THE USE OF CARFENTANIL IN DEER

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Introduction

The purpose of this paper is to review the available information on the use of the narcotic carfentanil for the immobilization of deer. Interest in this drug in Australia and New Zealand has been largely generated by the cessation of production of the fentanyl/azaperone formulation Fentaz (R) (SmithKline), which has been widely used in both countries for a number of years. A full review of the factors to be considered in the immobilization of deer has been provided elsewhere (English, 1988), with the present paper including the results of initial field use of carfentanil in Australian deer. It is stressed that this has not been a controlled experiment, and the information provided must be considered in that light.

Chemistry and Formulation

Carfentanil (R33799) is a carboxylated fentanyl (R4263) synthesized by Janssen Pharmaceuticals (Beerse/Belgium) in 1974. This ultra-potent opiate narcotic is reported to be 3 to 5 times the potency of etorphine (Janssen *et al* 1987), with a clinical potency 10,000 times that of morphine (Mather 1983). An early study on the use of carfentanil in African ungulates resulted in a calculation of the relative potencies of carfentanil, etorphine and fentanyl as 20:15:1, based on field experience (De Vos 1978). The only formulation currently available is Wildnil (R) (Wildlife Labs, Inc, PO Box 8938, Fort Collins, Colorado 80525 USA), which is carfentanil citrate 3 mg/ml in 10 ml ampoules. This concentration has been used to provide suitable dose volumes for the largest African animals, and is not entirely appropriate for smaller animals such as deer, given the very low dose rates and volumes of the 3 mg/ml preparation which are required. Until a lower concentration is perhaps provided, users will need to consider diluting the product to provide workable volumes for deer.

History of Use of Opioids

Opioids have been widely used in a number of countries to immobilize or anaesthetize a variety of species, both in captivity and for the capture of wild animals. In a recent review, Haigh (1990) notes that the first reports of the use of a synthetic opioid for animal capture described the use of diethyl-thiambutene (Themalon, May & Baker, Ltd) in the early 1960's. However, the low solubility of this drug was a problem (the dose required for an adult rhinoceros was 20 ml), and the advent of the oripavine derivative etorphine HCl (M99, Cyanamid, Willowdale, Ontario) revolutionized the chemical restraint and immobilization of wild animals. The volumes of etorphine required for immobilization of large herbivores were very small, with a feature of the drug being its marked potency relative to morphine - about 6000 times in some tests.

Etorphine is still widely used as Immobilon Large Animal (R) (C-Vet), with etorphine HCl 2.45 mg/ml and acepromazine maleate 10 mg/ml. This preparation is popular for use in deer in Great Britain (Fletcher, 1986), but because of strict controls on its availability in Australia it has mostly been used only in zoos in this country.

Very soon after the development of etorphine, fentanyl became available. First synthesized in 1960, fentanyl is a 4-amino-piperidine derivative which has been used in deer mainly as the preparation Fentaz (R), with fentanyl 10 mg/ml and azaperone 80 mg/ml. The success of Fentaz in the capture of wild deer in New Zealand (Hunter, 1981) resulted in wide acceptance of its value, either when used alone or with xylazine, not only for immobilization of deer but for procedures requiring anaesthesia such as semen collection and laparosopy for artificial breeding (Fennessy et al 1987).

Carfentanil was then produced just over a decade later, and is one of a new generation of narcotic agents now coming into use in both animals and man. Others include sufentanil (Sufenta, Janssen) and alfentanil (Alfenta, Janssen), with the latest opioid tested for wildlife immobilization being another 4-amino-piperidine derivative, A3080 (Anestall, Anesta Ltd), which has about half the potency of carfentanil but is extremely safe and fast acting (Haigh, 1990).

Field use of Opioids in Deer

The properties of opioids which make them so useful for the immobilization of deer are their relatively rapid induction time and their reversibility. Given the tendency of the narcotics when used alone to cause unwanted side effects (excitement and extrapyramidal effects) during induction, it has generally been considered necessary to combine them with a tranquilliser - hence the preparations such as Immobilon and Fentaz. These combinations have now been in use for many years, with dose rates well established for a number of cervid species.

The combination of Fentaz with xylazine has been a particularly successful initiative, with a quite remarkable degree of synergism obtained in the process. The dose rates of Fentaz recommended by the manufacturer for red deer are 1 ml/45 kg liveweight for quiet animals, up to 1 ml/22 kg for wild deer. Thus, a typical red deer stag on a farm may require 3 ml of Fentaz for immobilization in the open paddock. When combined with xylazine, the amounts required for immobilization of the same stag are 0.8 ml of Fentaz and 0.8 ml of Rompun 100 (Bayer)(Van Mourik *et al*, 1988). The same dose rate is cited for rusa stags, which has produced excellent results when immobilizing this species for velvetting in the open paddock (English, unpublished).

The reversibility of the narcotics when used for immobilization of animals remains one of their most desirable properties. By controlling the length of the immobilization, as a function of the nature of the procedure being undertaken, it has been possible to achieve an excellent safety record, providing certain basic precautions are taken - particularly in relation to the condition of the target animal (health status, mental or psychogenic state). The narcotic antagonists nalorphine (Lethidrone, Burroughs Wellcome) and levallorphan (Lorfan, Hoffman-LaRoche), have agonistic effects. Thus, special care must be taken with their use, especially if repeat doses are given, and the newer antagonists are now used almost exclusively.

Both diprenorphine (Revivon, C-Vet), and cyprenorphine (M285, Reckitt & Coleman) were produced at about the same time as etorphine, and the former is still used for the reversal of Immobilon LA where this is used to immobilize deer (Fletcher, 1986).

Naloxone (Narcan, Endo Labs) is a highly specific opioid antagonist with almost no agonistic side effects. It is now widely used to reverse the effects of all the narcotic immobilizing agents, with its only limitation being its short half-life (Haigh, 1990). Naltrexone (Sigma Chemical Coy) is also a specific opioid antagonist with a long half-life, and may prove to be the most acceptable reversal agent for carfentanil (Haigh, 1987). Nalmafene (Key Pharmaceuticals) is a naltrexone derivative which is also showing promise in the reversal of carfentanil and a new narcotic A-3080 (Stanley *et al* 1989).

Published dose rates of carfentanil

De Vos (1978) reported on the use of carfentanil on a total of 217 free-ranging animals in Africa, representing 20 different species. Provided that the animals were reasonably free from external stimuli there was very little excitement during induction, even when the carfentanil was used without a tranquilliser. However, he found that both xylazine and azaperone were valuable adjuncts to carfentanil in dosage ratios of 10:1 and 30:1 respectively. The dosage rates of carfentanil varied from about 1 µg/kg for elephants to about 10 µg/kg for the larger ungulates, with naloxone used for reversal in ratios of 6-10:1 for elephants and 2-4:1 for a variety of antelopes. He concluded that carfentanil is a powerful, yet safe morphine-like analgesic, with a wide therapeutic index, wide spectrum of action and reliability. He noted that the potency of carfentanil results in very small dose volumes - a 1 ml dart was used to immobilize animals as divergent as a 6000 kg elephant, an 800 kg eland and a 10 kg steenbok, with only the lengths of the needles varying.

Carfentanil has been used extensively in North America to immobilize a variety of ungulates in zoological collections, and in the wild. In many cases carfentanil was used alone, at dose rates of 5-20 µg/kg - for example Janssen *et al* (1987) reported that the mean effective dose for the family Cervidae was 13.6 µg/kg, and for the family Bovidae varied from 7.7 µg/kg in the subfamily bovinae to 29 µg/kg in the subfamily antelopinae. In a series of over 300 immobilizations, renarcotization occurred in about 5 % of cases, with the most rapid reversal and lowest rate of renarcotization being achieved with the concurrent use of nalmafene (given IV at 10 times the carfentanil dose) and diprenorphine (given IM at 5 times the carfentanil dose).

Karesh *et al* (1986) used carfentanil at 10-15 µg/kg to immobilize axis (chital) deer, with effective reversal using diprenorphine.

Wiesner (1984) used carfentanil to immobilize 268 animals in 33 species in a German zoo. Initial dose rates were based on an estimated 6-7 µg/kg body weight, with xylazine being used in conjunction with carfentanil if excitation or muscle spasms occurred, or if known sensitivity to morphine-like analgesics existed. The results published for satisfactory immobilization of red deer were 2.73-7.32 µg/kg of carfentanil (with a recommended dose rate of 5 µg/kg body weight) with xylazine at 92-278 ug/kg bodyweight. Fallow deer required 2.00-21.62 ug/kg carfentanil (recommended dose rate 10 µg/kg) with 125-213 µg/kg xylazine - several fallow deer immobilized with carfentanil alone exhibited severe excitation. Diprenorphine was used as the reversal agent IV at a ratio 13.5:1 for red deer and 14.7:1 for fallow deer (naloxone was very effective, but too expensive).

Much lower dose rates were reported by Stanley *et al* (1989) when carfentanil was used to immobilize trapped elk (*Cervus elaphus*) in Utah.

The immobilization ED50 for carfentanil was found to be 0.55 μg/kg body weight (and for A-3080 was 0.88 μg/kg bodyweight). These authors also used carfentanil to immobilize moose, with a standard injection of 4.5 mg carfentanil (estimated dose rate 1–2 μg/kg) resulting in an average down time of 4.5 minutes. Renarcotization followed reversal of carfentanil with IM injections of M50–50 at rates lower than 6:1.

A recent review which includes further information on the use of carfentanil in a number of species is provided by Franzmann and Lance (1988).

Thus, it is apparent that the dose rates for carfentanil in the literature vary quite widely, with the manufacturer of Wildnil recommending that a safe and effective range for the cervids is **5–10 μg/kg**, with the lower end of the dose range suggested for animals of quiet temperament or under confinement, or in poor physical condition. There is a statement that concurrent use of xylazine may produce variation in the dose response, but the above dose rate presumably applies to carfentanil used alone.

There is a further recommendation that reversal is accomplished with 7 mg of diprenorphine per 1 mg of carfentanil, or by using naloxone at **80–100 times** the carfentanil dose. However, Haigh (1990) points out that there is no information available on the pharmacokinetics of any opioid antagonist in any wildlife species, with widely varying doses given in the literature. In humans, naltrexone is 2–9 times as potent as naloxone, and nalmafene is more potent than naltrexone. Furthermore, some authors advocate that the antagonist dose should be based upon the size of the animal being treated, without any regard to the initial dose of immobilizing drug, whereas others consider that the ratio of antagonist to agonist is important.

In a preliminary study of naltrexone HCl for the reversal of carfentanil in ungulates, Haigh (1987) found that a ratio of 10:1 naltrexone:carfentanil produced rapid arousal, but there was a high proportion of "recycling" at 2–28 hours later. The dose of carfentanil used was 6–10 μg/kg for large species (above 150 kg body weight) and 12–17 μg/kg for ungulates between 20 and 110 kg – given in conjunction with either xylazine or the serotonin antagonist R51163. With subsequent work he established that a ratio of 100:1 naltrexone:carfentanil achieved excellent reversal with no renarcotization.

Carfentanil is generally slower to reverse that either etorphine or fentanyl. Users of Fentaz will be familiar with the rapid reversal achieved with IV naloxone in deer – rarely is an animal down for longer than 1 minute after antagonist treatment (although the concurrent use of xylazine, reversed with yohimbine 10 mg/ml (Reverzine, Parnell) may prolong the recumbency by 2–3 minutes). Carfentanil seems to be the most difficult of the opioids to reverse, with recovery times being often at least 4 minutes, irrespective of the antagonist used (Haigh, 1990).

The first sign of recovery after reversal is almost invariably an increase in the rate and depth of respiration (within 1 minute of IV naloxone (English, unpublished)), followed soon by ear twitching, eye movements and lifting of the head. Soon after that the animal will sit up or get to its feet, particularly if stimulated by sound or touch.

Experience with carfentanil in Australia

An inability to obtain Fentaz in 1989 resulted in a decision to import carfentanil as

Wildnil (R) from the United States. After using Fentaz alone for a number of years at recommended dose rates (in both red and rusa deer – the latter in particular being invariably immobilized in the paddock for velvetting), the Fentaz/xylazine mixture given by Van Mourik *et al* (1988) proved to be highly effective, and far cheaper than Fentaz alone, using only 0.8 ml Fentaz instead of 3 ml, with 0.8 ml of Rompun 100 (Bayer). Several hundred rusa and rusa/sambar hybrid stags were immobilized with this mixture, with excellent inductions (most were down in 4–5 minutes) and good reversal using naloxone at a total dose of 2–5 mg (half IV and half IM) and yohimbine IV (Reverzine at 1 ml/50 kg bodyweight).

Despite most stags regaining their feet in less than 3 minutes, it was noted that they remained drowsy for several hours, and would often lie down again if left undisturbed. It is therefore essential that elective procedures such as velvetting with immobilization be carried out late in the afternoon, so that recovery occurs during the cool of the evening. If this precaution is observed then problems with hyperthermia should not occur, even if the animals do lie down in the open for a period.

A smaller number of red deer stags were immobilized with the same mixture, with excellent results. In fact, the depth of anaesthesia which was almost invariably achieved suggested strongly that a lower dose of the Fentaz/xylazine mixture would have been effective on quiet farm stags, but there was no opportunity to test this to any extent.

Given the high cost of naloxone as Narcan (R) in 1 ml ampoules (0.4 mg/ml), it is very cost-effective to obtain the powdered drug by the gm from Sigma Chemical Company, PO Box 14508, St Louis, Missouri, USA 63178-9916, and to have this formulated locally in multi-dose ampoules at 5 mg/ml. Naltrexone is also available from the same source.

It was against this background of a very safe, relatively cheap and effective procedure that the impending cessation of Fentaz availablity induced the switch to carfentanil.

Carfentanil in rusa stags

There was an opportunity to use a carfentanil/xylazine mixture in rusa stags which had previously been immobilized using Fentaz/xylazine. These animals were injected using a Cap-Chur (R) Extra Long Range projector while coerced to approach a vehicle using bread. This was a routine with which they were very familiar, and they were not greatly disturbed by the process of darting and cutting velvet, at a rate of up to 8 stags per hour.

The dose rate of carfentanil which was initially chosen was at the lower end of the range quoted by Wildlife Labs – approximately 5 μg/kg, with 0.5 mg/kg body weight of xylazine. For an adult rusa stag of about 140 kg, 0.2 ml of Wildnil (3 mg/ml) gives a dose rate of about 4.3 μg/kg, with 0.7 ml of Rompun 100 (70 mg).

This dose was used on only one stag, with an induction lasting only 1.5 minutes and complete apnoea at 2.5 minutes. An immediate IV dose of 10 mg of naloxone, followed by a further dose of 5 mg naloxone and 3 ml of Reverzine 3 minutes later revived the stag, but he did not regain his feet for over 20 minutes.

Given the near death of the first stag, the dose of carfentanil was reduced to half that used initially, to be as near to **2 μg/kg** as was possible with visual estimation of bodyweight.

The dose of xylazine was reduced to **0.4 mg/kg** bodyweight.

A total of 60 adult rusa stags were immobilized using 0.1 ml of Wildnil and 50 mg of xylazine. Induction was invariably achieved within 5 minutes, with most being down in 4 minutes. A small number which failed to go down, and required re-darting, were found to have had less than the initial total dose due to dart failure - the detonator occasionally penetrates the rubber plunger in Cap-Chur darts, due possibly to inadequate lubrication of the syringe barrel.

Rusa/sambar stags

The carfentanil/xylazine mixture has also been used on a group of rusa/sambar hybrid stags, for removal of velvet antler and regrowth. These stags were too wary to be immobilized in the paddock, and were yarded for the procedure. It has become apparent that the stags of the tropical species remain much more anxious than do red deer stags, when confined in pens. Even deep xylazine sedation does not enable rusa and rusa/sambar stags to be approached in pens for the application of local analgesia - there is an unacceptable risk of damage to the velvet as the stags react to such attempts, creating both an economic and an animal welfare problem.

Thus, unlike red deer and fallow deer which are readily velvetted in pens using moderate xylazine sedation and local analgesia, it is customary to immobilize rusa and rusa/sambar stags for velvetting, whether in pens or the open paddock.

This resulted in an evaluation of the effects of confinement in pens on the dose rate of the carfentanil/xylazine mixture, compared to immobilization in the paddock. A number of the hybrid stags had in fact been done outside, with the dose rate quoted above for the rusa stags working very well (and estimating that the largest hybrid stags weighed about 200 kg).

When the dose of carfentanil **(2 μg/kg)** which was used in the open was used on a penned stag (standing quietly in a pen inside a shed, with little external stimulus), with 0.4 mg/kg of xylazine, there was an extremely rapid induction (less than 3 minutes) and a very deep level of anaesthesia.

The dose rate of carfentanil was then halved again to **1 μg/kg**, with 0.3 mg/kg xylazine. Induction was achieved in 4-6 minutes on a number of stags at this dose (0.05 ml of Wildnil and 40 mg xylazine), with no reaction to the cutting of velvet antler.

In a small number of stags the dose was reduced again by half - to about **0.5 μg/kg** carfentanil, with no further reduction in xylazine - 0.025 ml of Wildnil and 40 mg xylazine. These stags were "star gazing" at 4-5 minutes and recumbent at 8 minutes, and reacted slightly to velvetting and ear tagging. It was apparent that this was as low a dose of carfentanil as was practical or humane for velvetting without local analgesia.

In all rusa and rusa/sambar stags reversal was achieved using naloxone at 100 times the carfentanil dose, with half given IV and half IM, together with yohimbine IV (Reverzine at 1 ml/50 kg bodyweight). At the higher dose rates used in the open, it was common for stags to take 4-5 minutes to rise and move away, and they remained drowsy for several

hours, as with the Fentaz/xylazine mixture. However, at the lower dose rates used in the pens the reversal was more rapid, with the first signs of arousal at about 1 minute and regaining of feet inside 2 minutes.

Red deer and Wapiti

There has been less opportunity to evaluate the carfentanil/xylazine mixture on red deer or hybrids, since most stags are velvetted in pens using xylazine alone, with local analgesia. However, a total of 6 red deer stags and 2 hybrid stags have been immobilized in the open using a dose rate of **2 µg/kg** carfentanil and 0.5 mg/kg xylazine, with excellent results – induction times of 4–5 minutes with deep anaesthesia. There is a strong impression that the dose rate could be reduced for quiet stags in the open, and based on the results with the tropical stags, this should certainly be the case if red deer and hybrids are immobilized in pens – such as for semen collection.

The mixture has not so far been used on female deer of any species, but it seems reasonable to assume that the dose rate for quiet red deer hinds would be in the range **1–2 µg/kg**, with 0.5 mg/kg of xylazine – for such procedures as laparoscopy. Agitated females (dystocia, injuries) may require a higher dose, but it must be noted that prompt reversal could be required if the dose is too high.

Cost of carfentanil

When purchased in 1990 the cost of a 10 ml ampoule of Wildnil was US$265, with the cost of a US Narcotics Licence Fee at an additional US$35 – say A$375 per ampoule. At a dose rate of 1 ug/kg there are about 100 doses (average animal weight 150 kg) in an ampoule, which results in a cost price per deer of less than A$4.00 for carfentanil, and A$2.00 for xylazine. The cost of naloxone will depend on the formulation used, but can be as low as A$3.00 per deer. Yohimbine costs about A$2.50 per deer.

These 1990 rough costs should be verified against current prices, but it is apparent that the change from Fentaz to Wildnil need not be prohibitively expensive.

Human risk factor

Carfentanil is an extremely potent narcotic, with risk factors exceeding even etorphine. Thus, users must be fully aware of the dangers of accidental human exposure, and be prepared to take prompt action. In effect, the measures required are identical to those for fentanyl (Van Reenen 1981), although a higher total dose of naloxone may be required. Haigh (1990) points out that the medical literature suggests that a maximum dose of 2 mg of naloxone is required, followed by repeat doses in response to clinical signs – and concludes that this may be barely enough for the more potent narcotics such as carfentanil, where administration of a large ungulate dose to a human would be catastrophic. After the initial dose of naloxone the patient may show only brief signs of arousal, and it may be best to continue the administration of naloxone by intravenous infusion. . The situation may be even more complex if synergists such a xylazine are used, and it is highly likely that emergency medical personnel will not be familiar with the effects of these.

There is obviously need for great care in the handling and use of carfentanil, and

absolutely no place for its use by lay personnel.

Conclusions

Carfentanil is a very effective immobilizing agent, with a short induction period. On the basis of initial use in deer in Australia, there seems to be little reason for using carfentanil alone at the dose rates required – from 5–10 μg/kg. There is a very useful degree of synergism between xylazine and carfentanil, and further work should confirm that quite low dose rates of carfentanil (below 1 μg/kg) will be appropriate for quiet, penned red deer, when combined with xylazine at about 0.5 mg/kg. For the immobilization of red deer and rusa deer in the open, dose rates of 1–2 μg/kg carfentanil and 0.5 mg/kg xylazine should be effective, with a maximum of 2 μg/kg needed for wild or very anxious deer. Reversal without renarcotization can be achieved using naloxone or naltrexone at 100 times the carfentanil dose.

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