THE NARCOTIC AND ANALGESIC EFFECTS OF CARFENTANIL AND THEIR REVERSAL

Evan L Key
Veterinary Services Manager, Virbac Laboratories (NZ) Ltd

Carfentanil is a high potency opiate agonist, that is, an analogue of morphine or the endorphins, which act at μ_1 opiate receptors, mainly in the CNS

Carfentanil is formulated as ***Wildnil*** [1], containing 3mg/ mL carfentanil (as carfentanil citrate), and as ***Carfenzine 50/50*** [2], which contains 50 µg/mL carfentanil (as carfentanil citrate) with 50 mg/mL xylazine (as xylazine hydrochloride)

Carfentanil in these formulations provides consistent and powerful sedation and analgesia These actions are particularly marked for large cervines, which are more sensitive to carfentanil than to any other narcotic, including etorphine

The remarkable activity of this molecule is a product of all its characteristics, being very hydrophilic (which facilitates rapid absorption), extremely lipophilic (thus readily passing the blood-brain 'barrier'), with high μ_1 - opiate receptor affinity (giving agonist activity at very low concentrations) and stability in situ (providing prolonged action) As each of these features exceeds those of morphine and endorphins by several orders of magnitude, and the outcome is a mathematical product of these features, carfentanil can be stated to be about 30,000 times the potency of morphine

Basic research conducted by Janssen Laboratories, who originated the 'fentanyl' series (4-amino pyridines) of narcotic analogues, has shown that the molecule carfentanil has higher potency but no significant change to its toxicity, compared to fentanyl - thus safety margin is greatly enhanced

Relative Effects of Narcotics:

DRUG	ED_{50}, mg/kg FOR ANALGESIA	LD_{50}, mg/kg	SAFETY MARGIN (LD_{50}/ED_{50})	POTENCY RATIO
PETHIDINE	6 0	29 0	4 83	0 0018
FENTANYL	0 011	3 1	277	1 0
CARFENTANIL	0 00034	3 4	10,000	32 4

Although the exact ratios reported are specific to rats in which this research was conducted, comparable differentials between toxicity (LD_{50}) and potency (for analgesia) are applicable to other species, thus carfentanil has the widest safety margin of the narcotics available in N Z

Specifically considering potency for deer, carfentanil appears to be about 20 X the potency of fentanyl This implies that the dose of fentanyl in 1 mL of **Fentazin** [3], 0 4 mg = 400 µg, is equivalent to about 20 µg of carfentanil, which is provided by 0 4 mL of **Carfenzine 50/50** As typical label dosages of the latter product are approximately double the label dosages for Fentazin, the narcotic (=analgesic) dose delivered by label dosage of **Carfenzine 50/50** is about five times as great

Each of these products has its place in the management of deer, the point I wish to convey is that they should not be regarded as equivalent in potency or indications

Label dosage of **Carfenzine 50/50** gives consistently good analgesia, found adequate for velvet removal in clinical trials in N Z Carfentanil can impart profound sedation in stags for up to 2 or 3 hours, and if unreversed will continue to exert significant sedation for 12 hours or more To avoid prolonged recumbency and possible sequalae - such as respiratory and circulatory depression and misadventure during an incordinated phase of recovery - reversal at the completion of the procedure requiring sedation/analgesia is advised

For the reversal of carfentanil with naloxone, a standard ratio of prior narcotic dose to reversal/antagonist can be used, viz

For a **1 mg carfentanil narcotic dose, give 100mg naloxone** to reverse

Therefore for **Wildnil** ,

give	6mL **Narconil** [4] for each	1 mL **Wildnil**
	(50 mg/mL naloxone,	(3mg/mL carfentanil,
	x 6 = 300 mg)	x 1 mL = 3 mg)
or		
	1mL **Narconil** for each	0 167 mL **Wildnil**
	(50 mg naloxone)	(0 5mg carfentanil)

Administration of Narconil:

In a deeply narcotised (unconscious) patient, 50% of the reversal dose may be given intravenously, and the balance intramuscularly

As the rate of degradation in the body of carfentanil is slower than for naloxone, for heavy doses of carfentanil given as Wildnil, repeat dose(s) of naloxone may be needed, from 30 minutes to several hours after initial reversal of narcosis

Naloxone has a wide safety margin, 6 times these calculated dosages have been administered without untoward results

For reversal of **Carfenzine 50/50** ,

give 0 1 mL **Narconil** for each 1 mL **Carfenzine 50/50**
(5 mg naloxone) (0 05 mg carfentanil)
(plus xylazine reversal)

Naloxone does not reverse the effect of xylazine. After use of **Carfenzine 50/50** for immobilisation and analgesia in deer, *reversal of both components (carfentanil and xylazine)* is recommended

To prepare a complete reversal solution:

Add 1 0mL **Narconil** (Naloxone 50 mg/mL)
to 10 0 mL Yohimbine HCl 10 mg/mL solution for injection

Dosage:
(1 mL for each 80 kg bodywieght),
or 1 mL for each 1 mL **Carfenzine 50/50** previously administered

The latter regime, *dosage of reversal solution according to prior sedation dose* is recommended, rather than dosage by bodywieght

Administration:

A single intravenous injection usually gives a return to consciousness and standing posture within 2 - 5 minutes Renarcotisation is uncommon in **Carfenzine 50/50** sedated animals given intravenous reversal only However for slower but more prolonged action, 50% of the dose may be given intravenously and 50% intramuscularly

ALTERNATIVE ANTAGONIST FORMULATIONS ?

•**Narcan** [5] is 0 4 mg/mL Naloxone HCl supplied in 10 x 1 mL packages for narcotic reversal in humans

The relevant volumes to reverse as above are

750 vials	for each	1 mL **Wildnil**
125 vials	for each	0 167 mL **Wildnil**
12 5 vials (plus xylazine reversal)	for each	1 mL **Carfenzine 50/50**

2. Contran-H [6] contains 0 1 mg/mL Naloxone HCl

50 mL would be required to reverse the narcotic action of 1 mL **Carfenzine 50/50** Obviously this would be a toxic yohimine dose, so a safe and satisfactory reversal cannot be given

Therefore at present **Narconil** is the only realistic and effective dosage form of naloxone, for use in reversal of carfentanil products A mixed reversal product to suit **Carfenzine 50/50** as described above will be registered as an animal remedy in the near future

[1] ARB No 6427 P A R Class III Licensed to Virbac Laboratories (NZ) Ltd
[2] ARB No 6938 P A R Class III Licensed to Virbac Laboratories (NZ) Ltd
[3] ARB No 6409 P A R Class III Licensed to Parnell Laboratories NZ Ltd
[4] ARB No 6840 P A R Class II Licensed to Virbac Laboratories (NZ) Ltd
[5] Prescription Medicine Licensed to Boots Pharmaceuticals
[6] ARB No 6408 P A R Class II Licensed to Parnell Laboratories NZ Ltd