THE USE OF THE ORIPAVINE DERIVATIVE M. 99 FOR THE IMMOBILISATION OF THE BLACK RHINOCEROS (*DICEROS BICORNIS*) AND ITS ANTAGONISM WITH THE RELATED COMPOUND M. 285 OR NALORPHINE

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INTRODUCTION

The compound M. 99*, a derivative of the inactive opium alkaloid thebaine, is a potent analgesic with other morphine-like properties. The depressant effects of M. 99 are antagonised by the related compound M. 285** and by other morphine antagonists such as nalorphine†. M. 99 has been used, either alone or in combination with other drugs, for the successful immobilisation of many African mammals which have then been released by reversing the chemical restraint with nalorphine (Harthoorn and Bligh, 1965). The antagonist M. 285 has been substituted for nalorphine in Grant's zebra (*E. burchelli bohmi* Matschie) (King and Klingel, 1965), hippopotamuses (*Hippopotamus amphibius* Linnaeus) and elephants (*Loxondonta africana* Blumenbach) (Short — personal communication), and been equally effective.

The present trial was undertaken during routine drug-immobilisation and translocation of black rhinoceroses (*Diceros bicornis* Linnaeus) by the Kenya Game Department Capture Unit. The dose of phencyclidine†† normally used on these occasions was reduced to allow for the inclusion of M. 99 + hyoscine and, after the animals had been immobilised, the antagonists nalorphine and M. 285 were given. The result of M. 285 administration was not as expected and since this compound may be used extensively on rhinoceroses in the near future we are sounding a note of caution.

MATERIALS AND METHODS

Adult male and female black rhinoceroses, in good condition, were darted from an Alouette helicopter‡, or a land-rover, using a crossbow. Five animals were immobilised using a mixture of M. 99 + phencyclidine + hyoscine in 5 mls. of water (see Table 1). They were then lashed to a sledge in a position of lateral recumbency, winched onto a lorry and moved to holding pens at Kiboko, or Nairobi National Park. At varying times after capture the animals were given intramuscular injections of one or other of the morphine antagonists, nalorphine or M. 285. Prior to release they also received intramuscular injections of antibiotics (Streptomycin sulphate 2.5 g., Dihydro streptomycin sulphate 2.5 g., Procaine penicillin 3 mega units, Benzyl penicillin sodium 1 mega unit). The animals R_1 and R_2 received additional intramuscular injections of 60-80 mgms. of acepromazine‡‡ after the M. 99 had been antagonised with nalorphine.

RESULTS

Dart-drug immobilisation

The animals were chased for about a minute and a dart fired into the rump

* 6 : 14 endoetheno-7-α (-2-hydroxy-2-pentyl)-tetrahydro-oripavine hydrochloride.
** N-cyclopropyl methyl-6:4-endoetheno-7-(2-hydroxy-2-propyl)-tetrahydro-nororipavine hydrochloride. Reckitt and Sons Ltd., Hull, England.
† Lethidrone. Burroughs Wellcome and Co. Ltd., Euston Road, London, N.W.1.
†† Sernylan. Parke, Davis and Co., Hounslow, Middlesex, England.
‡ No. 8 Independent Reconnaisance Squadron, British Army.
‡‡ Acetylpromazine, Boots Pure Drug Co. Ltd., Nottingham, England.

at close range. Although catching vehicles and aircraft then retired to observe at a distance, the darted animals continued to trot briskly across country with the tail raised forwards over the back. The first sign of drug action occurred after 12-17 minutes, when the tail began to relax until it was hanging straight down. At this stage the animals swayed several yards sideways and gradually slowed down until they were almost marking time. They then toppled gently over sideways, sometimes righting themselves and moving a few yards before going down again and remaining recumbent 15-20 minutes after darting.

Clinical examination

The animals lay quietly unconscious on their sides (Fig. 4): the palpebral reflex was depressed and often absent, and the eyeballs fixed and either central or rotated medially. The pupils were dilated probably due to the atropine-like effect of hyoscine that was included to decrease the risk of bronchial effusion. There was some salivation, slight sweating on the neck and rectal temperatures ranged from 100-103°F.

The pulse and respiration rates are shown in Figs. 1-3. There was a tachycardia usually associated with a slight

TABLE 1

The effect of an M. 99 + phencyclidine + hyoscine mixture, followed by the morphine antagonists nalorphine and M. 285, on the black rhinoceros

ANIMAL			DOSE (mgm)					TIME FROM NARCOTIC INJECTION (mins)			Time from Darting to Standing
			NARCOTIC MIXTURE			ANTIDOTE					
	Sex	Weight (Kg) Estimated	M. 99	Phencyclidine	Hyoscine	Nalorphine	M. 285	To Immobilisation	To Antidote Injection	To Antidote Effect	
R_1	♀	700	1.3	550	85	400		15	38	43	
							3		138	—	250†
							4		288	—	343
R_2	♂	900	1.5	645	100	200		16	43	49	
						200			204	216	252††
R_3	♀	900	1.12	465	56		10	16*	68	81	
						200			132	152	
						200			327	337	369
R_4	♂	1100	1.4	600	100		15	20*	37	41	
						190			65	75	
							22		285	—	1080
R_5	♂	1000	1.2	500	100	200		17	90	95	180

† subsequently relapsed.

†† stood as soon as released.

* 1500 i.u. hyaluronidase injected with narcotic.

Body weights estimated from data provided by Kenya Fauna Research Unit.

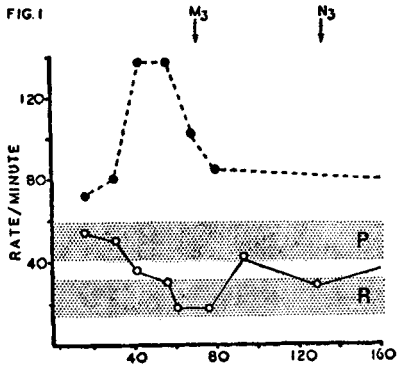

Fig. 1: The extreme values associated with the narcotic mixture in animal R_3
● = pulse; ○ = respiration; M_3 = intramuscular injection of M. 285 (10 mgms.); N_3 = intramuscular injection of nalorphine (200 mgms.)

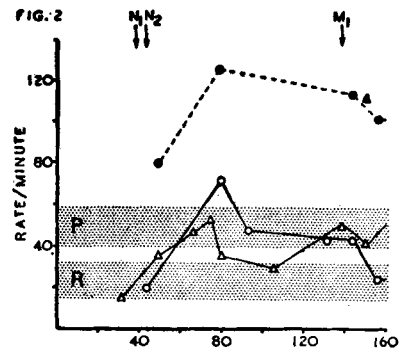

Fig. 2: The antagonism of M. 99 with nalorphine and the unmasking of the narcotic excitement due to phencyclidine
▲ = pulse of R_1; △ = respiration of R_1; N_1 = intramuscular injection of nalorphine (400 mgms.) to R_1; M_1 = intramuscular injection of M. 285 (3 mgms.) to R_1; ● = pulse of R_2; ○ = respiration of R_2; N_2 = intramuscular injection of nalorphine (200 mgms.) to R_2.

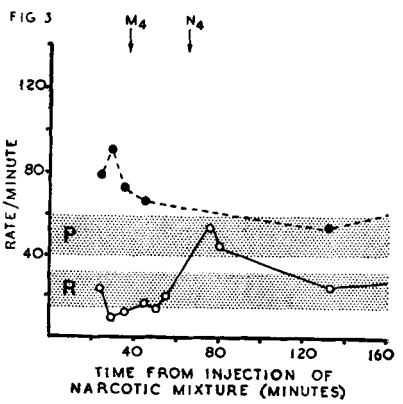

Fig. 3: The weak antagonism of M. 99 by M. 285 compared with nalorphine in animal R_4
● = pulse; ○ = respiration; M_4 = intramuscular injection of M. 285 (15 mgms.); N_4 = intramuscular injection of nalorphine (200 mgms.).

Figures 1-3: Variations observed in the pulse and respiration rates of black rhinoceroses during M. 99 + phencyclidine + hyoscine narcosis and after administration of nalorphine or M. 285.

The shaded areas on the graphs represent normal values:
P = pulse rate of a young adult *white* rhinoceros.
R = respiration rates of adult black rhinoceroses.

The heart rate was most easily obtained from the caudal pulse, which could not be recorded during bouts of struggling, muscle tremor, transportation and in animal R_1, which lacked a tail.

depression of the respiration rate, inspite of the exertion prior to capture. This prompted the administration of M. 99 antagonists within half an hour of darting to three of the animals (Figs. 1 and 2). The remaining two were given antidote 90 minutes after capture, and one of these showed a transient pronounced tachycardia which reached a peak 50 minutes after darting and was accompanied by a depression of respiration rate (Fig. 1).

The effects of nalorphine and M. 285 on M. 99-induced depression

Nalorphine

The intramuscular injection of nalorphine (200-400 mgms.) to animals R_1 and R_2 was followed by a pronounced lightening of central depression after five minutes. This was demonstrated by an increase in the amplitude and rate of respiration and accompanied by blinking, and muscle twitches which became co-ordinated into paddling movements of the limbs until the animal was struggling violently, thumping its head on the ground and occasionally squealing. This condition resembled the narcotic excitement caused by phencyclidine alone and the exertion was associated with a rise in rectal temperature to 104°F., sweating on the neck, brisket and back, muscle tremors, a further rise in pulse and respiration rates and mouth breathing (Fig. 2). The administration of acepromazine (60-80 mgms.) did not produce noticeable tranquillisation; the head was padded to avoid facial injuries and the animal lashed securely to the loading sledge as soon as possible.

M. 285

The intramuscular injection of M. 285 (10-15 mgms.) to animals R_3 and R_4 produced a barely perceptible lightening of sedation after ten minutes. It was demonstrated by small movements of the ears, limbs, and upper lip and the re-appearance of the palpebral reflex, but the narcotic excitement exhibited after nalorphine antagonism did not occur. The effect of M. 285 on pulse and respiration rates was difficult to assess because the trend towards normal values had started before it was administered (Figs. 1 and 3).

General effects of nalorphine and M. 285

The two animals (R_2 and R_5) in which nalorphine was used as the sole M. 99 antagonist showed no depressant effects that could be attributed to the antidote and rose immediately upon release, $2\frac{1}{2}$-4 hours after capture.

In contrast the increasing amounts of M. 285, given to antagonise the depressant effect of M. 99, merely prolonged the period of recumbency to 6-18 hours (animals R_3 and R_4). This effect was not related to the immobilising dose that had been used (see Table 1). Attempts to lighten sedation with nalorphine after M. 285 had been given (animals R_3 and R_4) had little effect apart from increasing the rate and amplitude of respirations, and the strength of the palpebral reflex in animal R_4. There was no suggestion of the narcotic excitement due to phencyclidine being unmasked in these two animals.

Radial paralysis as a sequel to prolonged recumbency

The administration of M. 285 failed to antagonise M. 99 and prolonged the period of recumbency, although the condition of the unconscious animals was quite satisfactory (R_3 and R_4). When the sedation wore off the animals had difficulty in rising and were then observed to stand on three legs with one forelimb carried limply, with the elbow dropped and the carpal joint flexed (Fig. 5). Any attempt to take weight on the affected limb was frustrated by the carpal joint knuckling over. A provisional diagnosis of radial paralysis was made, probably caused by bruising of the radial nerve between the rib cage and the dependent forelimb when the animal was lying on its side. The reason for a particular forelimb being affected was thought to relate to the critical position of the radial nerve between the chest and the forelimb and the length

of time spent lying on that side (see Table 2).

The milder case of radial paralysis recovered within a few hours, but the other animal (R_4) never recovered the use of the affected limb. On the second day of captivity, this animal could maintain the effort of standing on three legs for 45 minutes at a time, and would then collapse onto its brisket. As the period of recumbency was prolonged, the difficulty in standing was increased so that on the third day it could only stand for 30 minutes at a time, on the fourth for ten minute periods, and after that remained permanently recumbent. Although animal R_4 continued to eat and drink the prognosis was considered hopeless after a week and it was shot.

The recovery of the other four animals was uneventful.

DISCUSSION

Prior to this trial many black rhinoceroses had been successfully immobilised by the Kenya Game Department Capture Unit with the use of phencyclidine alone. However the dose of this drug required to stop an excited, galloping rhinoceros (adult bull required 0.75-1.00 g.) was at least 20% more than the same animal required when undisturbed, and was little short of the lethal dose especially when used on pregnant cows. The phencyclidine caused considerable narcotic excitement and when the animal went down it struggled violently and repeatedly thumped its head on the ground. A rise in rectal temperature, sometimes up to 106°F., profuse sweating, tachypnoea, muscle tremors and bruising of the head followed these exertions. During the second and third hours of recumbency the animal was quieter, becoming restless once more as consciousness returned when the frequent attempts to rise were thwarted by lack of equilibrium and knuckling over of the forelimbs. The animal was usually up within four

TABLE 2

The relationship between posture, period of recumbency and radial paralysis

Animal	LATERAL RECUMBENCY						Period of Recovery on Brisket (mins)	Total Period of Recumbency (mins)	Radial Paralysis
	Before Loading		During Transportation		After Unloading				
	Side	Time (mins)	Side	Time (mins)	Side	Time (mins)			
R_1	Left	45	Right	70	Left	60	60	235	None
R_2	Right Left	36 120	Right	80				236	None
R_3	Left	59	Right	90	Left	120	84	353	Right fore, slight
R_4	Left	20	Right	60	Left	300	680	1060	Left fore, severe
R_5	Right	20	Left	45	Right	15	60	140	None

Figure 4

Animal R_3 immobilised with the M. 99 + phencyclidine + hyoscine mixture. The leg hobbles are superfluous and there is no risk of self-inflicted injuries although the head is lying amongst rocks. Oxygen is being given intranasally because the ventilation rate is low despite the recent exertions of the animal.

hours of being darted and remained ataxic for a further four hours.

The use of the M. 99 + phencyclidine + hyoscine mixture appeared to be an improvement over phencyclidine alone. The safety of the immobilising dose was increased by reducing the amount of phencyclidine and by the ability to reverse the M. 99 in the mixture. The narcotic effect of this drug combination was not associated with excitement and animals that went down in rocky terrain could be left without any fear of self-inflicted injuries (Fig. 4). The following disadvantages were encountered: some depression of respiration which was considered undesirable in view of the exertion prior to immobilisation, and in one animal (R_3) a transient, pronounced tachycardia. The behaviour of the pulse and respiration rates of this animal resembled the response seen in only one of eleven Grant's zebra that had been sedated with an M. 99 + acepromazine + hyoscine mixture (King and Klingel, 1965).

The two morphine antagonists, nalorphine and M. 285, have produced similar effects in a variety of species. Nalorphine (200 μg/Kg) has reversed the depressant action of M. 99 (1-10 μg/Kg) in zebra, antelope and deer. In this trial it effectively antagonised M. 99 (1.5 μg/Kg) thereby unmasking the narcotic excitement associated with phencyclidine. The same M. 99 antagonism has been achieved with M. 285 in zebra (30-40 μg/Kg), and also in elephant and hippopotamuses (11-13 μg/Kg) which have been immobilised with doses of 0.9 and 1.8 μg/Kg M. 99 respectively

(Short, personal communication). Most of these animals have shown signs of sedation for some hours after antidote administration, which could be attributed to incomplete M. 99 antagonism, other ataractic drugs in the narcotic mixture, or M. 285 where this was used. However, in all cases the administration of nalorphine or M. 285 has shortened the period of recumbency, and often the animal has been on its feet within ten minutes of the intramuscular injection of the antagonist. In contrast, when M. 285 (10 μg/Kg) was given to the immobilised rhinoceros it did not effectively antagonise the M. 99 and, in the presence of phencyclidine, merely prolonged the period of recumbency. This could possibly be attributed to the depressant action of M. 285 demonstrated by hypokinesis in the guinea pig (E.D.50=13 μg/Kg) (Bentley, Boura, Fitzgerald, Hardy, McCoubrey, Aikman and Lister, 1965). It was also interesting to note that nalorphine could not antagonise M. 99 effectively after M. 285 had been given to the recumbent rhinoceroses.

The prolonged sedation of the rhinoceros after the administration of M. 285 was not thought to be harmful in itself, but the longer period of lateral recumbency increased the risk of radial paralysis. This condition is encountered in large domestic animals, and they experience the same difficulty in standing on three legs. The longer the animal is recumbent, the more cramped the sound limbs become until it is unable to stand without the support of slings. Although a crane has been used to sling a wild black rhinoceros in this condition the

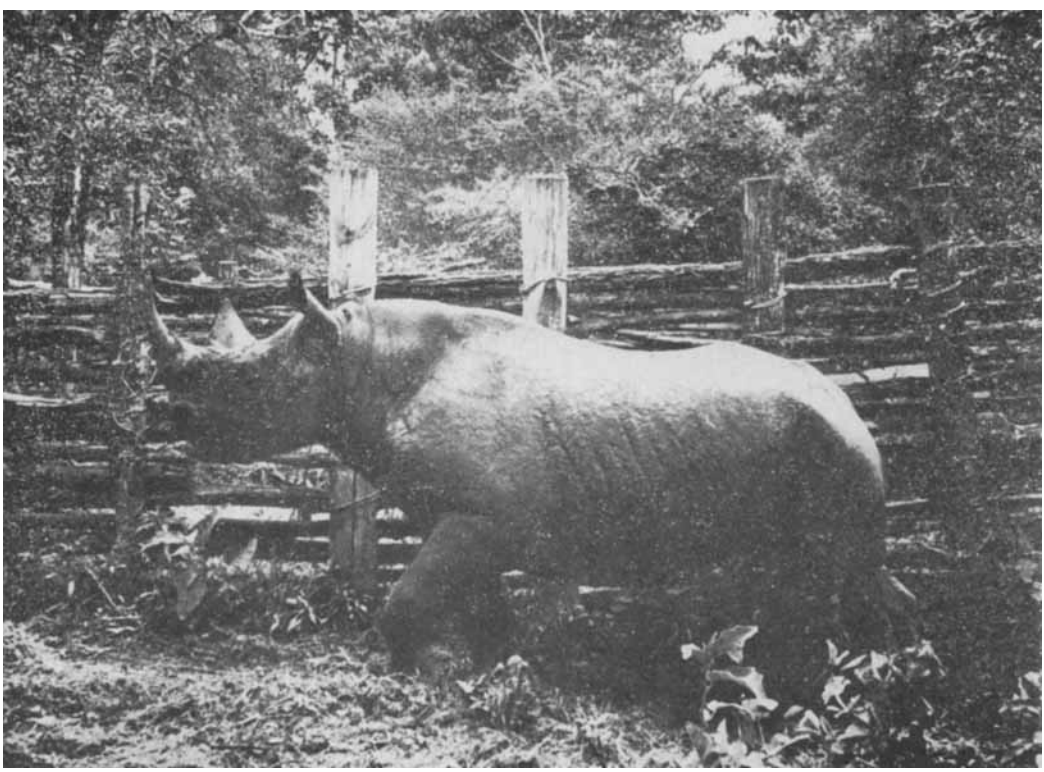

Figure 5
Animal R_4, twenty-four hours after immobilisation, with radial paralysis of the left forelimb.

result was unsuccessful.

It was concluded from this short trial that the M. 99 + phencyclidine + hyoscine mixture was safe and effective for the immobilisation of black rhinoceroses, provided that the animals were encouraged to their feet in the minimum possible time. This was best achieved by administering the morphine antagonist, nalorphine. Further improvements may be obtained if M. 99 becomes the dominant drug in the narcotic mixture, so that the animal is able to stand shortly after the morphine antagonist has been administered, and in these circumstances M. 285 may be a satisfactory antagonist.

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