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The Use of a New Oripavine Derivative with Potent Morphine-like Activity for the Restraint of Hoofed Wild Animals

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SUMMARY. The use of one of a series of oripavine derivatives (No. M.99) for the immobilization and capture of hoofed wild animals is described.

This substance, usually injected in combination with tranquillizer and hyoscine, is suitable for the restraint of all hoofed wild animals on which it has been used.

The very low mortality achieved originally with the use of tranquillizer/synthetic morphine/hyoscine mixtures has been maintained, while the speed of reaction has greatly increased.

The very much smaller bulk of this substance (approximately 0·2 ml. compared with 10 ml. equivalent of solution formerly needed has considerably increased the ease of injection through the use of much smaller projectile syringes.

The effect of this oripavine substance may be reversed with nalorphine.

THERE IS AN INCREASING need for reliable methods whereby large hoofed wild animals can be captured and handled for transportation from areas being developed for farming and habitation to the sanctuary of game reserves, for ecological and physiological investigations, and for veterinary attention.

The smaller African antelope can easily be captured by the projectile syringe technique using suxamethonium (Buechner, Harthoorn and Lock, 1960), but the use of paralysing drugs is less uniformly successful on the larger hoofed animals (Harthoorn and Lock, 1960). A mixture of tranquillizing, narcotic and parasympatholytic agents has been successfully used for the capture and transport of the Southern White Rhinoceros (Harthoorn, 1962, 1963). The drugs employed were chlorpromazine hydrochloride,* diethylthiambutene‡ and hyoscine§ in a mixture which permitted at least an eightfold margin between the minimum dosage necessary for capture, and the maximum safe dose (Harthoorn and Player, 1963). This mixture has since been used successfully by the members of the R.V.C. East Africa Expedition (1963).

The disadvantages of this drug mixture are: (a) the large amount of morphine or synthetic analgesic required, (b) the slow absorption of the large bulk of solution, and (c) the ballistic problems associated with projecting syringes of 10 or 20 ml. capacity.

At the suggestion of Sir John Gaddum (personal communication), the use of the bridged-ring oripavine derivatives (Bentley and Hardy, 1963) in place of morphine has been investigated.

**Largactil*, May & Baker Ltd.
‡*Themalon*, Burroughs Wellcome & Co.
§*Hyoscine*, Hyoscine hydrobromide B.P.

Their substitution for morphine in the mixture of drugs used in capturing large hoofed wild animals has been found largely to overcome the disadvantages listed above.

MATERIALS AND METHODS

Several members of the phenolic series of these compounds (which are properly regarded as derivatives of the alkaloid oripavine) have activities 5000–10,000 times greater than morphine (Bentley, 1964). It has been possible to test a number of these compounds, and so far M.99 (6, 14-endoetheno-7-α[2-hydroxy-2 pentyl]-tetrahydro-oripavine) has been the most effective, with the lowest incidence of side effects.

The hydrochloride salt of M.99* is its most convenient form as this will dissolve in water to give a strength of 5 mg./ml. at pH 5. The use of a concentrated solution is advisable because M.99 is adsorbed on glass and dilute solutions tend to lose their activity, and because the smaller volume permits the use of a small and accurate projectile syringe.

M.99 has been used in 2 combinations: (a) with acetylpromazine,‖ and (b) with 1-(1-phenylcyclohexyl piperidine monohydrochloride.¶

Combination A	
Acetyl promazine	20·0 mg. per 250 kg. body wt.
M.99	1·0 to 1·5 mg. per animal
Hyoscine	2·5 mg. per 250 kg. body wt.
Combination B	
Phencyclidine	100 mg. per 250 kg. body wt.
M.99	1·0 to 1·5 mg. per animal
Hyoscine	2·5 mg. per 250 kg. body wt.

Combination A was used for the more placid species which did not become greatly excited upon injection, or in response to M.99 These included zebra, wildebeeste, water-buck, tsetsebe and impala. For larger animals, such as the hippopotamus, white rhinoceros and elephant, whose reactions indicated the use of acetyl promazine, the effective amount of this tranquillizer was too bulky and only small quantities of it could be given completely to fill the projectile syringe.

Combination B was used on such very nervous animals as the black rhinoceros, kudu and eland, whose behaviour indicated the need of a more potent tranquillizing agent. Good results were obtained with phencyclidine provided the dose was such as to permit the animal to rise to its feet immediately upon receiving the antidote to M.99.

There was some overlap in the choice of the drug combination. Either Combination A or B was suitable for the capture of antelopes of 250–300 kg. bodyweight, immature zebra and rhinoceros. For highly nervous antelope such as kudu and nyala, the substitution of acetyl promazine by chlorpromazine, 3–4 mg./kg. bodyweight was advantageous.

RESULTS

Table I shows the results in a consecutive series of 24 animals. The variations in dosage rate are due principally to the problem of judging the bodyweight under field conditions. The weight estimation was revised at the time of capture and a proportion of the animals was weighed. In this series, the weights of impala were the easiest to judge, and those of elephant the most difficult, while those of zebra and wildebeeste were intermediate.

At about 4 μg. M.99 per kg. the impala (about 50 kg. bodyweight) went down very consistently, but they were able to rise and walk away if approached. Zebra (about 300 kg.

* 'M.99 (Reckitt)' (British Patent No. 937,214). Currently, small quantities are available for biological research and investigational purposes only, on request from Reckitt & Sons Ltd., Dansom Lane, Hull, England.

‖*Acetylpromazine*, Boots Pure Drug Co. Ltd.

¶*Phencyclidine*, Parke-Davis & Co. Ltd.

TABLE I

CASE HISTORIES OF THE RESTRAINT OF 24 HOOFED WILD ANIMALS

No.	Species	Sex	M.99 µg./kg.	Time to 1st apparent effects (min.)	Time to incapacitation (min.)	Position	Time from initial inj. to handling (min.)	Method of restraint	Lethidrone mg. kg.	Time interval inj. M.99 to first inj. of lethidrone (min.)	Reaction	Time to recovery (min.)	Remarks
1	Zebra	F	3·74	6	8	Leaning	17	None. Down in 25 min.	0·16	42·5	Up	0·5	Galloped out of sight at once
2	Zebra	M	2·68	2·7	8	Down	15	Rope round neck	0·05	23	Up and broke free	2·0	15 mg. Lethidrone only given to manoeuvre animal to the weighing scales. This caused sufficient resuscitation for it to break loose
3	Zebra	F	3·74	5	—	Walking	15	Held by head	—	None	—	—	Difficult to catch. Injection appeared to be subcutaneously
4	Zebra	F	3·74	13	—	Walking	—	—	—	—	—	—	Not quite catchable, although almost went down at 34 min.
5	Zebra	M	3·96	Unknown	8·5	Down	11·5	Up and caught by the ears	0·13	28	Up and walked	2·0	More Lethidrone may have been beneficial
6	Zebra	M	4·62	1	2	Down	3	Up—but down completely at 2½ min.	0·13	5	Up and standing	1·0	Injection probably intravenous
7	Zebra	M	3·96	Unknown	10·7*	Almost down	14·5	Caught by ear	0·14	23	Up and off	0·2	Broke free after catching the first time. Caught again by the ear immediately afterwards
8	Zebra	M	3·96	Unknown*	10·7*	Standing	14·5	None. Caught by ear	0·14	21	Off at a gallop	0·5	This animal was mounted and ridden without other restraint
9	Impala	M	4·18	4	6·7	Do	10	Caught by horn	0·26	25	Up and ran	2·5	Down in 6·7 min. but rose on approach and walked away
10	Impala	M	4·62	4	5·7	Down	8	Caught by horn	0·3	26	Up and ran	0·2	Down in 5·7 min. but rose on approach and walked away
11	Impala	M	4·84	7	21	Down	21	None	0·25	37	Rose in 30 sec.	0·5	Uneventful

8	Zebra	M	3·96	Unknown*	10·7*	Standing	14·5	None. Caught by ear	0·14	21	Off at a gallop	0·5	This animal was mounted and ridden without other restraint
9	Impala	M	4·18	4	6·7	Down	10	Caught by horn	0·26	25	Up and ran	2·5	Down in 6·7 min. but rose on approach and walked away
10	Impala	M	4·62	4	5·7	Down	8	Caught by horn	0·3	26	Up and ran	0·2	Down in 5·7 min. but rose on approach and walked away
11	Impala	M	4·84	7	21	Down	21	None	0·25	37	Rose in 30 sec.	0·5	Uneventful
12	Impala	M	4·40	5	8	Down	36	Held by horn	0·25	80	Remained lying	2·0	Uneventful
13	Giraffe	M	2·22	3·5	25	Walking	25	Caught by rope	0·12	27	Up and ran	0·5	Allowed to walk into rope held at breast height
14	Giraffe	M	2·22	4·5	12	Walking	15	Caught by rope	—	—	—	—	Died of regurgitation subsequent to bad casting
15	Giraffe	F	2·86	3·5	9·25	Walking	9·25	Walked into rope held breast high	0·15	27	Rose immed. Off at gallop	0·5	Uneventful
16	Giraffe	F	2·2	4·5	11	Walking	11	Walked into rope held breast high	0·15	23	Rose immed. Off at gallop	0·5	Uneventful
17	Giraffe	F	2·42	5	10	Standing	10	Walked into bush	0·15	22	Tried to rise once then remained on brisket	2·5	
18	Elephant	M	1·63	Unknown	14	Standing	15	None. Down in 34 min.	0·23	35	Trunk not mobile	7	Another 0·5 mg./lb. Lethidrone given at 46 min. Rose in 1 min.
19	Elephant	M	3·33	—	9·5*	Down	10	None	0·5	23	Very slow	180	Able but disinclined to rise. Injection of caffeine indicated but not available
20	Elephant	M	1·0	19	85	Standing	90	None almost down	0·05	120	Started to walk backwards	10	Estimated bodyweight 5000 kg. Remained on feet and fairly active
21	Kudu	F	6·32	12·5*	—	Walking	27	Caught by ear	0·1	—	—	—	Caught after surrounding Never really manageable.
22	Kudu	M	4·84	6	—	Down temporarily	27	Caught by the horn	0·2	37	Leapt up at once and made off	0·2	Cortensor† given i.v.

*Lost temporarily.

† *Cortensor*, 6-amylo- 2 Methyl- 2 heptaminol-HCl, Wander (Switzerland).

continued overleaf

TABLE I *continued*

No.	Species	Sex	M.99 µg./kg.	Time to 1st apparent effects (min.)	Time to incapacitation (min.)	Position	Time from initial inj. to handling (min.)	Method of restraint	Lethidrone mg./kg.	Time interval inj. M.99 to first inj. of lethidrone (min.)	Reaction	Time to recovery (min.)	Remarks
23	Wildebeest	F	3·74	7·25	—	Walking	25	Caught by the horn	0·1	35	Stood for 1·5 min. then galloped off	1·5	Not properly incapacitated and dose probably low
24	Waterbuck	M	5·50	—	—	Lying on side	12*	None	0·15	19	Up in ½ min. but down again	20	Dose too high. Observed alive on subsequent days

* Lost temporarily.

BLACK RHINOCEROS
Diceros bicornis bicornis Linnaeus

ELAND
Taurotragus oryx oryx Pallas

ELEPHANT
Loxodonta africana africana Blumenback

GIRAFFE
Giraffa camelopardalis wardi Lydekker

HARTEBEEST
Alcelaphus buselaphus jacksoni Thomas

HIPPOPOTAMUS
Hippopotamus amphibius amphibius Linnaeus

IMPALA
Aepyceros elampus elampus Lichtenstein

KOB
Adenota kob thomasi Sclater

KUDU
Tragelaphus strepsiceros strepsiceros Pallas

SABLE
Hippotragus niger niger Harris

SOUTHERN WHITE RHINOCEROS or WHITE (SQUARE-LIPPED) RHINOCEROS
Ceratotherium simum simum Burchell

TSETSEBE
Damaliscus lunatus lunatus Burchell

WATERBUCK
Kobus ellipsiprymnus ellipsiprymnus Ogilby

WILDEBEEST
Connochaetes taurinus albojubatus Thomas, and *Connochaetes taurinus taurinus* Burchell

ZEBRA
Equus burchelli antiquorum Hamilton Smith
Equus burchelli bohmi Matschie

NYALA
Tragelaphus angasi Gray

bodyweight) after injection at a dosage rate of approximately 4 μg. M.99 per kg., usually became rapidly ataxic and were easily approached and seized by the ear.

Giraffe were given a lower dosage rate with the intention of keeping them on their feet. All continued to walk, except one animal which was caught in a tree. Capture was effected with a rope held by several men at breast-height in the path of the giraffe.

The waterbuck (No. 24) received a dose prepared for another beast, and its reaction indicated that this dose (5·5 μg./kg. bodyweight) was rather high for this species. The female kudu (No. 21) on the other hand, remained difficult to catch after a dose of more than 6 μg. M.99 per kg.

Elephant No. 20 (see Fig. 1) eventually became immobile even at the low amount of less than 1 μg. M.99 per kg. bodyweight. After a long interval during which this animal walked in roughly concentric circles of half a mile in diameter, it eventually stopped and could be handled. Such low dosage rates may be employed if sufficient time is available between injection and handling.

REACTION TO M.99

The immediate reaction of the injected animal to the syringe, or penetration by the needle, is usually only slight and momentary, except in areas where animals have been harassed by hunters and are alert to danger. Nervous animals such as sable antelope will run as a herd for variable distances; others, such as zebra, will trot or walk for only 50 yards or so. The first visible signs of reaction to the drugs usually occur after 3 to 4 minutes. There is a slight ataxia and a tendency to move away from the herd or group of animals in which the animal was found. Once these signs have become apparent there is little likelihood of losing the quarry, as, if undisturbed, its progress will be erratic and mostly in circles.

Posture and gait soon become characteristic of the morphine-type influence. The forelegs are lifted high off the ground at every step, and paces become shorter so that the animal may actually mark time. The head of some, like the giraffe, is carried far back so that forward vision is masked. This action suggests the Straub-Hermann effect which is induced in certain experimental laboratory animals by drugs with morphine-like action. Frequently the animal is halted by a bush or a fallen tree. Sight is impaired by both M.99 and hyoscine, and visual accommodation is lost. The animal may be seized by horn or ear, as it will then approach a stationary person. Movements are soon perceived, however, and if startled an animal may canter for 20 or 40 yards before slowing to a walk. Hearing remains at normal acuity, and alarming sounds result in immediate flight reaction.

As the dose becomes fully adsorbed, or when large doses are used, most animals will stand with head drooped. Not infrequently they will seek out an object to lean against. Sometimes, particularly with the antelope, the animals will lie down in sternal recumbency from which they are usually able to rise at will. Lateral recumbency is very rare and occurs only with grossly excessive dosages. The mental reaction in many subjects is interesting: wild animals are naturally curious, and normally this interest is balanced by apprehension or fear. Under drug influence the latter are banished, leaving the curiosity unrestricted. In more cases than could be explained by random chance, injected animals have circled and approached the vehicle carrying the capture team, sometimes closely enough to touch the vehicle and be caught by a passenger's hand extended through a window.

Once seized, resistance is only rarely offered, and most animals will stand quietly when

held by horn or ear. Zebra and rhinoceros were mounted while otherwise unrestrained, and the full import of this may possibly be apparent only to those who have experienced the larger African ungulates in their own habitat! The bull rhinoceros in Fig. 1 was mounted without causing him any visible concern.

Few animals go down at the rates of dosage used by us, and this has a double advantage: first, the fallen animal is remarkably difficult to find even in 'short' grass of 3 to 4 feet high; secondly, in thick bush an animal usually reveals its position by stumbling or breaking dead twigs. Contact may be regained through listening quietly for sounds of its passage through the undergrowth. If the animal does go down it will, on nearly all occasions, assume sternal recumbency. This is of particular importance in ruminants which may otherwise regurgitate ruminal contents or become tympanitic. Ruminal movements are in complete abeyance under the influence of M.99, but expulsion of gas by eructation is possible if the animal is in a favourable position.

ANTIDOTE AND RECOVERY

The recumbent animal will usually rise within a minute or two of receiving an intravenous injection of nalorphine* which is a non-specific antidote to M.99 (see Table I).

The dose of nalorphine bears relation in the first place to the size of the animal rather than to the dose of M.99. This is due to dilution of the nalorphine in the animal body. The M.99 is highly selective for the receptor site, and 1 mg. for a 2000 kg. beast (see Fig. 1) is quite effective. The dose of nalorphine for animals of this size is 0·25 to 0·5 g. as compared with 40–60 mg. for a zebra immobilized with the same or higher dose of M.99.

The subject does not return quickly to complete normality after the nalorphine, and should not be exposed to the danger of predators for some 6 hours or so. Tranquillizers and hyoscine also tend to render an animal more susceptible to predation and for a longer period. In spite of this, there is no evidence of any marked animal, captured with M.99, being attacked soon after release. The disadvantage of prolonged depression may not be important when compared with the numbers of animals which succumb to the effects of a more easily metabolized but irreversible drug such as suxamethonium. It should also be noted that the antidote nalorphine is, itself, a respiratory depressant. In very large doses it may cause reactions very similar to those caused by the injection of morphine itself. If no reaction is observed after the injection of approximately double or treble the normal dosage of nalorphine, further doses should be withheld and direct C.N.S. stimulants used. All primary injections of nalorphine should be given intravenously to gauge their effect, although a final dose may be given intramuscularly to form a depôt against the needs of the immediate future. This has been our routine with some susceptible animals, such as giraffe, before their release.

Animals which have to be transported may be given small doses of nalorphine, followed immediately by a tranquillizer such as chlorpromazine. In this way the narcosis is reduced, and replaced by a sedation which makes the animal more easily transported. Control experiments on domestic livestock indicate that M.99 raises the blood pressure in conscious sheep (Harthoorn, 1965) and the heart rate in conscious sheep and donkeys (Harthoorn, 1964). These changes also appear to occur in wild ungulates, so that all stress should be avoided while the animal is under the influence of M.99. For wild animals, in particular, the drug should be regarded as a means of capture, after which it should be replaced with other drugs before stress such as crating and transport are inflicted.

**Lethidrone*, Nalorphine Hydrobromide, Burroughs Wellcome & Co.

USE OF TRANQUILLIZERS

M.99 excites some animals. In most species, the addition of 20 mg. of acetyl promazine per 250 kg. bodyweight is sufficient to offset this, but in other species, such as elephant, even this is unnecessary. For more nervous animals, this dose of acetyl promazine is insufficient and recourse must be had to high doses (about 3–4 mg. per kg. bodyweight) of chlorpromazine and/or phencyclidine. The addition of a large amount of chlorpromazine is useful in antelope such as nyala which are difficult to restrain on capture. The phencyclidine is effective in shortening the time interval between injection and immobilisation, especially in antelope such as kudu and nyala which tend to remain very active and difficult to catch. It is important that the phencyclidine is never given in doses sufficient to immobilize, since death will result in ruminants and prolonged immobilization will occur in rhinoceros.

DISCUSSION

The dose of M.99 may be varied according to the speed of immobilization required. In general, animals found on the plains may be given lower dosages because they can be kept in view easily and the time interval between injection and immobilization need not be very short. Higher doses must be given to animals living in bush country, but care is needed as maximum tolerable dosages for the wild ungulates are not yet known. Experimentally, 100 times the immobilizing dose permits spontaneous recovery in the goat (Harthoorn, 1965).

The details of 24 consecutive case histories of animals handled in December 1963 are given in Table I; although this report takes many more cases into consideration, the 24 animals in this Table were chosen as being the largest consecutive range. Doses have been increased somewhat since the series depicted in Table I, and 2 mg. M.99 are now usually given to adult zebras (*i.e.* about 7 µg. per kg.) so that they become completely immobilized in about 3 minutes. Larger doses should be avoided if the animals are to be released, as there may be a return of narcosis after the antagonistic action of the nalorphine has ceased. In animals too large to be man-handled, large doses that may be associated with a poor response to nalorphine will result in prolonged (possibly lateral) recumbency and rapid deterioration of the subject. When this occurs stimulants should be injected intravenously to induce the subject to rise to its feet.

Low doses were used for giraffes because there is little likelihood of losing sight of them. The death of giraffe No. 14 was due to regurgitation of ruminal contents, and this would not have happened had the head been held up or the animal kept on its brisket or on its feet. Giraffes normally never lower their heads to the ground, and they should not be subjected to this posture during handling. Elephants are more easily lost in difficult terrain, and the 90 minutes taken by elephant No. 20 to stop moving is far too long for practical purposes.

The results described here confirm the experimental evidence that the safety margin of the compound used is considerable. The dosages used range from 1 µg. to 6 µg. M.99 per kg. bodyweight, and the pattern of recovery indicated that the upper dosage rate can be considerably exceeded without endangering the life of the animal. The variations in dosage occurring in this series of 24 animals suggest that overdosage due to problems in weight estimation is unlikely.

CONCLUSION

The demand for methods of immobilizing large wild animals is increasing. They are required for research, conservation, veterinary assistance and for trapping for zoos. Irrespective of any personal opinion as to the ethics of catching animals for zoological gardens, the prime interest of the veterinarian is that the capture be performed with the least anxiety and distress to the animal. Methods of catching involving the running down of the quarry using motor-vehicles is still prevalent all over Africa, and apart from the heavy mortality that may be induced by this method, when carried out by the inexperienced, the hunting down of non-predatory animals by means of trucks cannot be condoned when other more humane methods are available.

Progress in methods of capture by drug immobilization has been rapid after the early start in Africa about 5 years ago. The method described results in negligible mortality, although no method will ever eliminate deaths among unhealthy animals. Many wild animals suffer from intensely debilitating conditions including muscular dystrophy (Jarrett, Jennings, Murray and Harthoorn, 1964), but no losses need occur among healthy stock.

Over a broad range of animals only about 2% failed to recover, and the few deaths that occurred were usually associated with misadventure irrelevant to this discussion.

The advantages of the oripavine series of compounds and of M.99 in particular over substances used previously are as follows:

Rapid adsorption.
Central narcotic and analgesic state with elimination of fear and anxiety.
Small bulk.
Soluble in water, and easily miscible with other substances such as hyoscine.
Lack of severe side reactions.
Maintenance of most postural reflexes.
Negligible depression of respiration.
Rapid reversion by the use of morphine-antagonists.
Effective in all large wild species of mammals.
Safety margin of several hundred per cent, and, therefore, avoidance of overdose due to faulty weight assessment.
Little variation of dosage rates between one species and another.
Stable as a dry powder in sterile phials.

The disadvantages are that it is a narcotic, and with improper use may be habit forming in man. It is rapidly adsorbed through mucous membranes and great care must be taken not to inhale traces of the powder. It is not readily destroyed, so that, until more information is available, the meat of animals that die or are killed under the influence of the compound cannot be sold and should not be eaten. The M-series of drugs are pharmacologically highly active, and several members have analgesic activities 5000–10,000 times greater than morphine in experimental laboratory animals (Bentley, 1964). These compounds should, therefore, be treated as dangerous drugs falling within the scope of the United Kingdom Dangerous Drugs Act of 1964, especially during the preparation of solutions.

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