Chemical immobilization in American black bears using a combination of nalbuphine, medetomidine, and azaperone

Lisa L. Wolfe[1,4], Heather E. Johnson[2], Mark C. Fisher[1], William R. Lance[3], David K. Smith[3], and Michael W. Miller[1]

[1]*Colorado Division of Parks and Wildlife, Wildlife Health Program, 4330 Laporte Avenue, Fort Collins, CO 80521, USA*
[2]*Colorado Division of Parks and Wildlife, 415 Turner Drive, Durango, CO 81303, USA*
[3]*Wildlife Pharmaceuticals, Inc., 1230 Ash Street, Windsor, CO 80550, USA*

Abstract: Safe and effective but unscheduled drug combinations are needed for wildlife immobilization in some jurisdictions. To this end, we evaluated a combination of nalbuphine HCl (40 mg/mL), medetomidine HCl (10 mg/mL), and azaperone tartrate (10 mg/mL)—referred to as NalMed-A (or NAM)—in 28 American black bears (*Ursus americanus*), captured during June to August 2014 as part of an ongoing study conducted in and around Durango, Colorado, USA. We effectively immobilized all bears; induction (mean $\pm$ SE) was 16.2 $\pm$ 0.9 minutes (n = 25) and reversal was 19 $\pm$ 1.6 minutes (n = 24). Advantages of NalMed-A included low delivery volume, good sedation quality, and effective reversal. Moreover, NalMed-A does not contain compounds regulated by the U.S. Drug Enforcement Administration, making it a useful unscheduled immobilization combination. Based on these and subsequent field experiences, our dosing recommendations are 0.5–1 mL NalMed-A/45.5 kg estimated body mass (0.44–0.88 mg nalbuphine HCl/kg, 0.11–0.22 mg azaperone tartrate/kg, and 0.11–0.22 mg medetomidine HCl/kg), and 5 mg atipamezole HCl/mg medetomidine for antagonism.

Key words: American black bear, atipamezole, azaperone, chemical immobilization, medetomidine, nalbuphine, sedation, tranquilizer, *Ursus americanus*

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Animal capture via chemical immobilization is an important element of wildlife management and research, including work on American black bears (*Ursus americanus*). In Colorado, USA, black bears are routinely immobilized and handled by wildlife officers and biologists to protect public safety, resolve human–bear conflicts, and gather data to refine population management. It follows that immobilizing drug combinations for black bears in Colorado must be both accessible and robust in order to perform across a wide range of conditions, including work in urban settings with bears that are extremely excited or agitated prior to receiving any capture drugs. These needs and usage patterns are common among jurisdictions across North America that are managing black bear populations.

The drug combinations most widely used for capturing and handling black bears include dissociatives (tiletamine hydrochloride [HCl] or ketamine HCl) or potent opioids (e.g., Bush et al. 1980, Gibeau and Paquet 1991, Kreeger and Arnemo 2012, Kreeger et al. 2013). In the United States, the possession and use of these drugs—classified as "controlled substances"—are strictly regulated by the U.S. Drug Enforcement Administration (DEA). The Veterinary Mobility Act (2014, H.R. 1528) amended the Controlled Substances Act to allow possession and field use of controlled substances by licensed veterinarians registered with the DEA. Under 42 CFR section 1301.12(a), each location of storage and use requires a separate registration, which complicates access to and field use of capture drugs. Use of scheduled drugs in the field is further complicated by requirements for secure storage (21 CFR §1301.71). Severe penalties can be imposed for violating DEA rules: according to the American Veterinary Medical Association "very few things cause more anxiety for veterinarians in practice than the possibility of running afoul of the DEA and Controlled Substances Act" (https://www.avma.org/KB/Resources/Reference/Pages/dea-registration).

To meet wildlife immobilization needs in Colorado and comply with federal rules, we have sought safe

[4]email: lisa.wolfe@state.co.us

and effective but unscheduled alternative drug combinations for wildlife work (Wolfe et al. 2014a, b). A combination of butorphanol tartrate, azaperone tartrate, and medetomidine HCl (BAM; Wildlife Pharmaceuticals Inc., Fort Collins, Colorado, USA) has been used to immobilize black bears throughout Colorado in urban and exurban settings (Wolfe et al. 2008 and unpublished data). Although its scheduling is lower than that of more potent opioids (Schedule CII) or dissociatives (CIII), butorphanol is a scheduled (CIV) drug and consequently BAM is still subject to DEA oversight.

We recently described a novel combination of nalbuphine HCl, medetomidine HCl, and azaperone tartrate (NalMed-A; Wolfe et al. 2014b) that was not subject to DEA regulations but otherwise showed attributes similar to BAM, including safety, efficacy, rapid antagonism, and small-volume delivery. Nalbuphine—an opiate κ agonist/μ antagonist—has pharmacological properties similar to butorphanol and produces mild analgesia and sedation with relatively few potential adverse effects (KuKanich and Wiese 2015). However, unlike butorphanol and the more potent opioids, abuse potential with nalbuphine appears quite low and consequently this opioid is not scheduled by the DEA (USDEA 2013). Medetomidine is a potent α_2 adrenoceptor agonist with sedative and analgesic properties antagonized by atipamezole (Jalanka and Roeken 1990). Medetomidine provides smooth induction and good muscle relaxation (Jalanka and Roeken 1990) that can be potentiated by the effects of opioids such as nalbuphine and butorphanol (Wolfe et al. 2008, 2014b). Azaperone—a butyrophenone—is a short-acting neuroleptic sedative that has been used to reduce stress from capture and handling in a number of species and can be used in combination with other drugs to synergize effective chemical immobilization (Colly 1992, Ebedes 1992). In addition to the simplified storage and use requirements for this drug combination, the components of NalMed-A are likely metabolized rapidly after recovery. A default withdrawal period of 30 days has been used for BAM; however, recent laboratory analyses did not detect butorphanol, azaperone, medetomidine, or atipamezole in liver or muscle of white-tailed deer (*Odocoileus virginianus*) after 11 days (W.R. Lance, unpublished data). A similar withdrawal time would be expected with NalMed-A.

To further our efforts to identify broadly useful, wildlife-immobilizing drug combinations that are safe and effective but unscheduled, we evaluated the field use of NalMed-A for chemical immobilization in black bears.

Methods

During June to August 2014, we immobilized 25 adult, free-ranging black bears (17 M, 8 F) as part of an ongoing study (Johnson et al. 2011; Colorado Division of Parks and Wildlife Animal Care and Use Committee file no. 01-2011) conducted in and around the town of Durango, Colorado, USA (elevation approx. 2,000 m above sea level), as well as 3 bears that were being relocated or euthanized as a result of human conflict.

The NalMed-A components were premixed in a single vial for ease of field use. The NalMed-A solution had final concentrations of 40 mg nalbuphine HCl/mL, 10 mg azaperone tartrate/mL, and 10 mg medetomidine HCl/mL. We initially extrapolated dosing from previous experience with BAM in >200 black bears (Wolfe et al. 2008 and unpublished data) and therefore used 1 mL NalMed-A/45.5 kg body mass for estimated dosages of 0.88 mg nalbuphine HCl/kg, 0.22 mg azaperone tartrate/kg, and 0.22 mg medetomidine HCl/kg.

We captured 23 research bears in cage traps and delivered drugs via intramuscular injection with a pole syringe (DAN-INJECT, Børkop, Denmark); 2 of the conflict bears were captured in culvert traps, and the remaining 3 bears were darted with CO_2-powered rifles (DAN-INJECT). We avoided injection placement in fat pads to insure consistent drug absorption. We visually estimated body mass for dosing, and we then weighed immobilized animals using a suspended scale to calculate actual dosages used. We measured induction as the time lapsed from NalMed-A injection until sternal recumbency or head down and unresponsive to stimuli (i.e., when we considered the bear as safe to handle).

Once the animal was immobilized, we took study-specific biometrics, blood via femoral venopuncture, and one or more sets of vital signs. We measured heart rate with a pulse oximeter (SurgiVet V3402; Smiths Medical PM, Inc., Waukesha, Wisconsin, USA) or via cardiac auscultation with a stethoscope. We measured respiration by observation of chest movement. We measured rectal temperature with a digital thermometer (FlashCheck; DeltaTrak, Pleasanton, California, USA). Although we used a pulse oximeter, oxygen saturation was monitored but not consistently

recorded under field conditions, in part because we routinely supplemented oxygen at 2 L/minute with an intransal canula (Roscoe Medical, Strongsville, Ohio, USA) to assure SpO_2 remained ≥90%. We monitored vital rates approximately every 10 minutes throughout the handling period. We fitted 8 adult female bears with radiocollars, and we monitored their posthandling survival for ≥6 months (as part of the ongoing survival study). We marked the remaining bears with ear-tags or transponder tags so they could be identified if recaptured or encountered as a mortality. We antagonized medetomidine with intramuscular injection of atipamezole HCl (5 mg/mg medetomidine HCl; Wildlife Pharmaceuticals, Inc.). We measured reversal as time lapsed from atipamezole injection until the animal was able to stand. We used mixed-effect models to estimate mean vital rates throughout the handling period. The fixed effect was an intercept-only model (to estimate mean values) and the random effect was individual bear, accounting for repeated measurements of the same animal taken during the handling process. We fit models with the package lme4 (Bates et al. 2013) using Program R (version 3.0.2; R Development Core Team 2013).

Results

All 28 black bears were successfully immobilized with the NalMed-A combination. The mean measured body mass of the bears was 66 kg (standard error [SE] = 5, range = 21–115 kg) and the mean volume delivered was 1.4 mL (SE = 0.1), equating to mean dosages of 0.8 mg/kg (SE = 0.3) nalbuphine HCl, 0.2 mg/kg (SE = 0. 01) azaperone tartrate, and 0.2 mg/kg (SE = 0.01) medetomidine HCl. Mean induction was 16.2 minutes (n = 25, SE = 0.9, range = 10–26 min). We considered quality of sedation to be good in all bears based on our ability to safely handle and sample the animals throughout the processing period ($\bar{x}$ = 40 min, SE = 3, range = 18–67 min). Only 3 bears required a supplemental dose (one-quarter of original dose) of NalMed-A for complete immobilization.

Based on vital-rate measurements of 25 bears taken throughout the immobilization period, mean respiratory rate was 7 breaths/minute (SE < 1, range = 5–14), mean heart rate was 40 beats/minute (SE = 2, range = 30–58), and mean rectal temperature was 38.3°C (SE = 0.1, range = 37.3–39.7°C). Mean reversal time was 19 minutes (n = 24, SE = 2, range = 7–36 min) after administration of intramuscular atipamezole. Bears were ambulatory and responsive but calm on reversal because only medetomidine was antagonized and nalbuphine and azaperone were still on board. Except for the 2 bears that were euthanized because of conflicts, we observed no mortalities within 1 week after release, and survival of telemetered bears was equivalent to that of other bears monitored during the Durango study (H.E. Johnson, unpublished data).

Discussion

Beneficial properties of NalMed-A as a chemical immobilization combination included low volume of delivery, good quality of sedation, and effective reversal. From our initial field assessments, NalMed-A appears to be an effective drug combination for immobilizing trapped or treed black bears. Moreover, in situations where use of scheduled drugs is precluded or unreasonably constrained by regulatory compliance, such as when used in the field by nonveterinary personnel, this combination offers the benefit of being unscheduled. Overall, the immobilization properties of NalMed-A in bears were similar to our experiences with BAM (Wolfe et al. 2008 and unpublished data). The concentration of NalMed-A allowed us to use a relatively low total drug volume for sedation (<2 mL for most individuals) that could be easily delivered with either a pole syringe or dart. We regarded the quality of sedation as sufficient for safe handling and sampling (e.g., blood draw, ear tag, and radiocollar placement). Three bears required supplemental NalMed-A for adequate immobilization, likely because their mass was underestimated. Unlike dissociatives, this combination is reversible with atipamezole alone, providing a smooth recovery. Although not used with these bears, nalbuphine can be antagonized with naltrexone (0.6 mg/kg; Wildlife Pharmaceuticals, Inc.), which may speed the rate of recovery.

Bears immobilized with NalMed-A showed respiratory rate depression similar to that reported for other drug combinations (Caulkett and Cattet 1997, Wolfe et al. 2008, Kreeger et al. 2013). Consequently, we recommend using supplemental oxygen when immobilizing black bears with NalMed-A. In addition, care should be taken to give intramuscular injections because medetomidine HCl is lipophilic and absorption from fat pads will be slow. In order to maximize the effectiveness of NalMed-A (and BAM)

immobilization in black bears, we preferentially use injection sites in the shoulder or leg and avoid injecting into the back or rump. Although not observed in the bears we immobilized, spontaneous arousal (Kreeger and Arnemo 2012) could occur in bears immobilized with NalMed-A.

We recognize that medetomidine dosage reported here is relatively high compared with that in other combinations used to immobilize black bears (e.g., Wolfe et al. 2008, Kreeger and Arnemo 2012). Black bears can be effectively immobilized with 0.5 mL NalMed-A/45.5 kg body mass (L.L. Wolfe, unpublished data), delivering a medetomidine dose (approx. 0.11 mg HCl/kg) similar to that originally described for butorphanol–azaperone–medetomidine (Wolfe et al. 2008). However, the occasional need for supplemental injections when using lower NalMed-A doses made this less well-suited for the circumstances in which our officers typically operated, and thus we sought to err on the side of a dosage that would result in a high probability of effective immobilization with a single administration. Based on initial observations, NalMed-A appears to be a promising drug combination for immobilizing bears and warrants further evaluation.

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