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The Use of Etorphine (M99) and Diprenorphine (M5050) For Anesthesia in a White Rhinoceros for the Removal of Growths on the Third Eyelid

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Zoo veterinarians have a difficult problem when dealing with restraint and anesthesia of exotic species. They are working with potentially dangerous animals and because of the great variety of species and relative lack of drug information on exotics, the problems of drug choice and dosage are much greater. Proper restraint is essential for the safety of the veterinarian and handlers and also that of the patient.

Some of the indications for restraint of wild animals are:

(1) animal management – manually forcing animals to walk to new areas; crating for shipment and relocation; dehorning; tagging; physical examination;

(2) diagnostic work – blood testing; tuberculin skin testing; radiography;

(3) treatment – antibacterial injection, wound therapy; antiparasitic treatment;

(4) surgery – dystocia; prolapsed rectum or vagina; bone fractures; etc.

A good deal of the restraint of the exotics is done by the use of manual restraints. Ropes, gloves, nets, snares, hand catching, push boards, crate training, and squeeze cages are standard methods of capture and restraint commonly used on wild animals. Often these methods of manual restraint cause injury or even death to the patient. Drugs have been used to supplement and replace many of these methods.

Qualities of an "ideal" drug for use in wild animals include the following characteristics:

(1) It should provide a wide margin of safety so that individual variation in response to the drug and error in weight estimation and dosage will be minimal factors.

(2) It should be useful in a wide variety of species.

(3) It should be potent and active in small volumes to produce the desired effects. This provides for rapid injection and makes use of projectile syringes possible.

(4) It should be effective and safe when administered either intravenously or intramuscularly. This is especially important when using dart syringes because a needle may enter a blood vessel when fired into a muscle.

(5) It should be reversible so that an animal can

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return to a normal state when a procedure is finished.

(6) It should depress the animals senses somewhat so that restraint does not lead to shock. This is important in exotics which are not accustomed to being handled by man.[11]

In 1963 a morphine related drug was developed called etorphine or M99* (part of the M-series).[15] Since its advent, etorphine has been widely used for restraint of wild species.

M99 (Etorphine) 6,7,8,14-Tetrahydro- -methyl- -propyl-6,14-endoethenooripavine- -methanol hydrochloride is a derivative of the opium alkaloid, thebaine.[9] It is a morphine-like agent with an analgesic potency that is 1,000 to 10,000 times greater than that of morphine.[7] Part of this may be due to the ability of etorphine to get into the brain much more rapidly than morphine. Relative to its analgesic effect, etorphine is considerably less toxic than morphine.

M99 has many desirable characteristics for use in exotic species.

(1) The margin of safety of M99 is extremely wide. The wide margin of safety precludes losses from overdosage and escapes the results of underdosage.

(2) M99 has been used in a wide variety of species of animals. These include species of *Bovidae* (antelope, cattle, goat, sheep), *Camelidae* (camel, llama), *Canidae* (dog, wolf), *Cervidae* (deer), *Elephantidae, Equidae* (zebra, horse, wild ass), *Felidae* (cheetah, lion), *Cynopithecidae* (Macaques, baboons), *Pongidae* (great apes), *Suidae* (swine), *Tayassuidae* (peccaries), *Ursidae* (bear), as well as the giraffe, hippopatamus, kangaroo, rhinoceros, tapir, crocodile, and turtle.[3]

(3) M99 is extremely potent. Doses of 0.5 to 8.0 mg. were used to immobilize 54 rhinoceroses weighing from 1800 to 5500 pounds.[16] An 11,000 pound elephant was successfully immobilized with 4.0 mg.[7]

(4) M99 is most often administered by a projectile syringe intramuscularly with satisfactory immobilization occurring usually within 5 to 15 minutes.[8] Satisfactory immobilization may occur as, (a) down in sternal recumbancy, (b) standing permitting safe approach and tolerance of routine capture techniques, (c) safe approach and response of animal to directional stimuli for planned movement or crating, (d) sufficient sedation and analgesia for minor surgical techniques. Typically the immediate response after injection depends on the usual flight response of the species darted. Clinically, a typical reaction of a properly dosed intramuscular injection of M99 is that the animal will walk slowly, develop an ataxic or "hackney" gait after a few minutes, then stop and stand in a "sawhorse" fashion with a dropped head and blinking eyelids. Often they stumble and fall or lie down and go into a deep sleep after several minutes. The immobilized state usually lasts from 30 to 60 minutes.[8]

(5) The effects of M99 are rapidly and completely reversible with antagonists such as M285* (Cyprenorphine) or M5050* (diprenorphine). Intravenous injection of M5050 abolishes the narcotic effect of etorphine usually within 20 minutes, often in seconds in certain species.[13]

(6) Etorphine and its antagonist are narcotic analgesics and produce analgesia, catatonia, some respiratory depression, inhibit gastrointestinal propulsion, have an antidiuretic effect, and block conditioned reflexes. It causes excitement, but this is minimized by its powerful action and rapid absorption. The effect on respiration of the doses required for immobilization is mild. Animals injected with M99 show an increased ability to endure pain. The extent of tranquilization and narcosis varies with species, individuals, and the dosage of M99.[1]

The action of etorphine in the body is still uncertain. It appears to act pre-synaptically in the cerebral cortex. The drug is excreted largely through the intestines from which reabsorption may occur.[8] Etorphine can cause bradycardia or tachycardia depending on the species and conditions.

Etorphine efficiency is greatly increased in combination with other agents depending on the species it is used on. Etorphine has been used in combinations with agents such as Xylazine, Acetylpromazine, Fentanyl citrate, Azaperone, Phencyclidine, Triflupromazine, Fluanisone, Hyoscine, Dimethylsulfoxide (DMSO). The addition of these tranquilizers and other compounds does not appreciably reduce the induction time or improve the immobilizing effects of etorphine; however the recovery is quite often smoother after the antagonist is given.

The effect of etorphine may be counteracted by narcotic antagonists such as Nalorphine, Cyprenor-

*M99 – American Cyanamid Company, Princeton, New Jersey.

*M285, M5050 – American Cyanamid Company, Princeton, New Jersey.

phine (M285), and Diprenorphine hydrochloride (M5050).

Cyprenorphine hydrochloride (M285) is related to etorphine and is a potent antagonist. It acts by competing for the receptor sites with etorphine by substrate competition. A certain concentration must be reached in the recipient animal's blood stream. Cyprenorphine is an antagonist but it also possesses a degree of agonist activity. Animals therefore often show some residual sedation when cyprenorphine is used as the etorphine antagonist.[8]

Diprenorphine (M5050) is a pure antagonist and produces virtually no residual sedation when used as an etorphine antagonist. It appears to have negligible effect on the heart, respiration or central nervous system and is therefore preferred to cyprenorphine. The recommended dosage ratio of M99 to M5050 is 1:2 respectively. This dose will completely reverse the effects of etorphine in about ½ to 4 minutes via intravenous injection. After injection of M5050 one should be prepared to deal with a fully conscious subject.[3]

Both M99 and M5050 have been tested on many species of animals under a wide variety of conditions and on various terrains. It is difficult, even impossible, to establish the usual well-controlled pharmacological studies conducted on new products. Therefore, when using M99, the user should be prepared for occasional unexpected results.[3]

The administration of M99 is somewhat unique in that it is safer to give the maximum dose rather than the minimum effective dose. Underdosing may cause hyperexcitability, hyperventilation, and severe alkalosis that may cause death. If too high a dose is given, a rapid reversal can be obtained by intravenous injection of M5050. If, for some reason, a vein is not accessible, use intramuscular or subcutaneous sites. These alternate routes will give a prolonged response time.[3]

The users of M99 should be familiar with clinical procedure such as monitering pulse and respiration, maintaining a patent airway, prevention of aspiration, relief of bloat, control of shock and hemorrhage, recognition of hyperventilation and heat exhaustion, etc.

If animals are recumbent for long periods of time, care should be taken to avoid eye damage. Shading and opthalmic ointments are useful in these cases.

Following M99 injections, brief periods of visual adjustment occur and it may be necessary to direct animals away from hazards (ravines, water holes, etc.).

The use of M99 in pregnant animals is not without risk. Its use should be avoided during mating seasons.

The ideal location for sites of injection of M99 are heavily muscled areas of the shoulder or croup. Care should be taken to avoid darting animals in the abdomen (intraperitoneally), thorax, or against bone.[12] Use a heavy initial dose and avoid subsequent fractional doses. Injection into fat deposits result in slow absorption. Needles of adequate length to hit muscle masses must be used.

Figure A—Pre-operative distance shot of left eye.

The use of M99 to restrain animals should not be done without considering the environmental temperature. The environmental temperature should not exceed 100°F. and one should restrict use in antelope, bison, and deer to days when the temperature is below 85° F.[13]

Lateral recumbency is hazardous in ruminants. M99 arrests rumination, but animals can release gas from a sternal position.

Side effects of M99 may be one or more of the following: increase in heart rate, increase in blood pressure, decrease in respiratory rate, muscle tremors, severe excitement due to underdosage, pupil dilation, salvation, teeth grinding, bellowing, increase in temperature, and rarely, bloat, emesis, and cyanosis. These symptoms are usually abolished after administration of M5050.[3]

Case Report:

Barbara, a 17 year-old female white (square-lipped) rhinoceros (Ceratherium simum) at the Catskill Game Farm, presented with growths on her third eyelid. Barbara's estimated weight was 1500 kilograms. The growths had a five year history of emerging in early June with the onset of warmer weather and regressing when cooler weather started in November. The growths were getting larger each summer as time progressed and were constantly irritated by flies. No similar previous cases are reported. The growths were elliptical with dimensions of approximately 4x3x3

Figure B—Pre-operative shot of right eye.

cm. Barbara was housed and on exhibit in a moat exposition with a male rhinoceros (Chippy). The make has never had any problems.

Barbara and Chippy arrived at the Catskill Game Farm in September 1962 being one of the first three pairs of white rhinos in the United States. They have never bred and since then it has been discovered that white rhinos will only breed on a herd basis in captivity. The only previous treatment given to these rhinos was in September, 1970 when the male was given testosterone and the female diethylstilbesterol to try to promote breeding, but without results.

Barbara's growths on her third eyelids had become an ugly eyesore to the public. The only thing that appeased the public was the evidence of topical treatment with various colored antibiotic sprays, powders, creams, and fly repellants. These showed evidence that the growths had been noticed and were being treated. However, they were of little value in reducing the growth's size. The growths appeared to be caused by a chronic irritation by flies with some unknown inciting factor. Since the growths seemed to be getting larger each year and were a public eyesore, it was decided to try to remove them.

Figure C—Post-operative and after M50-50 injection, before effect of drug.

On a cool morning in August, Barbara was kept inside the Rhino house. It was decided to use M99 as the sole anesthetic agent after consulting with the director of the National Zoo in Washington, D.C. The recommended dose was given as 1.5 to 3.0 mg. to immobilize an adult white rhinoceros.[6]

The first attempt at immobilization was made using 2.0 mg. of Etorphine in a projectile syringe with a 4.5 cm. barbed needle using a CO_2 pistol. The dart was aimed at and implanted intramuscularly in the right upper thigh muscles. Thirty minutes later, no reaction was observed; the dart was retrieved and was found not to have exploded.

The second attempt at immobilization was to slap a 14 gauge 1½-inch needle by hand into the thigh muscles, but the needle was plugged in the process and could not be used for an injection.

The third attempt and successful attempt for immobilization was done with 2.0 mg. etorphine in a dart syringe with a 6-cm. barbed needle using a dart gun (Cap-Chur equipment). The dart was fired and implanted in the right thigh muscles. No excess excitement was noted after firing. After approximately 8 minutes Barbara became ataxic and wandered around the cage with a hypermetric gait. She would occasionally lean against the wall. 16 minutes after etorphine injection, the patient reached sternal recumbency. Ropes were placed around her legs, nose and horn to aid in support and positioning.

The surgery consisted of placing a hemostat and clamping at the base of the mass in the third eyelid and then cutting above it with curved Mayo scissors. The entire nictitating membrane was not removed. The hemostatic clamp was left in place for a few seconds, then removed, and only minimal bleeding occurred. After removal of the growths a topical antibiotic-steroid opthalmic ointment was placed in the eye.

The surgery took 13 minutes after which 4 mg. of M5050 was injected into the ear vein. Sternal recumbency occurred 4 minutes 50 seconds after the antidote injection. Barbara began eating hay about 8 minutes after the antidote but was groggy for the next 4 hours. Quite often the white rhinoceros shows a slower response to M5050 when compared to other species.[6]

The growths were sectioned for histopathology and cultures and sensitivities were performed by the Cornell Diagnostic Lab. The histopathology revealed a specimen from an ovoid section of connective tissue covered with a focally ulcerated and hyperplastic squamous epithelium. Small lymphoid follicles and

lobules of glandular tissue were present. The striking feature was a massively dense eosinophilic inflammatory infiltrate found focally in about half the section. A less dense and diffuse sprinkling of eosinophils plus lymphocytes, macrophages, and neutrophils were present in the other half. Occasional necrotic foci were present surrounded by fibrosis, macrophages, eosinophils, neutrophils, and giant cells. Special stains were negative for etiological agents.

The final diagnosis was an eosinophilic inflammatory polyp in the nictitating membrane. This reaction should be expected in a host sensitized to insect bites, or due to wandering parasitic larva (Onchocerca or Habronema).

The cultures isolated *Pseudomonas aeruginosa* sensitive to colymycin, gentamycin, and polymyxin.

Six months post-operatively, the eye and eyelid appear normal and hopefully will remain so in the future.

Conclusion:

M99 may be used in captive and free ranging animals for any procedure that requires rapid immobilization, analgesia, sedation, and muscle relaxation.

M5050 is used to reverse the state of narcosis produced by M99. Under normal conditions ambulation usually occurs within 5 to 20 minutes. The antagonist may also be used in cases where severe bradycardia or respiratory depression occurs following M99 administration.

Figure D–Six months post-operative.

As a general rule: dose heavily with M99 and reverse its effect quickly. This will minimize the excitement stage and avoid over-exertion, exhaustion, injury, and possibly overdosing by repeated fractional doses.

In this case, M99 and M5050 were used successfully for anesthesia in a 17 year old female white rhinoceros to remove unsightly growths on the third eyelid.

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