Etorphine and Diprenorphine as Immobilizing and Reversing Agents in Captive and Free-Ranging Mammals

B. T. Alford, D.V.M.; R. L. Burkhart, V.M.D.; W. P. Johnson, D.V.M.

6482

SUMMARY

Etorphine, an opium alkaloid derivative of thebaine, and its specific antagonist, diprenorphine, were evaluated by research workers and zoo veterinarians in captive and free-ranging mammals.

An intramuscular injection of etorphine usually resulted in rapid immobilization, sedation, analgesia, and muscle relaxation in Equidae, Ursidae, Cervidae, and Bovidae, when given at the rate of 0.44, 0.5, 0.98, and 1.09 mg./45 kg. (100 lb.), respectively. Satisfactory immobilization was usually achieved within 5 to 15 minutes after intravenous administration of diprenorphine at twice the etorphine dosage.

Procedures performed after etorphine administration included dehorning, blood sampling, tail docking, antibacterial injection, radiography, orthopedic surgery, and obstetrical manipulation.

Side effects were commonly noticed in free-ranging mammals. The type and degree of reaction varied according to species and included tachycardia, bellowing, bradycardia, respiratory depression, opisthotonos, muscular tremors, mydriasis, and hyperpyrexia. Of 1,600 animals tested, 2.9% died as a result of severe heat prostration, inhalation pneumonia, respiratory depression, severe excitement due to underdosing, cardiac arrest, and inapparent disease.

RESTRAINT has long been one of the major problems facing veterinarians engaged in wildlife management and zoo practice. Animals that are injured or sick are often not properly examined and treated due to problems involving restraint. Proper restraint provides safety for the animal as well as for the individual involved in diagnosing and treating various disease conditions. Mechanical and manual methods of restraint currently being used include nets, squeeze cages, traps, and chutes. Such methods often result in injury or death to the animal or present a hazard to the handler.

Since their introduction in the early 1950's, tranquilizers have been widely used in wild animals. Although they have been useful for controlling fractious animals, other physical or chemical agents may be required for immobilization.

Early in 1963, a series of derivatives of the opium alkaloid, thebaine, were synthesized by British scientists.[5] These compounds were determined to be highly potent analgesics or analgesic antagonists. One compound in this series, etorphine hydrochloride[a] (Fig. 1), was found to possess morphine-like properties. Because of its immobilizing and analgesic activity at low dosages, it was initially evaluated in various species of free-ranging animals in Africa.[1,2]

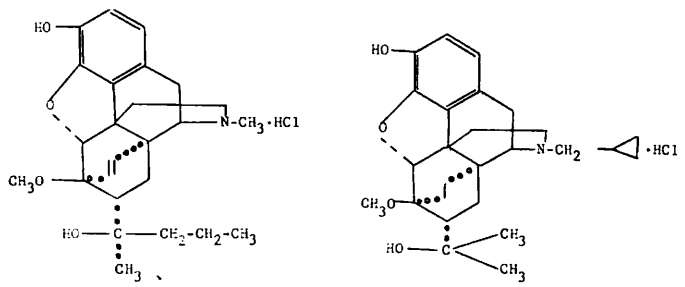

Fig. 1—Left—M-99 etorphine (6,7,8,14-tetrahydro-α-methyl-α-propyl-6, 14-endo-ethenooripavine-α-methanol hydrochloride).

Right—M-50-50 diprenorphine (N-(cyclopropylmethyl)-6,7,8,14-tetrahydro-7-α-(1-hydroxy-1-methylethyl)-6,14-endo-ethanonororipavine hydrochloride).

The action of etorphine resembles that of morphine in rodents, cats, dogs, and monkeys—causing analgesia, catatonia, respiratory depression, inhibition of gastrointestinal propulsion, and an antidiuretic effect.[5]

Preliminary Testing in the Laboratory

As part of our preliminary testing procedure to further evaluate the effectiveness of etorphine and the antagonist diprenorphine[b] (Fig. 1), laboratory studies were conducted in Beagle dogs. When etorphine was used in the dog, a phenothiazine tranquilizer such as methotrimeprazine[c] was also required to induce satisfactory analgesia and immobilization. This combination was found to induce neuroleptanalgesia (sedation, muscle relaxation, immobilization, and analgesia). The neuroleptanalgesia was rapidly reversed by administering the etorphine antagonist, diprenorphine.[5] In most cases, a

From the Agricultural Division, American Cyanamid Company, P.O. Box 400, Princeton, NJ 08540.

Presented before the Section on Laboratory Animals at the 110th Annual AVMA Meeting, July 16–19, 1973, Philadelphia, PA.

[a] M-99, American Cyanamid Company, Princeton, NJ.

[b] M-50-50, American Cyanamid Company, Princeton, NJ.

[c] Methotrimeprazine Hydrochloride, Lederle Laboratories, Pearl River, NY.

TABLE 1—Optimal Dosage for Certain Captive and Free-Ranging Mammals, Based on Data Submitted by Field Investigators

Species category	Etorphine (mg./45 kg. of body weight)*	Diprenorphine (mg./45 kg. of body weight)**
BOVIDAE		
Antelope— addax *(Addax nasomaculatus)*	1.09 (0.2-5.0)†	2.18 (0.4-10.0)
Sheep—bighorn *(Ovis canadensis)*	1.77 (0.19-13.3)	3.54 (0.38-26.6)
Domestic cattle *(Bos taurus)*	0.42 (0.11-2.0)	0.84 (0.22-4.0)
CERVIDAE		
Deer—fallow *(Dama dama)*	0.98 (0.23—12.0)	1.96 (0.46-24.0)
Moose *(Alces alces)*	0.98 (0.23-12.0)	1.96 (0.46-24.0)
Tule wapiti *(Cervus nannodes)*	0.98 (0.23-12.0)	1.96 (0.46-24.0)
ELEPHANTIDAE		
African *(Loxodonta africana)*	9.0 mg. (total adult dose)	18.0 (total adult dose)
Indian *(Elephas maximus)*		
EQUIDAE		
Horse *(Equus caballus)*	0.44 (0.11-4.32)	0.88 (0.22-8.64)
Mongolian *(Equus przewalskii)*	0.44 (0.11-4.32)	0.88 (0.22-8.64)
Zebra—Grevy's *(Equus grevyi)*	0.44 (0.11-4.32)	0.88 (0.22-8.64)
FELIDAE		
Cheetah *(Acinonyx jubatus)*	0.25 (0.21-2.0)	0.50 (0.42-4.0)
Lion *(Panthera leo)*	0.25 (0.21-2.0)	0.50 (0.42-4.0)
CANIDAE		
Wolf *(Canis lupus)*	(1.5-4.2)	(3.0-8.4)
URSIDAE		
Black bear *(Euarctos americanus)*	0.5 (0.05-4.17)	1.0 (0.10-8.34)
Grizzly bear *(Ursus horribilis)*	0.5 (0.05-4.17)	1.0 (0.10-8.34)
Polar bear *(Thalarctos maritimus)*	0.5 (0.05-4.17)	1.0 (0.10-8.34)
SUIDAE		
Wild boar *(Sus scrofa)*	1.1 (0.53-1.7)	2.2 (1.06-3.4)
CYNOPITHECIDAE		
Rhesus macaque *(Macaca mulatta)*	0.4 (0.12-2.0)	0.8 (0.24-4.0)
CAMELIDAE		
Camel—dromedary *(Camelus dromedarius)*	0.31 (0.23-1.2)	0.62 (0.46-2.4)
GIRAFFIDAE		
Giraffe *(Giraffa camelopardalis)*	0.31 (0.25-0.5)	0.62 (0.50-1.0)
MACROPODIDAE		
Kangaroo—long nosed *(Potorus tridactylus)*	0.35 (0.29-1.1)	0.62 (0.58-2.2)
HIPPOPOTAMIDAE		
Hippopotamus—pigmy *(Choeropsis liberiensis)*	6.0 mg. (total adult dose)	12.0
RHINOCEROTIDAE		
Rhinocerus—Indian *(Rhinoceros unicornis)*	1.0 mg. (total adult dose)	2.0
Black rhino *(Diceros bicornis)*	1.0 mg. (total adult dose)	2.0
White rhino *(Diceros simus)*	1.0 mg. (total adult dose)	2.0
TAPIRIDAE		
Tapir—Brazilian *(Tapirus terrestris)*	0.29 (0.16-4.0)	0.58 (0.32-8.0)
Malay *(Tapirus indicus)*	0.29 (0.16-4.0)	0.58 (0.32-8.0)

* Intramuscularly. ** Intravenously. † Range.

tranquilizer is not needed in combination with etorphine to immobilize captive and free-ranging mammals. Reports concerning the use of etorphine as an immobilizing and analgesic agent in wild animals indicated that some species reacted favorably to etorphine alone.[7,8] The addition of acepromazine maleate[d] to etorphine did not appreciably reduce induction time in the African elephant *(Loxodonta africana)*; however, with high doses of acepromazine, the amount of antagonist required to achieve recovery within a reasonable time was much higher.[9]

Field Trials and Results

To evaluate the compounds under field conditions in the United States, experimental samples of etorphine and diprenorphine were sent to 131 investigators, principally game biologists working in wildlife management programs and veterinarians involved in zoo and exotic animal medicine. A total of 1,600 reports were submitted on the efficacy and safety of the compounds in captive and free-ranging mammals. The reports covered 17 families and approximately 89 different species.

The principal aim of the investigation was to determine an optimal dosage for etorphine and diprenorphine in as many zoo and free-ranging animals as possible under various environmental conditions. The majority of the investigators used individual animal drug experience report forms, which served as a check list for observations and supplied pertinent information such as estimated animal weight, dosage, species, free ranging or captive, climatic conditions, purpose of test, immobilization time, surgical procedure performed, time required for return to pretreatment state, and mortality.

Etorphine and diprenorphine dosages used in the various animal species are given (Table 1). Variation in susceptibility to etorphine was observed among species. Among the more sensitive species were primates, elephants, hippopotamus, rhinoceros, tapir, and bears. Other species appeared to be moderately sensitive. Within the family Equidae, the Mongolian horse (*Equus przewalskii*) and African wild ass (*Equus asinus*) appeared to be least sensitive. Although the African elephant is larger than the Indian elephant, usually a smaller dosage is required to immobilize the African elephant. The administration of etorphine is unique in that it is safer to give the maximum dosage rather than the minimum effective dosage. Underdosing may

[d] Acepromazine Maleate Injectable, Ayerst Laboratories, Inc., New York, NY.

TABLE 2—Drug Effects in Captive and Free-Ranging Mammals After Treatment with Etorphine and Diprenorphine

Phase	No. of Cases	Overall estimate of effect				Successful reversal by diprenorphine
		Good	Fair	Poor	Dead	
I (1965–1967)	631	465	148		18	167/183
II (1967–1969)	539	382	133	4	20	487/493
III (1969–1971)	430	337	59	26	8	396/400
Total	1600	1184	340	30	46	1050/1076
Percentage of total		74.0	21.3	1.8	2.9	97.6

cause hyperexcitability, hyperventilation, and severe alkalosis that may lead to death.

It was concluded that satisfactory immobilization should be defined as sternal recumbency; standing, permitting safe approach, and tolerance of routine capture techniques; safe approach and response of animal to directional stimuli; or complete immobilization, sedation, and analgesia, allowing minor surgical techniques. The results are reported (Table 2). The estimate of effect was recorded as "good" in 74% of the cases reported; 21% of the cases were reported as "fair" and 2.1% were recorded as "poor." Of 1,600 animals for which reports were submitted, 2.9% died as a result of heat prostration, administration of other drugs in combination, inhalation pneumonia, severe excitement due to underdosing, severe respiratory depression, cardiac arrest, or inapparent disease. As experience was gained, the number of deaths and "fair" cases decreased (*see* Phase III, Table 2).

Free-ranging animals such as deer and antelope have a natural tendency to run prior to or at the time of "darting," which results in rapid increases in heart rate, respiratory rate, and body temperature, which appear to prolong induction time. Vigorous exercise during this period may result in sufficient stress to increase the likelihood of death. Neither age nor sex seemed to have any appreciable effect on drug response. In 97% (1,050/1,082) of the animals, the effect of etorphine was successfully reversed by the intravenous administration of diprenorphine at 2 times the dosage of etorphine.

Within the first 5 minutes after etorphine administration, most of the animals either had no signs of drug effect or developed ataxia, a hackney gait, or a friendly behavior pattern. Sheep and goats occasionally started chewing movements and horses usually paced in a counterclockwise direction. According to one investigator, the first sign of the drug's effect in 6 African elephants was inability to lift the tail. This was followed by progressive ataxia characterized by loss of control of the trunk and culminating in sternal or lateral recumbency.[10]

Side effects noticed after etorphine administration are listed (Table 3).

Some of the animals were immobilized only to evaluate the physiologic effects of the compounds; however, most of the animals were immobilized so that minor surgical procedures could be performed. A listing of procedures is given (Table 4).

TABLE 3—Some Side Effects Associated with the Use of Etorphine in Field Trials

Species category	Clinical observation
BOVIDAE	
Domestic cattle (*Bos taurus*)	Tachycardia, increased blood pressure, respiratory depression, muscular tremors, mydriasis, hypersalivation, teeth grinding, bellowing, bleating, bloat, and hyperpyrexia
Bighorn sheep (*Ovis canadensis*)	
EQUIDAE	
Mongolian horse (*Equus przewalskii*)	Tachycardia, increased blood pressure, respiratory depression, muscular tremors, and hyperpyrexia
Grevy's zebra (*Equus grevyi*)	
URSIDAE	
Black bear (*Euarctos americanus*)	Respiratory depression
Grizzly bear (*Ursus horribilis*)	
GIRAFFIDAE	
Giraffe (*Giraffa camelopardalis*)	Opisthotonos and regurgitation
CAMELIDAE	
Dromedary camel (*Camelus dromedarius*)	Opisthotonos and regurgitation

TABLE 4—Clinical and Surgical Procedures

MOST FREQUENTLY CITED	TREATMENT
Manually forcing animals to walk to new areas	Antibacterial injections
Crating animals for shipment	Wound therapy
Dehorning	Dipping or spraying for ectoparasites
DIAGNOSTIC	SURGICAL
Tuberculin skin test	Retained placenta
Collection of blood samples	Dystocia
Radiography	Prolapsed rectum or vagina
PREVENTIVE	Orthopedic surgery
Physical examination	Neurectomy
Hoof trimming	Tail docking
Rubber-tipping of horns	OTHER
Insertion of nose rings	Euthanasia
Application of leg bracelets	Tagging

When field work was first initiated and little information was available on etorphine, a number of investigators administered other drugs such as acepromazine maleate, atrophine sulfate, phencyclidine hydrochloride, and xylazine hydrochloride before, immediately after, or concurrently with etorphine. Acepromazine maleate was most commonly used in this manner. The addition of other compounds did not appreciably reduce the induction time or improve the immobilizing effects of etorphine; however, the recovery time was prolonged in those animals given the various combinations.

The effect of the antagonists, diprenorphine, and the specific morphine antagonist, nalorphine hydrochloride,[e] was evaluated, principally on the length of time required to reverse the narcotic effects of etorphine.

[e] Nalorphine hydrochloride, Merck and Company, Inc., Teterboro, NJ.

Several investigators used nalorphine when diprenorphine was not available. The most consistently satisfactory results were obtained at an etorphine-to-diprenorphine ratio of 1:2, e.g., 0.5 mg. etorphine/45 kg. body weight and 1 mg. diprenorphine/45 kg. body weight. Nalorphine required a ratio ranging from 1:10 to 1:20. Reversal of the narcotic effects of etorphine was usually obtained after intravenous administration with either antagonist; however, less residual narcosis was noticed after intravenous administration of diprenorphine. Several investigators indicated that intramuscular administration of the antagonist was satisfactory for routine use. Usually, within 5 to 20 minutes after diprenorphine administration, the central nervous system depressant effects of etorphine were reversed.

The ambulation time, which was defined as the lag period between the administration of the antagonist until the animal walked, varied according to animal species, environmental factors, and the type of drug used in combination with etorphine. Residual narcosis or incomplete reversal was normally noticed in those animals that were given exceptionally high dosages of other drugs in combination with etorphine. Some animals given various drugs in combination with etorphine required 24 hours or longer for complete recovery.

Safety

Laboratory studies were conducted to determine the parenteral median lethal dosage (LD_{50}) and median effective dosage (ED_{50}) of etorphine and to compare its effects in mice with those of morphine sulfate. Etorphine at all dosages resulted in the Straub tail effect (a stiff 90-degree erection of the tail) 5 to 7 seconds after injection vs. 3 to 5 minutes after injection of morphine sulfate. Morphine sulfate induced analgesia, Straub tail effect, and excitement.[4] The LD_{50}, ED_{50}, and therapeutic index are given (Table 5). The LD_{50} for morphine and etorphine was 546.6 and 74.1 mg./kg., respectively. The therapeutic index for etorphine was significantly higher than that for morphine (9.263 vs. 80.4).[3] Based on these results, it can readily be concluded that on a milligram per kilogram basis, etorphine is more effective and less toxic than morphine.

TABLE 5—Acute Toxicity and Effective Doses of Etorphine and Morphine After Their Parenteral Administration in Mice

Compound	LD_{50} (mg./kg.)	ED_{50} (mg./kg.)	Approximate therapeutic index
Morphine sulfate	546.6 (462.8–645.5)*	6.8 (4.5–10.2)	80.4
Etorphine hydrochloride	74.1 (59.2–93.5)	0.008 (0.0036–0.018)	9,263

* 95% Confidence limits in parentheses.

Tissue residue studies have not been conducted to determine a safe withdrawal period after treatment in various food-producing animals. Therefore, these compounds should not be administered to wild animals that might be used for food during the hunting season.

References

1. Alford, B. T., and Wozniak, L. A.: Neuroleptanalgesia in the Dog and Reversal by an Antagonist. J.A.V.M.A., 156, (Jan. 15, 1970): 208–212.
2. Bentley, K. W., and Hardy, D. G.: New Potent Analgesics in the Morphine Series. Proc. Chem. Soc., 220, 1963.
3. Blane, G. F., Boma, A. L. A., Fitzgerald, A. E., and Lister, R. E.: Actions of Etorphine Hydrochloride, (M99): A Potent Morphine-Like Agent. Brit. J. Pharmacol., 30, (1967): 11–22.
4. Hall, R. T., American Cyanamid Company, Princeton, NJ: Unpublished data, 1966.
5. Harthoorn, A. M.: Restraint of Undomesticated Animals. J.A.V.M.A., 149, (Oct. 1, 1966): 875–880.
6 Harthoorn, A. M., and Bligh, J.: The Use of New Oripavine Derivative with Potent Morphine-Like Activity for the Restraint of Hoofed Wild Animals. Res. Vet. Sci., 3, (July, 1965): 290–299.
7. Harthoorn, A. M.: The Use of a Neuromuscular Blocking Agent in Domestic Cattle. Vet. Rec., 74, (1962): 395–397.
8. King, J. M., and Carter, B. H.: The Use of the Oripavine Derivative M99 for the Immobilization of the Black Rhinoceros (*Diceros bicornis*) and Its Antagonism with the Related Compound M285 or Nalorphine. East African Wildlife J., 3, 1965.
9. Wallach, J. D., and Anderson, J. L.: Oripavine (M.99) Combinations and Solvents for Immobilization of the African Elephant. J.A.V.M.A., 153, (Oct. 1, 1968): 793–797.
10. Wallach, J. D., Frueh, R., and Lentz, M.: The Use of M.99 as an Immobilization and Analgesic Agent in Captive Wild Animals. J.A.V.M.A., 151, (Oct. 1, 1968): 793–797.