EVALUATION OF "DOMOSEDAN" IN FARMED RED DEER

A Preliminary Report

A L Bouma, P R Wilson and A M Alexander
Veterinary Faculty, Massey University

1. INTRODUCTION

There is always a desire amongst veterinarians for safer, more reliable and predictable methods of chemical restraint for deer. The requirements for such a drug can be broadly defined as:-

- ease of administration
- low-volume dose
- rapid onset of effect
- rapid recovery
- predictable sedative effect
- predictable duration of effect
- a dose-graded response
- analgesic properties
- inexpensive
- safe for both veterinarian and deer
- absence of untoward side-effects
- absence of tissue residues

Presently the drugs used for chemical restraint of deer include Xylazine ("Rompun", "Thiazine"), and a Fentanyl/Azaperone combination ("Fentaz"). In some instances a combination of Xylazine and "Fentaz" is used.

Xylazine satisfies most of the requirements listed above. Its major disadvantages include a variable effect at a given dose rate between deer, a variable rate of onset of activity between deer, and lateral recumbency predisposing to rumenal tympany. Recovery is sometimes slow, particularly if incremental doses are needed, and occasionally stags will die within 24 hrs of administration. (See elsewhere in this Proceedings).

"Fentaz" also fulfills most of the requirements above but Fentanyl is a potent narcotic and is therefore dangerous to humans at deer dose quantities, and it is expensive to purchase.

Recently detomidine hydrochloride ("Domosedan", Farmos Group Ltd.) has been introduced to New Zealand and is currently registered for use in horses and cattle. It has been used in Europe for a number of years and has proved popular amongst equine practitioners in New Zealand. Because of its attractive properties in the equine, it was considered appropriate to investigate the potential of this drug as a sedative/analgesic in deer. This paper discusses the pharmacology of "Domosedan" and summarises in brief an investigation of "Domosedan" in red deer that was carried out at Massey University.

2. PHARMACOLOGY OF "DOMOSEDAN"

Extensive studies of the pharmacology of "Domosedan" have been carried out overseas. Its cardiovascular and hypotensive effects, role in the

regulation of vigilance and pain, effects on the brain and its pharmacokinetics have all been quantified.

Detomidine, like Xylazine, is an alpha-adrenoceptor agonist. Both products are selective for alpha-2 receptors but Detomidine appears to have a greater affinity than Xylazine. Alpha-2 receptors are neuronal receptors on noradrenergic nerve endings and mediate inhibition of noradrenalin release. They also occur as post-synaptic receptors in vascular smooth muscle and in the central nervous system.

Stimulation of alpha-2 receptors causes inhibition of noradrenalin release at adrenergic nerve endings, aggregation of platelets and granule release, inhibition of lipolysis, inhibition of insulin release, contraction of vascular smooth muscle, inhibition of renin release at the kidney, and ocular hypotension. Stimulation of the receptors in the central nervous system causes cardiovascular depression, antinociception (analgesia), sedation and a decrease in noradrenalin turnover.

Trials with laboratory animals indicate that a marked hypotensive effect is produced if Detomidine is used in anaesthetised animals, but a minimal reduction of blood pressure occurs after administration in conscious animals. Xylazine produces a more significant degree of hypothermia than does Detomidine. Hypothermia has been shown to be more pronounced at low dose rates of Detomidine than at high dose rates. Detomidine does not induce loss of the righting reflex at any dose rate, whereas Xylazine induces the loss of this reflex even at relatively low dose rates. Analgesic effects of Detomidine in laboratory animals are greater than those produced by Xylazine.

Detomidine is a slightly basic lypophyllic chemical of small molecular size. This means it is tolerated well by tissues and that it targets the central nervous system. It is rapidly distributed following subcutaneous injection. Metabolism to hydroxylated products and their conjugates results in excretion via the kidney, while a small fraction is also excreted via the hepatoenteric system.

3. EXPERIMENTAL EVALUATION OF "DOMOSEDAN"

Evaluation was conducted in a series of nine component studies. These will be described and discussed in the following text.

3.1 Preliminary observations

In undertaking a study such as this it was necessary initially to establish simply whether or not the drug produced effects worthy of further investigation, and to ascertain an appropriate range of drug dosages to use for further investigation.

Six 1-year-old red stags were used for this purpose and were given doses ranging from 20-320 µg/kg. The deer were observed for several hours and notes made. On the basis of these observations it was decided to proceed with a detailed study.

3.2 Establishment of dose response curves

3.2.1 Sedative effects

The objective of this study was to establish a dose response curve in six trial deer. Over a period of weeks each deer was given 0, 40, 80, 160 or 240 µg/kg doses of "Domosedan", and these were compared with Xylazine at 400 µg/kg after intramuscular injection. This was a double blind trial so that the observers were unaware of which deer had received which dose rate and which drug. The following parameters were measured at 5, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 240 and 300 minutes after administration:

Sedation parameters:

- Heart-rate, by observation of the jugular pulse
- Respiratory rate
- Stance and steadiness
- Angle of neck
- Degree of eye closure
- Response to noise (loud bang)
- Withdrawal of head when approached
- Resistance to forced movement of the neck

Each of these parameters were graded and sedation and analgesia scores computed for each dose rate at each interval.

For example, the degree of eye closure was scored:

0 - normal, i.e. wide-open
1 - slightly drooped eyelids
2 - eyes half-closed
3 - eyes almost or completely closed

It was considered that such scores subjectively quantify the effects of the drug.

There was generally a dose-related effect on all parameters measured and these can be summarised:

1. Rate of onset of effects - higher dose rates resulted in a more rapid onset of effect.

2. Peak effects - higher dose rates resulted in a more rapid onset of peak effects whereas the peak effects of lower doses were delayed up to 45 minutes and were of a lower magnitude.

3. Duration of effect - even at low doses the effect on most parameters could still be observed after 240 minutes. For higher doses there were significant effects observable even after 5 hours.
4. Comparison with Xylazine - the effect of Xylazine at 400 µg/kg equates to a dose of 120 µg/kg of Detomidine. It was noted that both drugs had similar effects for each parameter measured, but in general the peak response to "Rompun" occurred later than the peak response to "Domosedan". Heart rate and respiration rate following "Rompun" were depressed for considerably longer than following the equivalent dose of "Domosedan", i.e. up to 5 hours. However, the response of ear twitches, angle of the neck, stance, eye closure, noise response, head withdrawal

and neck movement resistance after 5 hours were similar for "Rompun" and "Domosedan".

This finding may have significance in that the physiological parameters measured were depressed rather longer under "Rompun" than they were under the equivalent dose of "Domosedan".

It is also significant to note that lateral recumbency was not observed after Detomidine administration, even at high doses (320µg/kg).

Therefore from a sedation point of view, "Domosedan" would appear to have four potential advantages over Xylazine:

1. Onset of peak effect is advanced

2. Heart rate is depressed for a significantly shorter period

3. Respiration rate is depressed for a significantly shorter period

4. Lateral recumbency did not occur even at higher doses, thus preventing the risk of rumenal tympany, regurgitation and inhalation of rumen contents.

To produce an overall view of the effects of "Domosedan" and "Rompun", a sedation score was computed for each sampling time at each dose rate by pooling scores for angle of the neck, stance, degree of eye closure, response to noise, withdrawal of head and resistance to forced movement of the neck, in such a way that for each parameter the highest grade equated with the highest level of sedation. The sedation score so computed is presented in Figure 1.

3.2.2 Analgesic effects -

Analgesia was scored by grading the response to a prick with a 18-gauge needle in the gluteal region, and by response to pinching of the ear pinna with Ellis tissue forceps, such that 0 represented the normal response, i.e. immediate and obvious reaction, and 3 represented no response. Measurements were made concurrent with those of sedation indices in 3.2.1 above. It was apparent that there was a dose response pattern to analgesia similar to that for parameters indicating sedation, i.e. higher doses caused a more rapid onset of response and a more prolonged response. An analgesia score was computed by pooling data for both needle response and ear pinna pinch. The analgesia score computed is presented in Figure 2.

It is notable that Xylazine at 400 µg/kg produced a response equivalent to "Domosedan" at 120 µg/kg. This suggests that Xylazine has a slightly greater analgesic effect than sedative effect at a given dose when compared with "Domosedan".

The pattern of reduction of analgesic effect of "Domosedan" is similar to that for Xylazine.

3.3 Intravenous administration

Intravenous injections of 20 or 80 µg/kg "Domosedan" were evaluated in a manner similar to that described in 3.2.

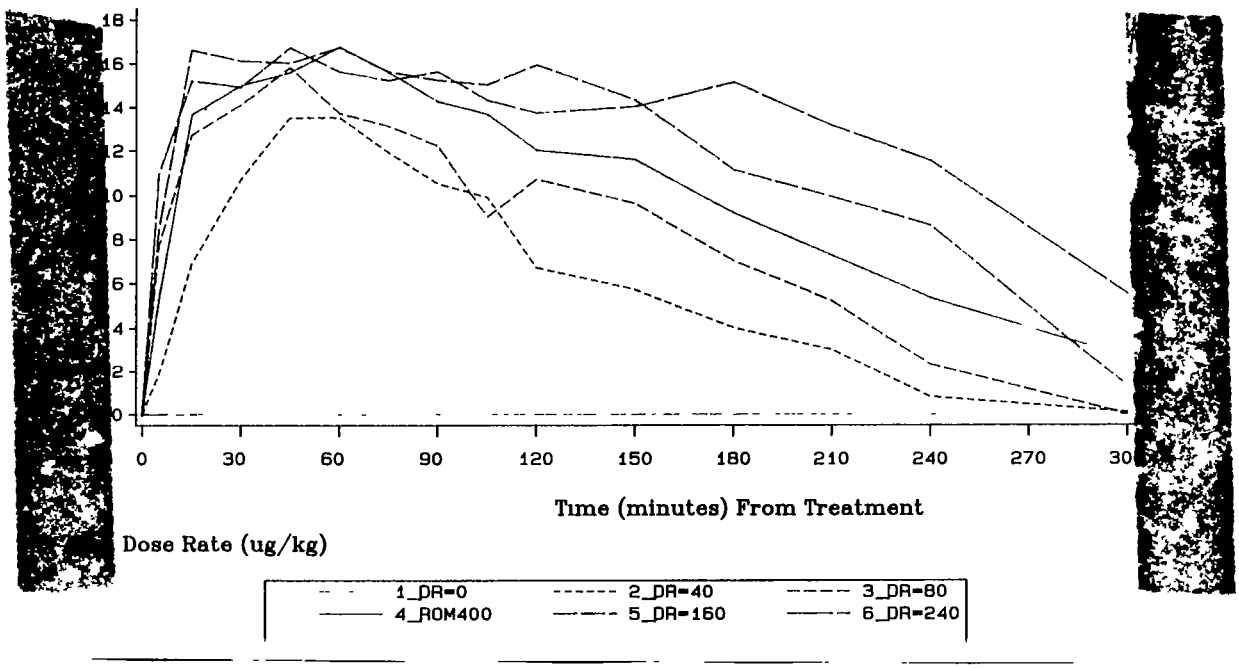

Figure 1. Sedation score following intramuscular detomidine administration

at 0, 40, 80, 160 and 240µg/kg and xylazine ("Rompun") at 400µg/kg

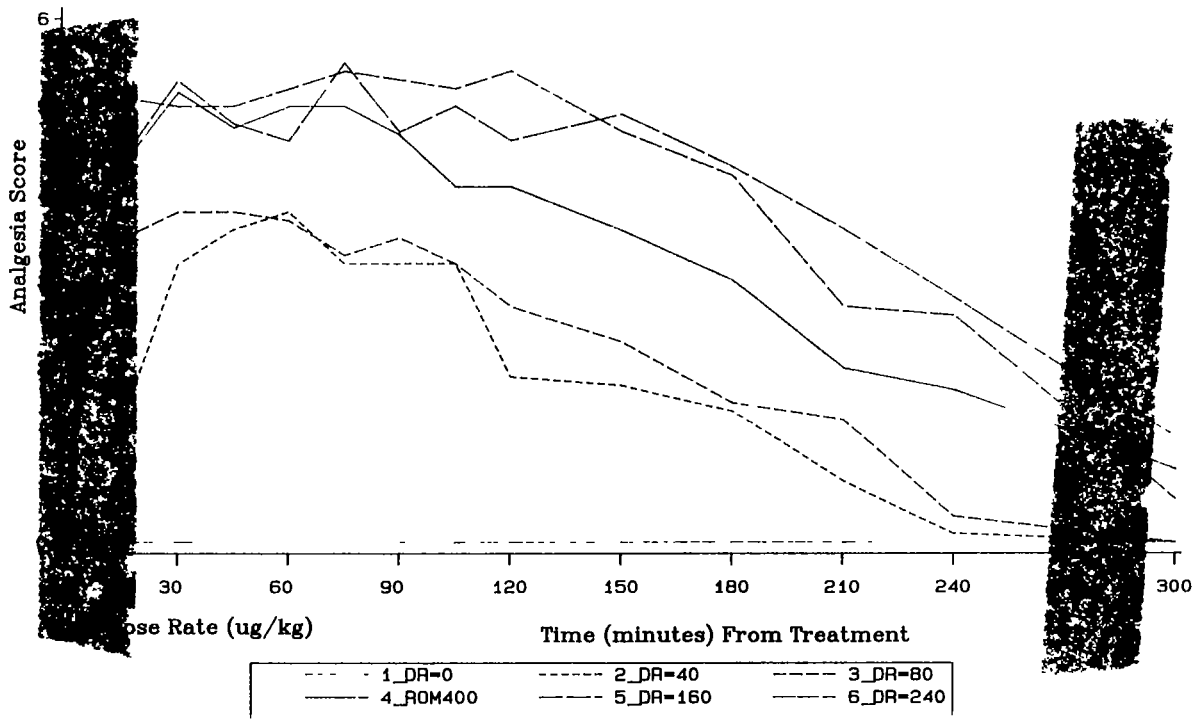

Figure 2. Analgesia score following intramuscular detomidine administration

at 0, 40, 80, 160 and 240µg/kg and xylazine ("Rompun") at 400µg/kg

The intravenous route proved to be effective and safe to the animal. All six deer became recumbent in less than 5 minutes after either dose. Analysis of sedation and analgesic properties suggest that two-thirds of the intramuscular dose is needed for similar effects. Recovery is also more rapid following intravenous administration.

3.4 Incremental doses

Field experience with Xylazine has shown that a number of deer require repeated injections to achieve the desired chemical restraining, sedative or analgesic effects. It was therefore considered necessary to examine the effect of incremental doses of "Domosedan" in deer.

Six deer were injected intramuscularly with 30 µg/kg "Domosedan" and left for 30 minutes. They were easily restrained in a standing posture and intravenous injection of 60 µg/kg of "Domosedan" was undertaken. All six deer became recumbent in less than 5 minutes. No untoward behavioural or physiological effects were observed.

3.5 Reversal of "Domosedan" using yohimbine hydrochloride

"Domosedan" has similar chemical and pharmacological properties to Xylazine. Since the latter drug is reversed in deer using yohimbine hydrochloride ("Recervyl") it was considered appropriate to examine the effect of this drug as a potential reversal agent for "Domosedan".

Six eighteen-month-old red stags were injected with "Domosedan", either at 120 or 160 µg/kg. After approximately 90 minutes, 0.25 µg/kg "Recervyl" was given to deer injected with 160 µg/kg "Domosedan" and 0.12 µg/kg "Recervyl" injected to those given 120 g/kg "Domosedan".

On three further occasions fourteen similar aged red deer stags were injected with doses 120-240 µg/kg. 30 minutes after "Domosedan" administration "Recervyl" at 0.25 µg/kg was administered intravenously. Heart rates and respiratory rates were recorded 15 minutes before "Recervyl" administration, and again 5 and 15 minutes following "Recervyl".

Of the original six deer, those given 0.25 µg/kg stood within 2 minutes. The remainder stood within 4 minutes. Heart rates increased from 30-40, to 80-90 beats per minute. The deer became obviously more alert.

However, results on the 14 other deer on each occasion were variable. Some deer stood within 1.3 minutes, others remained recumbent for 30 minutes. Therefore "Recervyl" does not appear to be a particularly reliable reversal agent for "Domosedan". The reasons for this apparent variability are unknown, but analysis of the data suggested that a more predictable response was achieved when a new bottle of reversa; drug was used. Poorer responses tended to occur when previously opened bottles were used.

3.6 Evaluation of "Domosedan" for clinical procedures

3.6.1 Velvet removal

A dose rate of 80 µg/kg was used to successfully restrain deer for the

purpose of removal of velvet antler. Because of the limited analgesic effect of "Domosedan" at that dose rate, local anaesthetic either as individual nerve blocks or ring blocks, was still required.

3.6.2 Liver biopsies

"Domosedan" was frequently used for experimental purposes as the sole means of restraint of animals during collection of liver biopsies. Dose rates used ranged from 60-160 µg/kg. Biopsies were taken from animals in a standing posture. "Domosedan" was considered to be an appropriate drug for this purpose.

3.6.3 Injuries

"Domosedan" was used for sedation of two deer with severely injured limbs requiring examination and treatment. One, with a compound fracture of the distal metacarpus, was very distressed but within 10 minutes of 170 µg/kg "Domosedan" he could be handled and examined with ease, with minimal withdrawal response during manipulations. The second animal, given "Domosedan" at 160 µg/kg, had a severe traumatic wound cleaned, surgically treated and bandaged, without pain withdrawal responses.

An observation of clinical responses was that several factors appear to affect the dose rate required to achieve a given level of sedation and analgesia. These include weather conditions, the temperament of the deer, background noise and animal habituation to yarding and handling. On grey, overcast days with low background noise level deer will require a relatively low dose. Conversely, it was noted that when animals were apprehensive, handled roughly or on a windy or very cold day, higher doses were necessary.

3.7. Safety evaluation

Fifty-three red and red-X-Wapiti 8-10-month-old stags on two commercial deer farms were injected with doses of "Domosedan" ranging from 120 to 240 µg/kg. Sedation and analgesia scores were computed as for Section 3.1 15 and 120 min after administration.

Observations revealed the following:-

- Sedation and analgesia scores for deer treated off-station were lower at both 15 and 120 min than equivalent responses observed in the study deer kept at Massey. The probable reason for this is that the Massey deer were of a uniform line and had received considerable handling.

- Marked differences in response between individuals were observed. Some animals became recumbent soon after injection, some remained recumbent for much longer periods than others, some animals appeared only mildly sedated. All animals administered with "Domosedan" 160 µg or more became recumbent. However, only 3 of 9 deer injected with 120 µg/kg became recumbent 15 minutes after injection.

- The responses of deer with Wapiti-type blood were more variable than for pure red deer.

These observations under the field environment are very similar to clinical observation of the response of deer to Xylazine.

3.8 Toxicity - overdosage

Six 18-month red stags were injected intramusculary with 480 µg/kg "Domosedan" and behavioural and physiological responses monitored for several hours. Analgesic and sedative effects were little different to those observed with 240 µg/kg. No adverse side effects were seen and it was possible to arouse all animals to stand unassisted 60 minutes after administration.

It would appear, therefore, that deer tolerate a "Domosedan" dosage of double that required to produce the maximal sedative and analgesic response.

Note: No studies were done to determine what dose may be fatal to deer as this was considered to be inappropriate. The study protocol was designed to reflect the practical possibility that some deer may receive an accidental second dosage if a group of animals was to be sedated at a given time.

3.9 Tissue residues

Ten rising two-year-old red stags were used in this study. Nine animals were injected intramuscularly with "Domosedan" at 240 µg/kg. Three animals were injected at 96, three at 48 and three at 24 hr before slaughter. The ten animals were despatched and liver, lung, heart, kidney, thymus, fat and skeletal muscle (including the injection site) were taken. All samples were frozen to await "Domosedan" analysis. At the time of writing results were not available.

4. CONCLUSIONS

The results of the studies performed indicate that "Domosedan" fulfills most of the requirements of a sedative for use in deer.

- It is easy to administer and the dosage volume is low
- The product appears safe and effective when administered by both the intramuscular and intravenous routes
- The onset of action is rapid
- Animal responses are relatively predictable but variation related to temperament and previous handling experience was observed
- The analgesic effect produced is similar to that observed with Xylazine
- Deer tolerate twice the normal maximum dosage without untoward effect

- The advantages this drug appears to have compared with Xylazine are a less prolonged depression of heart rate and respiration rate, and no deer developed lateral recumbency even at high dosages.

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