NEUROLEPTIC NARCOSIS OF LARGE WILD HERBIVORES IN SOUTH AFRICAN NATIONAL PARKS WITH THE NEW POTENT MORPHINE ANALOGUES M-99 AND M-183.

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Summary

The use of two of a series of bridged-ring oripavine derivatives (M-99 and M-183 Reckitt) for the immobilisation and capture of hoofed wild animals is described.

These substances are sometimes effective without the addition of synergists, as in the case of square-lipped rhino and elephant, but as a rule they are administered in combination with a tranquilizer and hyoscine.

The technique of neuroleptanalgesia has decided advantages over the majority of earlier drug-immobilising procedures and has proved highly successful when applied to a series of 439 animals, involving 16 different species, in South African National Parks. Mortality arising directly from drug reactions has been negligible, and of the order of 2-3 per cent.

The results of different drug combinations, which have been evolved for the capture of the different species, are discussed, and a composite table of dosage ranges is provided.

Introduction

The increased demand in recent years for more refined methods of field immobilisation and restraint of wild animals, for the purpose of veterinary and ecological research in situ, has compelled investigators to cast their net even wider in their search of suitable drugs.

The early range of drugs employed for incapacitating wild animals in the field included a wide range of muscle relaxants, reflex inhibitors, central nervous system depressants etc.[21 22 23 24]. These were applied, with varying degree of success, to a wide range of wild animals, but with few exceptions, they had the common disadvantage that their successful effect was to a large extent dependent upon accurate weight determination of the subject. This proved to be an insurmountable obstacle in the case of, particularly heavy animals. The action of the majority of these drugs was also irreversible, and in many instances, the large bulk of drug required to bring about the desired effect militated against its routine use in the field.

It was only when combinations of neuroleptic or ataractic and analgesic drugs with wide therapeutic index were adapted for animal immobilisation, that the high mortality rate incurred with older drug mixtures could be significantly reduced.

The pioneer work of Harthoorn[5] on the square-lipped rhinoceros, using a combination of morphine or diethylthiambutene (Themalon), hyoscine hydrobromide and a suitable tranquilizer, set the stage for the first really successful series of immobilising experiments on a particular species of wild animal, without fear of overdosage and resultant losses.

An important step forward was the fact that the narcotic action of one of the constituent drugs in the mixture could be reliably reversed, at any stage, through the intravenous or intramuscular injection of an antidote (Nalorphine hydrobromide).

One serious handicap which prevented the general application of neuroleptic narcosis in the animal field, was the large bulk of drug (analgesic) required to immobilise even a medium-sized ungulate in the wild state.

Different species also displayed varying reactions to the effects morphine, diethylthiambutene and other synthetic morphines, and a variety of tranquilizers had to be tested to find the correct combination of analgesic and neuroleptic agent which would bring about the proper state of central depression without an initial phase of hyper-excitement.

The advent on the scene of the bridged-ring oripavine derivatives M-99 and M-183 — thebaine-derived analgesics with morphine-like action, but extremely high potency — eliminated most of these practical difficulties.

After exhaustive field testing by a number of workers, it can safely be claimed that drug combinations including M-99 or M-183 are today without peer in the field of wild animal immobilisation, and these should be the drugs of choice for the capture of all large and medium-sized ungulates.

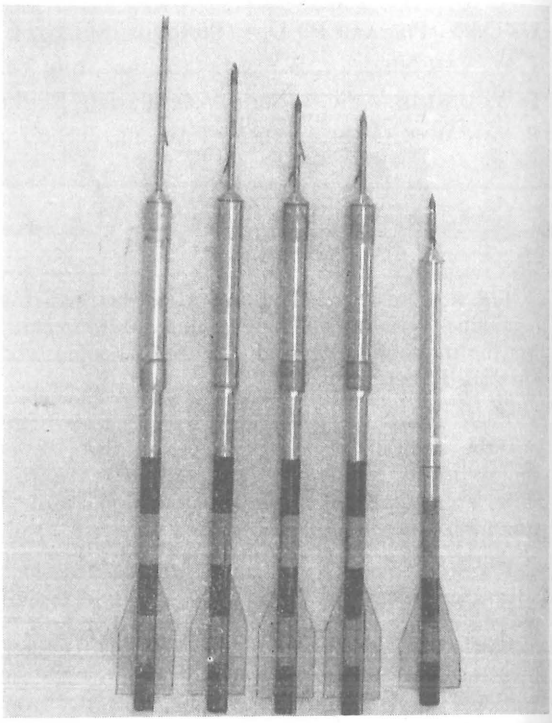
The successful application of M-99 drug mixtures for the restraint of particular hoofed wild animals has been reported on by Harthoorn and Player[10] — square-lipped rhinoceros; King and Klingel[14] — several species of equines; King and Carter[13] — black rhinoceros and Pienaar et al.[18] — African elephant. The initial series of experiments with M-99 in the Kruger Park, during which 7 different species of ungulates were successfully captured (with minor loss), was reported on by Harthoorn and Bligh[9].

It is the purpose of this paper to comment on the results of the protracted series of field trials with M-99 and M-183 which were initiated by us in December, 1963, and which eventually involved the capture of some 439 animals of 16 different species.

Material and Methods

With few exceptions, all the animals immobilised in this series, were injected by means of dart syringes (fig.) (i)), which were propelled by a powerful cross-bow (fig. (ii)), which was described by us in earlier papers[21] . For close-range work the Palmer Cap-chur pistol was found useful. Both the Palmer gas-propelled and powder-charged guns were, in our experience, not consistently accurate at long ranges, and have the added serious disadvantage that the loud report when fired, promotes the flight reaction of not only the darted beast, but also of associated animals in the herd. In comparison, the Van Rooyen cross-bow* is silent, causes no disturbance of the hunted animals and gives consistently accurate results at all ranges up to 120 yards, when used in combination with a good quality rangefinder**, and loaded with 3 cc. capacity dart syringes.

Fig. i



We also do not agree with Harthoorn[8] that a good quality cross-bow used in this manner, is essentially a specialist weapon. In fact, the converse is true, and cross-bows are at present used routinely by our game officers in preference to the 'Cap-chur' guns.

Animals, such as elephants, were sometimes stalked on foot, but as a rule darting was done from a vehicle (Land Rover of which the left front door and windscreen had been removed).

The following drugs were employed during the course of this study:

*Manufactured commercially by Mr. G. L. van Rooyen of "Southfields", P.O. Greytown, Natal, Republic of South Africa.

**Such as the 'Wild' hunter's range finder. (Manufactured by Wild Heerbrugg Ltd., Switzerland).

M-99

M-99 (Reckitt) is the code-name for the experimental drug 7oc-(1-R-hydroxy-1-methylbutyl)-6, 14-endoetheno-tetrahydro-oripavine hydrochloride (Synonym: Propylorvinol hydrochloride); currently manufactured and distributed in small quantities for biological research purposes only by Reckitt and Sons Ltd., Hull, England. This bridged-ring oripavine derivative is an analgesic of extremely high potency and may exhibit an activity 5,000 — 10,000 times greater than morphine.

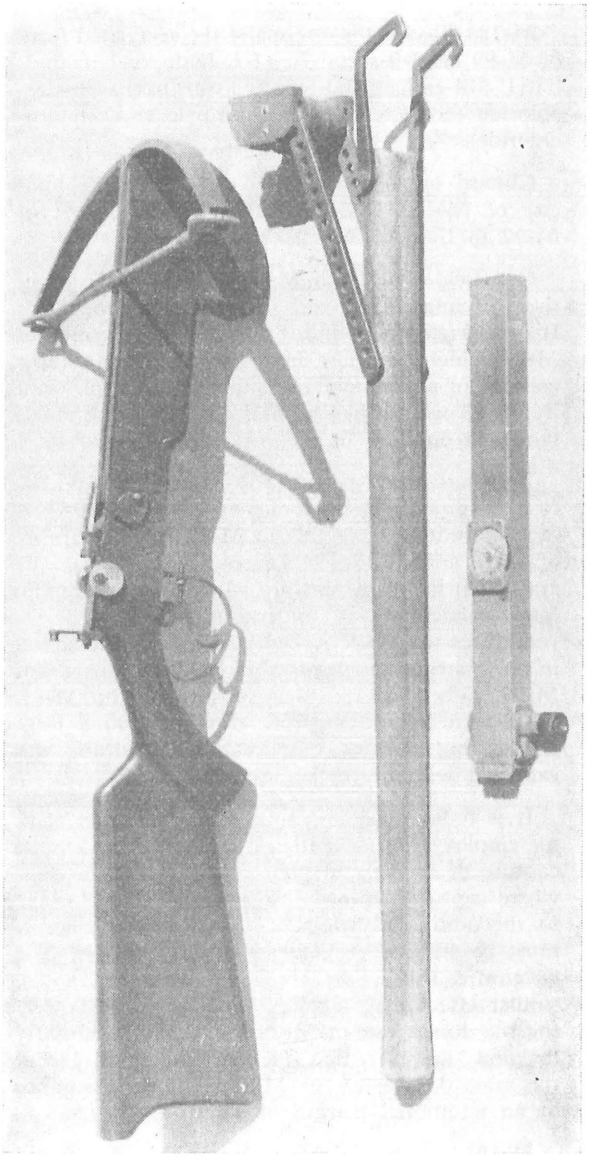
The small bulk of drug needed to produce the same effect as morphine or diethylthiambutene (Themalon), is an extremely valuable characteristic, and makes it possible to contain the total dose for even the largest animal (mature elephant bulls) in a 2 or 3 cc. capacity dart syringe. M-99 is rapidly absorbed after intramuscular administration and a central narcotic and analgesic state with elimination of fear and anxiety is induced within minutes in most species. The substance is sparingly soluble in water but stable aqueous solutions containing 4-5 mgm/ml. of the powdered base can be prepared, provided the water is acidified with N/1 HCl to pH4. M-99 is much more soluble in Dimethyl sulphoxide (D.M.S.O.*), an organic solvent with remarkable spreading properties. Solutions containing 10 mgm. or more of M-99 per ml. of solution may easily be prepared using D.M.S.O., and this was the technique employed when preparing solutions for the capture of elephant. M-99 in D.M.S.O. solutions should be treated with extreme care, as it is readily absorbed through the skin, but have the added advantage that induction is even more rapid than with watery solutions, and the addition of hyalase to the drug mixtures becomes unnecessary. Both aqueous and D.M.S.O. solutions of M-99 are readily miscible with other substances such as hyoscine hydrobromide, sernylan and most tranquilizing drugs.

M-99 has a wide therapeutic index and a safety margin of several hundred per cent in the case of most species. Dosage rates do not vary much from one species to another, and the action of the drug is rapidly and reliably reversed by the administration of the usual morphine antagonists such as Nalorphine hydrobromide and Lorfan, as well as the antagonist in the M-series of drugs, *M-285*.

Other advantages of M-99 are its lack of severe side reactions (there is a varying degree of respiratory depression and tachycardia), and the fact that most postural reflexes are maintained.

Darted animals usually go down on their briskets and maintain a position of sternal recumbency. This is to the advantage of ruminants as ruminal movements are inhibited under the influence of M-99. Expulsion of gas by eructation is possible if the animal maintains this favourable position, and bloating is not a serious complication. Elephants lying in a position of sternal recumbency

Fig. ii



*It has recently been found that D.M.S.O. may cause eye disturbances in a number of experimental animals subjected to prolonged contact with this substance.

soon develop symptoms of serious respiratory distress and it is essential that they should be assisted manually into a laterally recumbent position as soon as possible before a fatal state of anoxia is allowed to develop[18].

M-183

M-183 (Reckitt) is essentially the acetylated form of M-99 i.e. 3-0-acetyl-7œ-(1-R-hydroxy-1-methylbutyl)-614-*endo*etheno-tetrahydro-oripavine hydrochloride (Synonym: Acetyl-propylorvinol hydrochloride).

Clinical tests have revealed that the acute toxicity of M-183 is considerably less than that of M-99 in the case of rats and mice.

Our field trials with M-183 appear to bear out these findings in the case of many wild ungulates. It was a general finding that a dosage rate of M-99 which was just high enough to cause the collapse of an immobilised animal, was insufficient if M-183 was employed, and the stricken animals remained on their feet.

This was found particularly advantageous in the case of giraffe, and in our experience M-183 is quite definitely preferable to M-99 for the capture of these animals. M-99 causes severe tachycardia and a fall in blood pressure which may be rapidly fatal, particularly in undernourished giraffe. Several cases were experienced where giraffe collapsed in their stride and died while under influence of M-99. When M-183 was substituted for M-99, these toxic symptoms were eliminated to a large degree, and a series of more than 50 giraffe was captured without further loss.

It is today general practice in the Kruger Park to employ M-183 rather than M-99 for the capture of animals in poor condition, or in cases where captured animals are immediately subjected to the additional stress of long journeys, etc. It must be stressed that, except perhaps in the case of giraffe, this is not absolutely necessary, and a similar effect may possibly be achieved by lowering the dosage rate of M-99 somewhat. It is useful to know, however, that one can employ M-183 at the same dosage rate as M-99 with the assurance of an additional margin of safety.

M-183 is more soluble in water than M-99 and aqueous solutions containing 4 mgm/ml. solution were generally used by us. Cognisance should be taken of the fact however, that M-183 on sterilisation, and especially by autoclaving, is liable to hydrolyse partially and to give a mixture of M-183 and M-99.

Nalorphine hydrobromide.

Nalorphine hydrobromide or N-allylnormorphine hydrobromide is the morphine-antagonist which has been routinely employed in the Kruger Park experiments as an antidote for M-99 and M-183. The proprietary brand used was 'Lethidrone' (Burroughs-Wellcome).

Nalorphine rapidly reverses the morphine-like depression caused by the M-drugs when administered intravenously, and more slowly when an intramuscular injection is given. The dosage rate of nalorphine varies with the size of the animal and not so much with the dose of narcotic. Whereas 100 mgms. of nalorphine is normally sufficient to reverse the action of 2 mgms. M-99 in a captive zebra or wildebeest, 500 mgms. or more may be necessary to counteract the effect of a similar dose in the case of an adult square-lipped rhinoceros.

As is pointed out by Harthoorn[8], this is possibly due to the fact that M-99 is highly selective for the particular receptor centres of the central nervous system, and therefore suffers less from dilution in the animal body than its antagonist.

M-285

M-285 (Reckitt) is N-cyclopropylmethyl-7oc-(1-hydroxy-1-methylethyl)-6,14-endoetheno tetrahydro-nororipavine hydrochloride. (Synonym: N-cyclopropylmethyl-19-methyl-nororvinol). This substance is a highly potent specific morphine antagonist, but in contrast to Nalorphine hydrobromide, its action is very much less weight dependent. This is particularly true when it is employed to reverse the narcotic action of the M-drugs in large animals. It is probably, like M-99, more specific for the receptor sites in the central nervous system than nalorphine, and this characteristic makes it an essential requisite for the reversal of M-99 narcosis in elephants. The prohibitively large quantities of nalorphine which is necessary to antagonize the action of 4-7 mgm. M-99 in adult elephants (2 gms. and more) rules it out as a routine antidote. By contrast, only 40 mgms. of M-285 is necessary to effectively perform this function.

Scopolamine (Hyoscine hydrobromide).

Hyoscine hydrobromide is an alkaloid with parasympatholytic action somewhat similar to Atropine. It also has central depressant effects however, and has a potentiating action on ataractic and narcotic drugs and may counteract respiratory depression.

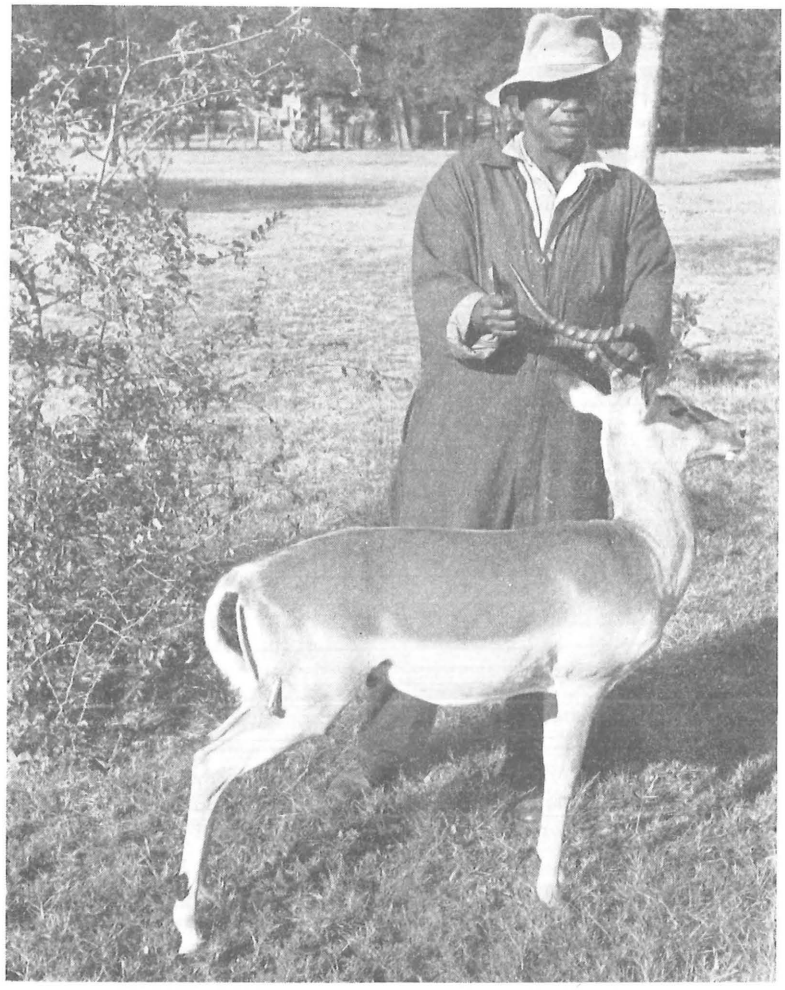
It has been found by us to be an essential adjuvant to drug mixtures employed for the capture of giraffe and even zebra, but for most other species it is not essential (although without it, the latent period after darting and before capture is extended). In some, like elephant, it might even be toxic, and is best left out[18].

Hyoscine hydrobromide is usually administered at a dosage rate which varies from 1-5 mgm/100 lbs. body weight.

Sernylan (Phencyclidine).

Sernylan (Parke Davis) is 1-(1-phenylcyclohexyl) piperidine monohydrochloride and is a centrally

Fig. iii



The crystalline substance is highly soluble in water, and aqueous solutions containing 100 mgm/ml. of the drug were prepared by us.

A disadvantage of hyoscine is that it causes a prolonged dilatation of the pupil and paralysis of the ciliary muscles. This causes photophobia and the animal is incapable of focusing on nearby objects. If released in such a semi-blinded state, its chances of survival must be reduced.

acting drug, the action of which varies according to dosage level.

At low dosages it causes a cataleptic state and at higher levels a condition resembling anaesthesia.

It may possibly be classified with the so-called 'Major' tranquilizers of Marsboom and Mortelmans[16], which also include the butyrophenones dehydrobenzperidol, fluanisone and others.

Harthoorn[7] considers that the term 'neuroleptic' should properly be reserved for this group of drugs which have a more intense akinetic activity than the true tranquilizers (ataractics), and which may produce a catatonic state which permits no concerted movement.

This is probably the correct approach, as sernylan, and even some of the butyrophenones employed by us, produce no state of true sedation. They certainly potentiate the action of M-99 and related drugs and effect the immobilisation of highly excitable ungulate species such as kudu, eland, and nyala, which in their absence remain ambulatory even under influence of large doses of M-99. Low dosage levels of sernylan should be administered in combination with M-99 (i.e. not more than 100 mgm/500 lbs. body weight), or the animal will fail to rise when the action of the M-99 is reversed with an antagonist.

It is also desirable to include a suitable tranquilizer in this mixture as Sernylan produces little or no sedation and the animal may thrash about severely and injure itself in the state of incoordination produced by the combined effect of M-99 and Sernylan.

Sernylan is highly soluble in water and stable aqueous solutions containing 100-200 mgm/ml. of the drug were prepared.

Fluanisone (R2028 base).

Fluanisone (Janssen) is the proposed name for 1-(3-(4-fluorobenzoyl)-propyl)-4-(2-methoxyphenyl)-piperazine. This butyrophenone derivative is, like the related Droperidol and Haloperidol (Janssen), a true neuroleptic drug of high potency. It is a strong inhibitor of learned reflexes, thus producing a typical state of catalepsy[16]. As such, dehydrobenzperidol (Droperidol) is 400 times more active in dogs than chlorpromazine and chlorprotixene, and 10 times more active than haloperidol. Droperidol has the shortest, and haloperidol the longest duration of action in this series. As in the case of Sernylan, aqueous solutions of Fluanisone are rapidly absorbed and hasten the induction of narcosis by narcotic or analgetic/cataleptic agents such as M-99.

At the dosage levels employed by us, Fluanisone does not cause any of the undesirable side effects of Sernylan, such as loss of balance, gnashing of the teeth etc.

In combination with M-99 and hyoscine hydrobromide, it induces a state of truly remarkable tractability in zebra, which persists for hours even after the morphine antagonist is administered, and the animal rises to its feet. In ruminants, however, fluanisone does not allay fear or nervous states as well as some phenothiazines, and it was noticed that buffalo, wildebeest and waterbuck, for instance, remained sensitive to handling. The potentiating action on M-99 in ruminants is as great as that of Sernylan however, and there is the added advantage that fluanisone causes no disturbance of heat regulatory mechanisms in this group.

Small synergistic doses of suitable phenothiazines would constitute an ideal combination with fluanisone or droperidol and M-99 for the capture of most species of heat-sensitive ruminants. This is highly desirable, as the usual doses of phenothiazines employed for the capture of these ruminants very often cause serious (often fatal) heat regulatory disturbances, particularly on hot days, in such species as waterbuck, buffalo, wildebeest, sable and others.

Fluanisone and Droperidol are both water-soluble drugs and stable aqueous solutions containing up to 40 mgm/ml. of these drugs were prepared by dissolving the requisite amounts in 1.5% Tartaric acid containing 0.05% Methylparaben and 0.005% Propylparaben as preservatives.

Tranquilizers.

A variety of tranquilizing or ataractic drugs were tested, and of these the phenothiazine derivatives chlorpromazine hydrochloride (Largactil, May and Baker), acetylpromazine (Boots) and trifluo-promazine (Siquil, Squibbs) were found most useful. Acetylpromazine because of its rapid absorption and fast action found the widest application, and is generally used in combination with M-99 (with or without Scopolamine) for the immobilisation of most ungulate species.

It produces very satisfactory sedation, and in combination with M-99 brings about a narcotic and analgesic state during which the animal is insensitive to pain and completely tractable. Animals have been branded (see fig. (iii)), castrated, and even partial hysterectomies have been performed under the influence of this drug mixture, after some additional local anaesthesia.

M-99 has a remarkable potentiating effect on tranquilizing drugs such as Acetylpromazine. Dosages of these phenothiazines which would normally not have the slightest visible influence on an animal when administered alone, effect a marked degree of tranquilization when injected in combination with M-99 or M-183. A total dose

of 50-60 mgms. of Acetylpromazine, for instance, is sufficient to produce a satisfactory state of sedation in even the largest elephant bull and higher doses induce a soporific reaction and a somnolent state from which the animal refuses to rise after the M-99 antagonist is administered[18].

It seems logical to conclude that M-99 plus acetylpromazine (or related neuroleptic agents) form true neuroleptanalgesic combinations under the influence of which even surgical intervention is possible in many species — a procedure which would not be possible with either drug alone.

Acetylpromazine causes toxic symptoms in many ruminants, even at fairly low dosage levels, and cognisance should be taken of the fact that serious, and often fatal, heat regulatory disturbances may follow its administration, particularly on hot days. The torticollis reported in waterbuck by Short and Spinage[19 20], is most likely also due to the effects of Acetylpromazine and is not a toxic symptom of M-99 per se.

In the case of highly-strung and nervous animals, such as kudu, eland, nyala, sable and others, it is advisable to use a tranquilizer of more potent, if slower, action. For this purpose, both chlorpromazine hydrochloride or trifluopromazine may be employed, and the latter has the added advantage that its influence on heat regulation is less drastic than that of acetylpromazine.

Discussion of Results

The reaction of ungulates to M-99 drug mixtures has been adequately reported on by Harthoorn and Bligh[9] and others, and will not be recapitulated.

A better purpose will be served by a discussion of drug mixtures applicable to individual species and the variation in dosage levels necessitated by differences in weight and sex of individuals.

(i) *Impala* (*Aepyceros melampus melampus* (Lichtenstein)).

A substantial number of impala has been successfully captured with the aid of the drug-immobilising technique. (See fig. (iii)). The following combination may be used for adult animals ranging from 100-165 lbs. in body weight.

0.5 mgm. M-99.
5 mgm. Acetylpromazine maleate.
5 mgm. Hyoscine hydrobromide.

Impala are rather sensitive to the action of M-99, and at this dosage rate they will usually lapse into a coma and die from anoxia within 30 minutes if no remedial measures are applied. The intravenous injection of 10 mgms. Nalorphine hydrobromide immediately after capture, is normally sufficient to prevent any such occurrence.

In more open country, the dose of M-99 may well be reduced to 0.25 mgm., and although the animal will remain ambulatory for a longer period*, there is no danger of excessive respiratory depression developing.

Total number of impala immobilised: 47 (33 males, 14 females).

Mortality: 2.

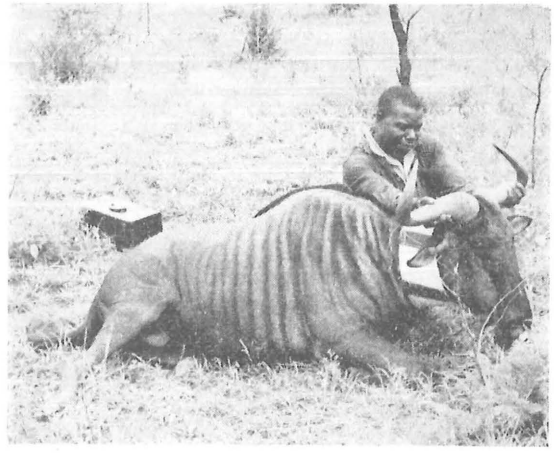
(ii) *Blue wildebeest* (*Connochaetes* (*Gorgon*) *taurinus taurinus* (Burchell)).

Wildebeest have been captured with almost infallible certainty and negligable loss with the following mixture (see fig. (iv)):

Adults (450 — 650 lbs.): M-99 — 2.0 mgms.
Acetylpromazine maleate — 20 mgms.
Hyoscine hydrobromide — 20 mgms.

1-2 *year old young* (200 — 450 lbs.): M-99 — 0.5 to 1.0 mgm.
Acetylpromazine maleate — 10 mgm.
Hyoscine hydrobromide — 10 mgm.

Fig. iv



In view of the successful application of Fluanisone in such cases where phenothiazine derivatives may cause toxic symptoms at higher dosage

*The addition of the enzyme Hyaluronidase (1500 i.u.) to the immobilising mixture, usually facilitates a more rapid induction.

levels, it may be desirable to reduce the Acetylpromazine dose by half and substitute an equivalent dose of Fluanisone.

The drug mixture for adult wildebeest would then read: M-99 — 2 mgms., Fluanisone — 10 mgms., Acetylpromazine — 10 mgms.

Total number of wildebeest immobilised: 124 (75 males, 49 females).

Mortality: 8. (Not all due to drug action).

(iii) *Zebra* (*Equus* (*Hippotigris*) *burchelli antiquorum* H. Smith)

The same drug-mixtures and dosage levels applicable to wildebeest above, may also be employed for the capture of adult zebra (550 — 750 lbs. body weight). (See fig. (v). In the case of these animals, Fluanisone is definitely preferable to Acetylpromazine or other phenothiazines, and induces excellent tranquilization even during the recovery phase post-nalorphine administration. This is particularly desirable when zebra have to be crated immediately for transport. Crates have to be fitted with padded shoulder supports to prevent the animal from moving forwards in characteristic manner during the recovery phase and injuring or breaking its neck.

Zebra foals of 1-2 years old have also been most successfully captured with a mixture comprised of:

M-183 — 1.0 mgms.
Fluanisone — 10 mgms.
Hyoscine hydrobromide — 10 mgms.

Darted animals usually exhibit first signs of ataxia within 3 minutes and could be caught and handled in less than 10 minutes.

Fig. v

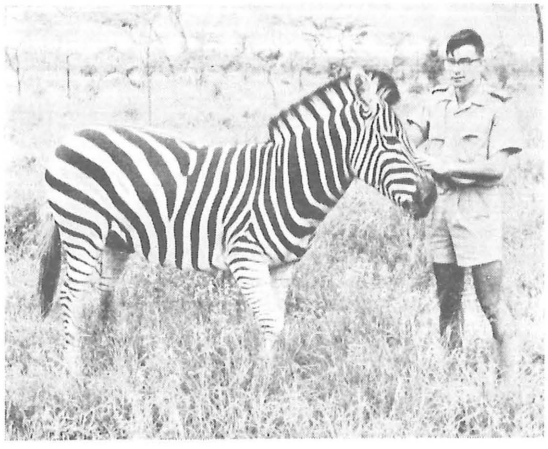
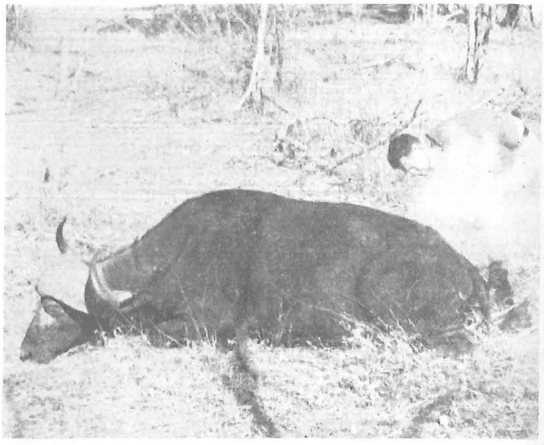


Fig. vi



Total number of zebra immobilised : 106 (60 males, 46 females).

Mortality: 7. (Only 2 directly due to drug action).

(iv) *Tsessebe* (*Damaliscus lunatus lunatus* (Burchell)).

A single tsessebe bull (estimated body weight 350 lbs.), was successfully captured and subsequently marked, using a mixture of 1.0 mgm M-99, 10 mgm. Hyoscine hydrobromide and 10 mgm. Acetylpromazine. The latter could well be substituted by Fluanisone 5 mgm. and Acetylpromazine 5 mgm.

(v) *Buffalo* (*Syncerus caffer caffer* (Sparrman)).

An effective and safe immobilising mixture for adult buffalo is the following (see fig. (vi)).

Adult bulls (1,500 — 2,000 lbs.) : 4 to 6 mgm. M-99.
Fluanisone 30 mgm.*
Acetylpromazine 20 mgm.
75 — 100 mgm. Hyoscine hydrobromide (Optional).

Adult cows (1,000 — 1,500 lbs.) : 3 to 4 mgm. M-99.
20 mgm. Fluanisone.
15 mgm. Acetylpromazine maleate.
50 mgm. Hyoscine hydrobromide (Optional).

* Buffalo have previously been successfully captured using M-99 with Acetylpromazine (20-25 mgms.) *or* Fluanisone (30-40 mgm.) alone, but in view of the synergistic action of the neuroleptic

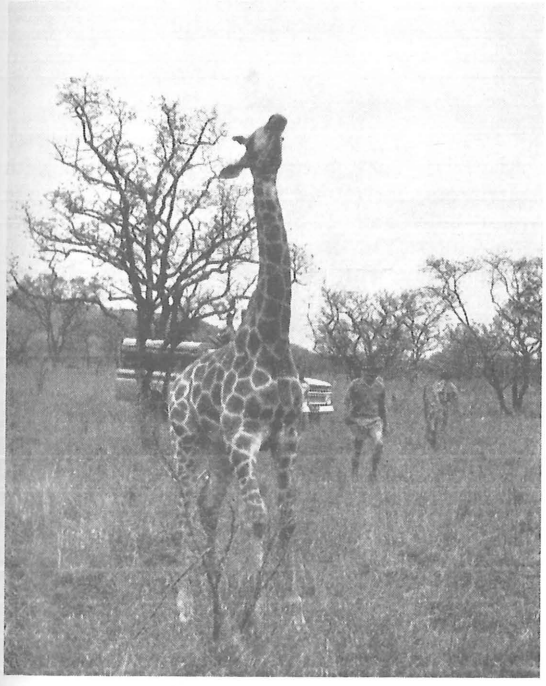
drugs and the unsatisfactory sedation achieved with Fluanisone alone, it is considered advisable to use a combination of the two drugs, both at a lower dosages level. In such cases the addition of hyoscine hydrobromide may well be redundant.

200 — 400 mgm. Nalorphine hydrobromide is the usual dose of antagonist administered. It is customary to inject some $\frac{3}{4}$ of the total dose of Nalorphine intravenously and the rest intramuscularly, to form a depôt against the needs of the immediate future.

Total number of buffalo immobilised : 19 (9 bulls, 10 cows).

Mortality: **0.**

Fig. vii



(vi) *Giraffe* (*Giraffa camelopardalis giraffa* (Boddaert)).

The oripavine derivative M-183 is a safer drug to use for the capture of giraffe than the related more potent M-99. The onset of its reaction is more gradual than that of M-99, and its effect is less drastic on cardiac function and respiration.

M-99 often causes a sudden fall in blood pressure, which may or may not be associated with acute cardiac failure. This is particularly true for giraffe in poor condition, and once they collapse, death follows almost inevitably.

It is essential to administer a dose of narcotic that will keep the animal ambulatory, as giraffe experience great difficulty in rising from the ground in a bemused state. They often exhaust themselves so much in their efforts to rise that they eventually succumb completely and die. In view of the risk of fatal hypotension, it is also essential to keep the animal on its feet.

While walking about in a condition of 'twilight sleep', it can easily be roped and led into a crate mounted on the back of a low trailer. (See fig. (vii)). Once in the crate, the morphine antagonist (100-200 mgm. Nalorphine) is immediately injected into the jugular vein, and 100-200 mgm. hydrocortisone (Vecortenol. Ciba) and some 12,000,000 i.u. long-acting penicillin are administered intramuscularly.

As soon as the animal's blood pressure returns to normal, which may be deduced from the prominence of the *Vena facialis,* the animal may be transported to the holding pen and released.

A completely safe and reliable drug combination for the capture of young giraffe in the 600 — 1,200 lbs. class, is:

M-183 — 2 mgms.
Acetylpromazine maleate — 20 mgms.
Hyoscine hydrobromide — 50 mgms.

For adult animals (1-1$\frac{1}{2}$ tons), the dose of M-183 would have to be increased to 4 or 5 mgms.

If giraffe have to be transported over long distances, it is very advisable to keep them in a holding pen for some time, until they are quite tame and will feed from the hand. This is often accomplished within 7-10 days. Giraffe should be transported individually in crates large enough to permit the animal to lie down and rise without difficulty. Frequent stops should be made en route, and the animals allowed to rest, to prevent fatal trauma in the extensor muscles of the fore legs[25].

Over smaller distances giraffe may be transported in smaller crates, provided they are trussed in a special harness, as is described by Riney and Kettlitz[17].

Total number of giraffe immobilised: 73. (35 bulls, 38 cows).

Mortality: 8. (Not all due to drug action).

(vii) *Hippopotamus* (*Hippopotamus ampbibius capensis* Desmoulins).

Drugs of the M-series, morphine and even diethylthiambutene (Themalon) in combination with chlorpromazine or acetylpromazine and hyoscine, are suitable for the capture of hippopotami on dry land, but are practically useless when the animals are in the water. The onset of the drug reaction is too rapid and the animals become completely immobilised, sink and drown.

On land, adult hippos (3,000 — 4,500 lbs. body weight) may be successfully immobilised with 4.0 — 5.0 mgms. M-99 without any adjuvants.

In the water, however, the only drug combination, which keeps the affected hippo buoyant for a sufficient length of time to allow a net to be brought in position and to haul it on to dry land before sinking, is Sernylan (Parke Davis), and a suitable tranquilizer[24].

A Sernylan-Chlorpromazine mixture gave very satisfactory results in the Kruger Park, and a number of hippo were successfully captured at a dosage rate of Sernylan 0.125 — 0.16 mgm/lb. and Chlorpromazine 0.25 — 0.4 mgm/lb. Chlorpromazine could conceivably be substituted with Trifluopromazine or Acetylpromazine.

Total number of hippo immobilised with M-99: 2.

Mortality: 1.

(viii) *Square-lipped Rhinoceros* (*Ceratotherium simum simum* (Burchell)).

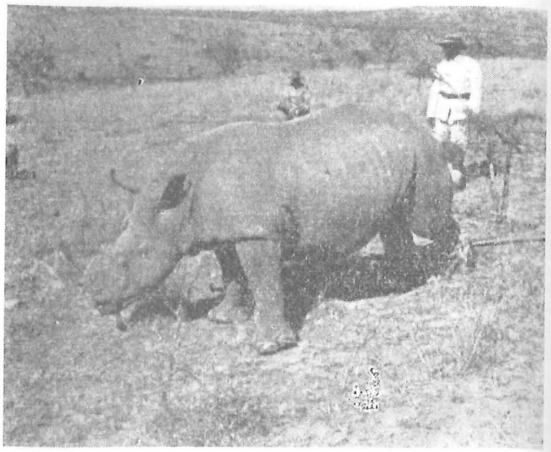
Circumstances have necessitated the capture of only 3 white or square-lipped rhino in the Kruger Park, but the long series which have been successfully immobilised in the Natal Parks[10], proved that adult beasts of this species (ranging from 3,000 — 5,000 lbs. body weight) may be safely and reliably restrained by the injection of 1.5 — 3.0 mgms. M-99, with or without adjuvants. (See fig. (viii)).

(ix) *Elephant* (*Loxodonta africana africana* (Blumenbach)).

Elephants are much more sensitive to the action of neuroleptic-narcotic mixtures than most other species. Compared with the dosage rate for M-99 in the case of most ruminant species (2.0 — 4.0μ gm./lb.), that for elephant is very much lower (0.47 x 0.67μ gm./lb.).

The optimum dosage rate of M-99 when combined with Acetylpromazine would appear to be 7-8 mgms. (total dose) in the case of the largest group of adult elephant bulls (weighing 12,000 — 15,000 lbs.), and 5-6 mgms. for the smaller class adult bulls and largest cows (7,000 — 12,000 lbs. body weight). (See fig. (ix)).

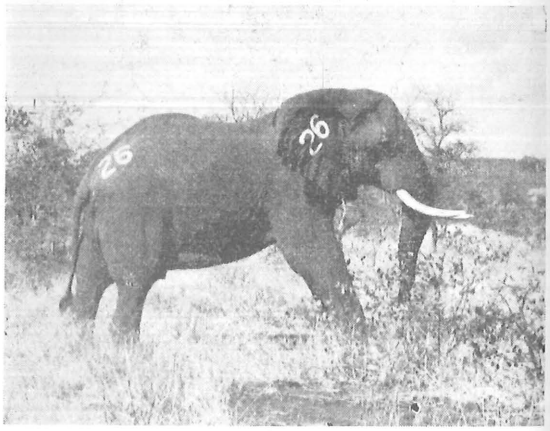
Fig. viii



M-99 is administered in combination with Acetylpromazine (50-60 mgms. (total dose) for the largest bulls and 40-50 mgms. for the smaller adult bulls). The latter may well be substituted by Fluanisone with even more satisfactory results.

Hyoscine hydrobromide apparently causes toxic reactions in elephant and it is best omitted from drug mixtures.

Fig. ix



Large amounts of Nalorphine are necessary to antagonise the effect of M-99 in these massive beasts and the antagonising action is to some degree weight dependent.

On the other hand, highly dependable reversal of narcosis is obtained in elephant with norori-pavine hydrochloride (M-285), and the optimum dose of antidote in the case of beasts immobilised with 5-8 mgms. M-99, seems to be in the region of 40-60 mgms. M-285. Elephants which go down in a sternal position when succumbing to the drug reaction, should be pulled over on their sides by means of a rope and truck, in the manner described by Pienaar et al[18], as soon as possible, in order to prevent fatal respiratory and circulatory collapse.

Total number of elephants immobilised: 34 (all bulls).

Mortality: 2.

(x) *Warthog* (*Phacochoerus aethiopicus sundevalli* Lönnberg).

An effective immobilising dose of M-99 for adult warthog (140-220 lbs.), is 1.0 — 1.5 mgms., in combination with 5-10 mgms. Hyoscine hydrobromide and 20 mgm. Acetylpromazine (or Fluanisone).

Total number of warthog immobilised: 2 (Boars).

Mortality: Nil.

(xi) *Waterbuck* (*Kobus ellipsiprymnus ellipsiprymnus* Ogilby).

A number of waterbuck have been successfully captured in the Kruger Park with neuroleptic-narcotic mixtures, but the therapeutic index is not particularly favourable in this species, and losses have been experienced elsewhere from heat-stroke and collapse, torticollis, cardiac failure, etc. Adult bulls (475 — 600 lbs.) have been captured with 3 — 3.5 mgm. M-99 and adult cows (350 — 500 lbs.) with 2 — 2.5 mgms. M-99, in combination with Acetylpromazine 20 mgms. and Hyoscine hydrobromide 20-30 mgms. (See fig. (x)). Until such time as Fluanisone or one of the other related butyrophenones prove to be a satisfactory substitute for Acetylpromazine (which causes the toxic reactions), it would be advisable to capture waterbuck with Succinyl-choline (Suxamethonium) at a dosage rate of 0.7 mgm./lb. in combination with Atropine or Hyoscine hydrobromide (5 mgm./100 lbs.).

Fig. x

Total number of waterbuck immobilised : 5 (4 males, 1 female).

Mortality: Nil.

(xii) *Red hartebeest* (*Alcelaphus buselaphus caama* (Cuvier)).

As in the case of wildebeest and tsessebe, red hartebeest may be captured with splendid success, using neuroleptanalgesic techniques.

Adult bulls (350 — 450 lbs.) require 1.0 mgm. M-99 and adult cows (280 — 380 lbs.) only 0.75 mgm. M-99 in combination with 10 — 15 mgm. Acetylpromazine and 10 mgm. Hyoscine hydrobromide. Fluanisone may be substituted for half the dose of Acetylpromazine and the Hyoscine may be omitted.

The dosage rates for hartebeest bulls may also be successfully applied to adult bontebok (280 — 350 lbs.) *Damaliscus dorcas dorcas* (Pallas), but here again the Acetylpromazine dose should be cut to the minimum and substituted with Fluanisone to prevent unwanted side reactions.

Total number of red hartebeest immobilised: 5 (4 males, 1 female).

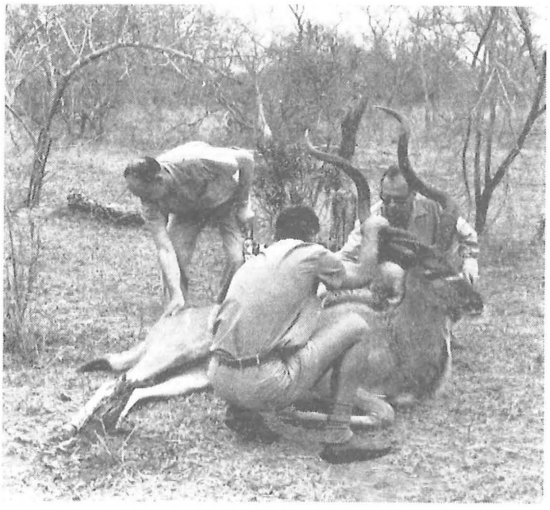
Mortality: Nil.

(xiii) *Kudu* (*Tragelaphus strepsiceros strepsiceros* (Pallas)).

Kudu, eland, nyala and their kin fall in the group of highly excitable animals, the behaviour of which upon darting indicate the need for a

more potent tranquilizing agent. The usual combinations of M-99 with acetylpromazine and hyoscine do affect these animals, but they remain ambulatory and keep on the move with a persistent trotting gait. Their sense of hearing is not impaired and they are easily startled and put to flight even in their bemused state. It is often very difficult to capture them unless they may be fortuitously roped.

Fig. xi



The most satisfactory drug combination for kudu used by us to date, and which does immobilise the animals, is the following. (See fig. (xi)).

Adult bulls (550-650 lbs.): M-99 — 4 mgms.
Sernylan — 75 to 100 mgm.
Trifluopromazine (Siquil) — 50 mgm.

Adult cows (280-400 lbs.): M-99 — 2.5 to 3 mgms.
Sernylan — 50 mgms.
Trifluopromazine — 50 mgm.

Hyoscine hydrobromide may also be added to this mixture at a dosage rate of 5 mgm./100 lbs. body weight, but is best omitted if the animal is to be released immediately after capture.

It seems likely, in the light of experience with other ungulate species, that the Sernylan in the above drug combination could be replaced by Fluanisone (40 — 50 mgms. total dose for bulls and 30 — 40 mgms. total dose for cows), with even more satisfactory results.

Number of kudu immobilised: 13 (10 bulls, 3 cows).

Mortality: 1.

(xiv) *Eland* (*Taurotragus oryx oryx* (Pallas)).

The same drug combination and dosage level employed for adult kudu bulls, may also be used for the capture of adult eland cows (500 — 850 lbs.). For adult bulls, weighing from 1,200 to 2,000 lbs., the dose of M-99 must be increased to 5 or 6 mgms., and that of Sernylan to 100 or 150 mgms. (alternative Fluanisone 50-60 mgms.). Trifluopromazine should also be used instead of Acetylpromazine. (See fig. (xii)). — Page 289.

Number of eland immobilised: 2 (1 male, 1 female).

Mortality: Nil.

(xv) *Sable* (*Hippotragus niger niger* (Harris)).

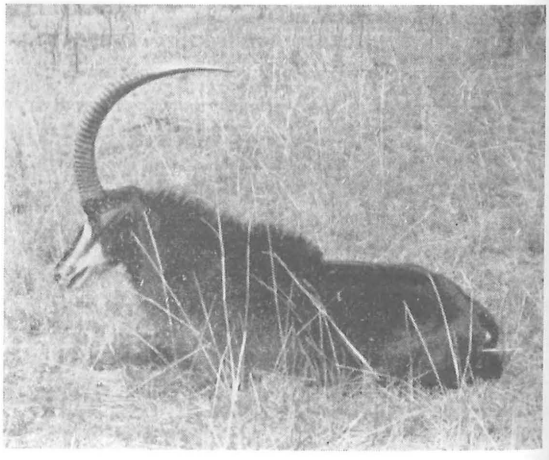
A provisional dose for adult sable antelope (450 — 550 lbs.), in the light of limited data available, would be: (See fig. (xiii)).

M-99 or M-183 — 2.0 mgms.
Hyoscine hydrobromide — 20 mgms. (Optional).
Trifluopromazine — 20 mgms.
Fluanisone — 10-20 mgms.

These dark-skinned animals develop toxic symptoms, associated with heat stroke, when injected with Acetylpromazine, and for this reason a low dose of Trifluopromazine in combination with Fluanisone is recommended.

A similar drug combination is proposed for the capture of Roan antelope (*Hippotragus equinus equinus* (Desmarest)), but for adult bulls, which

Fig. xiii



may weigh 600 lbs. and more, it may be necessary to increase the dose of M-99 to 3.0 mgms.

Number of sable immobilised: 2 (1 bull, 1 cow).

Mortality: 1.

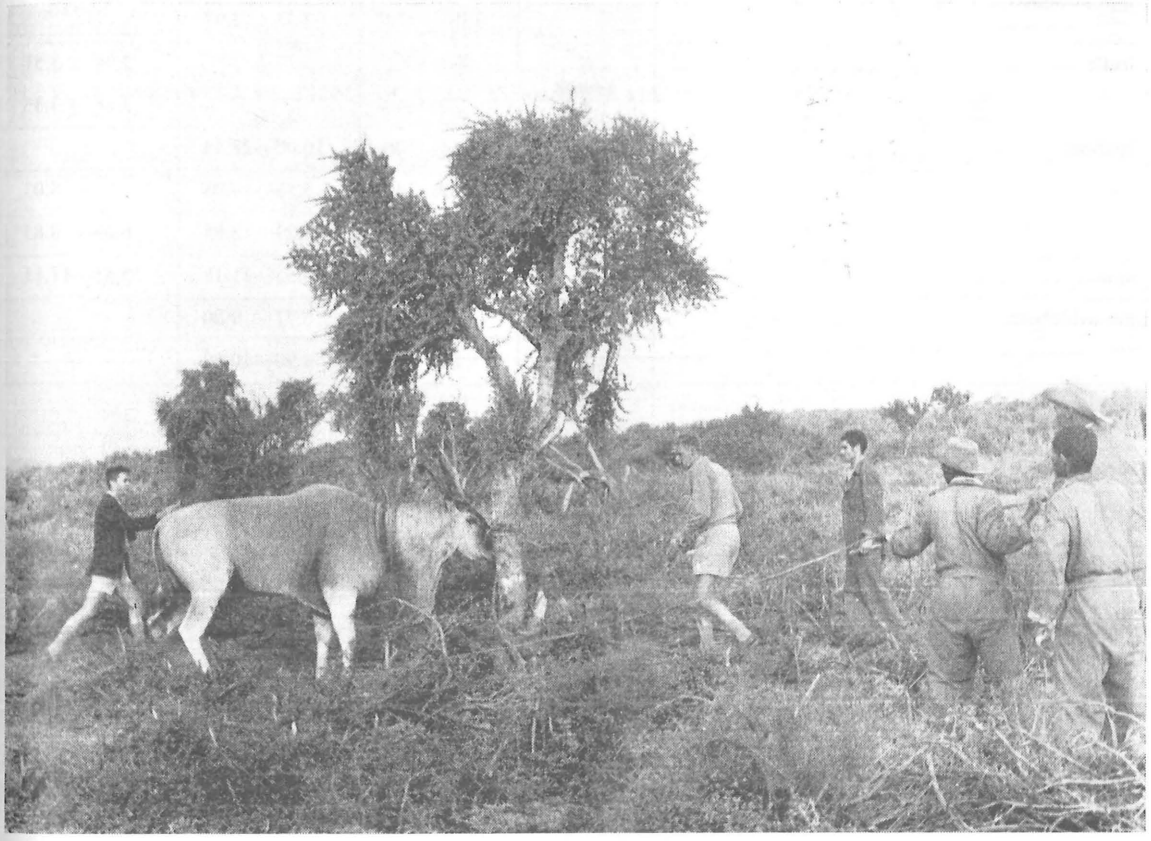
Number of roan immobilised: 1 (Young calf).

Mortality: Nil.

Discussion

It dose not fall within the scope of this paper to go into a detailed analysis of dose response curves, and with few exceptions, we have not as yet succeeded in establishing the minimum effective dose and LD-50 for M-99 or M-183 in our subject species. The table of optimum dosage levels provided below for 16 different species, will, in our opinion, form a practical guide on which more detailed studies can be based.

Fig. xii



ACKNOWLEDGEMENTS

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We also wish to thank Messrs. Parke Davis for a quantity of Sernylan received from them free of charge.

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TABLE 2.

OPTIMUM DOSAGE RATES OF M-99 AND M-183 (IN MG/KG) IN NEUROLEPTANALGESIC MIXTURES FOR 16 SPECIES OF WILD HOOFED ANIMALS IN SOUTH AFRICAN NATIONAL PARKS.

Species	Sex	Range adult body weight in Kg	Dosage rates in μg/Kg.	
			M-99	M-183
Elephant	♂	5443–6804	1.03– 1.47	
	♂	3175–5443	0.91– 1.89	
	♀	3175–5443	0.91 –1.89	
Square-lipped Rhinoceros	♂	1361–2268	0.88— 2.2	
	♂ & ♀	1134–1814	0.82— 2.2	
Hippopotamus	♂	1588–2041	2.45— 3.15	
	♀	1361–1724	2.32— 2.93	
Giraffe	♂ & ♀	907–1361		2.94— 5.51
	Young ♂ & ♀	272–544		3.68— 7.35
Warthog	♂ & ♀	64– 100	10.00—23.44	
Zebra	♂ & ♀	249– 340	5.88— 8.03	5.88— 8.03
	Young ♂ & ♀	113– 159	6.29— 8.85	6.29— 8.85
Impala	♂ & ♀	45– 75	5.55—11.11	5.55—11.11
Blue wildebeest	♂ & ♀	204– 295	6.77— 9.80	
	Young ♂ & ♀	91– 204	4.90—10.99	
Red Hartebeest	♂	158– 204	4.90— 6.32	
	♀	127– 172	4.36— 5.91	
Tsessebe	♂& ♀	113– 158	4.75— 8.85	
Buffalo	♂	590– 907	4.41—10.17	
	♀	454– 680	4.41— 8.81	
Waterbuck	♂	215– 272	11.02—16.28	
	♀	158– 227	8.81—15.82	
Kudu	♂	249– 295	13.56—16.06	
	♀	127– 181	13.81—23.62	
Eland	♂	544– 907	5.51—11.03	
	♀	227– 386	10.36—17.62	
Sable antelope	♂ & ♀	204– 249	8.03— 9.80	8.03— 9.80
Roan antelope	♂ & ♀	204– 272+	7.35—14.71	7.35—14.71

REFERENCES

1. BENTLEY, K. W. and HARDY, D. G. (1963). Proc. Chem. Soc. July. p. 220.
2. COLMAN-GREEN, G. (1963–65). Personal communications.
3. GRAHAM-JONES, O. (1964). Vet. Rec. Vol. 76, p. 1215.
4. HARTHOORN, A. M. (1962a). Journ. Amer. Vet. Med. Assn. Vol. 141, p. 1473.
5. HARTHOORN, A. M. (1962b). Can. J. Comp. Med. Vol. 26, No. 9, pp. 203–208.
6. HARTHOORN, A. M. (1963). Nature Cond. Vol. 198, p. 1116.
   HARTHOORN, A. M. (1965a). J. S. Afr. Vet. Med. Assn. Vol. 36, No. 1, p. 45.
8. HARTHOORN, A. M. (1965b). Application of Pharmacological and Physiological principles in restraint of wild animals. Wildlife Monographs. Vol. 14. March 1965.
9. HARTHOORN, A. M. and BLIGH, J. (1965). Res. Vet. Science. Vol. 6, No. 3. p. 290.

10. HARTHOORN, A. M. and PLAYER, I. C. (1964). The narcosis of the white rhinoceros. A series of eighteen case histories. Proc. Fifth Intern. Symp. Dis. Zoo Animals, 1963. Tijd Diergen. Vol. 89, p. 225.
11. HENSCHEL, W. F. (1963). Neuroleptanalgesia: A new anaesthetic technique. Lecture presented April 11, 1963, at the University of Michigan hospital.
12. JANSSEN, P. A. J., NIEMEGEERS, C. J. E. & SCHELLEKENS, K. H. L. (1965). Drug Res. (Arzneim-Forsch). Vol. 15, p. 104.
13. KING, J. M. & CARTER, B. H. (1965). East African Wildlife Journal. Vol. III. p. 19.
14. KING, J. M. and KLINGEL, H. (1965). The use of the oripavine derivative M-99 for the restraint of equines, and its antagonism with the related compound M-285. (In press).
15. LISTER, R. E. (1964). J. Pharm. Pharmacol. Vol. 16. p. 364.
16. MARSBOOM, R. and MORTELMANS, J. (1963). Small animal anaesthesia. Proceedings of Symposium in London July, 1963.
17. RINEY, T. and KETTLITZ, W. L. (1964). Management of large mammals in the Transvaal. Mammalia Vol. 28. No. 2. pp. 189–249.
18. PIENAAR, U. DE V., VAN NIEKERK, J. W., YOUNG, E., VAN WYK, P. and FAIRALL, N. (1966). The use of oripavine hydrochloride (M-99) in the drug-immobilization and marking of Wild African elephant (*Loxodonta africana* Blumenbach) in the Kruger National Park. (In Press).
19. SHORT, R. (1963–65). Personal communications.
20. SPINAGE, C. A. (1965). Personal communications.
21. VAN NIEKERK, J. W. and PIENAAR, U. de V. (1962.) Koedoe No. 5. p. 137.
22. VAN NIEKERK, J. W., PIENAAR, U. DE V. and FAIRALL, N. (1963). Koedoe No. 6. p. 126.
23. VAN NIEKERK, J. W., PIENAAR, U. DE V., and FAIRALL, N. (1963). Koedoe No. 6. p. 109.
24. VAN NIEKERK, J. W., PIENAAR, U. DE V., and FAIRALL, N. (1963). J. S. Afr. Vet. med. assn. Vol. 34. No. 3. p. 403.
25. VAN NIEKERK, J. W. (1965). A report on the capture and transport of giraffe in the Eastern Transvaal. (Unpublished report).

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