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THE USE OF THE MORPHINE-LIKE ANALGESIC CARFENTANYL* IN CAPTIVE WILD MAMMALS AT TIERPARK HELLABRUNN

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Introduction

In 1975, Janssen Pharamaceutica produced a new morphine-like analgesic called Carfentanyl (R 33799). It was derived from the piperidine-derivative Fentanyl. Fentanyl is between 20-40 times more potent than Morphine, depending on the species in which it is used[3,8,12,13] and Carfentanyl is considered to be more potent than this. In rats, Carfentanyl was found to be 20 times stronger than Fentanyl,[12] and de Vos[1] gives the subjective potencies of Carfentanyl: Etorphine: Fentanyl as 20:15:1.

So far Carfentanyl has been used in 24 mammalian species with variable results.[1,2,4,6,7,9,10,11] In common with other morphine-like drugs, its narcotic effects can be counteracted by the morphine antagonists[1,2,6,7] though in the dog,[4] rat[11] and guinea pig[9,10] the animals recovered without the use of an antagonist.

Due to Carfentanyl's propensity to cause varying degrees of CNS excitation during the induction phase various neuroleptics were combined with Carfentanyl to reduce or eliminate this undesirable side effect.[1,2,6,7]

Due to the favourable results of the field trials with Carfentanyl is was decided to test out the efficacy of the drug, with or without the neuroleptic Xylazine, on various mammalian species within the zoological gardens.

*Carfentanyl is the spelling used in Europe.

Materials and Method

The animals were all immobilized within the zoo, either in their stalls or outdoor enclosures, using a blowpipe and dart system.* The initial dosage rates of Carfentanyl[a] used were based either on previous work,[3,9] or on an estimated 6-7μg. Carfentanyl/kg body weight. Depending on the animal's reaction subsequent immobilizations were undertaken using the same or a higher or lower dosage rate.

If excessive excitation occurred during the induction phase, or if muscle spasms or rigor were apparent during the narcosis, or if from previous experience with[14] it was known that the species was particularly sensitive to the C.N.S. stimulatory effects of the morphine-like analgesics, then Xylazine hydrochloride[b] was used with the Carfentanyl. The initial dosage rate used for Xylazine was that which was found to be satisfactory in combination with "Large Animal Immobilon" in that particular species.[14] Again depending on the animal's reaction, in subsequent immobilizations the dose rate of Xylazine used would be varied.

In some species Atropine sulphate[c] was used in conjunction with the Carfentanyl, to reduce salivation and to reduce gastric/rumenal motility.

Hyaluronidase[d] (150 i.n.) was added to all darts to ensure a rapid uptake of the drug from the tissues into the circulation, this ensured a rapid induction time.

The animals were darted either in the shoulder, neck or hindquarter regions, where the largest muscle masses are situated and there is less likelihood of damage being done to some vital structure.

After darting, the animal was kept under observation, but from a distance so that excitement induced by the presence of people was kept to a minimum. Once the

*Telinject Blowpipe and Dartsystem, Telinject Veterinarmdizinische Spezialgerate GmbH.

**Hamadryas Baboon, Red Kangaroo, Polar Bear, Kulan, wild Boar, Barasingha, Pere David's Deer, Giraffe, Kudu, Nyala, Nilgai, American Bison, Yak, Dorcas Gazelle, Blackbuck.

animal became recumbent, it was approached to determine the level of narcosis. The levels were determined as follows:

1. U: little or no effect.
2. L: unsatisfactory. The animal was not sedated enough. Ataxia was seen and the animal would even lie down, but on being approached the animal was capable of defensive behaviour and/or being ambulatory.
3. S: satisfactory level of sedation. The animal was effectively immobilized and could be handled without struggling. The animal remained responsive to noxious stimuli. This level was ideal for crating, transportation and for minor surgical procedures. Ungulates tended to remain in sternal recumbency.
4. O: this level was deep enough for surgical procedures to be undertaken, but without excessive respiratory or cardiovascular depression.
5. T: excessive respiratory depression occurred. Prompt administration of the antidote was required, often with manual resuscitative procedures to prevent the animal from dying.

If the level of narcosis was too light an additional dose of Carfentanyl, with or without Xylazine, was sometimes given. If the level became too deep, prompt administration of Diprenorphine hydrochloride[α] with or without physical stimuli occurred, either to lighten the narcosis or to obtain complete reversal depending on the circumstances. All ruminants were placed in sternal recumbency to reduce the danger from regurgitation or bloat.

Once the handling procedures were finished the antidote diprenorphine was given. The initial dosage rate used was that, which was found to be effective against the required "Large Animal Immobilon" dosage for that particular species.[14] If the response was not adequate, more diprenorphine would be given until the immobilization was sufficiently reversed and the animal returned to normality. The antidote was administered intravenously. If after reversal of the immobilization the animal showed signs of the Carfentanyl's effects returning eg. ataxia, high stepping gait, excitement etc., then more diprenorphine would be given by blowpipe (a quantity equal to that originally given to produce reversal of the immobilization). If the species was prone to having relapses into the neuroleptanalgesic state some time after the administration of the antidote, then a small quantity of diprenorphine would be given subcutaneously as this would prolong the time during which effective levels of diprenorphine would be in the circulation within the body, therefore preventing the relapse. If an animal came out of the immobilization spontaneously then no diprenorphine would be given unless "hang-over" symptoms were apparent.

In addition to diprenorphine, Levallorphan[A] and Naloxone[B] were tested as antagonists to the Carfentanyl induced narcosis.

Results

A total of 268 animals from 33 species of mammal were immobilized during the period 1979-1982 using Carfentanyl. The results of 235 immobilizations in 18 species of mammal are shown in Table 2. These are those species of mammals in which the S level of narcosis was repeatedly obtained. This level was satisfactory for normal handling and minor operational procedures. The animals usually became recumbent and were sufficiently sedated, so that no reaction occurred on handling, but noxious stimuli would provoke response. Palpebral, anal and often aural reflexes were present. The other 15 species** are not included in this paper as further work is required in those species before assumptions can be made about safe dosage levels.

The recommended dosage levels shown in Table 2 are those found to give an effective S level of immobilization and are not the statistical means. In this case the statistical

TABLE 1

Showing the results of these immobilizations resulting in an S level of narcosis

Species	n	Carfentanyl dosage rate µg/kg body weight (Range)	Xylazine dosage rate µg/kg body weight (Range)	Recommended dosage rate Carfentanyl µg/kg body weight	Diprenophine iv Xylazine mg. total dose/animal	Carfentanyl mg/mg.
Brown bear *Ursus arctos*	3	10.00-20.00	28-40	11.8	5	6
Gray Wolf *Canis lupus*	5	2.35-3.09	—	2.7	2 mg Atropine	13.67
Muntjac *Muntiacus muntjac*	3	6.25-6.36	45-62	7.0	0.5	25.8
Axis deer *Axis axis*	4	3.75-7.60	125-139	3.75	5	8.0
Fallow deer *Dama dama*	41	2.00-21.62	125-213 (Seven animals without)	13.3	10	14.7
Red deer *Cervus elphus*	41	2.73-7.32	92-278	5.0	10	13.5
Elk *Alces alces*	16	2.86-10.50	18-105	3.3	10	10.5
White tailed gnu *Connochaetes gnou*	7	5.88-7.69	58.8-76.9	6.7	10	4.5
Defassa Water buck *Kobus ellipsiprymus defassa*	7	3.12-7.27	50-91	5.3	10	11.5
Springbock *Antidorcas marsupialis*	5	5.62-10.34	111-227	10.3	5	26.5
Impala *Aepyceros melampus*	7	5.13-10.91	128-182	6.0	5	10.0
Chamois *Rupricapra rupricapra*	24	10.20-18.18	77-91	13.3	2	13.5
Tahr *Hemitragus jemlahicus*	11	0.49- 5.71	60-142	0.9	5	101
Alpine ibex *Capra ibex ibex*	10	3.66- 7.78	61-194	4.3	5	22.8
Markhof *Capra falconeri*	29	3.12-10.0	49-333	5.0	5	4.3
Barbary sheep *Ammotragus lervia*	5	2.72- 6.0	50-110	5.0	5	4.3
Europ. Mouflon *Ovis ammon musimon*	8	6.57-14.89	158-278	10.5	5	12.

means have little value practically as they would take into consideration dose rates that induced either insufficient or excessively deep levels of narcosis. An additional dose of Diprenorphine 1.5 mg was given to each animal s. c., to help prevent any recurrence of narcosis due to the re-cycling of the Carfentanyl.

In Table 3, the types and incidence of the adverse reactions are recorded. One animal (A Barasingha) died as a consequence of the use of Carfentanyl, resulting in an overall

TABLE 2

Showing the type and incidence of adverse side effects seen when Carfentanyl was used, either with or without Xylazine

Species	No. of animals	% total immobil.	Side effects	Carfentanyl dosage rate low	NS*	high	Xylazine used	Comments
Wolf	2	40	Tachypnoea		+		–	
Brown bear	3	100			+	+		Serious hang-over symptoms 24-36 hours after immobilization
Fallow deer	1	2	Excessive excitement during induction		+		–	
	7	17	Muscle spasms	+		+/–		
	2	5	Opisthotonus		+	–/+		
	1	2	Penile prolapse		+	–		
	6	15	Excessive salivation		+	+/–		
	5	12	Tachypnoea		+	+		Low Xylazine dose
	1	2	Gasping respiration	+		–		
	2	5	Long hang-over		+			
White tailed gnu	3	37	Tachypnoea	+	+			
Waterbuck	1	14	Generalized muscle rigidity	+	+			
Chamois	5	21	Excessive excitement during induction		+	+		high stepping gait follow by animals crawling around on their knees
	3	12.5	Tachypnoea		+		+	
Thar	1	9	Excessive salivation			+	+	
	1	9	Tachypnoea		+	+		
	2	18	Long hang-over	+			+	very high Xylaine dose
Alpine ibex	1	10	Paralysis of tongue		+	+		
	1	10	Excessive salivation		+	+		
Markhor	1	4	Muscle spasms	+		+		
	1	4	Generalized muscle rigidity	+		+	+	same animal as above
	5	17	Paralysis of tongue		+	+	+	high Xylazine dose
	2	7	Excessive salivation		+		+	one animal had a very high dose of Xylazine
	1	3	Regurgitation of human contents		+		+	
Barasingha	1	–	Death		+			

*NS: Dosage rate, which usually gave the S level of immobilization

mortality of 0.4%.

The effective dose of Diprenorphine given i. v. is given as a ratio with the Carfentanyl dose, as this varies between the different species.

Cyprenorphine;[1,6] Diprenorphine;[6] Nalorphine[6,7] and Naloxone[1,2] have all been used as antagonists to Carfentanyl. Our trials with Levallorphan in Red Deer, Elk and Mouflons, as the antidote to Carfentanyl had poor results, as the recovery period was very much longer than when Diprenorphine was used. Naloxone was used in 1 Red Deer with good results, but its high cost limits its use in the field. Also in the rat the effects of Naloxone wore off after 80 mins. and the signs of sedation and respiratory depression returned,[11] indicating that it has only a short term effect, Diprenorphine was found to be a very good and effective antagonist to the Carfentanyl, with the recovery period being from a matter of seconds to 5 mins.

Spontaneous recovery has been observed in the dog,[4] rat[11] and guinea pig[9,10] with no antagonist being required. In our trials 3 Wolves and 6 of the Fallow Deer spontaneously stood up after 20-25 mins., but in the majority of the immobilizations the antagonist was given before the animals showed signs of recovery. The ratio of Diprenorphine:Carfentanyl in comparison to that with LA Immobilon is very high.[14] In wild Wildebeest Diprenorphine was found to be effective at a rate of 3.5-5.0 times the dose of Carfentanyl,[6] which is in agreement with our results of 4.5 times. Hofmeyer found that if insufficient Diprenorphine was given, then the animal remained soporific, disorientated and exhibited abnormal grazing behaviour for up to 15 mins., after which time the animal would become re-orientated and return to the herd.[6] This effect was not

noted in this series of immobilizations, but this may be due to a tendency to give high doses of Diprenorphine initially.

De Vos found that excessively high doses of Carfentanyl resulted in residual CNS

Discussion

From Table 1, it can be seen that the dosage rates of Carfentanyl, Xylazine and Diprenorphine are species specific. The effects of Carfentanyl have also been found to be species specific. In Guinea pigs analgesia only is induced,[9,10] while in rats analgesia, exophthalmia, increased muscle tonus and catatonia were observed.[11] In the Grey Seal the plane of anaesthesia progressively deepens and unlike in other species does not reach a steady state at a specific level of narcosis.[2] This results in the animal becoming apnoeic due to profound respiratory depression leading to death unless immediate reversal of the narcosis is undertaken. In Bruchell's zebra even at high doses, the animal did not become recumbent, although the sedation was deep enough for the animal to be captured.[2,6]

The effects of Carfentanyl in the species presented here were very similar to those observed by de Vos.[1] In the ungulates, Brown Bear and Wolf a state of analgesic hypnosis was induced. All animals lay down if sufficiently immobilized at the S level, with the ungulates adopting sternal recumbency. At higher dosage rates the animals lay in lateral recumbency.

The Carfentanyl-induced excitations, with or without extrapyramidal stimulation, seen by previous workers,[1,2,6,7] were only observed by us in the Fallow deer and Chamois during the induction phase. In the affected animals no Xylazine had been used. In the wild Kob[7] and wild Waterbuck[1] the use of Xylazine and Azaperone did not reduce the Carfentanyl induced excitations, but certainly at the dosage rates used in the species presented here, this problem did not arise. This difference may be due to the calming effects of captivity on our animals.

It has been found that the amount of neuroleptic required, varies with the rate of Carfentanyl used.[1,4,6,7,9,10,11] Excessive doses of the neuroleptic will result in prolonged hang-over periods. De Vos found that by using higher dosage rates of Carfentanyl, the amount of Xylazine required in the Gemsbok was reduced, alleviating the problems found with high doses of Xylazine. This factor governs the lower limit of the Carfentanyl dosage rate. Carfentanyl with Xylazine was found to be safe in 2 immature Red Deer. One 4 week old calf (body weight 21 kg) was immobilized with 0.1 mg Carfentanyl + 1 mg Xylazine giving an L level of narcosis. Another calf, 6 weeks old (17.3 kg) was immobilized with 0.1 mg Carfentanyl + 2 mg Xylazine giving an 0 level of narcosis. In both animals, no side effects were apparent and recovery was uneventful and complete. depression after the antidote had been given.[1] This effect may be due to the fact that the antagonism is competitive and therefore in such instances, the reversal of the narcosis is not 100%. Due to this fact the dosage rates of Carfentanyl used, were those at the lower effective levels, to prevent this effect from occurring.

From Table 2, it can be seen that the majority of the adverse side effects seem to occur when the dosage rate of Carfentanyl or Carfentanyl/Xylazine used, was that which would in other animals of that species induce a satisfactory level of narcosis. These reactions may therefore be due to the individual's idiosyncratic sensitivity to the effects of Carfentanyl. In certain cases, such as tachypnea in the White-tailed Gnu and the Wolf, the incidence is high enough to allow one to assume that it is a normal reaction of that species to Carfentanyl. Lingual paralysis is a side effect caused by Xylazine. Also it was noted that excessively high doses of Xylazine caused prolonged recovery times, as its narcotic effects were not reversed by the Diprenorphine. In general, the side effects could be eliminated either by adjusting the dosage rates of

Xylazine and/or Carfentanyl or by including Atropine in the dart.

The mortality rate can be considered to be very good as it is so low (0.4%). It should be emphasized that Carfentanyl is highly toxic to man and great care must be taken when employing it in immobilizing wild or captive animals; also the antidote Naloxone should always be readily available.

Due to these favourable results further work is being undertaken at Tierpark Hellabrunn, in order to expand the knowledge of the use of Carfentanyl in both the aforementioned species and in other mammals. It is considered that Carfentanyl is both an efficacious and safe analgesic to use in the 18 species named in Table 1.

Summary

The use of the morphine-like analgesic, Carfentanyl in wild mammals is discussed and the results of 235 immobilizations in animals from 18 species of mammal are presented. It is concluded that Carfentanyl has great potential as an immobilizing agent in wild mammals either alone or in combination with the neuroleptic Xylazine. Diprenorphine as 'Revivon' is used as the antagonist against Carfentanyl.

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Products Mentioned in Text

a. Carfentanyl: 10 mg/ml diluted to 1 mg/ml Janssen Pharmaceutica

b. Xylazine hydrochloride: 'Rompun' 500 mg powder dissolved to give 100 mg/ml. Bayer Leverkusen.

c. Atrophine sulphate: 'Atropinum Sulphuricum 1%' 10 mg/ml. Wirtschaftsgenossenschaft Deutscher Tierarzte eG..

d. Hyaluronidase: "Kinetin" 150 i.u. as powder, Schering AG Berlin/Berkamen.

a. Diprenorphine hydrochloride: "Large Animal Revivon" 3 mg/ml. Reckitt and Colemann, U.K.

A. Levallorphan: "Lorphan" 1 mg/ml. Roche.

B. Naloxone Hydrochloride: "Narcanti" D 4mg/ml. Winthsop.