

USE OF THE CATALEPTOID ANESTHETIC CI-744 FOR CHEMICAL RESTRAINT OF BLACK BEARS

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Abstract: Warner-Lambert/Parke-Davis and Company have developed a new drug combination known as CI-744 (to be marketed for veterinary use as Tilazol TM). CI-744 is a 1:1 ratio of the phencyclidine hydrochloride (Sernylan) analogue tiletamine hydrochloride and a non-phenothiazine tranquilizer, zolazepam hydrochloride. Field trials of CI-744 in 39 black bears (*Ursus americanus*) showed its effects to be similar to a 1:1 mixture of Sernylan and promazine hydrochloride. However, CI-744 provides the advantages of shorter restraint time, faster recovery, less salivary and respiratory secretion, and ease of use (no supplemental drugs were needed). Based on 25 immobilizations (22 bears) for which complete and accurate data are available, mean values of 4 important parameters were: induction time, 7 minutes; restraint time, 81 minutes; emergence time, 36 minutes; total down time, 117 minutes. Mean dosage rate was 4.1 mg/kg, but the optimum for routine field work is about 4.0 mg/kg.

Field research on large mammals has been greatly facilitated by the development of chemical restraint techniques. However, species differ in their responses to particular drugs and no single drug works well on all species. In field work, the investigator usually desires a drug that is absorbed rapidly after intramuscular injection, provides adequate restraint with a minimum of troublesome side effects, and has a wide margin of safety. In addition, the drug's effects should be reasonably predictable and permit a quick recovery, and the drug itself should be chemically stable over a wide range of temperatures.

Succinylcholine chloride (Anectine, Burroughs Wellcome; Sucostrin, Squibb) has been used alone or in combination with a barbiturate anesthetic in several studies applying chemical restraint to bears (Erickson 1957, Black 1958, Craighead et al. 1960, Sticklely 1961, Troyer et al. 1961, Jonkel and Cowan 1971, Rogers et al. 1976). Succinylcholine is a short-acting neuromuscular blocking agent without anesthetic properties. It is difficult to use because dosage is extremely critical and multiple injections may be fatal (Pearson et al. 1968, Hamilton 1974, Rogers et al. 1976). Aqueous solutions are unstable and must be refrigerated. Barbiturates generally are unsatisfactory for field use because of their critical dosages, profound depression of the central nervous system, and the prolonged recovery required.

Some researchers working with bears (Flygar et al. 1967; Larsen 1967, 1971; McCaffrey et al. 1976; Miller and Will 1976) have successfully employed the potent morphine derivative M99 (Etorphine, American Cyanamid). The great advantage of this drug is that its effects can be reversed in a few minutes by the specific antagonists M50-50 or M285 (Diprenorphine or Cyprenorphine, American Cyanamid). However, the effects of M99 are somewhat unpredictable. Underdosed animals may exhibit a brief period of excitation, or may

become drowsy and then revive unexpectedly (Miller and Will 1976; G. Kuehn, Los Angeles Zoo, personal communication). High doses depress heart and breathing rates and deep body temperatures (Larsen 1971). M99 is subject to strict regulations in the United States and currently may be sold only to licensed veterinarians.

Beginning in the late 1960s, phencyclidine hydrochloride (Sernylan, originally Parke-Davis, now Bio-Ceutic) has been the chosen drug in a number of bear studies (Lentfer 1968; Craighead et al. 1971, 1976; Kistchinski and Uspenski 1972; Piekielek and Burton 1975; Amstrup and Beecham 1976; Glenn et al. 1976; Pearson 1976). Sernylan is the prototype of a group of compounds that may be characterized as cataleptoid anesthetics. These compounds produce a state of waxy rigidity without complete muscular relaxation. The degree of anesthesia varies with dosage and may reach the stage of unconsciousness. Even at clinical dosage levels, however, the eyes remain open and certain reflexes (corneal, palpebral, laryngeal, pharyngeal, pedal, and pinnal) are intact (Beck 1972). Although Sernylan meets most of the criteria for a good bear drug, recovery is prolonged, salivation and respiratory secretion may be excessive, tetanic convulsions occasionally occur, and thermoregulation may be impaired (Lentfer 1968, Pearson et al. 1968, Seal and Erickson 1969, Larsen 1971, Beck 1972, Hamilton 1974). These side effects can be minimized or controlled by administering light doses or supplemental drugs, but such efforts often have other undesirable effects and prolong the handling procedure.

In the course of ecological studies on black bears in the San Bernardino and San Gabriel Mountains of southern California, we have been fortunate to work with Warner-Lambert/Parke-Davis and Company in the evaluation of a new drug combination known as CI-744 (to be marketed for veterinary use as Tilazol TM). CI-744 is a 1:1 ratio of the Sernylan analogue tiletamine

hydrochloride and a non-phenothiazine derivative tranquilizer, zolazepam hydrochloride (C. Beck, Warner-Lambert/Parke-Davis and Company, personal communication). The development and pharmacology of these drugs have been described by Chen et al. (1959, 1969), Beck (1972), and Conner et al. (1974).

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METHODS AND MATERIALS

CI-744 was received from Warner-Lambert/Parke-Davis and Company as bulk powder. It was dissolved in distilled water to a concentration of 300 mg/ml. Bears were captured in culvert traps or Aldrich foot snares. The weight of each bear was estimated visually and, after the first few trials, CI-744 dosage was routinely calculated at 4.4 mg/kg. A syringe mounted on the end of a pole was used to inject the drug into the rump, thigh, or shoulder musculature. After a bear was immobilized, it was weighed on a spring scale, measured, tagged, and given a prophylactic dose (5 ml/50 kg) of long-acting antibiotic (Bicillin, Wyeth). Rectal temperature and heart and breathing rates were recorded during most immobilization episodes, usually within 30 minutes of achieving restraint, but no attempt was made to monitor these parameters at regular intervals. The age of each bear was initially estimated on the basis of tooth wear and was later checked in most individuals by counting cementum layers (Stoneberg and Jonkel 1966, Willey 1974) around the root of a third premolar tooth.

CI-744 was evaluated primarily in terms of the following parameters: induction time, from injection to loss of head-lifting response when mechanically stimu-

lated; restraint time, from loss of head-lifting response to beginning of head-lifting response; emergence time, from first head-lifting response to standing position; total down time, from loss of head-lifting response to standing (restraint time plus emergence time); dosage rate, mg/kg needed to produce restraint. Data on these parameters were obtained for each episode of immobilization. However, the tabular data presented here pertain only to those 25 episodes for which complete and accurate records were obtained after single injections. Mean values for immature (1-3 years old) and adult (4+ years old) bears were compared statistically using the Student's *t*-test.

RESULTS

A total of 39 different bears, all judged to be in good health, were immobilized in the field with CI-744 between August 1974 and November 1976. Ten immature (9 male, 1 female) and 12 adult (all male) bears provided the 25 immobilization episodes for our data on time parameters and dosage rates. The immature female and 2 adult males contributed 2 episodes each. Twenty of the 25 episodes reported occurred in the months May-October, and 5 occurred in November-December.

Estimated weights of the bears tended to be slightly lower than the true weights. As a result, the average dosage rate was 4.1 mg/kg. Mean dosage rates for immature and adult bears were not significantly different ($P > 0.05$). However, mean induction, restraint, and total down times all were significantly ($P < 0.05$) shorter for immature than for adult bears, whereas mean emergence times were nearly identical (Table 1).

Scatter diagrams and regression equations were prepared to obtain estimates of how closely induction, restraint, and emergence times were correlated with dosage rate and body weight. Data points were widely scattered in each case and only the following positive correlations were statistically significant: restraint time/dosage rate ($Y = 34.9X - 63.6$, $r = +0.44$, $P < 0.05$); emergence time/dosage rate ($Y = 14.6X - 24.5$, $r = +0.49$, $P < 0.05$); restraint time/body weight ($Y = 0.44X + 21.9$, $r = +0.53$, $P < 0.01$).

Eight immature (7 male, 1 female) and 22 adult (20 male, 2 female) bears provided 37 episodes in which rectal temperature and heart and breathing rates all were recorded 1 or more times during the restraint period. Means for these parameters in the immature and adult bears were not significantly different ($P > 0.05$). Means, standard errors, and ranges derived from the pooled observations ($N = 49$) were: rectal temperature, 38.1 ± 0.1 C (36.9 - 39.2); heart rate, 113 ± 16

Table 1. Weights, dosages, and time parameters for 25 immobilization episodes using CI-744 in black bears. Data are derived from 10 immature and 12 adult bears. SE = Standard Error.

Age-class	Weight (kg)	Dosage (mg/kg)	Induction (minutes)	Restraint (minutes)	Emergence (minutes)	Total down (minutes)
Immature bears						
\bar{X} (N = 11)	85**	4.1	4.6*	60**	37	97*
Range	46-116	3.0-5.3	3-11	31-139	10-70	41-176
SE	±6	±0.2	±0.8	±10	±6	±12
Adult bears						
\bar{X} (N = 14)	176**	4.2	8.2*	98**	35	133*
Range	122-244	3.5-4.9	3-17	25-174	13-59	38-207
SE	±8	±0.1	±1.1	±11	±3	±12
All bears						
\bar{X} (N = 25)	136	4.1	7.0	81	36	117
Range	46-244	3.0-5.3	3-17	25-174	10-70	38-207
SE	±10	±0.1	±0.8	±8	±3	±9

*P > 0.05.

**P > 0.01.

beats/minute (87 – 155); breathing rate, 11 ± 4 breaths/minute (4 – 20).

DISCUSSION

Explanations for the observed differences (or lack of them) between immature and adult bears, with respect to the time parameters studied, are largely speculative. Although variability in our data and in those of other investigators is great, some trends are evident. Young, lightweight polar bears (*Ursus maritimus*) (Larsen 1971) and other mammals (Seal and Erickson 1969) have been observed to require higher dosage rates of Sernylan than adults to achieve restraint and have been noted to recover more quickly. Larsen (1971) attributed the higher dosage rates and quicker recovery to the higher metabolic rate of younger bears. The shorter mean induction and restraint times observed in the younger bears injected with CI-744 also might be due in part to higher metabolic rates. However, a factor of major importance may be the amount of body fat in the individual animal. Fat may account for a greater percentage of body weight in older, heavier bears and may serve as a nonmetabolic reservoir for the drug, thereby increasing both the time required for the drug to reach effective levels in the brain and the time required for its elimination from the body. Unfortunately, we do not have sufficient data to compare bears in specific age-classes at different seasons and to analyze the effects of increasing fat deposits. Since some tiletamine may be excreted without being metabolized (F. Eads, Warner-Lambert/Parke-Davis and Company, personal com-

munication), another consideration is that any impairment of kidney function that might occur in older bears would also increase excretion and restraint times.

The lack of a statistically significant difference between the mean emergence times of immature and adult bears may be an artifact of our small sample size and the relatively imprecise end point of emergence. We therefore refrain from speculating on any pharmacodynamic implications. However, the observation that restraint and emergence times increased with dosage rate seems explicable on the basis that the drug was metabolized and/or excreted at a constant rate by the animal. If so, larger doses required a longer time to be eliminated from the body, and restraint and emergence times were prolonged.

The observable sequence of effects of CI-744 was similar to that described for Sernylan by Pearson et al. (1968). Bears in culvert traps often assumed a sitting position soon after injection, though this action did not seem to be a response to the drug *per se*. Drooping of the head and a slow swaying motion, together with slight salivation and/or nystagmus, usually indicated the first stages of induction. Coordination was lost in posterior to anterior sequence and was regained in reverse order. Compared with the reports of other investigators (Lentfer 1968, Pearson et al. 1968, Seal and Erickson 1969, Larsen 1971) and our own experience with Sernylan, salivary and respiratory secretions were slight to moderate and posed no problem for the bears. Induction time was similar to that of Sernylan, but emergence was much more rapid and restraint was of shorter duration.

Piekielek and Burton (1975) achieved comparably short restraint times with Sernylan by administering very light doses (0.55 – 0.73 mg/kg). However, their induction times were quite long (\bar{X} = 30 minutes), and the results of drugging were probably less predictable. Seal and Erickson (1969) recommended the use of promazine hydrochloride (Sparine, Wyeth) in a 1:1 ratio with Sernylan to promote muscle relaxation, prevent convulsions, and control hyperthermia. While this combination is effective, it is our impression that promazine potentiates the action of Sernylan and lengthens total down time. The combination of zolazepam with tiletamine to make CI-744 has the same synergistic effect, but tiletamine has only about one-half the potency of Sernylan and is not so long-acting (Beck 1972).

No convulsions occurred in bears immobilized with CI-744. Heat stress was minimized by working in the shade during daylight hours, and ambient temperatures for our series of immobilization episodes ranged from 4 to 28 C. There was considerable variation in rectal temperatures and in heart and breathing rates. Although some of this variation might have been due to different dosage rates or to the circumstances of immobilization and handling, the available data are not sufficient to demonstrate consistent relationships. The rectal temperatures of bears immobilized with CI-744 were virtually the same as those Hock (1957, 1960) reported for nonhibernating, unanesthetized bears. Heart rates were notably higher than those reported for sleeping bears in summer (Folk 1967, Folk et al. 1972) and were comparable to those of bears in "a very active state" (Folk 1967:76). This tachycardia may have been due to the influence of tiletamine on cardiovascular regulatory centers in the brain (Chen et al. 1969). We are not aware of any published data on breathing rates in resting bears, but Chen et al. (1969) found that tiletamine did not cause respiratory depression in monkeys at anesthetic dosages, which is probably true for bears also. In our experience, the effects of CI-744 on rectal temperature and on heart and breathing rates are similar to the effects of Sernylan and Promazine in combination.

The optimum dosage rate of CI-744 for routine field work with adult black bears appears to be about 4.0 mg/kg. Younger bears may require 4.4 mg/kg to provide adequate restraint. As a matter of procedure, this latter dosage rate is probably the best for routine use because some degree of control will be achieved with a good injection even if the weight of the bear is slightly underestimated. CI-744 has at least a 3-fold safety margin, as

does Sernylan (Pearson et al. 1968), and overestimation of weight usually will result only in somewhat longer restraint and emergence times. The maximum dosage rate applied to a bear in our study was estimated to be approximately 9.5 mg/kg. In this instance, an 83-kg female with 3 8-month-old cubs was restrained for 91 minutes (emergence time not recorded). Warner-Lambert/Parke-Davis and Company have a limited amount of data on the use of CI-744 in other Ursidae. The indications are that a dosage rate of about 4.4 mg/kg is generally satisfactory for the restraint of all species (C. Beck, Warner-Lambert/Parke-Davis and Company, personal communication).

Although we did not attempt definitive tests, most of the bears we worked on appeared to be in a state of surgical anesthesia (Conner et al. 1974) for much of the restraint period. Minor surgery was performed on 1 5¼-year-old female (weight, 98 kg) to implant a temperature-sensitive transmitter subcutaneously. This bear was adequately anesthetized for the procedure with an initial dose of 5.8 mg/kg and a supplemental dose of 1.4 mg/kg administered 48 minutes later. Restraint lasted 144 minutes.

The development of tolerance for CI-744 was observed in 2 young males (siblings) over a period of 10 months while they were maintained in an outdoor enclosure. One (age, 2¼ years) required 2.4 times as much CI-744 for restraint on its fourth exposure (16 May 1976) as on its first exposure (20 July 1975). The second bear exhibited a 2.8-fold increase in dosage requirement over the same period after receiving 5 previous exposures. Both bears subsequently required about twice the dosage rate of Sernylan and promazine that we have found to be effective (2 mg/kg instead of 1 mg/kg). Seal and Erickson (1969) also noted increased tolerance for Sernylan as evidenced by increasing dosage requirements for restraint.

In Summary, we find that the advantages of CI-744 compared with the Sernylan-promazine combination are (1) shorter emergence and restraint times; (2) less salivary and respiratory secretion; and (3) greater ease of use, because two drugs do not have to be mixed and supplemental drugs (such as atropine) are not needed.

Aqueous solutions of CI-744, freshly prepared at a concentration of 300 mg/ml, are pale yellowish brown. We have noted some darkening with age, though potency does not seem to have been affected. Refrigeration probably should be used to maintain long-term potency.

LITERATURE CITED

- AMSTRUP, S. C., AND J. BEECHAM. 1976. Activity patterns of radio-collared black bears in Idaho. *J. Wildl. Manage.* 40(2):340-348.
- BECK, C. C. 1972. Chemical restraint of exotic species. *J. Zoo Anim. Med.* 3:3-66.
- BLACK, H. C. 1958. Black bear research in New York. *Trans. N. Am. Wildl. Conf.* 23:443-461.
- CHEN, G., C. R. ENSOR, AND B. BOHNER. 1969. The pharmacology of 2-(ethylamino)-2-(2-thienyl)-cyclohexane • HCl (CI-634). *J. Pharmacol. Exp. Therap.* 168(1):171-179.
- , D. RUSSELL, AND B. BOHNER. 1959. The pharmacology of 1-(1-phenylcyclohexyl) piperidine • HCl. *J. Pharmacol. Exp. Therap.* 127(3):241-250.
- CONNER, G. H., R. W. COPPOCK, AND C. C. BECK. 1974. Laboratory use of CI-744, a cataleptoid anesthetic, in sheep. *Vet. Med./Small Anim. Clinician* 1974(April):479-482.
- CRAIGHEAD, J. J., F. C. CRAIGHEAD, JR., J. R. VARNEY, AND C. E. COTE. 1971. Satellite monitoring of black bear. *BioScience* 21(24):1206-1212.
- , M. HORNOCKER, W. WOODGERD, AND F. C. CRAIGHEAD, JR. 1960. Trapping, immobilizing and color-marking grizzly bears. *Trans. N. Am. Wildl. Conf.* 24:347-363.
- , J. R. VARNEY, F. C. CRAIGHEAD, JR., AND J. S. SUMNER. 1976. Telemetry experiments with a hibernating black bear. Pages 357-371 in M. R. Pelton, J. W. Lentfer, and G. E. Folk, Jr., eds. *Bears — their biology and management*. IUCN Publ. New Ser. 40.
- ERICKSON, A. W. 1957. Techniques for live-trapping and handling black bears. *Trans. N. Am. Wildl. Conf.* 22:520-543.
- FLYGAR, V., M. W. SCHEIN, A. W. ERICKSON, AND T. LARSEN. 1967. Capturing and handling polar bears — a progress report on polar bear ecological research. *Trans. N. Am. Wildl. Conf.* 32:107-119.
- FOLK, G. E., JR. 1967. Physiological observations on subarctic bears under winter den conditions. Pages 75-85 in K. Fisher and F. South, eds. *Mammalian hibernation III*. Oliver and Boyd, Edinburgh.
- , M. A. FOLK, AND J. J. MINOR. 1972. Physiological condition of three species of bears in winter dens. Pages 107-124 in S. Herrero, ed. *Bears — their biology and management*. IUCN Publ. New Ser. 23.
- GLENN, L. P., J. W. LENTFER, J. B. FARO, AND L. H. MILLER. 1976. Reproductive biology of female brown bears (*Ursus arctos*), McNeil River, Alaska. Pages 381-390 in M. R. Pelton, J. W. Lentfer, and G. E. Folk, Jr., eds. *Bears — their biology and management*. IUCN Publ. New Ser. 40.
- HAMILTON, R. B. 1974. A brief and cursory summary of some trapping, marking, and handling techniques for black bear. *Proc. Eastern Workshop on Black Bear Manage. and Res.* 2:40-46.
- HOCK, R. J. 1957. The metabolic rates and rectal temperatures of active and "hibernating" black bears. *Fed. Proc.* 16:440.
- . 1960. Seasonal variation in physiological functions of arctic ground squirrels and black bears. Pages 151-177 in C. P. Lyman and A. R. Dawe, eds. *Mammalian hibernation I*. Harvard University Press, Cambridge.
- JONKEL, C. J., AND I. MCT. COWAN. 1971. The black bear in the spruce-fir forest. *Wildl. Monogr.* 27. 57pp.
- KISTCHINSKI, A. A., AND S. M. USPENSKI. 1972. Immobilization and tagging of polar bears in maternity dens. Pages 172-180 in S. Herrero, ed. *Bears — their biology and management*. IUCN Publ. New Ser. 23.
- LARSEN, T. 1967. The trapping and study of polar bears, Spitsbergen, 1966. *Polar Rec.* 13(86):589-593.
- . 1971. Capturing, handling, and marking polar bears in Svalbard. *J. Wildl. Manage.* 35(1):27-36.
- LENTFER, J. W. 1968. A technique for immobilizing and marking polar bears. *J. Wildl. Manage.* 32(2):317-321.
- MCCAFFREY, E. R., G. B. WILL, AND A. S. BERGSTROM. 1976. Preliminary management implications for black bears, *Ursus americanus*, in the Catskill region of New York State as the result of an ecological study. Pages 235-245 in M. R. Pelton, J. W. Lentfer, and G. E. Folk, Jr., eds. *Bears — their biology and management*. IUCN Publ. New Ser. 40.
- MILLER, R. L., AND G. B. WILL. 1976. Use of M99 Etorphine and antagonists to immobilize and handle black bears. Pages 225-234 in M. R. Pelton, J. W. Lentfer, and G. E. Folk, Jr., eds. *Bears — their biology and management*. IUCN Publ. New Ser. 40.
- PEARSON, A. M. 1976. Population characteristics of the arctic mountain grizzly bear. Pages 247-260 in M. R. Pelton, J. W. Lentfer, and G. E. Folk, Jr., eds. *Bears — their biology and management*. IUCN Publ. New Ser. 40.
- , R. M. BRADLEY, AND R. T. MCLAUGHLIN. 1968. Evaluation of phencyclidine hydrochloride and other drugs for immobilizing grizzly and black bears. *J. Wildl. Manage.* 32(3):532-537.
- PIEKIELEK, W., AND T. S. BURTON. 1975. A black bear population study in northern California. *California Fish and Game* 61(1):4-25.
- ROGERS, L. L., C. M. STOWE, AND A. W. ERICKSON. 1976. Succinylcholine chloride immobilization of black bears. Pages 431-446 in M. R. Pelton, J. W. Lentfer, and G. E. Folk Jr., eds. *Bears — their biology and management*. IUCN Publ. New Ser. 40.
- SEAL, U. S., AND A. W. ERICKSON. 1969. Immobilization of Carnivora and other mammals with phencyclidine and promazine. *Fed. Proc.* 28(4):1410-1419.
- STICKLEY, A. R., JR. 1961. A black bear tagging study in Virginia. *Proc. Annu. Conf. Southeast. Assoc. Game and Fish Commissioners* 15:43-54.
- STONEBERG, R. P., AND C. J. JONKEL. 1966. Age determination of black bears by cementum layers. *J. Wildl. Manage.* 30(2):411-414.
- TROYER, W. A., R. J. HENSEL, AND K. E. DURLEY. 1961. Live-trapping and handling brown bear. *Proc. Alaska Sci. Conf.* 12. 16pp.
- WILLEY, C. H. 1974. Aging black bears from first premolar tooth sections. *J. Wildl. Manage.* 38(1):97-100.