THE EFFECTS OF XYLAZINE AND FENTANYL ON VARIOUS HORMONES AND METABOLITES IN KARAKUL SHEEP AND A BLESBOK

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ABSTRACT

Xylazine and fentanyl are commonly used in combinations for immobilisation of wild antelope. In order to ascertain the effects of the combination of these drugs on certain metabolites and hormones in ruminants, blood was sampled from 8 karakul sheep (4 experimental and 4 control) and one tame blesbok (*Damaliscus dorcas phillipsii)* for 30 min before and after immobilisation. The samples were assayed for glucose, free fatty acids, insulin, thyroxine, triidothyronine, progesterone and oestrogen. Significant changes, after the administration of xylazine and fentanyl, were recorded in circulating concentrations of glucose, which increased, and free fatty acids and insulin, which decreased. The other hormones tested were not affected within the sampling period. It is suggested that the combination of xylazine and fentanyl may act directly on pancreatic Beta cells to inhibit the secretion of insulin, which will consequently affect circulating concentrations of glucose and free fatty acids.

Key words: Drugs, metabolites, hormones, sheep

Marais A.L.; Van der Walt J.G.; Skinner J.D. **The effects of xylazine and fentanyl on various hormones and metabolites in Karakul sheep and a blesbok.** *Journal of the South African Veterinary Association* (1991) 62 No. 1, 17-19 (En.) Mammal Research Institute, University of Pretoria, 0002 Pretoria, Republic of South Africa.

Pharmacological immobilisation of free-ranging and captive wildlife has provided a relatively safe and easy way of obtaining blood samples and various measurements for physiological studies. Clarke & Doughton[4] found that although chemical restraining drugs differ widely in physiological side-effects, this method was preferable to manual physical restraint of wild animals. They are thus in agreement with Wesson et al.[18] who reported on the influence of chemical immobilisation and physical restraint on white-tailed deer *(Odocoileus virginianus).*

However, side-effects of drug administration can influence homeostatic mechanisms responsible for maintaining normal serum biochemical and hormone concentrations[7 10 18]. It is therefore imperative to determine possible side-effects before embarking on a physiological study using chemical restraint.

Xylazine hydrochloride has been used for immobilisation of deer (*Capreolus* spp.)[11 17] and combinations of xylazine and ketamine hydrochloride, fentanyl citrate and etorphine for restraint of moose *(Alces alces),* deer *(Cervus elaphus nelsoni)*[15] and various African ungulates[19].

Xylazine is an alpha-2 adrenergic agonist with sedative, analgesic and muscle relaxant properties[9] and is widely used in biomedical research and veterinary medicine. Various studies on dogs (*Canis familiaris)*[8], sheep *(Ovis aries)*[3] springbok *(Antidorcas marsupialis)*[11] and goats *(Capra hircus)*[1 13] conclude that xylazine causes a fasting hyperglycaemia. Garcia-Villar et al.[6], reporting on the pharmacokinetics of this drug, indicated that there were remarkably small interspecific differences in the action of xylazine administered either intramuscularly or intravenously.

Fentanyl citrate is described as a pethidine analogue with pharmacologic actions similar to morphine[2]. This drug is effective for the chemical restraint of large herbivores when mixed with a suitable tranquilliser to counter the respiratory depression caused by fentanyl citrate[19].

No published information was available on the physiological side-effects of xylazine and fentanyl used in combination for immobilisation of wild animals. The present experiment was designed to determine the effects of these drugs on a group of ruminants in order to validate their suitability as pharmacological restraining agents in a physiological study.

Karakul sheep (n = 8) weighing ca 40 kg (4 experimental and 4 control) were trained to stand in metabolic crates and were handled regularly prior to the experiment to minimise sampling stress. Jugular catheters were inserted 24 h prior to the experiment and were filled with heparinised saline to prevent blood clotting. Blood was collected using an automatic suction pump connected to a fraction collector, at a rate of 1 ml min^{-1}, as described[16]. After 40 min collection, an intramuscular injection of a combination of 2,5 mg of xylazine (Rompun, Bayer, SA) and 5 mg of fentanyl (Sublimaze, Janssen Pharmaceutica Pty Ltd), or saline in the case of control animals, was administered. Thereafter, blood was collected for a further 40 min before administration of the narcotic antidote, nalorphine (Lethidrone, Wellcome, SA).

The samples were kept on ice before centrifugation, whereafter they were pooled into 4 pre-injection (A B C D) and 4 post-injection (E F G H) samples of 10 ml each. Free fatty acids (FFA) and glucose were determined on the day of the experiment, and aliquots of the remaining pooled plasma were stored at -20°C awaiting assay for insulin, thyroxine, triidothyronine, progesterone and oestrogen (Diagnostic Products Corporation, Johannesburg, SA). Glucose was determined with the GOD-Perid kit (Boehringer Mannheim (Pty) Ltd, Johannesburg, SA) and the FFA were determined colorimetrically according to a des-

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Received: November 1989 Accepted: October 1990

cribed method[5]. All chemicals used were of analytical grade.

One tame blesbok *(Damaliscus dorcas phillipsii)* was available from which to draw blood samples without being stressed. A jugular catheter was inserted one day prior to the experiment. Blood samples were taken 4 times at 10 min intervals before an intramuscular injection of a combination of xylazine (5 mg) and fentanyl (10 mg) was administered, and 4 times at 10 min intervals thereafter. The samples were treated in the same way as for the sheep samples, and subsequently assayed for insulin, free fatty acids and glucose.

Results were analysed using the Student's t-test.

Circulating serum concentrations of glucose remained constant (~3 mM) in the control animals throughout the sampling period, while in the experimental animals, a significant increase of at least 2 mM ($p < 0,001$) was recorded after the injection of xylazine plus fentanyl (Fig. 1).

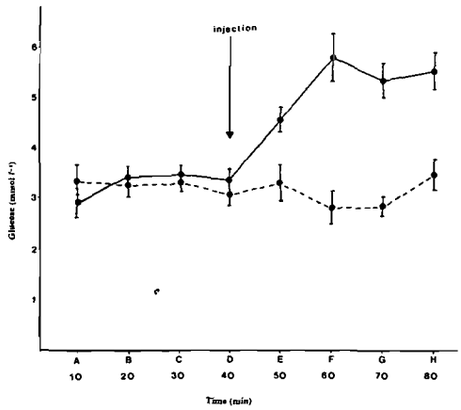

Fig. 1: **Circulating concentrations of glucose (----) before (ABCD) and after (EFGH) injection of xylazine and fentanyl. Control animals (----) received a saline injection**

A significant decrease of almost 0,1 mM ($p < 0,001$) in the serum concentration of free fatty acids was noted after the injection in the experimental animals, while the control animals remained constant at ~0,2 mM. The control animals did not react to the saline injection (Fig. 2).

A significant decrease in serum insulin concentration of over 50 u IU ml^{-1} ($p < 0,001$) was found in the experimental animals after the injection, while concentrations remained constant in the control animals (Fig. 3).

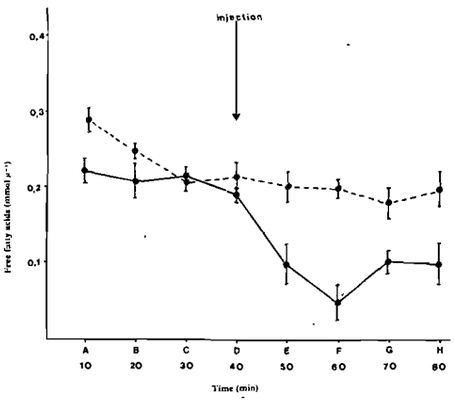

Fig. 2: **Circulating concentrations of free fatty acids (----) before (ABCD) and after (EFGH) an injection of xylazine and fentanyl. Control animals (----) received a saline injection**

No significant changes were recorded in serum concentrations of thyroxine and triidothyronine, either after the administration of the drugs, or between experimental and control animals.

Serum concentrations of progesterone and oestrogen remained constant both before and after drug administration and between control and experimental animals.

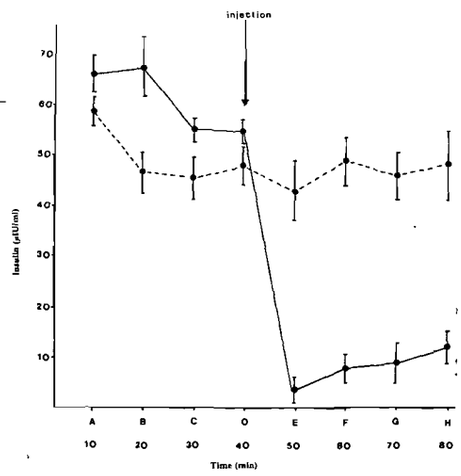

Fig. 3: **Circulating concentrations of insulin (----) before (ABCD) and after (EFGH) an injection of xylazine and fentanyl. Control animals (----) received a saline injection**

Plasma glucose concentrations in the blesbok increased from 1,9 mM to 3,2 mM after the injection of xylazine and fentanyl, while FFA levels dropped from ~0,1 mM to ~0,06 mM. Once again the most dramatic change was the decrease in serum insulin concentrations from ~30 μIU ml^{-1} to ~ 3 μIU ml^{-1}.

The depression of insulin and elevation of glucose concentrations in plasma are typical responses to sympathetic stimulation[3]. Thus, it appears that the hyperglycaemia and hypoinsulinaemia associated with the administration of xylazine and fentanyl may be a sympathetic response mediated via alpha-2 receptors in the brain, rather than those in the pancreas. The present study supports the observations of Nolan et al.[14] that the effect of xylazine on insulin is mediated by the alpha-2 adrenergic receptor.

However, as no significant changes were recorded in hormones secreted by the thyroid or gonads, either before or after immobilisation, it would appear that the combination of xylazine and fentanyl acts directly on receptor sites in the pancreas to inhibit insulin secretion. This supports the hypothesis of Greene et al.[9] that one of the sites of action of xylazine is the pancreatic Beta cell and that the mechanism may involve modulation of calcium transport.

The present results therefore suggest that xylazine and fentanyl should not be used for physiological experiments necessitating pharmacological restraint, where either insulin secretion or plasma glucose and FFA concentrations are critical variables.

ACKNOWLEDGEMENTS

This research was supported by a grant from the Foundation for Research Development.

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