Treatment of heartwater: potential adverse effects of furosemide administration on certain homeostatic parameters in normal sheep

A S Shakespeare[a], F Reyers[a], S R van Amstel[a], G E Swan[b] and J S van den Berg[a]

ABSTRACT

Diuretics, in particular furosemide, are generally recommended as a supportive treatment in the advanced stages of heartwater in ruminants. However, after what appeared to be possible adverse effects accompanying its use in field cases of heartwater, the effects of this drug on certain blood and urine parameters were investigated in normal sheep at the same dose rates. Diuresis with concomitant natriuresis was significant after furosemide administration, as was the expected plasma volume decrease. Other significant changes included metabolic alkalosis, hypokalaemia and reduced blood ionised calcium. The difference in duration of the diuretic effect and the duration of the changes in blood parameters from *c.* 3 h and *c.* 6 h respectively make it difficult to determine a time interval between successive treatments with furosemide. It appears that the probable cause of death of sheep with heartwater is a drastic reduction in blood volume and decreased cardiac output that leads to general circulatory failure. A therapeutic approach that involves further loss of plasma volume due to diuresis appears contradictory. The added effects of potentiating respiratory alkalosis and the terminal drop in blood ionised calcium seen in heartwater-affected animals indicate that the use of furosemide in supportive treatment of this disease is not warranted.

Key words: alkalosis, diuresis, furosemide, heartwater, hypokalaemia, sheep.

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INTRODUCTION

Heartwater (cowdriosis) is a major cause of stock losses in southern Africa[2]. It is a tick-borne disease of cattle, sheep, goats and certain wild ruminants and is caused by a rickettsia, *Cowdria ruminantium*. The disease is typically characterised by high fever, mucosal petechiation, nervous signs, brain and lung oedema, hydropericardium, hydrothorax and eventual death.

Terminal stages in heartwater in sheep apparently involve a sudden drop in plasma volume (PV) following peripheral vaso-collapse[3,10]. A fall in systolic[10] and diastolic[3] blood pressure and a decrease in cardiac output[17,18] just before death may enhance vaso-collapse in the advanced stages of the disease. There is also a terminal decrease in plasma proteins (especially albumin) over and above the fluid loss, indicating that there is a relatively larger protein loss to the effused fluids[18]. The effused fluids have albumin and globulin concentrations almost as high as blood values[18], sodium levels in excess of those in serum and potassium levels far in excess of those in serum. The osmolality of the effused fluid is greater than that of plasma, and the effused fluid coagulates on exposure to air, indicating that even the very large molecule, fibrinogen, diffuses across the endothelial membranes[3,11]. The limited morphological endothelial cellular changes do not correlate with the permeability defect nor the volume of effused fluids that develop in heartwater[2,16,17,21]. Other significant changes in the disease involve an increase in blood pH (respiratory alkalosis)[2,19,23,24], hypokalaemia, decreased serum ionised calcium[22] and nephrosis of varying severity[2,11].

In the advanced stages of heartwater in sheep, especially when neurological signs and respiratory distress are evident, supportive treatment, especially in the form of diuretics, has been recommended and is commonly used in the belief that these drugs would limit or relieve the profuse oedema and effusion that was believed to drown the animal 'in it's own fluid'[1,20]. On account of the ease of administration, furosemide has been the preferred diuretic, at a dose rate extrapolated from small animal medicine, between 2.5 to 10 mg/kg body mass (BM) at 6 hourly intervals[1,5,20].

Furosemide has been reported to decrease plasma volume (PV) by dehydration[4,14], increase blood pH (metabolic alkalosis)[24], and cause hypokalaemia[8,9,24], hyponatraemia, hypochloraemia[8] and a decrease in serum ionised calcium[8,14].

Sodium, chloride and potassium normally pass down an electrochemical gradient from the renal tubular fluid into the tubule cell[24]. An ATP-dependent sodium pump (Na^+, K^+-ATPase), located at the basolateral border of the cell, maintains a favourable sodium electrochemical gradient across the luminal membrane[24]. Sodium moves across the basolateral membrane via this active pump, whereas chloride is believed to move passively from the cell into the peritubular interstitium, possibly coupled in part to potassium[24]. Furosemide has been shown to inhibit the Na^+-Cl-K co-transport process in the luminal membrane. Sodium and chloride reabsorption is therefore prevented and thus resorption of other eletrolytes such as potassium, calcium and magnesium, in particular, but possibly also hydrogen, ammonium, bicarbonate and phosphate is inhibited[14,24]. The generation and maintenance of a hypertonic renal interstitium is therefore compromised and the gradient for passive water movement from the descending limb of the loop of Henle and the medullary collecting duct is removed[24]. Free water clearance and the ability to maximally concentrate urine are markedly decreased[24].

The possibility therefore exists that the use of furosemide in the treatment of heartwater may exacerbate the pathophysiological alterations found in the advanced stages of the disease and may even contribute to the demise of the animal. Experience with and without the use of this drug in similar field cases of

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heartwater suggested that the use of furosemide actually hastens the death of the animal.

English *et al.*[5] compared oral and intravenous administration of furosemide at 1 mg/kg BM and 0.5 mg/kg BM, respectively, given once a day for 5 days in normal sheep, and, although slight diuresis was noted, no other side-effects or changes were reported. The dose rate in this trial was chosen at 5 mg/kg BM, firstly to enhance any potential side-effects that may occur; secondly, the figure is half the recommended maximum value used in small animals, and thirdly, significant diuresis is needed since this is the main objective for the use of this drug[5].

The objective of this trial was to establish whether furosemide administered to healthy sheep at the dose regimens recommended for the treatment of heartwater caused dehydration, diuresis, change in blood pH, natriuresis, kaliuresis and calciuresis as reported in other species, and to establish to what degree these occurred.

MATERIALS AND METHODS

Seven 3-year-old Mutton Merino wethers of approximately equal mass were used in this study. A 2×2 cross-over design was used with a wash-out period of 6 days between treatments. A parallel control group of 2 sheep was used. The animals were randomly allocated to individual metabolic crates in a controlled environment room. According to the crate numbers, 3 groups of sheep were formed receiving 5 mg/kg BM of furosemide (Lasix7, Hoechst Ag-Vet) (Group 1, $n = 3$) intravenously once, or 5 mg/kg BM of furosemide (Group 2, $n = 2$) intravenously twice with a 6-h interval between the 2 treatments, or no treatment (Group 3, $n = 2$). Phase 2 of the experimental design occurred 6 days later, with treatment protocols for Groups 1 and 2 exchanged. Throughout the trial, fresh, clean water was on offer to each sheep *ad libitum*.

Venous blood and urine samples were collected from each sheep at $-24, -\frac{1}{4}, \frac{1}{4}, \frac{1}{2}$, 1, 2, 4, 6, $6\frac{1}{4}$, 7, 8, 10, 11, 16 and 24 h. Total urine was collected and recorded from a separate container below each metabolic crate where a sieve mechanism separated the urine from the faeces. Blood was drawn into evacuated lithium heparin tubes (Radem Laboratories, South Africa), a sample of which was used to determine haematocrit (Jouan Haema-C micro-haematocrit centrifuge, SA Scientific). The remainder was centrifuged at 3200 rpm for 10 min and the plasma used to measure total serum proteins,
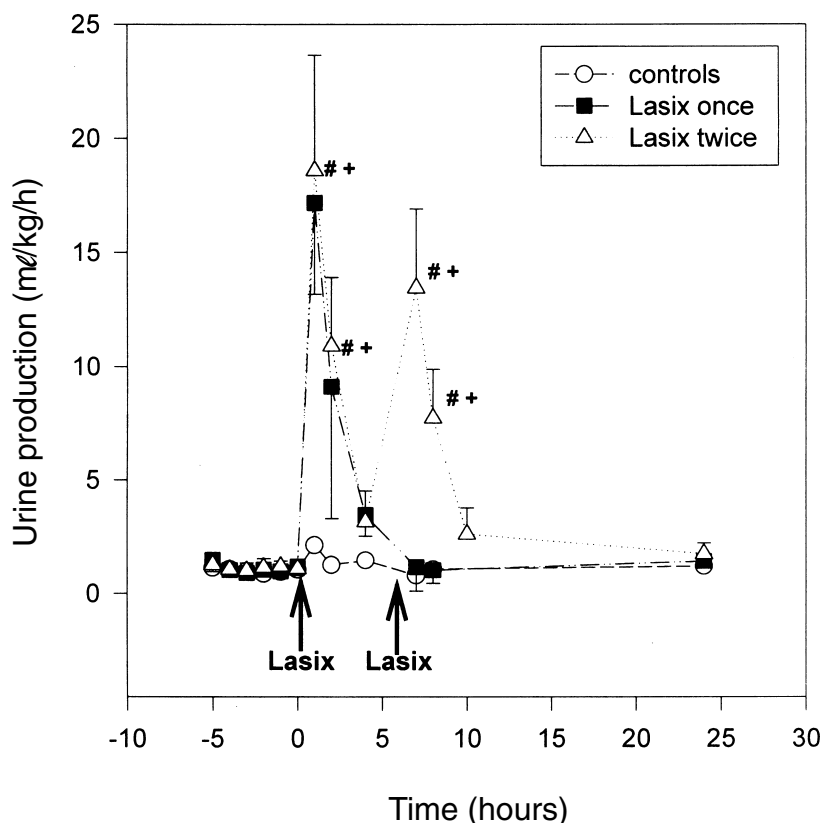
osmolality, sodium, potassium, ionised calcium and creatinine. A 2nd blood sample was drawn into a heparinised 2 mℓ syringe and evaluated for blood gas, bicarbonate and pH on an Acid-base Laboratory analyser ABL3 3 (Radiometer, Copenhagen). Urine samples were analysed for specific gravity, osmolality, sodium, potassium and creatinine.

Creatinine and total protein were determined on a Technicon RA 1000 system (Technicon Instruments Corporation, USA), sodium and potassium on a Nova 1 ion-selective electrode analyser (Nova Biochemical, USA) and ionised calcium on a Nova 8 analyser. Osmolality was determined on a freezing point depression osmometer (Osmometer 800 c 1, SLAMED, Medical Electronic Distributors, South Africa).

Urine production was calculated as the average urine produced over a fixed period (*i.e.* 1 h), per kg BM for all sheep in a specific group. Percentage plasma volume change (% ΔPV) was calculated as follows[6] :

$$\%\Delta PV = \left(\frac{TSP_a}{TSP_0} - 1 \right) \times 100$$

where TSP_a = total serum protein at time 'a' h and TSP_0 = total serum protein at time '0' h and fractional excretion of a

substance $y_{(FEy)}$ was expressed as a percentage without units as follows:

$$FEy = \frac{Uy/Sy}{Ucr/Scr} \times 100$$

where Uy = concentration of substance y in urine (mmol/ℓ), Sy = concentration of substance y in serum (mmol/ℓ), Ucr = concentration of creatinine in urine (mmol/ℓ), and Scr = concentration of creatinine in serum (mmol/ℓ).

Statistical evaluation of the data was performed on an interlinked commercial statistical software package (Sigmastat, Jandel Scientific Software, USA). The data were tested for normality and equal variance by the Kolmogov-Smirnov and Levene's median tests respectively. In order to compare groups of data in the same treatment groups at different stages, the Friedman 1-way repeated measures analysis of variance was used. To isolate the group or groups that differed from the others, a Bonferroni or Dunn's multiple-comparison procedure, comparing all groups against a control group (at $t = 0$ h) was applied. Significance was set at $p < 0.05$.

RESULTS

Urine production as calculated in mℓ/kg BM/h is presented graphically in Fig. 1.

Fig. 1: **Urine production** (mℓ/kg BM/h) **fluctuations with the use of furosemide** (Lasix) **at 5 mg/kg BM intravenously in normal sheep** (# = significantly different ($p < 0.05$) from t = 0 h within each group; + = significantly different ($p < 0.05$) from the control sheep at comparable times).

Table 1: Percentage urine of water intake (09:00 – 17:00) **in the 2 groups of sheep treated with furosemide and the control sheep.**

Pen number	1st treatment day			2nd treatment day		
	Urine volume (ml)	Water intake (ml)	% Urine	Urine volume (ml)	Water intake (ml)	% Urine
1 Group 1	2065	1483	139	3337	1900	176
2 Group 1	1332	1317	101	2445	1767	138
3 Group 1	1462	1983	74	2682	1917	140
4 Group 2	2545	1550	164	2079	1700	122
5 Group 2	2058	1183	174	1714	1350	127
6 Control	687	1283	54	613	1383	44
7 Control	514	1200	43	394	1167	34

Administration of furosemide to sheep significantly increased urine production for up to 4 h after each treatment. Within the 1st 6 h after furosemide administration, the sheep produced an average of 6.07 ml/kg BM/h of urine, (controls 1.23 ml/kg BM/h), the difference being highly significant. For the 6 h following the 2nd dose of furosemide, the sheep produced significantly less urine (4.61 ml/kg BM/h). This rate of urine production was still significantly higher than the controls. Urine volume as a percentage of free-water intake on the experimental days (Table 1) was 43.75, 112.6 and 158.4 % for the control sheep, those sheep given furosemide once, and those treated twice respectively.

Changes in haematocrit and total serum proteins (TSP) are shown in Table 2, with only TSP evincing significant changes after each furosemide treatment. Percentage plasma volume change revealed distinct troughs with drops of –8.86 and –11.47 % between 1 and 2 h after the respective furosemide treatments. The 2nd decrease was greater and of longer duration than the 1st.

Venous blood pH became significantly more alkaline (Fig. 2) with each furosemide treatment. This alkalosis was metabolic in nature as seen by the blood bicarbonate values (Fig. 3). The blood pH and bicarbonate were raised for longer with the 2nd treatment.

Serum sodium decreased in all 3 groups of sheep with small but significant changes (Fig. 4). Recovery to normal was slow, with the control group showing what appeared to be a slight rebound to greater than normal values at 10 h after initiation of treatment compared to the other sheep. In the group of sheep that was treated twice, serum sodium was maintained at a low level that was significantly different from the other groups between 11 and 16 h after the initial treatment at 0 h.

Serum potassium (Fig. 5) showed more definite and significant troughs after each
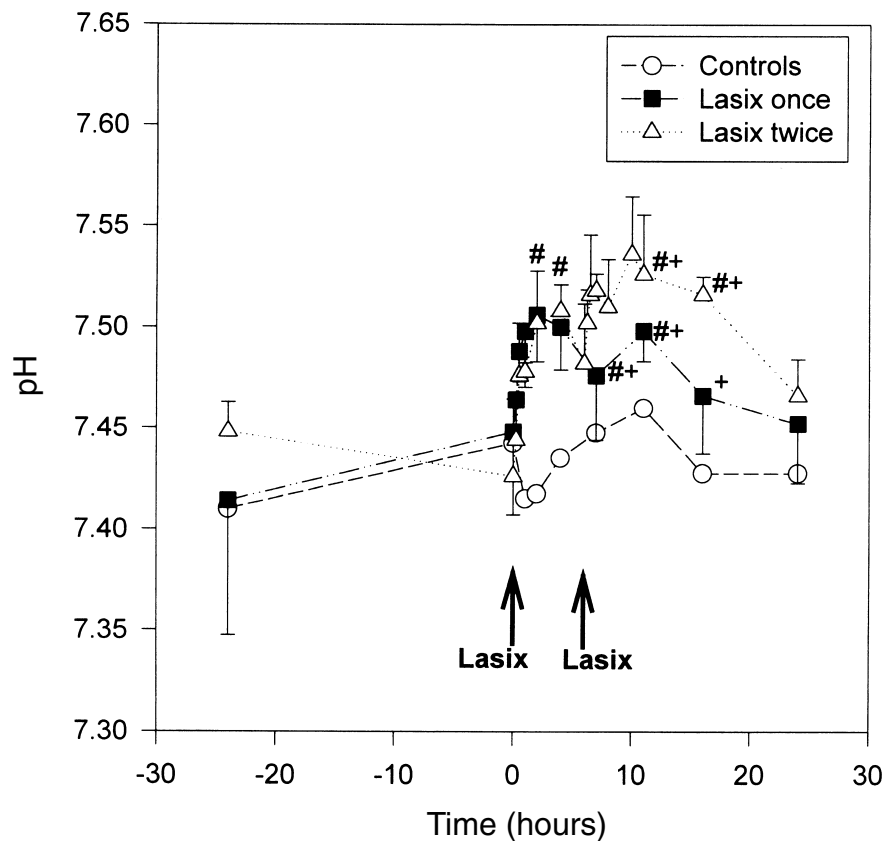

Fig. 2: **Venous blood pH fluctuations with the use of furosemide** (Lasix) **at 5 mg/kg in normal sheep** (# = significantly different ($p < 0.05$) from t = 0 h within each group; + = significantly different ($p < 0.05$) from the control sheep at comparable times).

treatment, with the 2nd dose of furosemide enhancing and extending hypokalaemia, whereas serum ionised calcium, although decreasing, did not differ significantly from the control values.

Urine specific gravity (Fig. 6) and urine osmolality (Fig. 7) confirmed significant urine dilution following each furosemide treatment. The control sheep also showed an increase in urine dilution following the initial furosemide treatment of the other sheep but not after the 2nd treatment. Percentage osmolality creatinine clearance ratios (Fig. 8) within 1 h of each furosemide administration were both striking and significant.

Natriuresis was significant (Fig. 9) after each furosemide treatment, whereas kaliuresis (Fig. 10), although exhibiting similar but smaller peaks, was only significant after the 2nd treatment.

DISCUSSION

Diuresis

The results clearly demonstrate that the diuretic response in sheep to intravenous furosemide at 5 mg/kg BM is very large, almost instantaneous, peaking within 1 h of administration and with a duration of between 2 and 3 h. A second, similar dose of furosemide, given 6 h after the first,

Table 2: Mean haematocrit and total serum protein variations in 2 groups of sheep treated with furosemide and the control group.

t (h) from initial treatment	Haematocrit (%)			Total serum proteins (g/ℓ)			Mean percentage plasma volume change		
	Controls	Furosemide once	Furosemide twice	Controls	Furosemide once	Furosemide twice	Controls	Furosemide once	Furosemide twice
–24 h	30.6	32.5	31.2	62.4	68.8	66.6	–4.77	–4.22	–3.57
0	30.8	31.7	31.8	59.4	65.9	64.2	0	0	0
¼		29.7	30.9		68.0	65.4	—	–2.95	–1.74
½		32.5	30.8		69.2	66.4	—	–4.85	–3.31
1	30.5	31.2	31.7	60.5	69.3	68.7	–1.77	–4.99	–6.52
2	30.4	32.7	30.2	61.5	72.9*	69.9*	–3.45	–9.68	–8.04
4	31.1	32.1	31.7	61.0	70.0	67.9	–0.26	–5.9	–5.39
6			33.0			66.7	—	—	–3.75
6¼			32.5			68.0	—	—	–5.58
6½						63.0	—	—	–7.74
7	29.5	32.6	33.9	59.3	64.9	72.6*+	+0.08	+1.51	–11.47
8			35.0*			70.8*+	—	—	–9.21
10			33.6			69.0+	—	—	–6.87
11	29.8	31.4	33.6	57.5	65.7	68.9+	+4.16	+0.34	–6.79
16	31.5	32.8	33.6	59.1	65.0	65.5	+0.59	+1.35	–1.98
24	21.1	31.7	30.3	60.4	64.9	65.3	–1.66	+1.54	–1.62

* = significantly different ($p < 0.05$) from t = 0 within each group of sheep.
+ = significantly different ($p < 0.05$) from the control group of sheep at the identical time.

also elicits a strong diuretic response, but with a slightly diminished peak from *c.* 17 mℓ/kg BM/h to *c.* 14 mℓ/kg BM/h. This slight reduction in the diuretic response could be due to tolerance to the drug but it is more likely that the dehydration caused by the 1st furosemide administration left reduced body water reserves to respond to the 2nd furosemide injection.

The slight increase in urine voided by the control group of sheep during the 2 experimental days from a normal 1.01 mℓ/kg BM/h to 1.23 mℓ/kg BM/h is probably because sheep do 'follow like sheep', and when the other groups of sheep urinated and drank water, so too did the watching controls. This was confirmed by observation by the investigators during the experimental days.

Urine production other than during the 2 experimental days of the trial was constant at *c.* 1.08 mℓ/kg BM/h for all the sheep, which compares well with published reference ranges[15].

Hydration

Assessment of hydration status using haematocrit (Ht) was unsatisfactory. Peripheral pooling of red blood cells or splenic sequestration of these red cells could have dampened the effective haematocrit changes.

Total serum protein values (TSP), on the other hand, demonstrated significant shifts in hydration status after each furosemide administration, with dehydration being greater and lasting longer after the 2nd dose. Percentage plasma volume change (%ΔPV), being a mathematical manipulation of TSP, produced
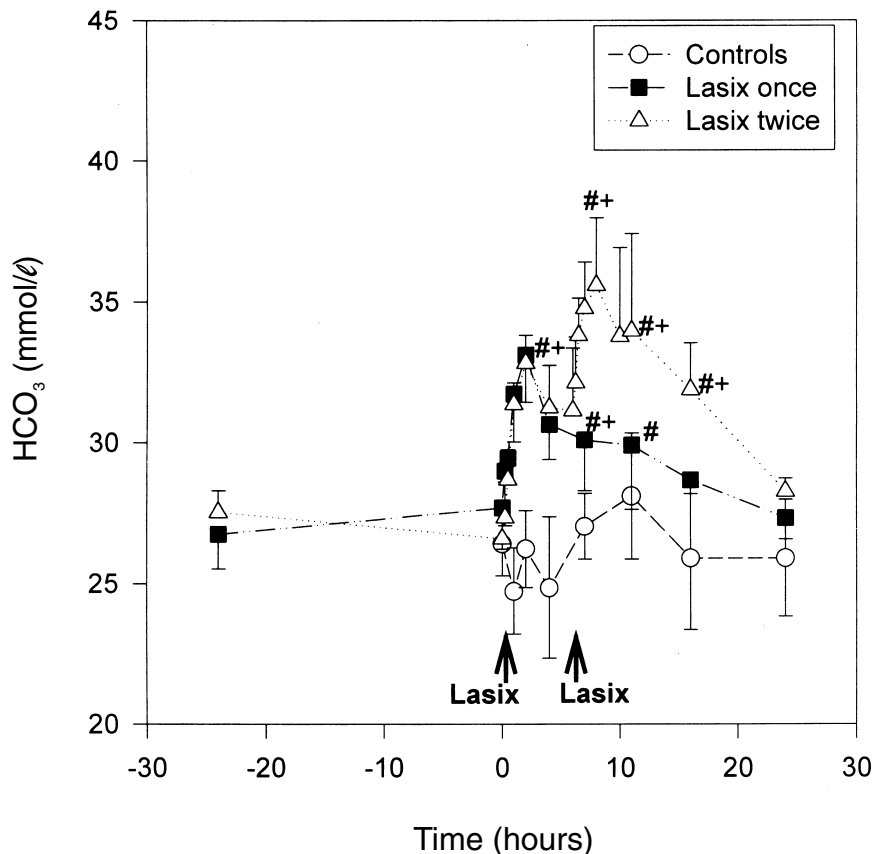

Fig. 3: Venous blood bicarbonate fluctuations with the use of furosemide (Lasix) **at 5 mg/kg in normal sheep.** (# = significantly different ($p < 0.05$) from t = 0 h within each group; + = significantly different ($p < 0.05$) from the control sheep at comparable times).

similar yet inverted results. The 2nd trough showed a percentage plasma volume drop of close to 12 %. This confirms the effectiveness of furosemide as a diuretic in sheep.

The control sheep, while mimicking the others and producing increased amounts

of urine exhibited, according to TSP and %ΔPV, mild but non-significant dehydration after the initial furosemide treatment of their treatment peers. However, after the 2nd furosemide administration, the control sheep showed a reversed trend with an increased or

positive hydration status. The initial increase in urine production by the controls possibly exhausted fluid reserves (including bladder urine retention) and with the continued stimulus to drink water by imitating the other sheep, a temporary period of increased hydration could have resulted.

It is not uncommon to find total body water losses anywhere between 6 and 12 % in sick animals[7]. Unfortunately, water losses are not evenly distributed throughout all the body compartments. The greatest loss is from the extracellular fluid (ECF) with the plasma volume (PV) being the most severely depleted[7]. With total body water losses of around 6 %, ECF losses range around 35 % with plasma loss in the 40 % range[7]. Such severe losses of blood volume will cause peripheral vasoconstriction and result in hypovolaemic shock. Van Amstel *et al.* in 1988 and 1994 recorded terminal percentage plasma volume losses of 25 % in sheep and 18 % in calves with heartwater[21,23]. If the 12 % plasma loss caused by the 2 furosemide treatments in normal sheep is transposed to sheep suffering from heartwater, the dehydration status can only be made worse and hasten the vascular collapse that plays a role in the death of these animals. In marked contrast to the large losses in ECF with total body water decrease, the intracellular water pool is only slightly altered and may even increase in volume by up to 9 %[7,12]. The measured increase in total muscle water content with severe dehydration in calves[7] support this. Movement of fluids into the cells at the expense of the ECF volume and against the increased extracellular osmotic pressures is of negative survival value and is due in part to decreased cellular metabolism causing alterations in energy charge and ion transport, increased intracellular osmolality and subsequent cellular swelling[7].

In sheep affected with heartwater, a fall in intravascular protein levels occurs owing to losses into other compartments that would dampen any TSP rise due to dehydration and subsequently cause %ΔPV determinations to be of no value in determining the hydration status of the sick sheep.

Blood parameters

Metabolic alkalosis resulting from repeated furosemide administration in normal sheep cannot bode well for the use of the drug in sheep with heartwater, which already have respiratory alkalosis[2,19,23,24].

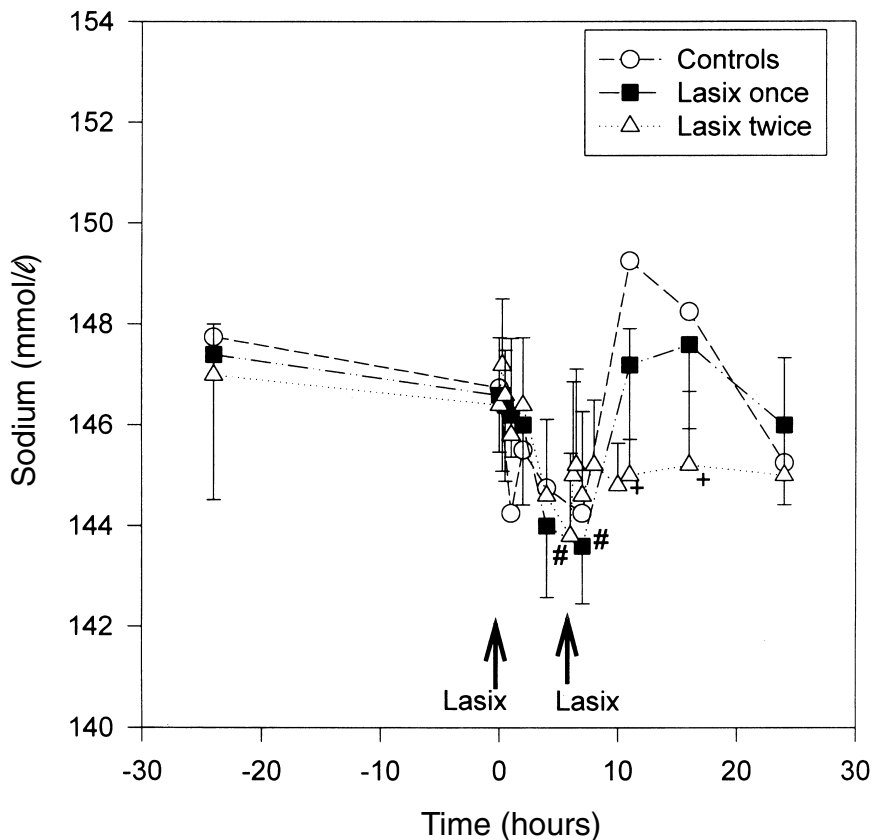The decrease in serum ionised calcium, although not significant, was expected, since both metabolic alkalosis and the

Fig. 4: **Serum sodium variation with the use of furosemide** (Lasix) **at 5 mg/kg in normal sheep** (# = significantly different ($p < 0.05$) from t = 0 h within each group; + = significantly different ($p < 0.05$) from the control sheep at comparable times).
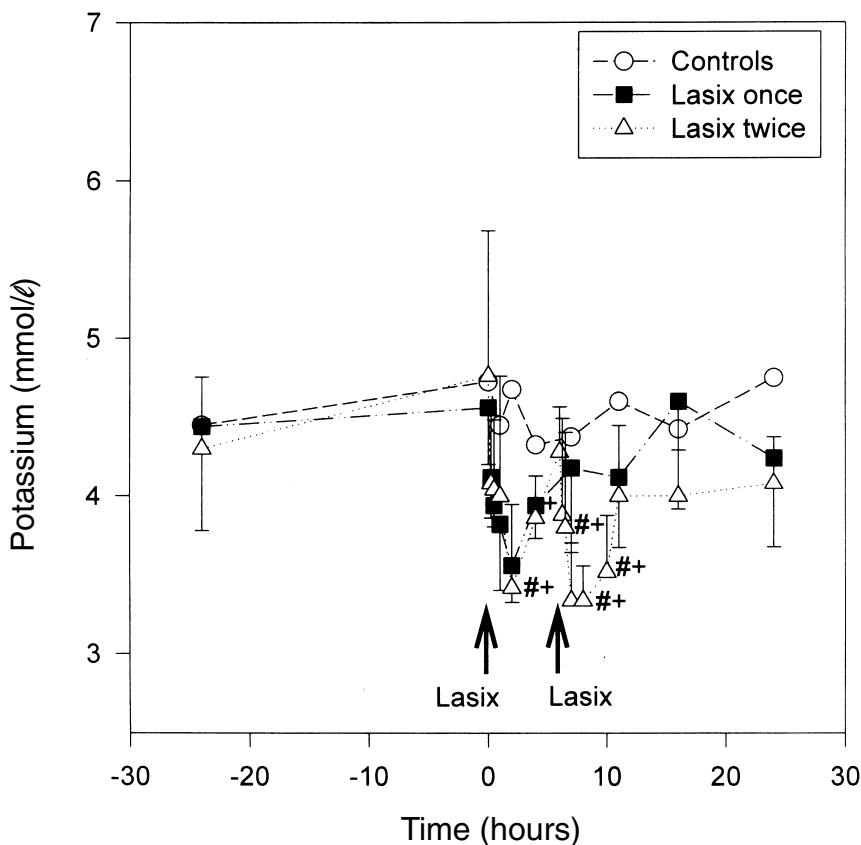

Fig. 5: **Serum potassium variation with the use of furosemide** (Lasix) **at 5 mg/kg in normal sheep** (# = significantly different ($p < 0.05$) from t = 0 h within each group; + = significantly different ($p < 0.05$) from the control sheep at comparable times).

increase in total serum proteins as a result of the furosemide will result in more serum calcium being bound to albumin. By adding this decrease to the drastic fall in ionised calcium to 70 % of pre-infection levels in heartwater-infected sheep[22], the use of furosemide in the treatment of the disease will probably hasten death.

The increase in blood pH will decrease serum potassium levels by driving potassium intracellularly. In addition to this, the increased loss of the electrolyte in the urine owing to the diuretic action of furosemide, plus the decreased intake of potassium owing to anorexia experienced in diseased states, will potentiate any existing hypokalaemia seen in heartwater cases and will further complicate the cardiac problems that occur in these patients[3].

Hyponatraemia recorded in the treated sheep is due to the strong natriuresis that resulted from furosemide administration. The control sheep exhibited no natiuresis and their mild decrease in serum sodium is possibly due to the positive hydration status they experienced. The rebound in serum sodium levels in the control sheep, although not significant, is possibly due to the body making use of the most prolific vascular ion and the ion most easily regulated in ruminants to quickly try and re-establish normal osmotic and electro-gradient potentials.

Urine parameters

Very dilute urine was produced by the administration of furosemide to normal sheep, with specific gravity measurements often dropping below 1.010. The dilute urine took over 5 h to recover to normal SG values, in stark contrast to the 2–3 h taken for urine production to normalise. This slower return could possibly be due to 2 principal effects:
i)   total body water was easily corrected via an easily accessible water source, whereas electrolyte replacement depends on a slower mechanism such as ion exchange and diet and/or
ii) a mild 'wash-out' effect could have occurred, owing to the natriuresis, in the renal medulla, where ion retention may be less easily regulated than ADH water control.

Percentage creatinine clearance ratios indicated that there was the expected marked natriuresis and milder kaliuresis. The lack of significant potassium loss via the kidney was surprising since it is reported that short-term, high-dose furosemide causes increased potassium excretion. The second dose of furosemide did increase urinary potassium loss that could be exacerbated by additional furosemide use.
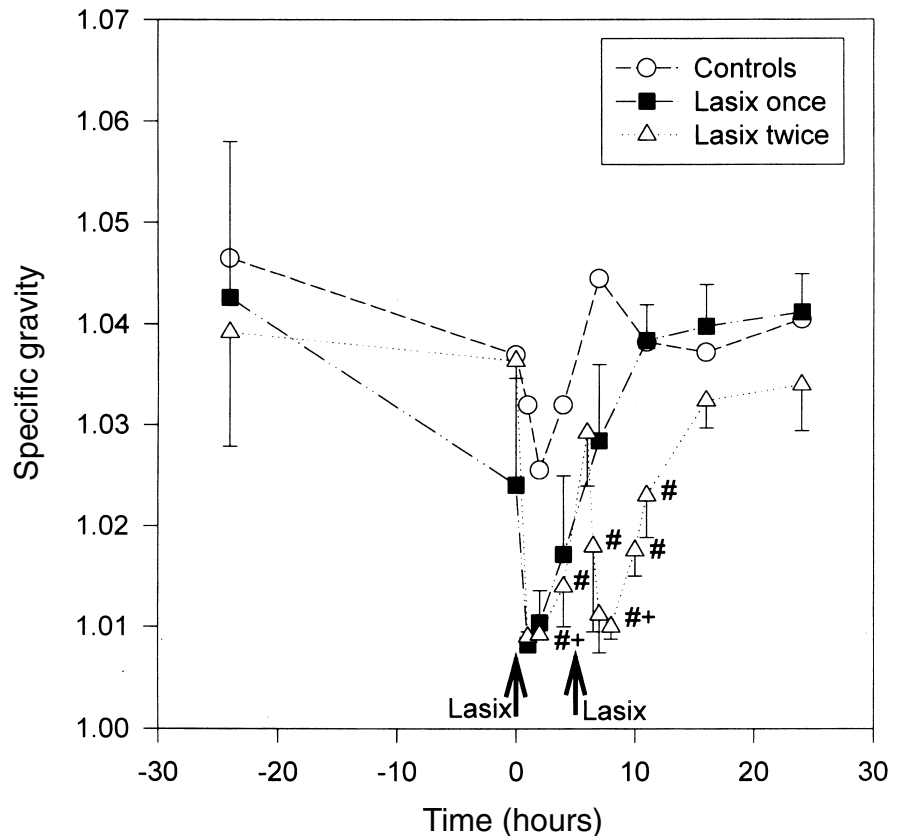

Fig. 6: **Urine specific gravity variation with the use of furosemide** (Lasix) **at 5 mg/kg in normal sheep** (# = significantly different ($p < 0.05$) from t = 0 h within each group; + = significantly different ($p < 0.05$) from the control sheep at comparable times).
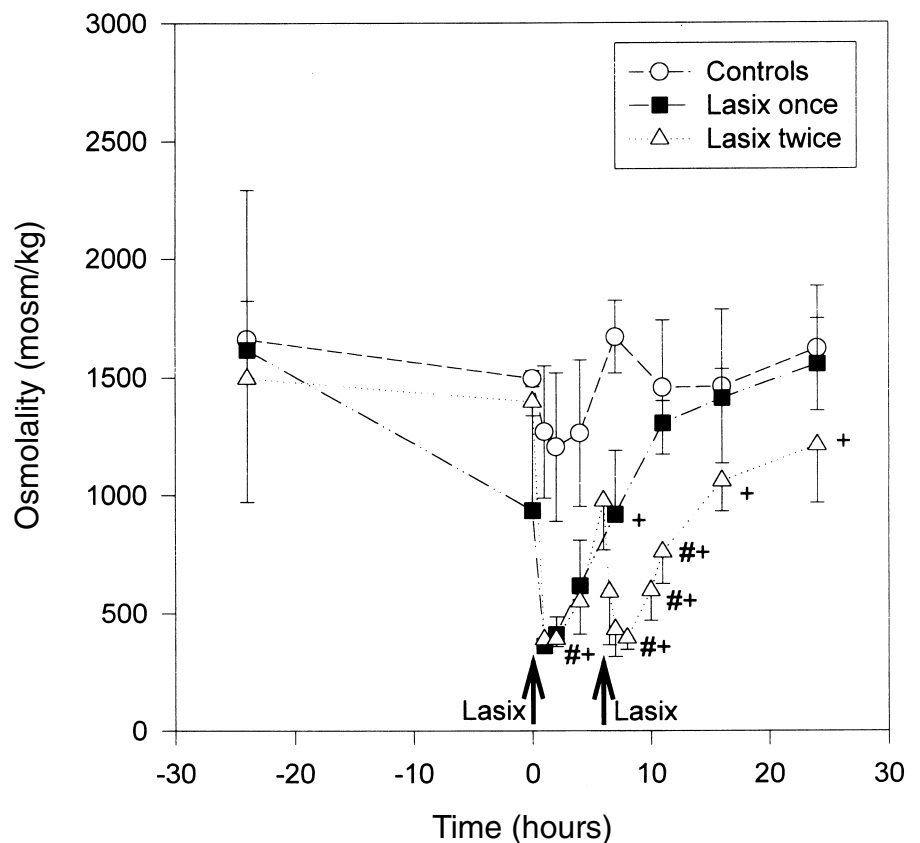

Fig. 7: **Urine osmolality variation with the use of furosemide** (Lasix) **at 5 mg/kg in normal sheep** (# = significantly different ($p < 0.05$) from t = 0 h within each group; + = significantly different ($p < 0.05$) from the control sheep at comparable times).

CONCLUSIONS

Diuresis in normal sheep is readily accomplished with furosemide given intravenously at the dose generally used to treat heartwater cases, and the duration of the diuretic effect is sustained for *c.* 3 h. To maintain a sustained diuretic effect, the interval between successive administrations of furosemide would have to be reduced to 2–3 h. However, changes in blood and urine parameters with furosemide treatment extend for *c.* 6 h and beyond, so a reduction in the interval between treatments could potentiate and enhance these changes and could become detrimental to the sick animal.

The relatively high protein and electrolyte content of the effused fluid in advanced cases of heartwater will encourage fluid withdrawal from the vascular compartment, which leads to blood volume reduction, loss of blood pressure and eventually circulatory failure that causes the death of the animal[17]. Diuresis in these advanced cases of the disease, although probably severely dampened by the already reduced vascular volume, is certainly detrimental and even contra-indicated. The diuresis arguably reduced the intravascular fluid component, thereby increasing the intravascular osmotic effect, which should draw the fluid portion of the effused fluids back into circulation and thereby decrease pulmonary and brain oedema and increase blood pressure. However, if the fluid portion of the effused fluid is drawn back into the vascular compartment, the extravascular protein and electrolyte, which are already greater than the plasma values, will be further increased with a subsequent increase in osmotic pressure and the whole process will be reversed. Treatment with diuretics would be advantageous if the effused fluid in heartwater cases was mainly fluid of low oncotic pressure and low osmolality.

To make matters worse, the side-effects of furosemide administration (such as metabolic alkalosis, hypokalaemia and a decrease in serum ionised calcium levels), could potentiate these changes experienced in animals suffering from heartwater.

In the sick animal affected by heartwater, a degree of nephrosis[13] is likely, which could significantly alter the pharmacodynamics of furosemide and subsequently its effect and duration. The decreased TSP due to protein loss to the effused fluid in heartwater cases could also affect the pharmacodynamics of the drug by presentation of more unbound drug to the kidneys and the lungs.
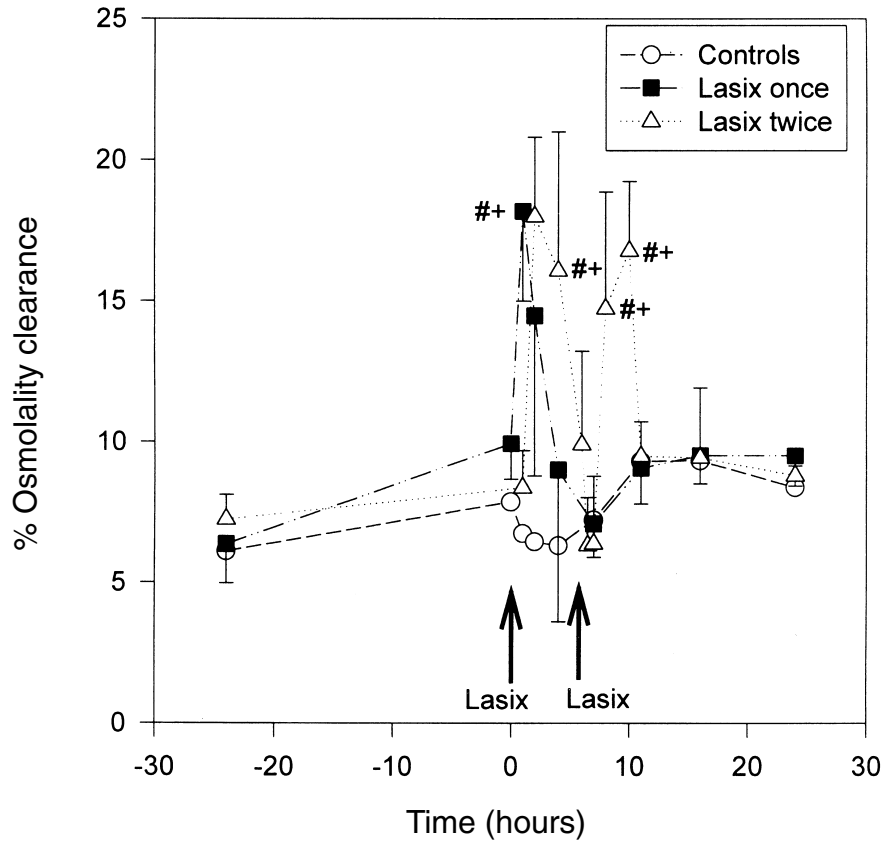

Fig. 8: **Osmolality clearance ratio variation with the use of furosemide** (Lasix) **at 5 mg/kg in normal sheep** (# = significantly different ($p < 0.05$) from t = 0 h within each group; + = significantly different ($p < 0.05$) from the control sheep at comparable times).
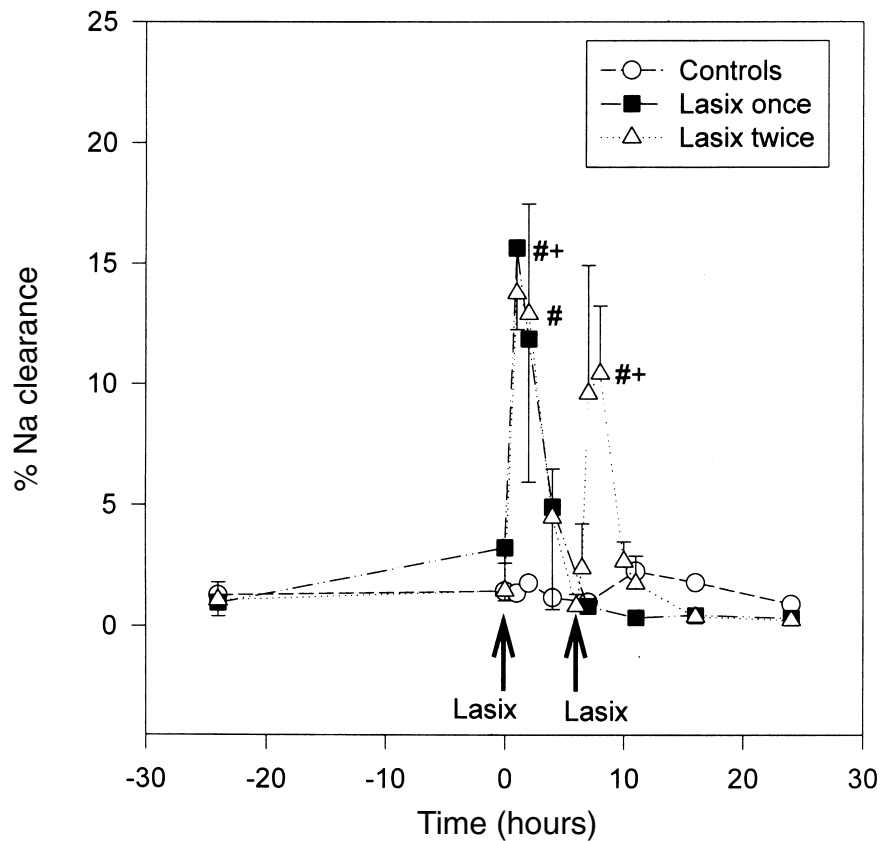

Fig. 9: **Sodium clearance ratio variation with the use of furosemide** (Lasix) **at 5 mg/kg in normal sheep** (# = significantly different ($p < 0.05$) from t = 0 h within each group; + = significantly different ($p < 0.05$) from the control sheep at comparable times).

Fig. 10: **Potassium clearance ratio variation with the use of furosemide** (Lasix) **at 5 mg/kg in normal sheep** (# = significantly different ($p < 0.05$) from t = 0 h within each group; + = significantly different ($p < 0.05$) from the control sheep at comparable times).
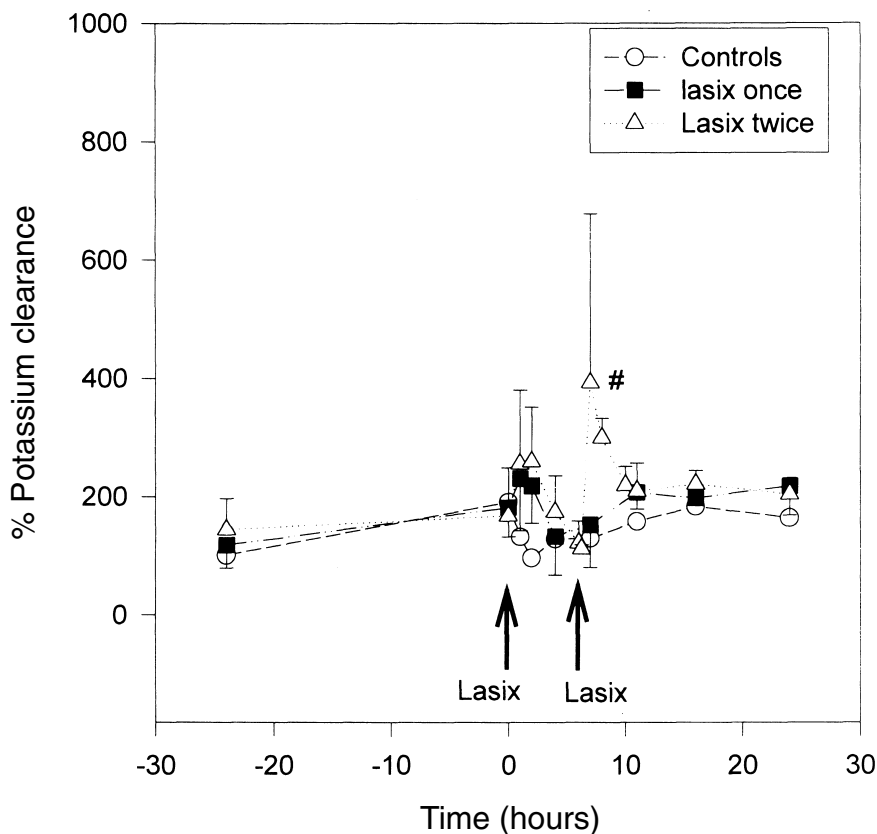
It is apparent from the above findings and the reported pathogenesis of heartwater that supportive treatment with furosemide is of no benefit and may hasten or even cause the death of the patient. The use of diuretics, in particular furosemide, to treat the oedema that develops in heartwater, is based on a misconception and lack of understanding of the pathogenesis of the disease.

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