

A NEW POTENT ANALGESIC FOR CHEMICAL IMMOBILIZATION OF GEMSBOK *ORYX GAZELLA GAZELLA*

V. DE VOS

Division of Nature Conservation

Private Bag X404

Skukuza

1350

Abstract – The successful chemical immobilization of gemsbok *Oryx gazella gazella* with a new potent analgesic, R33799 (Janssen Pharmaceutica), and the major sedative xylazine hydrochloride (Rompun; Bayer) is described.

Evidence, which is presented, show that the R33799 – xylazine mixture is an improvement over previously used drug mixtures for the immobilization of gemsbok. The following optimal dosage rates and application are recommended: 10–20 µg R33 799 per kg + 100 µg xylazine per kg deep intramuscularly.

It is concluded that with the use of the above-mentioned drug mixtures and deposition site, almost predictable short induction periods of about 5 minutes or less can be achieved.

High dosage levels of xylazine was found to produce a delayed or persistent somnolent state which has the disadvantage of a long and hazardous recovery phase, especially in predator prone surroundings.

Results show that the action of R33799 could be effectively reversed with the usual morphine antagonists.

Propionylpromazine (Combelen; Bayer) was found to be a useful post-capture tranquilizer.

Introduction

The gemsbok *Oryx gazella gazella* is generally considered difficult to capture successfully with chemical compounds (Ebedes 1969; Pienaar 1973; Smuts 1973; Harthoorn 1976). Harthoorn (1976) maintained that the gemsbok has always been considered a difficult animal to capture being of nervous temperament and therefore reacting with excitement to mixtures of morphinomimetic substances containing suboptimal quantities of tranquilizers. Pienaar (1973) also states that the gemsbok can be captured with conventional neuroleptic – analgesic drug combinations, but the captured animals are almost invariably less tractable than roan or sable, and resist handling to a great deal.

The advent of the highly potent, thebaine derived analgesic, oripavine hydrochloride (Etorphine, or M-99; Reckitt) and subsequently of xylazine hydrochloride (Rompun; Bayer) did much to relieve the situation (Ebedes 1969; Smuts 1973; Young & Whyte 1973). Ebedes (1969), however, found the average induction time, i.e. time elapsing from injection of drugs to recumbency, for 64 animals to be 23,6 minutes. Shorter induction times, but on average still well in excess of 10 minutes, were found by Smuts (1973) and Young & Whyte (1973), utilizing etorphine with high Rompun dosage levels. The high Rompun dosages, however, had the disadvantages of a long and hazardous recovery phase (Smuts 1973). The etorphine-xylazine mixtures therefore still posed some disadvantages for gemsbok immobilization and the search continued for better drug mixtures.

In the meantime the firm "Janssen Pharmaceutica", Beerse, Belgium, synthesized and screened for analgesic activity a novel series of 4-substituted derivatives of fentanyl (Van Daele, de Bruyn, Boey, Sanczuk, Agten & Janssen 1976; Van Bever, Niemegeers, Schellekens & Janssen 1976). Some of these compounds were found to be extremely potent analgesics characterized by unusually high safety margins, surpassing the performance of fentanyl comfortably under laboratory conditions (van Bever *et al.* 1976). This claim was borne out in practice under field conditions when 20 species of animals were tested with one of these drugs, R33799 (De Vos 1978). De Vos (1978) also concluded that R33799 is the most powerful, yet safest, morphine-like analgesic for a wide range of ungulates and pachyderms in the field today. Three gemsbok were also included in these trials and it was concluded that R33799 holds high promise as the drug of choice for the capture of gemsbok.

When gemsbok therefore had to be caught in the Mountain Zebra National Park, Republic of South Africa, it was taken as an ideal opportunity for further tests on R33799 in combination with xylazine as an immobilization "cocktail" for these animals. This report documents the findings of this investigation.

Material and Methods

The newly developed compound, known by its manufacturing number R33799 only, was developed by Janssen Pharmaceutica as part of a novel series of N-4-substituted 1-(2-arylethyl)-4-piperidinyl-N-phenylpropanamides and is a 4-substituted derivative of fentanyl. R33799 was supplied free of charge for experimental purposes by Janssen Pharmaceutica, Beerse, Belgium. The drug was supplied in 1 ml ampoules as a pharmaceutical solution of 10 mg/ml. For more accurate dispensing when small quantities were needed, the drug was diluted down to 5 mg/ml or 1 mg/ml.

Other drugs that were used in conjunction with R33799 included the following:

Xylazine hydrochloride. Syn: Rompun (Bayer, Leverkusen, Germany). This thiazine derivative was used for its known sedative, analge-

sic (central acting) and synergistic effects on etorphine (M99) and fentanyl in capturing nervous and aggressive antelope species (Smuts 1973). The drug substance was made up to concentrations of 100–500 mg/ml in the solvent provided with the drug.

Propionylpromazine. Syn.: Combelen (Bayer, Leverkusen, Germany). This phenothiazine derivative was used for its long acting potent sedative action (Westhues & Fritsch 1965). Propionylpromazine was supplied as a 1% solution for injection.

Naloxone hydrochloride. Syn: Narcan (Supplied free of charge for experimental purposes by Endo Laboratories, Inc. New York). This is a potent narcotic antagonist synthesised from oxymorphone hydrochloride, a narcotic analgesic. It was used for its known excellent antagonistic properties on a wide dosage range of etorphine and fentanyl, and its wide safety range making overdosage extremely unlikely (Blumberg, Dayton & Wolf 1965; Martin 1967; Smuts 1975).

Cyprenorphine. Syn: M285. (Reckitt and Sons, Ltd., England). This morphine derivative was used for its known potent antagonistic action against morphine and morphine-like analgesics and its wide therapeutic index (Harthoorn 1973).

The immobilizing drugs were administered by means of one millilitre capacity springloaded projectile syringes fitted with barbed needles (De Vos, van Rooyen & Kloppers 1973). A hypodermic-projectile rifle (Powder charged Cap Chur Gun; Palmer Chemical and Equipment Company, Atlanta, Ga.) was used to propel these syringes.

Operations were restricted to the Mountain Zebra National Park (MZNP). Drug reactions were tested on 13 gemsbok as listed in Table 1. The three gemsbok that were immobilized previously in the Kalahari Gemsbok National Park, Republic of South Africa, and cited in a previous study (De Vos 1978) is also included in this report for the sake of completeness.

The subject animals were essentially free-ranging and were darted from a helicopter. The MZNP gemsbok were caught as part of an animal reduction programme and were translocated to holding pens immediately afterwards where observations were continued. The Kalahari gemsbok were caught for marking purposes and were released immediately afterwards.

Estimates of the weight of immobilized animals were derived from a combination of experience and known adult liveweight records by Wilson (1968) and Von La Chevallerie (1970).

Induction time is taken as the time for an animal to become immobilized after injection.

Results and Discussion

A total of 16 free-ranging gemsbok were immobilized with the trial mixtures as shown by Table 1.

In a review of chemical immobilization Harthoorn (1976) stressed the fact that immobilization techniques have actually been orientated to

Table 1
The chemical immobilization of gembok using a new potent analgesic, R33799, and xylazine hydrochloride

| No. | Sex | Mass est. kg. | Immobilization Drugs | | | Analgesic | | | Analgic Antagonist | | | Recovery time ^a | Comments |
|---------|-----|---------------|--------------------------------|------------------------------------|--------------------------------------|--|----------------|-----------------------------|---------------------------------|------------------------|---|----------------------------|----------|
| | | | Analgic (R33799) Total dose mg | Analgic (R33799) Dosage rate µg/kg | Neuroleptic (xylazine) Total dose mg | Neuroleptic (xylazine) Dosage rate µg/kg | Induction time | Cyprenorphine Total dose mg | Cyprenorphine Dosage rate µg/kg | Naloxone Total dose mg | Naloxone Dosage rate µg/kg | | |
| 1. | ♀ | 70 | 2.0 | 28.5 | 4.5 | 600.0 | 2.5 | 6.0 | 85.7 | 4.5 | Pronounced somnolent during recovery phase. Released afterwards. | | |
| 2. | ♂ | 180 | 2.25 | 12.5 | 4.5 | 250.0 | 6.5 | 12.0 | 66.6 | 3.0 | Pronounced somnolent during recovery phase. Released afterwards. | | |
| 3. | ♂ | 130 | 1.75 | 13.3 | 20 | 156.0 | 8.0 | 11.0 | 84.4 | 2.5 | Pronounced somnolent during recovery phase. Released afterwards. | | |
| 4. | ♂ | 50 | 1.0 | 20.0 | 25 | 500.0 | 15.0 | 7.5 | 150.0 | 5. | Darted low down in hind leg. Dart wound bleed profusely afterwards. Only faint signs of somnolence during recovery phase. In captivity afterwards. | | |
| 5. | ♂ | 50 | 1.0 | 20.0 | 25 | 500.0 | 3.5 | 7.5 | 150.0 | 11.0 | Pronounced somnolent during recovery phase. In captivity afterwards. | | |
| 6. | ♀ | 100 | 1.0 | 10.0 | 25 | 250.0 | 4.0 | 7.5 | 75.0 | 9.0 | Pronounced somnolent during recovery phase. In captivity afterwards. | | |
| 7. | ♀ | 140 | 2.0 | 14.3 | 25 | 140.0 | 3.0 | 7.5 | 53.6 | 4.5 | Moderately somnolent during recovery phase. In captivity afterwards. | | |
| 8. | ♂ | 150 | 2.0 | 13.3 | 15 | 100.0 | 4.5 | 7.5 | 50.0 | 4.0 | Moderately somnolent during recovery phase. In captivity afterwards. | | |
| 9. | ♂ | 180 | 2.0 | 11.1 | 15 | 83.3 | 4.5 | 7.5 | 41.7 | 2.5 | Moderately somnolent during recovery phase. In captivity afterwards. | | |
| 10. | ♀ | 130 | 2.0 | 15.3 | 15 | 115.4 | 8.0 | 7.5 | 57.7 | 3.0 | Dart hit abdomen. Moderately agnostic during recovery phase. In captivity afterwards. | | |
| 11. | ♂ | 160 | 2.0 | 12.5 | 15 | 93.8 | 9.0 | 7.5 | 46.9 | 2.0 | Dart jumped out immediately after impact. Moderately agnostic during recovery phase. In captivity afterwards. | | |
| 12. | ♂ | 190 | 2.0 | 10.5 | 15 | 78.9 | 5.0 | 7.5 | 39.5 | 2.5 | Faint signs of somnolence detected during recovery phase. In captivity afterwards. | | |
| 13. | ♀ | 140 | 2.0 | 14.2 | 10 | 71.4 | 5.5 | 7.5 | 53.6 | 1.5 | Moderately agnostic during recovery phase. Propionylpromazine administered to counteract these symptoms effectively. In captivity afterwards. | | |
| 14. | ♂ | 180 | 2.0 | 11.1 | 10 | 55.5 | 4.5 | 7.5 | 41.7 | 1.0 | Severely agnostic during recovery phase. Propionylpromazine administered to counteract these symptoms effectively. In captivity afterwards. | | |
| 15. | ♀ | 140 | 2.0 | 14.2 | 10 | 71.4 | 11 | 7.5 | 53.6 | 1.9 | Dart needle embedded in median crest of sacrum. Severely agnostic during recovery phase. Propionylpromazine administered to counteract these symptoms effectively. In captivity afterwards. | | |
| 16. | ♂ | 175 | 2.0 | 11.4 | 10 | 57.1 | 5 | 7.5 | 42.9 | 0.75 | Moderately agnostic during recovery phase. Propionylpromazine administered to counteract these symptoms effectively. In captivity afterwards. | | |
| Average | | 135.3 | 1.8 | 13.4 | 20.3 | 195.2 | 6.2 | 7.5 | 65.9 | 9.7 | 78.9 | 3.0 | |

^a Recovery time = time from administration of antidote to recovery to a standing position.

Time in minutes.

producing as short an induction as possible, commensurate with safety. Ebedes (1969), using etorphine hydrochloride in combination with other drugs found the average induction time for 64 gemsbok to be 23,6 minutes. Ebedes also reported 75% of the animals being satisfactorily immobilized and 52% immobilized and captured in less than 15 minutes. Shorter induction times, but on average still well in excess of 10 minutes, were found by Smuts (1973) and Young & Whyte (1973) utilizing etorphine hydrochloride with high xylazine dosage levels. An average induction time of 6,2 min. representative of a range of 2,5–15 min, which was achieved in the present trials with R33799 (Table 1), must therefore be considered remarkably short. A total of 56% actually had induction times of 5 min or less. The relatively long induction times which were recorded were every time associated with questionable circumstances (Table 1). No. 4 bled profusely from the dart wound directly afterwards and it is believed that an unknown quantity of drug was lost through seepage. In the case of No. 11 the dart jumped out immediately after impact, leaving insufficient time for the full dose to be administered. No's 10 and 15 were hit on sites (abdomen and bone) which is notoriously reputed for slow absorption and therefore slow induction periods. In this respect Ebedes (1969) declared that the site of injection is important and has a direct relationship to effective and rapid immobilization in the gemsbok. The rest of the cases showed persistent short induction times, with an average of 4,7 minutes. On the basis of this evidence it can therefore be concluded that with the use of R33799, provided good intramuscular deposition of the drug is made, almost predictable short induction periods of about 5 min or less can be achieved.

During the field trials R33799 dosage rates varying from 10,0–28,5 $\mu\text{g}/\text{kg}$ was used without ill effect. It must therefore be concluded that R33799 has a very wide safety margin or therapeutic index for gemsbok, and largely precludes losses from overdosage and escape from underdosage. De Vos (1978) also concluded that high dosage rates of R33799 seem to absorb the effects of variables better than lower rates, and produce consistent short times for the induction phase in a wide variety of wild animal species tested. This means that when a short induction period is considered necessary, high dosage levels of R33799 can be used with confidence and safety.

The induction phase terminated in a state of analgesic hypnosis which was characterised in each case by sternal recumbency (Fig. 1). If given sufficient time this invariably proceeded to a state of lateral recumbency. This is ascribed mostly, however, to the effect of xylazine.

Initially xylazine hydrochloride was used as an additive to R33799 at dosage levels as recommended by Smuts (1973) and Young & Whyte (1973). Their recommendations amounted to about 40 mg–50 mg of xylazine for an adult gemsbok, which means a dosage rate of about 250–300 $\mu\text{g}/\text{kg}$. In the field trials under investigation, pronounced somnolence for prolonged periods afterwards was achieved with all dosage



Fig. 1. Gemsbok immobilized with R33799 and Xylazine, showing good tractability.

rates of xylazine in excess of $150 \mu\text{g}/\text{kg}$. A moderate somnolent state was found from 150 down to about $100 \mu\text{g}/\text{kg}$. In all cases of pronounced somnolence and sometimes also with moderate somnolence the animals rose to an upright position without undue difficulty and some of them even trotted off, seemingly normal. If, however, left undisturbed, the animals invariably lay down, eventually going over onto their sides in a deep sleep. In this position bloating occurred invariably. In most cases the animals could, however, be aroused with harsh external stimuli. In one case (No. 6) the animal could not be moved after she went down the second time and had to be propped up in a sternal position. This animal eventually got up after about 6 hours and survived. This agrees with the views of Smuts (1973) that a high xylazine dosage has the disadvantage of a long and hazardous recovery phase.

Low dosage levels of xylazine (Table 1), however, led to an agonistic state in the animals that were held over in captivity. This was characterized by excitement and continuous running to and fro along the sides of the holding pens, even to the extent of rubbing and butting against the sides. In these cases superficial abrasions were caused and over-exertion was imminent.

This general peripheral reflex irritability was, however, effectively reduced with the intramuscular administration (dart syringe) of about 100 µg propionylpromazine per kg body weight. A tranquilized state was sustained for about two hours with the animals emerging gradually from their indifferent state afterwards.

At a dosage rate of 100 µg/kg, xylazine was found to provide just about the right level of muscular relaxation to ensure good tractability without complicating the recovery phase unduly.

Results show that the action of R33799 was effectively reversed with the usual morphine antagonists (Table 1). An average recovery time of three minutes to standing in an upright position was noted. When relatively low dosages of xylazine was used as an adjunct to R33799, the reversal was found to be near complete, leaving the animal in a state of effective awareness of his surroundings. This poses a definite advantage in predator prone surroundings. De Vos (1978), however, found that extremely high dosages of R33799 may cause a residual state of central nervous depression which is not entirely reversible with antidote injection. This may cause increased vulnerability to predators.

Based on the evidence from the field trials as outlined, the use of R33799 + xylazine must be considered an improvement over previously used drug mixtures for the immobilization of gemsbok. The following optimal dosage rates and application is recommended: 10–20 µg R33799 per kg + 100 µg xylazine hydrochloride per kg deep intramuscularly. The higher dosage rates of R33799 are for free-ranging hyper-excited animals or where a very short induction period is considered a prerequisite.

Gemsbok that have adapted to captive conditions, or tame or undisturbed animals require lower dosages. It is also recommended that lower dosage levels be given to animals that are being released in predator-prone surroundings. When placed in captivity it is recommended that propionylpromazine be administered at a rate of 100 µg/kg prior to arrival at the holding pens. As antagonists to R33799, naloxone at three times or cyprenorphine at four times the total dose of R33799 is recommended. Although diprenorphine (Reckitt and Sons, Ltd., England) is not listed as an antagonist, it can be used with equal success in dosage slightly less than cited for cyprenorphine.

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