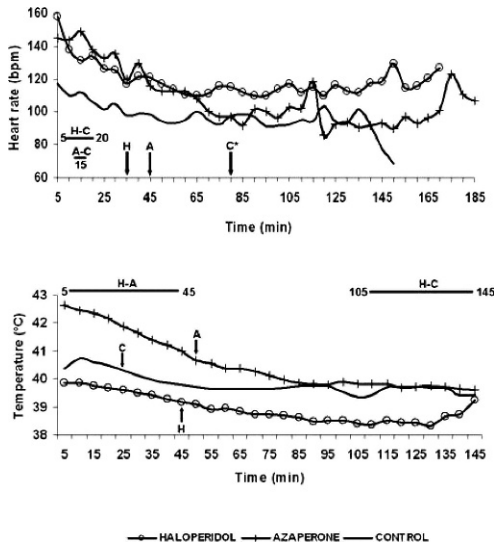
FIGURE 1. Mean heart rate and rectal temperature of captured chamois. C=control, H=haloperidol, and A=azaperone. Arrows indicate stabilization of different treatment groups. C* indicates stabilization of control group in the study of López-Olvera et al. (2007). Bars indicate significant differences ($P<0.05$) between groups.

operidol: $22.50\pm5.60\%$). The haloperidol group displayed lower temperatures than the azaperone-treated (at 5–45 min) and the control (105–150 min) groups. Temperature stabilized earlier in the control group (at 25 min) than in the treated ones (azaperone, 50 min; haloperidol, 45 min).

Erythrocyte count, PCV, and HGB and total protein (TP) concentrations decreased over time in both treated groups, which also displayed lower values of these parameters from 1 hr posttreatment onward. Serum creatinine concentration increased in the control and the azaperone-treated, whereas chloride concentration increased only in the control group. The haloperidol-treated group displayed lower values of serum creatinine, chloride, and sodium concentrations than the control group from 2 hr posttreatment onward. Both treated groups displayed a stronger increase and had higher values of aspartate aminotransferase (AST) and creatine kinase (CK) than the control group at 3 hr posttreatment (Table 1).

The remaining parameters (WBC, serum cortisol, glucose, cholesterol, triglycerides, lactate, bilirubin, and urea concentrations and alkaline phosphatase activity) did not differ between treatments. Three animals receiving high doses of haloperidol (0.38 mg/kg) and azaperone (1.69 mg/kg and 2.5 mg/kg) had extrapyramidal signs, opistotonos, trembling, and tremors.

Heart rate is considered an objective way of assessing the status of the autonomic nervous system when confronted with stressors (Hopster and Blokhuis, 1994). Nevertheless, it can be influenced by numerous factors, with some authors indicating its physiologic variability as a better stress indicator than heart rate itself (Porges, 1985). Red deer (*Cervus elaphus*) treated with phenothiazines also displayed a higher heart rate than control animals (Diverio et al., 1996), which was attributed to the reflex tachycardia secondary to hypotension caused by the tranquilizers (Plumb, 2002). The lack of stabilization of heart rate record in the control group, and the lower interindividual coefficients of variation in the tranquilized chamois suggest a more homogeneous response induced by the tranquilizers.

Physical activity and stress-induced hyperthermia increase body temperature in physically captured and restrained animals; this is an anticipatory response that can increase temperature by 1–1.5 C in the first 10 min (Bakken et al., 1999). Thus, body temperature was already increased and it was starting to decline when monitoring began in our study. Because of this, tranquilizers would only modulate hyperthermia, but not prevent it. The later stabilization of temperature in both treated groups (Fig. 1) could be due to a lack of effect of the tranquilizers over central thermoregulation, as previously reported in wildebeest (*Connochaetes taurinus*) and domestic goats (*Capra hircus*) for haloperidol (Fick et al., 2006 and 2007). Azaperone seemed to worsen hyperthermia probably due to paradoxical excitement (Ebedes and Raath, 1999).

TABLE 1.   Mean hematologic and serum biochemical values of the captured chamois. Different letters (A, B, C, D) indicate statistically significant differences ($P<0.05$) between means within each treatment group (rows). Different italicized numbers (*1*, *2*) indicate statistically significant differences ($P<0.05$) between means of different treatment groups within each time (columns). Reference values (central 95% interval) for Southern chamois captured with the same protocol are provided (López-Olvera et al. 2006a).

Parameter[a]	Reference values for time 0 (López-Olvera et al. 2006a)	Treatment	Time 0	1 hr	2 hr	3 hr
RBC count ($\times10^{12}$/l)	12.12–17.20	Control	14.98	15.36 *1*	15.05 *1*	14.66
		Haloperidol	14.38 A	13.52 B*2*	13.71 B*2*	13.87 B
		Azaperone	14.75 A	13.75 B	13.32 B*2*	13.85
PCV (l/l)	0.43–0.56	Control	0.471	0.473	0.471 *1*	0.465
		Haloperidol	0.468 A	0.440 B	0.439 B	0.443 B
		Azaperone	0.465 A	0.431 B	0.413 B*2*	0.441
Hemoglobin (g/l)	147.0–183.8	Control	178.2	180.8	181.0 *1*	176.4
		Haloperidol	176.0 A	164.7 B	165.1 B*2*	166.1 B
		Azaperone	175.8 A	165.2 B	159.0 B*2*	167.0
Total protein (g/l)	53–86	Control	66.93	67.89 *1*	66.30 *1*	69.59 *1*
		Haloperidol	65.07 A	60.39 B*2*	57.96 B*2*	57.81 B*2*
		Azaperone	63.64 A	57.98 B*2*	59.15	58.65 *2*
CK (IU/l)	254–2,795	Control	2,801.35 A	5,787.59	7,188.96 B	10,655.21 B*1*
		Haloperidol	2,093.21 A	7,562.67 B	15,170.52 C	18,160.61 D
		Azaperone	1,293.66 A	6,939 B	12,531.65 C	19,252.68 D*2*
AST (IU/l)	134–475	Control	326.20 A	354.13 A,B	364 B,C	493.13 C
		Haloperidol	297.59 A	447.76 B	670.24 C	847.36 D
		Azaperone	220.59 A	475.17 B	655 C	817.33 D
Creatinine (mmol/l)	70.72–159.12	Control	136.93 A	154.92 B	161 B*1*	167.96 B*1*
		Haloperidol	127.79	130.05	131.96 *2*	129.49 *2*
		Azaperone	133.85	155.73	157.65	153.37
Chloride (mmol/l)	98.4–127.1	Control	100.19 A	104.10	103.38	109.30 B*1*
		Haloperidol	102.44	102.61	103.04	101.87 *2*
		Azaperone	98.49	102.35	105.58	103.40
Sodium (mmol/l)	122–169	Control	140.91	142.85	140.55	147.44 *1*
		Haloperidol	143.47	140.98	139.58	137.44 *2*
		Azaperone	140.03	141.52	143.87	140.85
Potassium (mmol/l)	3.9–7.2	Control	5.61	5.75 A	5.55	4.92 B
		Haloperidol	5.93 A	5.30 B	4.94 C	4.49 D
		Azaperone	5.98 A	5.34 B	4.95 B,C	4.30 C

[a] RBC = erythrocyte; PCV = packed-cell volume; CK = creatine kinase; AST = aspartate aminotransferase; IU = international units.

However, the lower temperature values of the haloperidol-treated group at the end of the monitoring period could be related to vasodilation-induced heat dissipation, as previously reported for phenothiazines (López-Olvera et al. 2006b, 2007).

Splenic contraction and peripheral vasoconstriction caused by the catecholamines on α-adrenergic receptors in the smooth muscle of the splenic capsule and blood vessels induce an increase in RBC count, PCV, HGB, and TP (Plumb, 2002). These parameters decreased only in the treated groups, probably due to the α-adrenergic blockade caused by the tranquilizers, inducing vasodilation, secondary hemodilution, and splenic sequestration of RBCs (Jain, 1993). The results observed for serum creatinine, chloride, sodium, and potassium concentrations could also be explained by vasodilation of renal arterioles and improvement of renal perfusion induced mainly by haloperidol and, to a lesser extent, azaperone. This effect has been previously reported in chamois tranquilized with acepromazine (López-

Olvera et al., 2007). The leukogram followed a biphasic pattern characteristic of stress, with initial lymphocytic leukocytosis due to epinephrine and then corticosteroid-induced leukocytosis with neutrophilia and lymphopenia (Jain, 1993).

Serum activities of lactate dehydrogenase, alanine aminotransferase, and, especially, CK and AST are good predictors of capture myopathy (Williams and Thorne, 1996). They increase due to damage related to poor tissue perfusion induced by catecholamine vasoconstriction, which increases muscle-cell permeability, decreases heat dissipation, and causes hypoxia. The stronger increase and the higher values observed in the treated chamois could be due to higher muscle stress caused by the appearance of adverse effects of butyrophenones, such as extrapyramidal signs, restlessness, isotonic contractions, allotriophagia, and trembling or stiffness (Ebedes and Raath, 1999).

To summarize, haloperidol demonstrated some effective action in inhibiting the sympathetic-adrenal-medulla axis, as suggested by heart rate, and improved renal function during stress response, as shown by creatinine, chloride, sodium, and potassium, but azaperone was not as protective. The higher increase of serum muscular enzyme activity in both tranquillizer-treated groups suggests that they would not prevent exertional myopathy. Taken as a whole, the results suggest a low safety margin of butyrophenones in this species. Because neither haloperidol nor azaperone improved the effects of acepromazine (López-Olvera et al., 2007) we can not recommend their use at the doses assessed in this study as first-choice neuroleptics in chamois. Additionally, because better results have been observed with butyrophenones in other species, the observed sensitivity could be characteristic of the tribe *Rupicaprini*, and it should be taken into account before using butyrophenones with other species of this tribe.

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