EFFECTS OF ENVIRONMENTAL TEMPERATURE ON PHARMACOKINETICS OF, AND CLINICAL RESPONSE TO XYLAZINE IN GOATS.

A Thesis

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Doctor of Philosophy.

by

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DECLARATION

I, **Eddy Geoffrey Mosoti Mogoa**, do hereby declare that this thesis which I submit to the University of Pretoria, for the degree of Ph.D has not been submitted either in part or as a whole by me for a degree to any other university and my promoters: Prof. A. Guthrie - Equine Research Centre, Prof. G. F. Stegmann - Department of Surgery, and Prof. G. Swan - Department of Pharmacology and Toxicology, bear testimony to that.

Signed..... Date 26.05.99

Dedicated to my wife Judith Waithera, son Eric and daughter Alainer.

Thank you for understanding and bearing with my long periods of absence.

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ABSTRACT

The clinical use of xylazine may result in morbidity and mortality in small ruminants, and it was suspected that exposure to changes in environmental temperature may contribute to these effects.

Xylazine hydrochloride was administered intravenously at a dose of 0.1 mg/kg to a group of six indigenous domestic goats with a mean body mass of 28.2 kg. Xylazine was administered at a room temperature of 14° C and relative humidity of 33%, at 24° C and a relative humidity of 55%, and at 34° C with a relative humidity of 65%. The following variables were evaluated: clinical behaviour, cardiopulmonary function, haematology, acid-base balance, plasma glucose and insulin, body temperature, and the pharmacokinetic characteristics of xylazine.

Xylazine administration resulted in transient restlessness, followed by sedation, muscle relaxation, and salivation. The onset of these clinical signs was not influenced by environmental conditions.

Administration of xylazine resulted in a transient increase in respiratory rate in the 24 and 34° C environments. In the 14° C environment, the respiratory rate

decreased significantly ($p<0.05$) from baseline and continued to decrease for the full duration of the 60 minutes observation period. Heart rate decreased in all three environments, but this decrease was only significant in the 14° C environment for the duration of the observation period.

Changes in haemoglobin concentration, haematocrit, red blood cell count and mean red blood cell volume were significantly ($p<0.05$) different 15 minutes after xylazine administration and continued to be so for the duration of the observation period. Total serum protein changed significantly ($p<0.05$) in the 24° and 34° C environments from 15 minutes after xylazine administration. The white cell count changed significantly ($p<0.05$) from 15 minutes after xylazine administration for the duration of the observation period in all three environments.

Significant ($p<0.05$) changes occurred after xylazine administration in acid-base balance and arterial blood gas variables independent of environmental conditions. Arterial pH and the partial pressure of oxygen decreased significantly within 5 minutes of xylazine administration, and the partial pressure of carbon dioxide, total carbon dioxide and base excess increased significantly ($p<0.05$).

Environmental conditions had no observable influence on plasma glucose and

insulin concentration. Significant ($p<0.05$) changes occurred in all three environments.

Environmental conditions had no influence on body temperature in the control (untreated) animals. Following the administration of xylazine, the body temperature of the goats in the 14 and 24° C environments was significantly ($p<0.05$) lower than that of the goats in the 34° C environment. The maximum decrease in oesophageal temperature of 1.57° C was observed 60 minutes after xylazine administration to goats maintained in the 14° C environment.

Environmental conditions had no influence on all of the pharmacokinetic parameters of xylazine hydrochloride evaluated.

It is concluded that apart from changes in body temperature, changes that occurred in clinical and pharmacokinetic variables after xylazine administration, were independent of the three environmental temperature and humidity conditions.

OPSOMMING

Die kliniese gebruik van xilasien mag lei tot morbiditeit en mortaliteit by kleinvee, en die vermoede het bestaan dat blootstelling aan skommelinge in omgewingstemperatuur hiertoe mag bydra. Die doel van hierdie studie was om die invloed van temperatuur en relatiewe humiditeit op 'n verskeidenheid van kliniese veranderlikes en die farmakokinetika van xilasien hidrochloried in bokke te bepaal.

Xilasien was intraveneus toegedien teen 'n dosis van 0.1 mg/kg aan 'n groep van ses inheemse, gedomestiseerde bokke met 'n gemiddelde liggaamsmassa van 28.2 kg. Eerstens is xilasien toegedien by 'n temperatuur van 14° C en 'n relatiewe humiditeit van 33%, tweedens by 24°C en 'n relatiewe humiditeit van 55%, en laastens by 34° C met 'n relatiewe humiditeit van 65%. Die volgende veranderlikes is geëvalueer: kliniese gedrag, kardiopulmonale funksie, hematologie, suur-basis balans, arteriële bloedgasse, plasma glukose en insulien, liggaamstemperatuur en die farmakokinetiese eienskappe van xilasien.

Xilasientoediening het aanvanklik 'n kort periode van rusteloosheid veroorsaak gevolg deur kalmering, spierverslapping en speekselvloei. Die aanvang van hierdie kliniese tekens was nie deur verandering in eksperimentele omgewingstoestande beinvloed nie.

Toediening van xilasien het die asemhalingstempo aanvanklik verhoog by die 24 en 34° C omgewingstoestande, waarna dit weer begin daal het. By 14° C het die asemhalingstempo betekenisvol ($p< 0.05$) gedaal vanaf die basislyn gedurende die 60 minute observasietydperk. Harttempo het ook tydens al drie omgewingstoestande gedaal. Die harttempo het slegs tydens die 14° C omgewingstoestand statisties betekenisvol ($p<0.05$) vir die volle duur van die observasietydperk gedaal.

Veranderinge in hemoglobienkonsentrasie, hematokrit, eritrosiettelling en gemiddelde eritrosietvolume het betekenisvol ($p<0.05$) verander, 15 minute na toediening van xilasien vir die volle duur van die observasietydperk. Totale serum proteien het tydens 24 en 34° C omgewingstoestande betekenisvol ($p<0.05$) verander vanaf 15 minute na toediening. Die witseltelling het ook vanaf 15 minute na toediening vir die duur van die observasietydperk by al drie omgewingstoestande betekenisvol ($p<0.05$) verander.

Betekenisvolle veranderings ($p<0.05$) in die suur-basis balans en arteriële bloed gas veranderlikes het onafhanklik van omgewingstoestande na toediening van xilasien voorgekom. Arteriële pH en parsiële suurstofdruk het betekenisvol ($p<0.05$) binne 5 minute na toediening van xilasien gedaal, terwyl die parsiële druk van

koolsuurgas, totale koolsuurgas en basisoorskot betekenisvol ($p<0.05$) verhoog het. Eksperimentele omgewingstoestande het geen invloed op plasma glukose en insulien vlakke gehad nie. Statisties betekenisvolle veranderinge ($p<0.05$) het wel by dié veranderlikes na xilasientoediening in aldrie omgewingstoestande voorgekom.

Omgewingstoestande het geen invloed op liggaamstemperatuur in die kontrole groep (onbehandelde) bokke gehad nie. Die toediening van xilasien het tot 'n betekenisvolle daling in liggaamstemperatuur by 14 en 24° C omgewingstoestande gelei in vergelyking met die veranderinge wat by die 34° C omgewingstoestand waargeneem is. 'n Maksimale daling van 1.57° C in oesofageale-temperatuur het 60 minute na die toediening van xilasien aan bokke by die 14° C omgewingstoestand voorgekom.

Die eksperimentele omgewingstoestande het geen invloed op plasma halflewe en volume van verspreiding van xilasien gehad nie.

Ten slotte dit gevind dat, afgesien vir veranderinge in liggaamstemperatuur, het afwykinge in kliniese en farmakokinetiese veranderlikes na xilasientoediening onafhanklik van die eksperimentele omgewingstoestande plaasgevind.