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Authors: Kreeger, Terry J., and Seal, Ulysses S.

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Zoogeographic Region, Unipub, New York, 560 pp.) and since there is evidence that unilateral renal aplasia may have some genetic background then such an occurrence may have further impact on an already genetically-compromised species. In this particular case, however, the female wolf was an unsuccessful breeder and thus has not contributed any further to the present gene pool. Unknown, however, is the prevalence of this abnormality in the existing gene pool, its mode of inheritance, complete pattern of expression and long term effect on successful propagation of this species.

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Failure of Yohimbine Hydrochloride to Antagonize Ketamine Hydrochloride Immobilization of Gray Wolves

Terry J. Kreeger, Department of Fisheries and Wildlife, University of Minnesota, St. Paul, Minnesota 55108, USA; **and Ulysses S. Seal,** Research Service, Veteran's Administration Medical Center, Minneapolis, Minnesota 55417, USA and Departments of Biochemistry and Fisheries and Wildlife, University of Minnesota, St. Paul, Minnesota 55108, USA

The indolealkylamine, yohimbine hydrochloride (HCl), has been used to antagonize ketamine HCl–xylazine HCl anesthesia in a variety of wild and domestic animals (Jessup et al., 1983, J. Am. Vet. Med. Assoc. 183: 1339–1340; Hsu and Lu, 1984, J. Am. Vet. Med. Assoc. 185: 886–888; Jacobson and Kollias, 1984, Proc. Am. Assoc. Zoo Vet., p. 57; Kitzman et al., 1984, Am. J. Vet. Res. 45: 875–879; Jacobson et al., 1985, J. Am. Vet. Med. Assoc. 187: 1195–1198; Mech et al., 1985, J. Wildl. Dis. 21: 405–410; Ramsay et al., 1985, J. Wildl. Dis. 21: 396–400). Although the ability of yohimbine HCl to antagonize xylazine HCl sedation has been well established (Hsu, 1981, J. Pharmacol. Exp. Ther. 218: 188–192; Kitzman et al., 1982, Am. J. Vet. Res. 43: 2165–2169; Jensen et al., 1983, Proc. Am. Assoc. Zoo Vet., pp. 65–66; Hsu and Schulaw, 1984, J. Am. Vet. Med. Assoc. 185: 1301–1303; Hatch et al., 1985, Am. J. Vet. Res. 46: 371–375; Jessup et al., 1985, J. Am. Vet. Med. Assoc. 187: 1251–1253; Renecker and Olsen, 1985, J. Am. Vet. Med. Assoc. 187: 1199–1201), the ability of yohimbine HCl to antagonize ketamine HCl anesthesia is equivocal. "Arousal times" (the ability to regain righting reflex) were shortened significantly in domestic cats anesthetized with 20.0 mg/kg ketamine HCl, then given 0.25 mg/kg yohimbine HCl. Ambulation times, however, were lengthened (Hatch et al., 1983, Am. J. Vet. Res. 44: 417–423). Also, yohimbine HCl (0.5 mg/kg) failed to antagonize ketamine HCl (10.0 mg/kg) anesthesia in rhesus monkeys (Lynch and Line, 1985, Lab. An. Sci. 35: 417–418). Coyotes anesthetized with 2.0 mg/kg xylazine HCl and 4.0 mg/kg ketamine HCl, then given 0.2 mg/kg yohimbine HCl, appeared to have a residual ketamine HCl effect which emerged after the antagonism of xylazine HCl (Kreeger and Seal, 1986, J. Wildl. Dis. 22: 604–606). The purpose of the present paper was to determine if yohimbine HCl could antagonize ketamine HCl anesthesia in gray wolves (*Canis lupus* L.).

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Ten adult gray wolves (five female, five

TABLE 1. Head up and walk times of gray wolves anesthetized with 25.0 mg/kg ketamine HCl, then given 0.2 mg/kg yohimbine HCl.

Wolf no.[a]	Sex	Weight (kg)	Head up time (min)		Walk time (min)	
			Yohimbine HCl	Control	Yohimbine HCl	Control
210	F	32	5	20	100	91
204	F	29	5	26	46	80
35	F	30	7	9	80	47
142	F	30	1	1	69	50
212	F	28	4	20	128	130
245	M	35	8	5	108	164
246	M	40	7	10	169	106
247	M	35	5	5	102	92
213	M	38	7	16	118	132
229	M	42	8	38	132	92
Mean ± SE		33.9 ± 1.5	5.7 ± 0.7[b]	15.0 ± 3.6[b]	105.2 ± 11.0	98.4 ± 11.5

[a] Each individual served as its own control with different treatments given on alternate weeks.
[b] Values significantly different at $P < 0.05$.

male) were housed in outdoor kennels in east-central Minnesota, fed commercial dry dog chow supplemented with road-killed deer, and provided water ad libitum. In January 1986, the wolves were anesthetized with 25.0 mg/kg ketamine HCl (Ketaset®, Bristol Laboratories, Syracuse, New York 13201, USA) given intramuscularly via gas-operated dart pistol or pole syringe. Exactly 15 min after the animal was considered immobilized, each received either 0.2 mg/kg yohimbine HCl (Sigma Chemical Co., St. Louis, Missouri 63178, USA), or an equivalent volume of its vehicle via the cephalic vein. Yohimbine HCl was prepared by dissolving it in sterile, distilled water with mild heating (<50 C), then diluting with sterile 50% dextrose to achieve a 5% dextrose solution containing 5 mg/ml yohimbine HCl.

A technician injected the yohimbine HCl or vehicle and determined head up time (HUT) and walk time (WT) without knowing which animal received which substance in a single blind paradigm. HUT was the time from injection of yohimbine HCl or vehicle to when the animal raised its head from lateral recumbency; WT was the time from injection of yohimbine HCl or vehicle to when the animal could walk in a directed, coordinated manner of its own accord as well as negotiate objects in its path and respond appropriately to humans and to other wolves. One wk later, each animal was given the alternate solution that it received the previous week, thus serving as its own control. Statistical analysis was by Student's paired t-test and Wilcoxon matched pairs test. Means are reported with standard errors.

The mean induction times (time from initial injection to immobilization) were 5.5 ± 0.4 min for the first trial and 4.3 ± 0.4 min for the second trial and were not significantly different ($P > 0.05$). Test and control HUT's were significantly different ($P < 0.02$). There was no difference between test and control WT's ($P \geq 0.56$) (Table 1). Male control WT's (117.2 ± 13.8) were significantly greater than female control WT's (79.2 ± 14.8) ($P < 0.03$). Though not significant, WT's for males given yohimbine HCl (125.8 ± 11.9) were noticeably longer than female WT's (84.6 ± 13.9) ($P \geq 0.16$). The pattern of recovery was the same regardless of treatment: the animal initially raised its head, then forequarters; then after a variable period of time, raised its hindquarters. All animals had palpebral and corneal reflex-

es both when immobilized and after they raised their heads. Female wolf no. 142 had the shortest HUT's due to her being only "lightly immobilized" with the given dose of ketamine HCl. Administration of either yohimbine or its vehicle initiated almost an immediate response in this animal. No adverse effects were noted in either group during recovery.

Yohimbine HCl is classified as an alpha$_2$-adrenergic antagonist (Goldberg and Robertson, 1983, Pharmacol. Rev. 35: 143–180) although it may interact with cholinergic (Zetler and Thorner, 1973, Pharmacology 10: 238–251), serotonergic (Sanghvi and Lershon, 1970, Eur. J. Pharmacol. 11: 125–129), or dopaminergic (Scatton et al., 1980, J. Pharmacol. Exp. Ther. 215: 494–499) receptors.

The mode of action of ketamine HCl appears to be quite complex and remains to be elucidated. Ketamine HCl has central (Leeuwin et al., 1984, Br. J. Pharmacol. 82: 339–347) as well as peripheral (Maleque et al., 1981, J. Pharmacol. Exp. Ther. 219: 638–645) anticholinergic activity. Ketamine HCl also can increase the release of dopamine from nerve terminals (Havdala et al., 1980, Anesthesiology 53: S57), stimulate serotonin release (Wright, 1982, J. Am. Vet. Med. Assoc. 180: 1462–1471), reduce synaptic excitation via N-methylaspartate receptors (Anis et al., 1983, Br. J. Pharmacol. 79: 565–575), and bind sterospecifically to opiate receptors (Finck and Ngai, 1982, Anesthesiology 56: 291–297).

Consequently, many substances besides yohimbine HCl have been investigated as possible ketamine HCl antagonists. Cholinesterase inhibitors, such as physostigmine and neostigmine, have decreased sleeping times in humans given ketamine HCl (Balmer and Wyte, 1977, Br. J. Anaesth. 49: 510; Toro-Matos et al., 1980, Anesth. Analg. (Cleve.) 59: 764–767). Physostigmine shortened anesthesia time, but did not reverse analgesia, in rats given ketamine HCl (Lawrence and Livingston, 1979, Br. J. Pharmacol. 67: 426). Physostigmine did not shorten ketamine HCl-induced anesthesia in domestic cats (Hatch and Ruch, 1974, Am. J. Vet. Res. 35: 35–39). Naloxone, an opioid antagonist, reduced the duration of ketamine HCl analgesia in rats (Lakin and Winters, 1978, Proc. West. Pharmacol. Soc. 21: 27–30). Like yohimbine HCl, 1-amphetamine and 4-aminopyridine shortened arousal times in cats anesthetized with ketamine HCl, but did not shorten walk times or reduce ketamine HCl-induced cataleptic motor impairment (Hatch and Ruch, 1974, op. cit.; Hatch et al., 1983, op. cit.). Thus, if consciousness in mammals is mediated by multiple control mechanisms, administration of drugs having selective activity on one neurotransmitter system might only partially antagonize the actions of an anesthetic.

This hypothesis appears to have been substantiated in the present study. The HUT for wolves given yohimbine HCl was markedly less than the control HUT and wolves given yohimbine HCl appeared capable of movement sooner than when given the vehicle. This movement, however, was not directed or otherwise controlled. If the effects of ketamine HCl are mediated by several receptors, yohimbine HCl could have antagonized only a subset of these receptors, or acted as a stimulant to overcome some of the effects of anesthesia. These observations are consistent with previous findings (Hatch et al., 1983, op. cit.).

The differences between female and male WT's were interesting. In a previous study, female lynx (*Lynx canadensis* Kerr) immobilized with the cyclohexane, phencyclidine, had significantly shorter immobilization times than did males (Berrie, 1972, J. Wildl. Manage. 36: 994–996). Although time of day could affect receptor populations and subsequent response to anesthesia (Jhanwar-Uniyal et al., 1986,

Life Sci. 38: 473–482), all wolves in this study were immobilized during the same time period for both trials. At the time of this study, wolves were entering their reproductive season. It is possible that the hormone milieu associated with reproduction could alter receptor populations or sensitivity, resulting in a differential response to the immobilizing drugs. In ovariectomized rats, exogenous administration of ovarian steroids increased beta-adrenergic receptors in the cerebral cortex, hypothalamus, and anterior pituitary (Petrovic et al., 1985, Life Sci. 37: 1563–1570). Further research would be required to ascertain a similar phenomenon in wolves.

Although previous investigations have claimed that yohimbine HCl "antagonizes" ketamine HCl-induced anesthesia (Hatch, 1973, Pharmacol. Res. Commun. 5: 311–320; Hatch and Ruch, 1974, op. cit.), this claim depends on one's definition of "reversal" or "antagonism." From a field biologist's viewpoint, it would seem reasonable to define antagonism of anesthesia as the point when the animal is capable of defense or escape. At any point before this, the animal could be subject to predation, intraspecific aggression, or accident. In this study, we chose intentionally to define antagonism of anesthesia as when the animal appeared to be physically and mentally "normal." By this definition, we have concluded that yohimbine HCl does not antagonize ketamine HCl-induced immobilization of gray wolves.

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