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Authors: Semple, Hugh A., Gorecki, Dennis K. J., Farley, Sean D., and Ramsay, Malcolm A.

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PHARMACOKINETICS AND TISSUE RESIDUES OF TELAZOL® IN FREE-RANGING POLAR BEARS

Hugh A. Semple,[1,4] Dennis K. J. Gorecki,[1] Sean D. Farley,[2] and Malcolm A. Ramsay[3]

[1] College of Pharmacy and Nutrition, University of Saskatchewan, 110 Science Place, Saskatoon, Saskatchewan, Canada, S7N 5C9

[2] Alaska Department of Fish and Game, 555 Raspberry Road, Anchorage, Alaska, USA, 99518

[3] Department of Biology, University of Saskatchewan, 112 Science Place, Saskatoon, Saskatchewan, Canada, S7N 5E2

[4] Corresponding author (e-mail: hsemple@kinetana.com)

ABSTRACT: A pharmacokinetic and tissue residue study was conducted to assess the risks associated with human consumption of polar bears in arctic Canada that have been exposed to the immobilizing drug Telazol®, a mixture of tiletamine hydrochloride and zolazepam hydrochloride. Twenty-two bears were remotely injected with about 10 mg/kg of Telazol®. Following immobilization, serum samples were collected serially at regular intervals until the bears awakened. Sixteen of the bears were relocated and killed under permit by local hunters at various times from 0.5 to 11 days after dosing. Serum, kidney, muscle and adipose tissue samples were collected immediately after death. All samples were stored at −70 C until analysis by HPLC. The concentration-time data of tiletamine and zolazepam in serum during the immobilization period were fitted to curves by computer and the pharmacokinetic parameters assessed. In addition, the serum and tissue samples collected at the time of death were analyzed for both parent drugs, for one metabolite of tiletamine (CI-398), and for three metabolites of zolazepam (metabolites 1, 2 and 4). A one-compartment model with first-order absorption and elimination best fit the time-series data for the drugs in serum during the immobilization period. This model gave half-lives (mean ± SE) for tiletamine and zolazepam of 1.8 ± 0.2 h and 1.2 ± 0.08 h, respectively, clearance values of 2.1 ± 0.3 $l \cdot h^{-1} \cdot kg^{-1}$ and 1.1 ± 0.1 $l \cdot h^{-1} \cdot kg^{-1}$, and volumes of distribution of 5.2 ± 0.6 l/kg and 1.8 ± 0.2 l/kg. The concentrations of both drugs and their metabolites declined rapidly to trace levels by 24 h post-dosing, although extremely low concentrations of some metabolites were encountered sporadically over the entire sampling period. In particular, zolazepam metabolite 2, remained detectable in fat and muscle tissue at the end of the study, 11 days after dosing. It was concluded that during immobilization, both tiletamine and zolazepam levels decline rapidly in a monoexponential fashion, and their pharmacokinetic parameters in polar bears are similar to those observed in other species. Tissue levels of the drugs and their metabolites declined sufficiently rapidly that individuals eating meat from exposed bears would be unlikely to experience pharmacological effects from the drugs. Nevertheless, slight exposure to the drugs and/or their metabolites might be possible for an indeterminate time after dosing.

Key words: Immobilization, pharmacokinetics, polar bear, Telazol®, tiletamine, tissue residues, *Ursus maritimus*, zolazepam.

INTRODUCTION

Telazol® is an injectable drug product widely used as a veterinary anesthetic and immobilizing agent in certain mammalian species. Chemically, the preparation is a combination of equal parts of tiletamine hydrochloride (henceforth tiletamine), a dissociative anesthetic, and zolazepam hydrochloride (henceforth zolazepam), a minor tranquilizer (Fig. 1). The dissociative anesthetic, when used alone, can cause convulsions, which are normally prevented by combining the drug with a weak anticonvulsant such as a tranquilizer. Thus, smooth induction of and recovery from anesthesia is assured.

Each year, Telazol® is used to anesthetize several hundred free-ranging polar bears (*Ursus maritimus*) as part of various research and management programs in the United States, Canada, Greenland and Svalbard. There is no doubt that, compared with other available products, Telazol® represents a superior anaesthetic for use in research on polar bears, both in terms of safety for the researchers and the reduced risk of accidental deaths to bears (Stirling et al., 1989). However, Telazol® is still listed as an experimental drug in Can-

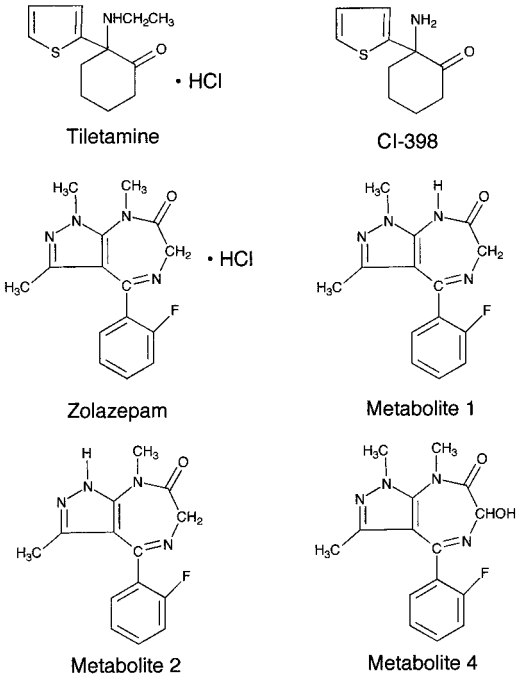

FIGURE 1. Structures of the constituent drugs of Telazol®, tiletamine and zolazepam, and their metabolites CI-398 (of tiletamine), zolazepam metabolite 1, zolazepam metabolite 2 and zolazepam metabolite 4.

ada and has not yet been approved for routine use (Bureau of Veterinary Drugs, Health Protection Branch of Health and Welfare, Ottawa, Ontario, Canada). In particular, no data are currently available on the residency time of the drugs and their respective metabolites in the tissues of animals after they have been anesthetized.

Native people in the Canadian arctic kill more than 600 polar bears each year. For these people, information on Telazol® residency time is essential for assessing the health hazards associated with eating polar bear tissue. Consequently, several native communities in the Northwest Territories and Nunavut (Canada) have requested their territorial governments to commission appropriate studies to determine Telazol® residency time in polar bear tissue.

This project was undertaken to evaluate the pharmacokinetic properties of both constituent drugs of Telazol®, tiletamine and zolazepam, in order to determine how long drug residues are likely to remain in tissues and fluids of polar bears after immobilization. Samples of serum, muscle, fat, and kidney were collected from several bears, killed between 0.5 and 11 days after being immobilized with Telazol®, and analyzed for the parent drugs. The muscle, fat and kidney samples also were analyzed for one metabolite of tiletamine and three of zolazepam.

MATERIALS AND METHODS

Chemicals

Drug standards of tiletamine, Lot #013928 and zolazepam, Lot #013922, were the gift of Fort Dodge Laboratories (Fort Dodge, Iowa USA). Standards of CI-398, ripazepam and three different zolazepam metabolites were the gift of Park-Davis (Ann Arbor, Michigan, USA). The Telazol® used for immobilizations was obtained from A.H. Robins Co. (Richmond, Virginia, USA) (1992) and Fort Dodge Laboratories Inc. (1993 and 1994). The ethyl acetate and acetonitrile used in assays were HPLC grade (OmniSolv, BDH Inc., Toronto, Ontario, Canada), while all other chemicals were reagent grade.

Administration of Telazol® and collection of tissue samples

All animal procedures were carried out according to Canadian Council on Animal Care guidelines as assessed by the University Committee on Animal Care and Supply (University of Saskatchewan, Saskatoon, Saskatchewan, Canada). The general field-sampling protocol was proposed by the Bureau of Veterinary Drugs (Health Protection Branch of Health and Welfare, Ottawa, Ontario, Canada) and called for three male bears to be sampled at each of five time periods (0.5 days, 1 day, 2 days, 5 days, and 10 days) after administration of Telazol®.

The fieldwork was based out of Resolute (Nunavut, Canada; 74.5°N; 95.0°W). That site was chosen because of the presence there of the Polar Continental Shelf Project (Ottawa, Ontario, Canada) research facility, which offered superb logistical support, and because of the interest in the project expressed by the members of the Resolute Hunter's and Trappers Association (HTA; Resolute, Nunavut, Canada). The Resolute HTA offered 16 of their assigned polar bear tags for use in the Telazol® study. In addition to these 16 bears (A to M, T to V), serial blood samples for the first 1 to 5 hr after administration of Telazol® were taken from an additional six bears (N to S) which

were not killed. Fieldwork began in the spring of 1992 and was completed in the spring of 1994.

We used a Bell 206B helicopter (Bell Helicopter Textron, Montreal, Quebec, Canada) to search for polar bears in 1992 and a Bell 206L model in 1993 and 1994. All male polar bears sighted were captured and sampled. Each animal was anaesthetized by remote injection of Telazol® using standard methods identical to that of research and management programs currently in operation within Canada (Stirling et al., 1989). On completion of sampling, the bears were placed in a side-recumbent position facing away from the wind and left to recover normally.

"Time of dosing" was recorded as the time when the first injection of Telazol® was administered. Some bears required a second administration of drug during the initial capture operation, but "Time of dosing" was recorded when the first injection occurred.

As soon after initial anesthetization as safely possible, an indwelling peripheral venous catheter (Angiocath, Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA) was inserted into either a cephalic or sublingual vein. The catheter allowed us to collect serial samples of blood into evacuated glass tubes (Vacutainer, Becton, Dickinson and Company for subsequent analyses. An initial blood sample was taken immediately after installation of the catheter and serial samples were taken approximately every 20 min if logistical constraints allowed. Serum samples were usually collected for at least 2.5 hr after initial administration of Telazol®. If the bear showed signs of imminent arousal, further Telazol® was administered intra-muscularly, but then no further serial blood samples were taken. The total amount of Telazol® administered was the sum of all injections. Blood samples were kept at 5 C until evening. In the field laboratory blood samples were separated by centrifugation, the serum was decanted into individually labeled polypropylene vials, and stored at −20 C. Within 3 wk of collection the samples were archived at −70 C.

Unmarked bears were assigned a unique identifying number, which was applied as a tattoo to each upper lip. Body mass was determined by weighing the bears with an electronic load cell (accuracy ± 0.5 kg; Sensi-Tech Ltd., Saskatoon, Saskatchewan, Canada). Standard morphometric measures (axillary girth and straight line length) also were taken. A vestigial premolar tooth was extracted from each bear for age determination by counting annual cementum depositions (Calvert and Ramsay, 1997).

Each polar bear was fitted with a small (circa 50 g) VHF radio transmitter (Holohil Systems Ltd., Woodlawn, Ontario, Canada) in each ear to facilitate relocation. The radios had a 5 mm diameter nylon bolt extending from the rear, which was inserted through a hole punched in each ear and fastened with a nylon nut fitted over the bolt. Leather washers abutted the ear to keep the pressure of the radio's mass distributed over the ear surface. The ear punch used to perforate the ear was the same as that used to fit standard ear tags to bears handled in other research programs. The radios had no external antenna but could be detected by receiving equipment mounted on the helicopter at a distance of >10 km when flying at >500 m elevation above sea level.

Killing of polar bears and tissue sampling

Each bear captured was randomly assigned a time for relocation based on the sampling protocol. However, weather and cloud ceiling often constrained when actual flying could be carried out so that the time of relocation for some bears differed from the intended time.

Bears were relocated by returning to the general vicinity of initial capture and then searching for the radio signals using the helicopter. When a bear was re-sighted, a researcher and a licensed native hunter assigned by the Resolute HTA were dropped onto the sea ice near the bear allowing the hunter to shoot the bear with a center-fire rifle. As soon as the bear was shot, the helicopter landed nearby and tissue samples were collected. The time when the bear was shot was recorded as "time of kill". Tissue samples were collected within 20 min of the "time of kill" and stored at −20 C until archived at −70 C within approximately 2 wk of collection. The samples collected were serum (taken via heart puncture), kidney (saggital sections), muscle (*biceps brachii* from right forearm), and adipose tissue (base-of-tail depot).

All bears killed were part of the annual polar bear quota legally assigned to the Resolute HTA. No bears were killed in addition to this quota. The pelt from each bear was retained by the HTA and assigned to a registered native hunter for disposal. The accompanying hunters were paid a salary through the HTA for the days spent assisting us.

Analytical methods

High performance liquid chromatography (HPLC) was employed in the analysis as it offered a technique that could be used to measure both drugs simultaneously. A procedure was developed whereby both substances were

extracted from the fluids and tissues and separated chromatographically (Gorecki et al., 1994). In addition to separating the two compounds from one another, both were resolved from any interfering substances such as endogenous substances and metabolites. Furthermore, adequate sensitivity was achieved to measure the low levels of these compounds likely to be found hours after administration. The method was also modified to measure one metabolite of tiletamine and three metabolites of zolazepam in polar bear tissues.

The analytes tiletamine and zolazepam, and an internal standard (pindolol) were extracted into ethyl acetate from alkalinized serum or tissue samples (borate buffer, pH 9.5). Samples were back-extracted into 1 ml of 0.1 M HCl, basified with 0.1g sodium borate and re-extracted into ethyl acetate. The solvent was evaporated under nitrogen and the residue was reconstituted in either a solution of one part acetonitrile to three parts water for serum samples, or mobile phase for tissue samples.

Chromatographic separation of tiletamine, zolazepam and internal standard was accomplished under isocratic conditions using an octylsilane (C_8) reverse phase column (Merck LiChrospher 60 RP-select B, 250 × 4 mm, 5 μm, EM Separations, Gibbstown, New Jersey, USA) and a mobile phase of 26 parts acetonitrile to 74 parts sodium phosphate buffer (0.05 M, pH 6.8), pumped at 1 ml/min and monitored with an ultraviolet detector at 233 nm (Model 480, Waters Corp., Milford, Massachusetts, USA). Samples (70 μl) were injected using a Model SIL-9A autoinjector (Shimadzu Corp., Kyoto, Japan) and the data were recorded on a Model CR601 Chromatopac integrator (Shimadzu Corp., Kyoto, Japan). The retention times were 9.6–9.8 min for pindolol, 12.3 to 12.6 min for zolazepam, and 18.5 to 19.2 min for tiletamine.

Polar bears are large and formidable predators. Consequently, serum samples from nonanesthetized polar bears were unavailable. Therefore, for standard curve preparation 3% bovine serum albumin (BSA) was used as a serum substitute because a true blank serum sample could not be employed. To verify that 3% BSA was suitable, it was compared to polar bear serum obtained from a killed bear which had been immobilized 11 days previously. Similar blank chromatograms were obtained with no interfering peaks. For tiletamine, the method was linear from 10–2,000 (r = 0.9999) and for zolazepam, 2–4,000 (r = 0.9997) ng/ml serum. The extraction efficiency of both drugs was 88%. In 1 ml of serum, the limits of quantitation were 10 ng/ml of tiletamine (RSD 18%) and 2 ng/ml of zolazepam (RSD 12%).

Zolazepam and tiletamine levels in tissues were determined by the external standard method because of the variability associated with the extraction of the internal standard pindolol. Nonetheless, performance parameters were similar to those for our serum assays.

Because there was insufficient sample to identify the metabolite peaks by the usual procedures, only those peaks having a retention time corresponding to that of an authentic standard metabolite peak and which were completely resolved from other peaks were quantitated as if they were representative of that metabolite. Peaks representative of one tiletamine and three different zolazepam metabolites were quantitated. Chromatographic separation of the Telazol® compounds, the potential metabolites and ripazepam (internal standard) was accomplished by modifying the mobile phase to 16 to 84 ratio (volume to volume) acetonitrile to 0.05 molar sodium phosphate buffer. To achieve a pH of 5.5, the sodium phosphate buffer contained 52 parts NaH_2PO_4 to 48 parts $NaHPO_4$ The extraction procedure employed for the quantitation of tiletamine and zolazepam was modified to increase extraction efficiency of the metabolites. To 1.5 g of tissue with 300 μl of a 1 μg/ml aqueous solution of ripazepam homogenized in 6 ml of 0.5 M sodium borate buffer, pH 9.5, was added 10 ml of ethyl acetate, followed by vortexing for 20 min. The phases were separated and the organic layer was removed, followed by a repeat of the extraction on the aqueous layer. The organic extracts were pooled, acidified with 2 ml of 0.1 M HCl and back-extracted, followed by a repeat of this step. The acid fractions were pooled, basified with 0.2 g of sodium borate and re-extracted into 12 ml of ethyl acetate, evaporated under nitrogen and reconstituted in 200 μl of one to four parts mixture of acetonitrile and water. The retention times following a 70 μl injection were 22.8 to 24.5 min for CI-398, 24.4 to 26.5 min for zolazepam metabolite 1, 27.6 to 29.2 min for zolazepam metabolite 4, 32.4 to 33.9 min for zolazepam metabolite 2, 43.4 to 46.3 min for tiletamine, 50.5 to 52.4 min for ripazepam (internal standard), and 56.7 to 59.0 min for zolazepam. The quantitation of the various metabolites was based on the internal standard method of quantitation using the peak height ratio of drug to internal standard. Standard curves were constructed and fitted by linear regression to determine slopes, intercepts and correlation coefficients for the metabolites. The limits of quantitation and detection, respectively, for each of the metabolites were, in ng/ml, 27 and 12 for CI-398, 13 and 4 for zolazepam metabolite 1, 11 and 2 for zolazepam metabolite 2, and 13 and 4 for zola-

zepam metabolite 4. Tiletamine (CI-398) and zolazepam (1, 2 and 4) metabolite concentrations were also determined in fat, kidney and muscle samples obtained from 16 different polar bears killed at various times after Telazol® administration.

Pharmacokinetic methods

Concentrations of both drugs were dose-adjusted to a total dose of 10 mg/kg by multiplying each raw concentration by 10/dose in mg/kg in order to allow meaningful comparisons of data between animals. Using the computer program WinNonlin (Scientific Consulting Inc., Apex, North Carolina, USA), one-compartment curve-fits were performed on the dose-adjusted concentration vs. time data, and the pharmacokinetic parameters were determined in accordance with standard methods (Gibaldi and Perrier, 1982). Serum concentrations of both drugs at kill time were predicted and compared with observed values. Predictions were calculated from the mean values of the pharmacokinetic parameters from the fitted data, according to the equation $C_{pt} = [k_a D/V_d(k_a - k)](e^{-kt} - e^{-k_a t})$ where C_{pt} is the serum concentration of drug at time t after dosing, k_a is the first order absorption rate constant, k is the first order elimination rate constant, V_d is the apparent volume of distribution, and D is the dose of drug administered. Tissue and serum concentrations of both drugs and their metabolites at time of killing were compared.

RESULTS

Of the bears that were killed, four were sampled in 1992, 10 in 1993, and two in 1994 (Table 1). All were males collected in the latter half of April or early May of each year except for Bear T which was collected in November, 1993. Ages ranged from 3 to 22 yr and body mass varied between 133 and 384 kg. The dosage of Telazol® administered ranged between 5.1 mg/kg and 14.1 mg/kg with a mean dosage of 8.9 mg/kg. An additional six bears were sampled for pharmacokinetic analysis but not killed, in April of 1992 (Table 1). All but one of these (Bear R, a subadult) were adults, two of the group were females (Bears O and P).

Zolazepam and tiletamine concentrations were determined in the serum of all 22 different polar bears handled. The serum concentrations of both zolazepam and tiletamine showed a monotonic decline in the period immediately following drug administration (Fig. 1 and Fig. 2). In order to characterize the concentration-time profiles, one-compartment (monoexponential) curve fitting, with first-order absorption and first-order elimination, was applied to the pooled time-series data. Only bears for which sufficient samples were available and for which the absorption of drug was sufficiently rapid that the maximum serum concentration (C_{max}) occurred at the first or second sampling time (i.e., Bears A, C, D, E, N, O, Q, R, S) were used in these procedures. First-order absorption was assumed as absorption from an intramuscular injection is usually considered to be approximately first-order (Gibaldi and Perrier 1982, p32). Biexponential curve-fitting was also conducted on the data, however most curves were best fit by a one-compartment model. Table 2 shows the pharmacokinetic parameters derived from the data analyses for tiletamine and zolazepam.

Serum concentrations of tiletamine and zolazepam at the time the bears were killed were predicted from our kinetics model and compared with measured values (Table 3). The observed serum concentrations were higher than predicted for tiletamine in two of 14 cases, and for zolazepam in six of 14 cases. This pattern held even when the kinetic parameters of the bear with the slowest elimination were used for the predictions (not shown).

Tissue concentrations of tiletamine and its metabolite CI-398 and zolazepam and its three metabolites, Z-1, Z-2 and Z-4, were determined in the tissues that might be consumed, including kidney, fat and muscle samples from 16 polar bears killed after immobilization with Telazol®. The dose-corrected data from these determinations are shown in Table 4. Traces of drug and metabolites, especially zolazepam and its metabolites in kidney, tiletamine, zolazepam, Z-2 and Z-4 in fat, and tiletamine, zolazepam and Z-2 in muscle persisted throughout most of the sample

TABLE 1. Summary of sampling protocol, age, mass, and Telazol® administered for free-ranging polar bears handled in the Canadian Arctic. Bears are ordered by the interval of time between the injection of Telazol® and the collection of tissue samples.

Name	Age (y)	Date of initial capture	Hours between dose and kill	Days between dose and kill	Body mass (kg)	Telazol® delivered (mg)	Telazol® dosage (mg/kg)
Bears killed							
BEAR-T	9	93.11.09	12.7	0.5	329	3,000	9.1
BEAR-G	3	93.05.02	12.8	0.5	133	1,400	10.6
BEAR-U	12	94.04.15	20.4	0.8	384	2,600	6.8
BEAR-B	9	92.04.20	27.6	1.2	321	2,800	8.7
BEAR-J	6	93.04.29	28.6	1.2	180	2,000	11.1
BEAR-M	13	93.05.01	34.0	1.4	351	1,800	5.1
BEAR-L	9	93.04.24	46.6	1.9	287	4,000	14.0
BEAR-D	11	92.04.29	52.7	2.2	358	3,000	8.4
BEAR-C	22	92.04.23	52.9	2.2	310	2,000	6.5
BEAR-K	>7	93.04.23	63.4	2.6	324	2,500	7.7
BEAR-V	7	94.04.15	91.4	3.8	255	3,600	14.1
BEAR-A	5	92.04.16	121.4	5.1	167	2,200	13.1
BEAR-H	18	93.04.22	172.7	7.2	299	2,000	6.7
BEAR-I	8	93.04.22	174.3	7.3	287	2,000	7.0
BEAR-F	9	93.04.20	242.7	10.1	344	2,000	5.8
BEAR-E	8	93.04.18	266.8	11.1	266	2,200	8.3
Bears not killed							
BEAR-N	18	92.04.23			386	3,600	9.3
BEAR-O	16	92.04.23			153	2,000	13.1
BEAR-P	5	92.04.26			120	1,400	8.8
BEAR-Q	12	92.04.26			326	3,000	9.2
BEAR-R	2	92.04.26			129	1,800	13.9
BEAR-S	7	92.04.28			237	3,000	12.7

period. With only four exceptions (one sample of tiletamine in fat, three samples of Z-2 in fat), however, the concentrations of all analytes in all tissues measured fell below 100 μg/kg after 24 hr post-dosing.

DISCUSSION

There is little pharmacokinetic information on the constituents of Telazol in the literature; the only quoted information comes from data produced by the manu-

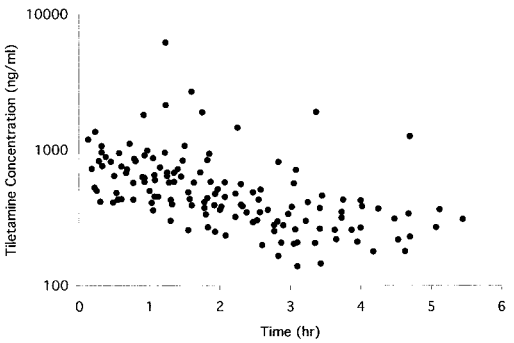

FIGURE 2. Dose-corrected serum concentration of tiletamine in 22 free-ranging polar bears versus time after administration of Telazol®.

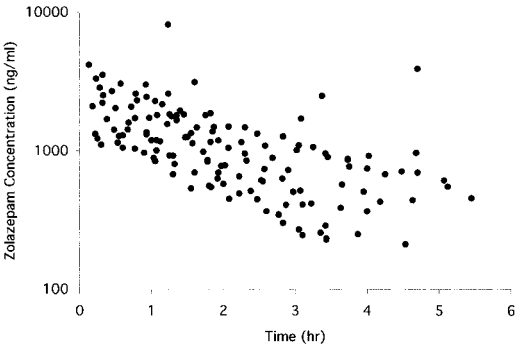

FIGURE 3. Dose-corrected serum concentration of zolazepam in 22 free-ranging polar bears *versus* time after administration of Telazol®.

TABLE 2. Mean pharmacokinetic parameters (± SE) of tiletamine and zolazepam determined from 9 free-ranging polar bears for which sufficient number of sequential serum samples were available to characterize the concentration versus time profile.

Parameter	Tiletamine	Zolazepam
k (hr^1)[a]	0.42 ± 0.04	0.58 ± 0.04
$t_{1/2}$ (hr)[b]	1.8 ± 0.2	1.2 ± 0.08
V_{ss} (l/kg)[c]	5.2 ± 0.6	1.8 ± 0.2
AUC (mg 1 hr^{-1} kg^{-1})[d]	2.50 ± 0.19	5.29 ± 0.71
Clearance (1 hr^{-1} kg^{-1})[e]	2.1 ± 0.29	1.1 ± 0.1

[a] Elimination rate constant.
[b] Elimination half life.
[c] Steady-state volume of distribution.
[d] Area under the concentration versus time curve.
[e] Total body clearance.

TABLE 3. Observed concentrations of tiletamine and zolazepam in the serum of free-ranging polar bears at selected intervals after the administration of Telazol® and those concentrations predicted by our kinetics model.

BEAR #	Kill time (hr post-administration)	Observed tiletamine (μg/kg)	Predicted tiletamine (μg/kg)	Observed zolazepam (μg/kg)	Predicted zolazepam (μg/kg)
Bear-T	12.7	966	6.10	196	1.83
Bear-G	12.8	20	5.86	44	1.72
Bear-U	20.4	NA[a]	0.28	NA	0.02
Bear-B	27.6	—[b]	0.02	122	<0.01
Bear-J	28.6	—	0.01	2	<0.01
Bear-M	34.0	—	<0.01	—	<0.01
Bear-L	46.6	—	<0.01	—	<0.01
Bear-D	52.7	—	<0.01	5	<0.01
Bear-C	52.9	—	<0.01	4	<0.01
Bear-K	63.4	—	<0.01	—	<0.01
Bear-V	91.4	NA	<0.01	NA	<0.01
Bear-A	121.4	—	<0.01	—	<0.01
Bear-H	172.7	—	<0.01	—	<0.01
Bear-I	174.3	—	<0.01	—	<0.01
Bear-F	242.7	—	<0.01	—	<0.01
Bear-E	266.8	—	<0.01	—	<0.01

[a] Not analyzed.
[b] Not detected.

facturer that developed the product (Lin et al., 1993). In the investigation described here, most curves for both drugs were best fitted by a one-compartment model, and the resulting half-lives in this group of polar bears (Table 2) were similar to those in other species. The tiletamine half-life of 1.8 hr compares with 2 to 4 hr reported in the cat, 1.2 hr in dogs, 1 to 1.5 hr in monkeys and 30 to 40 min in rats, while the zolazepam half-life of 1.2 hr was shorter than for dogs (4 to 5 hr), cats (4.5 hr) or rats (3 hr) but similar to that in monkeys (1 hr) (Lin et al., 1993).

In every case where measurable concentrations were present in the serum at kill time, the concentrations of both drugs were lower than those of the last sample taken while the animal was immobilized. Nevertheless, the concentrations at kill time were higher than the predictions based on the one-compartment model (Table 3). We speculate that the elimination rate constant calculated from the one-compartment curve fits may relate to distribution, not elimination, and that the elimination half-life in most bears would become apparent only after the animals have awakened. In dogs, the structurally-related drug phencyclidine has a distribution phase lasting about 4 h, followed by a longer elimination phase with a half-life of about 5 hr (Woodworth et al., 1985). The large scatter of the drug serum data (Fig. 1 and Fig. 2) also suggest that there may be considerable individual variation in drug elimination rates.

Rather than being correlated to serum concentrations of the drugs, tissue concentrations of the drugs and some metabolites appeared to decline rapidly during the first 24 hr after dosing, then to remain at trace levels for an extended period (Table 4). In general, concentrations tended to decline over time although tiletamine persisted in muscle tissue at very low levels. This may indicate tight drug binding to these tissues, although the extractability of both drugs indicates that the binding was not covalent. CI-398, the tiletamine metabolite disappeared from kidney, fat and muscle tissue quite quickly, while the zolazepam metabolites persisted for longer periods in all three tissues. Zolazepam metabolite 2 persisted at the highest levels, having a concentration of 64 μg/kg in fat tissue in Bear

TABLE 4. Dose-adjusted drug and metabolite concentrations in kidney, fat and muscle tissue from free-ranging polar bears at selected intervals after the administration of Telazol®.

BEAR #	Kill time (hr post-dose)	Tiletamine (μg/kg)	CI-398[a] (μg/kg)	Zolazepam (μg/kg)	Z-1[b] (μg/kg)	Z-2[b] (μg/kg)	Z-4[b] (μg/kg)
KIDNEY:							
Bear-T	12.7	21	87	151	212	621	84
Bear-G	12.8	39	—	61	—	37	D
Bear-U	20.4	92	39	29	42	20	D
Bear-B	27.6	2	—	2	11	—	—
Bear-J	28.6	—[e]	—	13	—	D	D
Bear-M	34.0	—	64	2	22	—	21
Bear-L	46.6	—	—	10	D	14	—
Bear-D	52.7	—	—	3	20	26	22
Bear-C	52.9	—	—	2	—	D	D
Bear-K	63.4	—	—	—	—	—	D
Bear-V	91.4	—	—	—	—	—	—
Bear-A	121.4	D[f]	—	70	D	26	D
Bear-H	172.7	—	—	—	D	—	D
Bear-I	174.3	—	—	—	—	—	—
Bear-F	242.7	—	—	—	—	—	—
Bear-E	266.8	—	—	—	—	—	—
FAT:							
Bear-T	12.7	1,093	—	348	21	D	—
Bear-G	12.8	813	—	31	D	122	14
Bear-U	20.4	770	—	449	—	—	—
Bear-B	27.6	—	D	—	—	11	—
Bear-J	28.6	—	—	11	—	—	—
Bear-M	34.0	28	—	29	—	20	—
Bear-L	46.6	8	—	11	—	32	D
Bear-D	52.7	9	—	—	—	190	15
Bear-C	52.9	5	—	—	—	101	—
Bear-K	63.4	15	—	7	—	97	14
Bear-V	91.4	—	—	23	—	—	—
Bear-A	121.4	352	D	53	—	27	—
Bear-H	172.7	17	—	15	D	19	13
Bear-I	174.3	—	—	—	—	154	18
Bear-F	242.7	—	—	—	—	32	—
Bear-E	266.8	—	—	—	13	64	D
MUSCLE:							
Bear-T	12.7	923	—	219	68	266	D
Bear-G	12.8	53	—	42	—	27	D
Bear-U	20.4	—	—	22	D	D	—
Bear-B	27.6	5	—	—	—	D	—
Bear-J	28.6	5	—	7	—	D	—
Bear-M	34.0	9	—	—	—	—	—
Bear-L	46.6	3	—	7	—	18	—
Bear-D	52.7	6	—	—	—	14	21
Bear-C	52.9	9	—	1	—	17	—
Bear-K	63.4	2	—	—	—	—	—
Bear-V	91.4	—	—	37	—	—	—
Bear-A	121.4	18	—	46	D	21	—
Bear-H	172.7	4	—	1	—	D	—
Bear-I	174.3	5	—	—	D	—	—
Bear-F	242.7	3	—	—	—	10	—
Bear-E	266.8	6	—	—	—	D	—

[a] A metabolite of tiletamine.
[b] A metabolite of zolazepam.
[c] Not detected.
[d] Detected, but below the limit of quantitation.

E, which was killed 267 hr post-dosing. We cannot preclude the possibility that some of the persistent low concentrations detected could have been artifact, but they were not a consistent feature of the samples examined even from the treated animals in this study. Therefore, it would be impossible to determine even with blank control samples whether a detected peak was artifact. Further studies with later kill times would be required to determine how long measurable concentrations of drug and metabolites persist in these tissues, and data from more bears at earlier killing times would be required to adequately characterize the decline of drug concentrations in all tissues.

Given that some drug and/or metabolites may persist in tissues that might be eaten, some further estimates are necessary to help establish the risk of consuming meat of animals that had previously been drugged. After one day, the concentrations of all analytes were less than 500 μg/kg. Therefore, an estimated drug or metabolite concentration of 500 μg/kg would be a conservative figure to use in an estimate of exposure one day after dosing. If a generous 500 g meal of polar bear muscle were to be consumed, the dose of drug would be 250 μg. An average human weighs 70 kg, so the dose would be 250 μg/70 kg = 3.6 μg/kg. Although there is no literature on the use of Telazol® in humans, the review by Lin et al. (Lin et al., 1993) indicates that over a range of >100 species, over one half of which were mammals, the lowest dose of Telazol® alone used to achieve an immobilizing effect was more than 1 mg/kg. Given that the dose of each drug in the mixture at a Telazol dose of 1 mg/kg would be 500 μg/kg, the maximum expected exposure of a human would be more than two orders of magnitude less than the minimum effective dose. This would be rapidly metabolized and mostly eliminated. Given the lack of data on humans, it is impossible to assess the risk of toxicity from this exposure, but it appears highly unlikely that a human consuming polar bear meat from an animal killed more than 24 hr after darting would experience a pharmacological effect from either tiletamine or zolazepam.

Higher exposure to drugs from consuming the meat could occur if the animal had been dosed less than 24 hr prior to being killed, or if meat from the area of the injection site was consumed. Regarding the latter possibility, the darting process tends to create a large hematoma on the shoulder, which could impede the diffusion of drug away from the injection site, thus leaving higher concentrations at this location. A colored injection solution could be used to warn anyone butchering an animal away from that site.

A number of uncontrollable factors, including the variability in dosing levels and sampling times, the short interval over which samples could be taken, and the small number of animals studied limited the characterization of the pharmacokinetics of zolazepam and tiletamine in serum and tissues of free-ranging polar bears. Nevertheless, valuable information germane to the original purpose of the project has been uncovered. The serum concentration vs. time profiles of both drugs in the polar bear do not appear to differ greatly from those in other species such as the dog. Both drugs and some metabolites, while quickly cleared from some tissues, may be retained in others and tiletamine in particular may be retained for an extended period at low concentrations in muscle tissue, so that an individual consuming meat from a killed animal could be exposed to very low doses of the drugs and or their metabolites.

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