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SOME PHYSIOPATHOLOGICAL FEATURES OF EXPERIMENTAL *HOMERIA GLAUCA* (WOOD & EVANS) N. E. BR. POISONING IN MERINO SHEEP

C. BUTTON[1], F. REYERS[2], D. G. A. MELTZER[1], MARIA S. G. MÜLDERS[1] and VALERIE M. KILLEEN[1]

ABSTRACT

BUTTON, C., REYERS, F., MELTZER, D. G. A., MÜLDERS, MARIA S. G. & KILLEEN VALERIE M., 1983. Some physiopathological features of experimental *Homeria glauca* (Wood & Evans) N. E. Br. poisoning in Merino sheep. *Onderstepoort Journal of Veterinary Research*, 50, 191–196 (1983).

Five Merino sheep were dosed 3 g/kg of dry, finely-milled *Homeria glauca* (Natal yellow tulp) plant material. An electrocardiogram was recorded and the arterial and central venous blood pressure, blood gases, haematological variables, plasma electrolytes (Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^- and PO_4^{2-}) and a variety of serum enzymes and chemical constituents were measured hourly until death (3 sheep) or until sheep were *in extremis* (2 sheep).

Heart rate rose progressively as a result of sinus and, later, ventricular tachycardia. Systolic blood pressure rose, but there was little change in the mean and diastolic arterial pressures and central venous pressure. There was progressive hypoxaemia, hypercarbia and acidaemia with depletion of plasma bicarbonate. Haemoconcentration, hyperkalaemia and hypochloraemia were found along with rising serum creatinine and plasma glucose. Rises in serum enzymes indicated widespread tissue damage. Electrocardiographic recordings were being made at the moment of death in 3 of the 5 sheep. In these 3 sheep the cause of death was ventricular fibrillation.

INTRODUCTION

Poisoning of animals by plants containing cardiac glycoside-like toxins is an important problem in southern Africa and is responsible for large losses of livestock, especially cattle. The plants incriminated, their distribution, the circumstances resulting in intoxication, the clinical and pathological features and some aspects of treatment have been described (Steyn, 1949; Naudé, 1969; Vahrmeijer, 1981; Joubert & Schultz, 1982). However, prior to the present study, the physiopathology of plant-related cardiac glycoside poisoning had not, to our knowledge, been investigated in a systematic fashion. The purpose of the following investigation was to broaden knowledge in this field. An increased understanding of the physiopathology of the toxic syndrome was required to make more rational treatment possible. With this objective in mind, haematological, cardiorespiratory and certain blood biochemical variables as well as serum electrolytes and blood gases, were measured in 5 experimental sheep poisoned with milled *Homeria glauca* plant material. Known locally as the Natal yellow tulp, *H. glauca* was chosen because a lethal dose usually kills sheep in less than 1 day (J. P. J. Joubert, personal communication, 1982). The main toxic principle in *H. glauca* has been identified as a bufadienolide, 1α, 2α-epoxyscillirosidin (Naudé & Potgieter, 1971).

MATERIALS AND METHODS

The subjects in this trial were 5 Merino sheep (3 wethers and 2 ewes) (Table 1). The sheep were kept on a grass pasture during the day and fed lucerne (alfalfa) hay at night. Three days before the commencement of each trial the sheep were fasted overnight. The following morning, 48 hours before the administration of toxic plant material, they were anaesthetized by means of intravenously administered pentobarbitone sodium. After skin preparation an incision was made over the left jugular groove. The left jugular vein and carotid artery were catheterized with silastic catheters of our own making. The lengths of the catheters was such that the tips were in the anterior vena cava and aortic root. The catheters were kept patent by daily flushing with heparinized saline (500 units/mℓ). The necks of the sheep were bandaged between the time of surgery and toxin administration to prevent displacement of the catheters.

TABLE 1 Details of the experimental sheep

Sheep No.	Sex	Permanent incisors	Body mass (kg)	Time of dosing to death (h)
1	W	2	32,5	27,75*
2	W	0	37,0	2,2
3	F	2	39,0	>7,5**
4	F	2	32,5	5,0
5	W	2	39,1	4,0

W = wether; F = female;

* Sheep killed with pentobarbitone sodium
** Sheep was not being observed at moment of death

Approximately 48 hours after surgery, the body mass of each sheep was recorded and the sheep placed in a sling which permitted it to stand, but not to move away. The arterial and venous catheters were connected to precalibrated pressure transducers* via 3-way taps.

In this way blood samples could be collected and the catheters flushed without disconnecting the transducers. Alligator clip electrodes were clipped onto the skin over the heart on the left side of the thorax and over the right jugular vein to record a base:apex electrocardiogram (EKG). Pulsatile and mean arterial pressure, mean central venous pressure and EKG were recorded on a multichannel physiological recorder**. Respiratory rate (RR) was counted by watching thoracic and abdominal movements, and rectal temperature (RT) was monitored with a clinical thermometer.

The sheep were allowed approximately 30 minutes to become accustomed to restraint in the sling, then 2 control recordings were made of arterial blood pressure, mean central venous pressure, EKG, RR and RT, with 10 minutes between the 2 control measurements. Two sets of control blood samples were drawn concomitantly: heparinized arterial blood for blood gas and acid base analysis, for haematological analysis and for determination of total plasma proteins; arterial blood in Anderson's solution (Anderson, 1969) for determination of plasma glucose and phosphate; arterial blood without anticoagulant for determination of serum sodium, potassium, magnesium, calcium, chloride and creatinine as well as the enzymes lactate dehydrogenase (LD) (EC*** 1.1.1.27), α hydroxybutyrate dehydrogenase (α HBD) (Isoenzymes 1 and 2 of LD), creatine kinase (CK) (EC 2.7.3.2), γ glutamyl transpeptidase (GGT) (EC 2.3.3.2), glutamate dehydrogenase (GD) (EC 1.4.1.3) and sorbitol dehydrogenase (SD) (EC 1.1.1.14).

* Statham P50
** Siemens-Elema Mingograf, Model 62
*** Enzyme code number

[1] Department of Physiology, Pharmacology and Toxicology, Faculty of Veterinary Science, University of Pretoria, P.O. Box 12580, Onderstepoort 0110

[2] Department of Medicine, Faculty of Veterinary Science, University of Pretoria

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Blood gas samples were immediately stored in iced water. Analysis was carried out within 30 minutes, by means of a blood-gas analyser*. Red and white blood cell counts were performed, with an electronic counter**, haemoglobin determination on a haemoglobinometer***, and packed cell volumes, using a microhaematocrit centrifuge****. Plasma and serum for biochemical and electrolyte assay were harvested within less than an hour and samples were deep frozen for later analysis.

Serum electrolytes were measured by atomic absorption spectrophotometry*****, and plasma inorganic phosphate was determined with a commercially available kit******. Serum enzymes were assayed with commercially available kits*******. Plasma inorganic phosphate and serum enzymes were measured spectophotometrically********.

After all the control samples had been taken, the sheep were given finely-milled *H. glauca* plant material suspended in water at the rate of 3 g/kg body mass, by stomach tube. The plant material, sent from Estcourt, Natal, had been picked during the flowering stage and air-dried.

Blood pressures, EKG, RR and RT were recorded and blood samples collected hourly. Blood pressures and EKG were monitored more frequently when deterioration in the physical status of the animals became evident. Recordings were also made and blood samples collected at the moment of death in 3 of the 5 sheep. In Sheep 1 and 3, which lived longer than Sheep 2, 4 and 5, the recordings and samples made closest to death were pooled with the data from the 3 agonal recordings and samples referred to above. The pooled sample was called the "death" sample and the sample immediately preceding it was also pooled and called Sample 4. The 3 hourly samples which preceded Sample 4 were designated Samples 3, 2 and 1, respectively. Earlier data from the longer-lived Sheep 1 and 3 were thus not included in statistical calculations or graphs (see Results).

Means and standard deviations were calculated for the various pooled samples. Analysis of variance (Steel & Torrie, 1960) was used to determine whether the differences in means between the control data and data after administration of toxin were significant.

RESULTS

The sheep showed the following *H. glauca* intoxication-associated symptoms, listed in their approximate order of appearance: restlessness; chewing movements or audible tooth grinding sometimes with frothy saliva showing at the lips; fine muscle tremor; frequent urination; frequent defaecation with the passage of formed faecal pellets; free-gas bloat; grunting; groaning and struggling.

Heart rate increased steadily and significantly during the course of intoxication (Fig. 1). In the earlier stages this was the result of sinus tachycardia and, in later

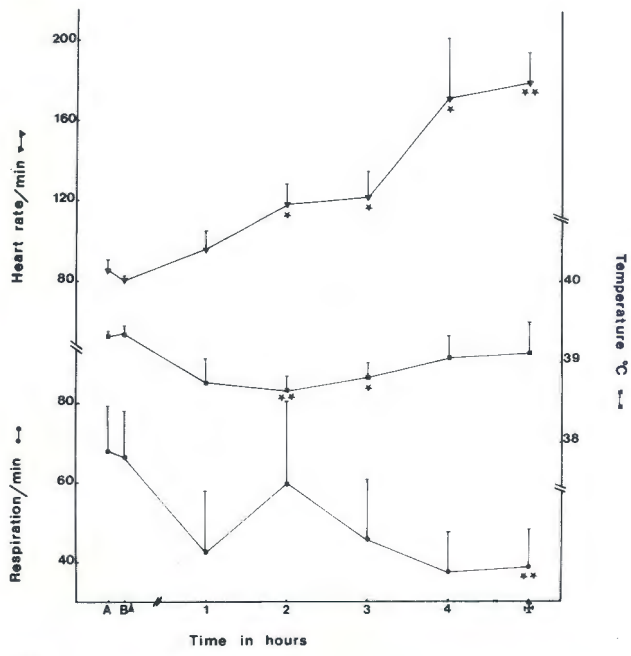

FIG. 1 Mean ± SD of heart rate, respiratory rate and rectal temperature for 5 sheep poisoned by *H. glauca*. Stars indicate that the mean was significantly different from the control values A and B. *P < 0,05 **P < 0,01. The arrow head indicates toxin administration and the cross indicates death

stages, of ventricular tachycardia. Individual rates as high as 250 beats per minute were recorded. Other transient arrhythmias included atrio-ventricular dissociation, ventricular ectopic beats, and, in one instance, ventricular flutter. Ventricular fibrillation was recorded in the 3 sheep from which recordings were taken at the time of death (Fig. 2).

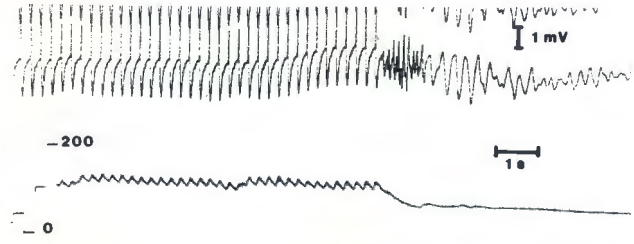

FIG. 2 Electrocardiogram (top trace) and arterial blood pressure (bottom trace) from sheep No 5. The recording was taken at the time of death when ventricular fibrillation occurred

Respiratory rate (Fig. 1) declined gradually during the course of the trial. Deep, slower grunting or groaning respiration was evident during the later stages of intoxication. Several sheep had apparent respiratory crises with approximately 1–2 minutes of apnoea, during which they appeared to be dying, only to recover somewhat thereafter.

Rectal temperature (Fig. 1) declined slightly soon after administration of the toxin, but increased towards control values terminally.

A significant rise in systolic blood pressure (Fig. 3) occurred coincidentally with the tachycardia referred to above. Mean arterial and diastolic arterial blood pressures showed only slight, non-significant and late rises. Central venous pressure declined initially, but rose towards control pressure towards the end (Fig. 3).

During the course of intoxication, the sheep developed significant and progressive mixed metabolic and respiratory acidosis (acidaemia with depletion of plasma bicarbonate and hypercarbia) as well as hypoxaemia (Fig. 4).

* Radiometer Model PHM 72
** Coulter Model DN
*** Coulter Haemoglobinometer
**** Ecco Model E2/12
***** Varian Atomic Absorption Spectrophotometer Model AA 275
****** Phosphorus Auto/Stat Kit, Pierce Chemical Company
******* Monotest, Boehringer Mannheim Diagnostica
******** Ames Pacer Spectrophotometer

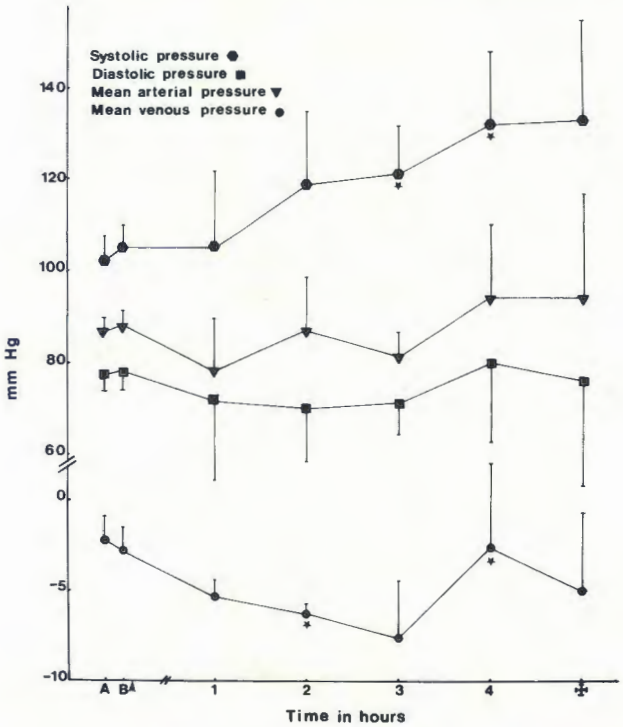

FIG. 3 Mean ± SD of systolic, mean and diastolic arterial blood pressure and mean central venous pressure for 5 sheep poisoned by *H. glauca*. Stars indicate that the mean was significantly different from the control values A and B. *P < 0,05 **P < 0,01. The arrow head indicates toxin administration and the cross indicates death

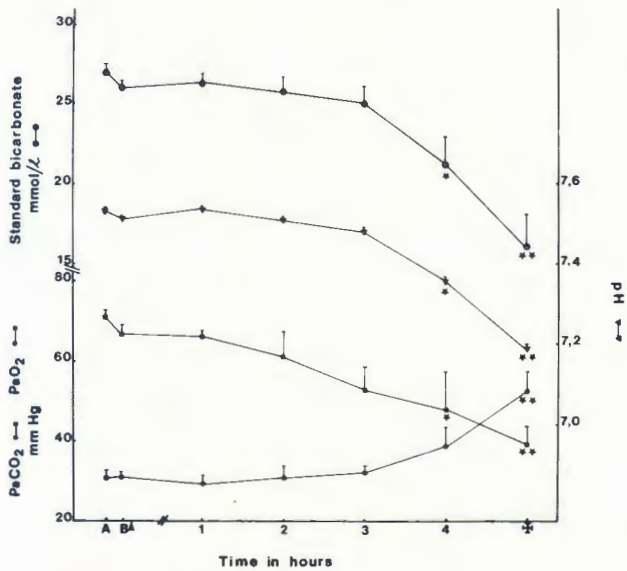

FIG. 4 Mean ± SD of arterial blood standard bicarbonate, pH, partial pressure of oxygen and carbon dioxide for 5 sheep poisoned by *H. glauca*. Stars indicate that the mean was significantly different from the control values A and B. *P < 0,05 **P < 0,01. The arrow head indicates toxin administration and the cross indicates death

Progressive haemoconcentration was evidenced by increases in haematocrit, red cell count and haemoglobin (Fig. 5), and by a rising concentration of total plasma proteins (Fig. 6). The white cell count also rose during the earlier stages of the trial (Fig. 6).

Serum sodium concentrations declined slightly during the trial but serum potassium concentrations increased steadily, with the terminal concentrations being hyperkalaemic in 4 out of the 5 sheep (Fig. 7). In Sheep 3,

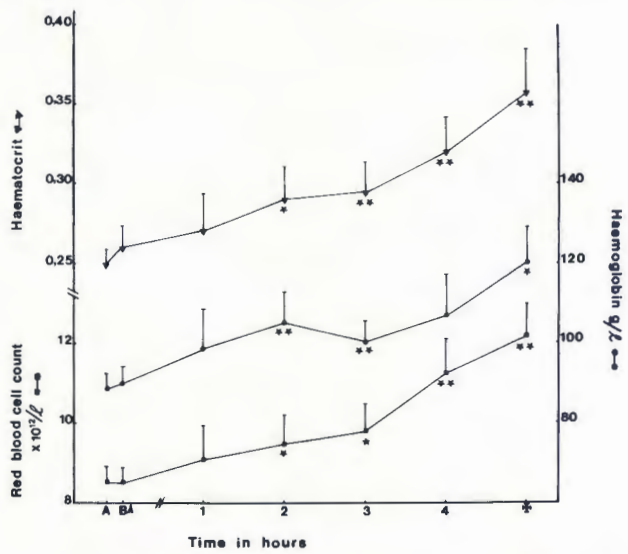

FIG. 5 Mean ± SD of haematocrit, haemoglobin and red blood cell counts for 5 sheep poisoned by *H. glauca*. Stars indicate that the mean was significantly different from the control values A and B. *P < 0,05 **P < 0,01. The arrow head indicates toxin administration and the cross indicates death

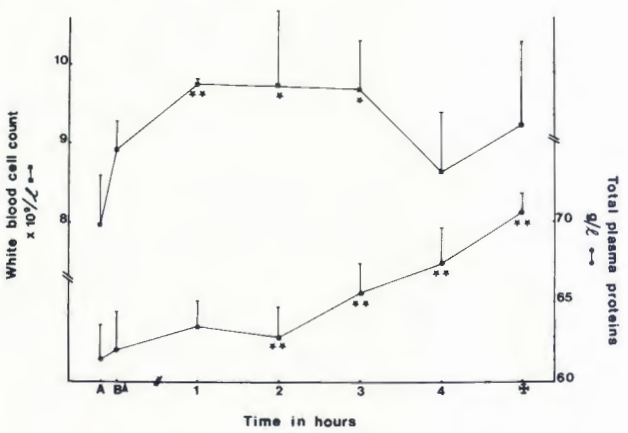

FIG. 6 Mean ± SD of white cell count and total plasma proteins for 5 sheep poisoned by *H. glauca*. Stars indicate that the mean was significantly different from the control values A and B. *P < 0,05 **P < 0,01. The arrow head indicates toxin administration and the cross indicates death

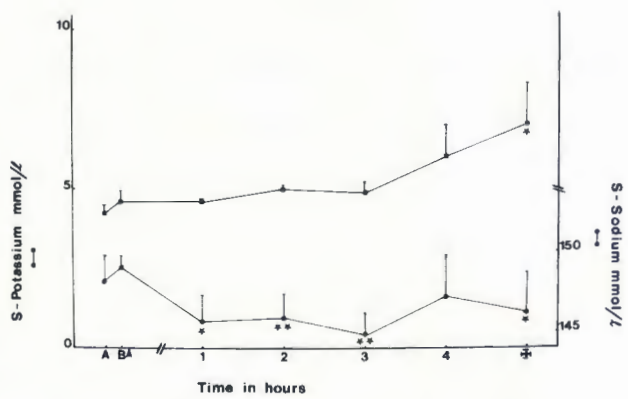

FIG. 7 Mean ± SD of serum potassium and sodium for 5 sheep poisoned by *H. glauca*. Stars indicate that the mean was significantly different from the control values A and B. *P < 0,05 **P < 0,01. The arrow head indicates toxin administration and the cross indicates death

from which the last sample was taken before death, the serum potassium concentration was within normal limits. The highest individual potassium concentration measured was 10,9 mmol/ℓ in Sheep 4 at the moment of death. Serum calcium and magnesium concentrations both rose slightly during the course of the trial (Fig. 8), but only the terminal magnesium concentrations increased significantly ($P < 0,05$) above control values. There was a marked and significant ($P < 0,01$) fall in serum chloride, while plasma inorganic phosphate declined initially but rose back to control concentrations terminally (Fig. 9).

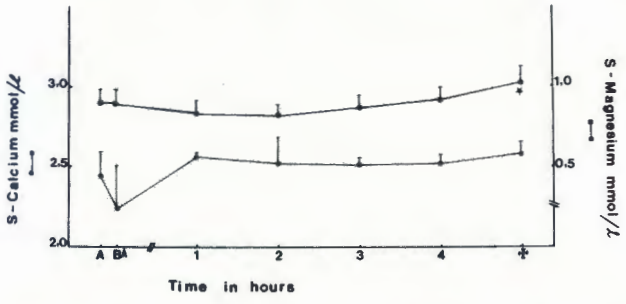

FIG. 8 Mean ± SD of serum magnesium and calcium for 5 sheep poisoned by *H. glauca*. Stars indicate that the mean was significantly different from the control values A and B. *P < 0,05 **P < 0,01. The arrow head indicates toxin administration and the cross indicates death

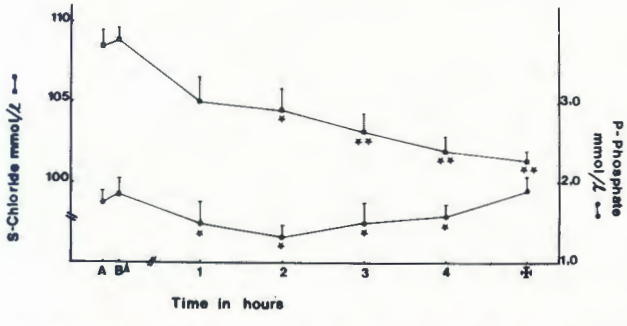

FIG. 9 Mean ± SD of serum chloride and plasma phosphate for 5 sheep poisoned by *H. glauca*. Stars indicate that the mean was significantly different from the control values A and B. *P < 0,05 **P < 0,01. The arrow head indicates toxin administration and the cross indicates death

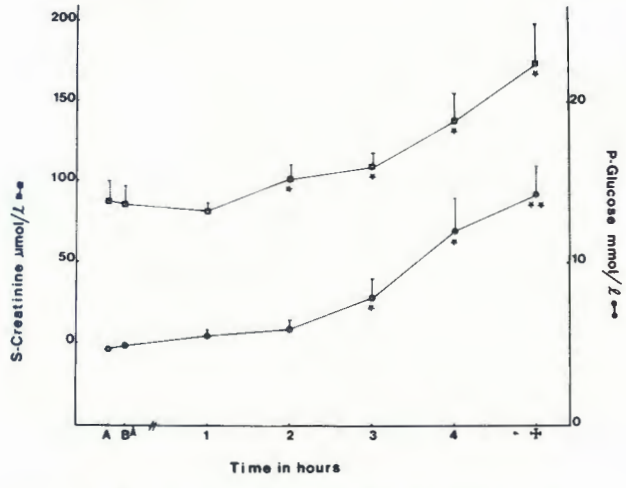

FIG. 10 Mean ± SD for serum creatinine and plasma glucose for 5 sheep poisoned by *H. glauca*. Stars indicate that the mean was significantly different from the control values A and B. *P < 0,05 **P < 0,01. The arrow head indicates toxin administration and the cross indicates death

Serum creatinine and plasma glucose concentrations both rose progressively and significantly during the course of the trial (Fig. 10). The highest individual terminal plasma glucose concentration was 19 mmol/ℓ in Sheep 2, which died 2,2 hours after toxin was administered.

The serum enzymes α HBD and LD increased in parallel to reach concentrations significantly ($P < 0,01$) above control concentrations. The α HBD:LD ratio remained practically constant, varying between extremes of 0,55 and 0,59 (Fig. 11). Serum CK declined not significantly initially but increased terminally towards control concentrations (Fig. 11). Serum GGT concentrations rose steadily during the trial. Serum GLD and SD increased gradually, but not significantly (Fig. 12).

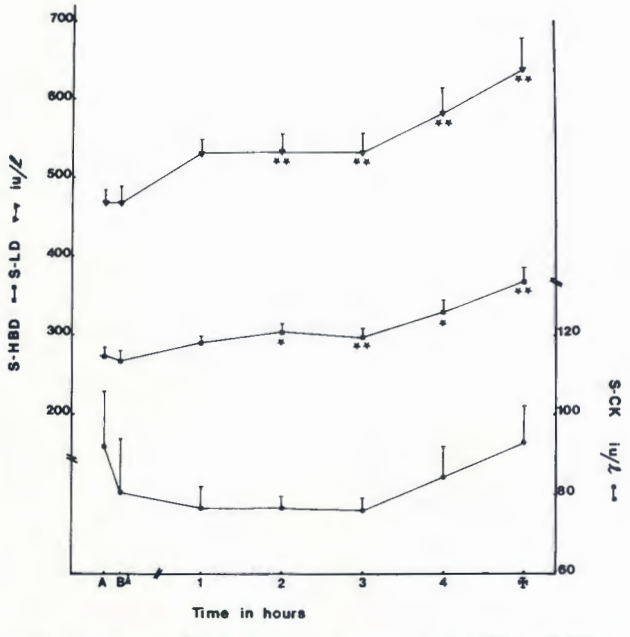

FIG. 11 Mean ± SD for the serum enzymes LD, HBD and CK for 5 sheep poisoned by *H. glauca*. Stars indicate that the mean was significantly different from the control values A and B. *P < 0,05 **P < 0,01. The arrow head indicates toxin administration and the cross indicates death

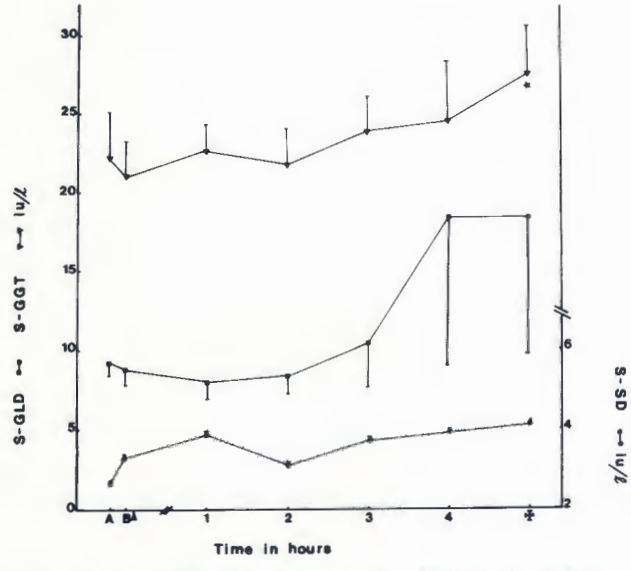

FIG. 12 Mean ± SD for the serum enzymes GGT, GLD and SD for 5 sheep poisoned by *H. glauca*. Stars indicate that the mean was significantly different from the control values A and B. *P < 0,05 **P < 0,01. The arrow head indicates toxin administration and the cross indicates death

DISCUSSION

The clinical signs of *H. glauca*-induced intoxication in this trial were similar to those which have been described previously (Steyn, 1949; Naudé & Potgieter, 1971; Vahrmeijer, 1981). The absence of diarrhoea in all 5 sheep supports the statement by Naudé & Potgieter (1971) that, unlike other cardiac glycoside-containing plants, *H. glauca* does not induce diarrhoea. The cardiac arrhythmias resulting from plant-related cardiac glycoside poisoning, described earlier by Pretorius, Van der Walt, Kruger & Naudé (1969) and by Schultz, Naudé & Pretorius (1975), were similar to the arrhythmias found in the present study. Ventricular fibrillation was the terminal lethal event in the 3 sheep that were being recorded at the moment of death. It seems likely that ventricular fibrillation is the usual cause of death in such animals poisoned by cardiac glycoside-containing plants. This statement is supported by the fact, generally recognized by farmers and veterinarians, that the stress experienced by such animals when they are being treated frequently precipitates their sudden death. It is probable that the sudden deaths referred to above were also the result of ventricular fibrillation.

Cardiac arrhythmias, including ventricular fibrillation, can be explained by the inherent arrhythmogenicity of cardiac glycosides, exacerbated by such influences as hypoxaemia, acidosis and hyperkalaemia. It is likely too that plasma catecholamines are elevated in advanced intoxication. Indirect evidence for this in the present trial was the tachycardia, elevated systolic blood pressure, and hyperglycaemia recorded. Catecholamines are well known for their arrhythmogenicity. Protection from lethal ventricular fibrillation with antiarrhythmic drugs or β adrenergic blockers might well prolong the lives of intoxicated animals long enough to enable slower-acting antidotes such as activated charcoal to take effect. The possible role of catecholamines and the potential role of antiarrhythmics in treatment obviously warrant more study.

The rise in systolic blood pressure in this trial was probably the combined effect of tachycardia, positive inotropism by the bufadienolide toxin and peripheral vasoconstriction. As was mentioned earlier, a strong suspicion exists that catecholamines are released during intoxication. The α adrenergic effects of adrenaline and nor adrenaline would result in viscerocutaneous vasoconstriction. The β_2 effects of adrenaline open blood vessels in skeletal muscle and this could be the reason why mean and diastolic arterial pressures did not rise as high as systolic pressures. The early drop in central venous pressure was probably the result of hyperkinetic circulation, and the subsequent rise the result of a failing circulation.

Both the hypoxaemia and the hypercarbia noted indicate pulmonary dysfunction. Lung oedema is a well-recognized necropsy finding in animals dying of plant-related cardiac glycoside intoxication (Naudé & Potgieter, 1971). The acidosis noted was primarily metabolic and was presumably the result of hypoxaemia and tissue hypoperfusion with lactic acid generation. The question of whether the lung oedema is secondary to cardiac failure or is due to primary pulmonary endothelial damage should be posed at this stage. The fact that there was severe pulmonary dysfunction with only mild rises in central venous pressure indicates a primary pulmonary vascular lesion. Haemoconcentration as evidenced by rises in formed blood elements and in total plasma proteins is likely to be the result of a shift in fluid from the intravascular compartment to extravascular tissues. This too may be a sign of a diffuse increase in vascular permeability.

The marked rises in serum potassium and the milder decrease of serum sodium are most likely the results of inhibition of the membrane Na:K pump which is powered by ATP, and of acidaemia. Cardiac glycosides bind to and inhibit membrane Na:K ATP-ase, so reducing the amount of ATP available to power the pump (Smith & Willerson, 1971). The result is that less potassium is pumped back into the cell and less sodium is pumped out, with a corresponding increase in extracellular potassium and decrease in sodium.

Hyperkalaemia is a well-known finding in severe digitalis poisoning in man, e.g. attempts at suicide (Smith & Willerson, 1971; Smith & Haber, 1973). Inasmuch as animals frequently ingest lethal quantities of cardiac glycoside-containing plants, animal poisoning should perhaps be equated with suicidal ingestion of cardiac glycosides in man. The distinction between mild (therapeutic) digitalis intoxication and massive (suicidal, animal) intoxication is important inasmuch as potassium supplementation is advocated in the former and contraindicated in the latter (Smith & Willerson, 1971). Treatment of animals poisoned by cardiac glycoside-containing plants, with oral potassium chloride and activated charcoal, has recently been advocated (Joubert & Schultz, 1982). Whether the success achieved in this trial should be ascribed to the use of activated charcoal, potassium chloride or the mixture of both cannot be determined from the available literature. The results of the present study indicate that if potassium salts are to be used in cardiac glycoside poisoning of animals, it would be advisable to monitor serum potassium. Certainly intravenous administration of potassium salts to an already hyperkalaemic animal will hasten or precipitate death.

The mild rises undergone by both serum calcium and magnesium are not likely to have affected the animals adversely. Inasmuch as hypercalcaemia and hypomagnesaemia exacerbate digitalis intoxication (Seller, Cangiano, Kim, Mendelssohn, Brest & Swartz, 1970; Hoffman & Bigger, 1980), the rise in magnesium could be considered beneficial and the slight rise in calcium potentially deleterious.

The decrease in serum chloride and depletion of plasma bicarbonate indicate in widening of the anion gap*. The mean control anion gap was 17,4 mmol/ℓ and the mean gap at death was 34,8 mmol/ℓ. An increased anion gap indicates the presence of anions other than chloride or bicarbonate. The unmeasured anion in the present study was likely to have been lactate generated as a result of tissue hypoxaemia and anaerobic metabolism. The initial minor decline and later slight rise in plasma inorganic phosphate were unlikely to have affected the sheep adversely.

The marked rise in plasma glucose is indicative of the severe stress to which the animals were subjected and is probably the result of the release of both catecholamines and cortisol. The marked rise in serum creatinine indicates renal dysfunction with a decline in glomerular filtration rate. This in turn can probably be linked to autonomically mediated renal vasoconstriction.

The progressive rise of LD and αHBD indicates widespread tissue damage. The fact that αHBD (equivalent to iso-enzymes I and II of LD and found most abundantly in the kidney and myocardium) (Schmidt, 1979) rose in parallel with LD indicates that damage to kidney and/or myocardium was of the same order as in other tissues of the body. The fact that CK rose only slightly also indicates that there was no great damage to cardiac or skeletal muscle.

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* The anion gap = serum $(Na^+ + K^+) - (C\ell^- + HCO_3^-)$

The minor rises in GGT, GLD and SD all indicate a degree of acute liver damage (Schmidt, 1979), possibly the result of hypoxaemia.

CONCLUSIONS

At or near the time of death from *H. glauca* intoxication, sheep suffer ventricular tachycardia, arterial hypertension, hypoxaemia, hypercarbia, acidaemia, hypochloraemia and hyperkalaemia. They are also hyperglycaemic and have raised serum creatinine concentrations. Serum enzyme concentrations suggest that there is liver damage, and damage to other tissues. In short, the *H. glauca* toxin results in deranged function of the cardiovascular system, lungs, kidneys and liver.

The immediate cause of death is ventricular fibrillation which is the result of inherent arrhythmogenicity of the bufadienolide in *H. glauca*, exacerbated by hypoxaemia, hypercarbia, acidaemia, hyperkalaemia and probably also by increased plasma catecholamines.

It may be hazardous to administer potassium salts to animals poisoned by cardiac glycoside-containing plants unless those animals are first shown to be normo- or hypokalaemic. Anti-arrhythmic agents, oxygen parenteral fluids and systemic alkalinizers might help prolong the lives of affected animals so that slower acting antidotes such as activated charcoal may be given a chance to work.

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