

## THE TREATMENT OF HEARTWATER

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### ABSTRACT

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This paper reviews the available literature on the treatment of heartwater and draws comparisons with results obtained from recent work on experimentally-induced heartwater in sheep, calves and mice.

### INTRODUCTION

The successful treatment of field cases of heartwater remains a problem because of the advanced stage of the disease in which the animal is usually presented and because of ineffective supportive therapy. Such supportive therapy has been largely empirical in nature, based mainly on experience and observation, and seldom based on established pathophysiological findings.

### SPECIFIC TREATMENT

A variety of drugs has been used with varying success against *Cowdria ruminantium* both *in vitro* and *in vivo*. A classification of these agents is shown in Table 1.

#### Antiseptics—Aldehydes

##### Formalin

Alexander (1931) reported on the use of formalin given intravenously at a dose rate of 1-3 ml in cattle. He stated that at this dose rate the rickettsiae were not destroyed since subinoculation of blood from such treated cattle to sheep resulted in clinical disease. He was, however, convinced that this treatment, when used in conjunction with calcium and magnesium, had some beneficial effect on the course of the disease and that the mortality among treated animals was appreciably lower than anticipated. He advised that the formalin treatment be repeated on two consecutive days but warned that diarrhoea in treated animals should be expected.

#### Heavy metals

##### Arsenic

Ronse (1935) as cited by Neitz (1940b) reported a beneficial effect on the course of *Rickettsia prowazeki*-induced disease in guinea pigs with the use of an anti-mony-arsenical compound, Std. 386 B. As a result of this observation Neitz (1940b) used both an arsenical compound (Neosalvarsan) and Std. 386 B in sheep artificially infected with heartwater. He observed no beneficial effect but rather an enhancement of symptoms and a shortened course of the disease which resulted in death. This prompted him to conclude that both compounds stimulate the development of *Rickettsia ruminantium* and this is underscored by the fact that smear diagnosis is facilitated in animals in which these compounds were used.

#### Anaplasmodastat (antiviral)

##### Dithiosemicarbazone (gloxazone)

Du Plessis (1981) and Syngé & Scott (1976) reported on the successful use of gloxazone in the treatment of clinical cases of heartwater. Work done by Du Plessis (1981) suggests that it may sterilize the infection thus interfering with immunity. Syngé & Scott (1976) re-

TABLE 1 Classification of agents used in the specific treatment of heartwater

Group classification	Generic name
Antiseptics—Aldehydes	Formalin
Heavy metals	Arsenicals
Anaplasmodastat (antiviral)	Dithiosemicarbazone
Antibiotics:	
1. Penicillins	Procaine penicillin Ampicillin
2. Aminocyclitols	Spectinomycin
2.1 Aminoglycosides	Streptomycin Neomycin Kanamycin Gentamycin Amikacin Tobramycin Netilmycin
3. Tetracyclines	Tetracycline Chlortetracycline Oxytetracycline Doxycycline Rolitetracycline (pyrrolidinomethyltetracycline)
4. Chloramphenicol	Chloramphenicol
5. Macrolides	Tylosin
6. Polymyxins	Polymyxin E (colistin)
Antimicrobials Sulphonamides	Sulphanilamide Sulphathiazole Sulphadimidine Sulphadiazine Uleron [4-(4'-aminobenzosulfo- namide) benzol-sulfonedime- thylamide] Sulphamerazine Sulphapyridine
Potentiated sulphonamides	Trimethoprim
Biologicals	Hyperimmune serum

ported that relapses occurred in sheep treated with single doses of gloxazone and that repeated daily treatments are necessary, however, they did not comment on dose rates employed. Camus & Barré (1982), in their review on heartwater, drew attention to the fact that the toxicity of the compound prevents its general use, and it will not be developed as a product because of this.

#### Antibiotics

##### 1. Penicillins

Penicillin G was reported to be ineffective against heartwater *in vivo* by Haig (1952), and Du Plessis (unpublished data). Haig (1952) suggested that it had some effect against *Cowdria ruminantium in vitro*. Syngé & Scott (1976) and Uilenberg (1983) found ampicillin to be completely without effect in clinical cases of heartwater.

Penicillin is used in the production of the heartwater vaccines (Oberem & Bezuidenhout 1987) and in the tissue cultures of Bezuidenhout, Paterson & Barnard

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(1985) to prevent contamination without any obvious effects on the organism.

## 2. Aminocyclitols

### *Spectinomycin*

Syngé & Scott (1976) used spectinomycin in clinical cases of heartwater without any success.

### 2.1 Aminoglycosides

The use of streptomycin in clinical cases of heartwater is ineffective (Syngé & Scott, 1976). Du Plessis (1984), in an unpublished trial, tested members of the aminoglycoside group both *in vitro* and *in vivo* (in mice) with the results shown in Table 2.

TABLE 2 The efficacy of some aminoglycosides in experimentally-induced heartwater in mice

Aminoglycoside	Efficacy	
	<i>in vitro</i>	<i>in vivo</i>
Streptomycin	—	—
Neomycin	+	—
Kanamycin	+++	—

— No effect  
+ Slight effect  
+++ Moderate effect

In a recent study of experimentally-induced heartwater in sheep and mice, members of the aminoglycoside antibiotics (as indicated in Table 1) were used for the specific treatment of *Cowdria ruminantium* (Oberem, unpublished data, 1986). Results showed these antibiotics to be entirely ineffective when used alone or in combination with dimethylsulphoxide (DMSO) to try and enhance their penetration ability.

From this it would seem that the aminoglycoside group, despite having a similar mechanism of action to the tetracyclines (Sande & Mandell, 1980), are not effective *in vivo*. Several factors could be responsible for this including the dose, time of treatment and the bio-availability of the drug within the animal. The aminoglycoside antibiotics are very polar and thus not very lipid-soluble and this results in a poor penetration ability (Sande & Mandell, 1980). Agents which enhance such penetration by acting as "carriers" may play an important role in increasing the efficacy of these antibiotics. Such "carriers" include DMSO and the polymixin antibiotics (Brayton, 1985).

## 3. Tetracyclines

### *Tetracycline, chlortetracycline (aureomycin), oxytetracycline, rolitetracycline, doxycycline*

The use of tetracyclines in clinical cases of heartwater has been reported by Haig, Alexander & Weiss (1954), Karrar & El Hag Ali (1965), Poole (1961a), Weiss, Haig & Alexander (1952), Uilenberg (1983) and Immelman & Dreyer (1982). From these reports it is clear that the tetracyclines as a group are effective for the specific treatment of heartwater. However, successful therapy will depend on several factors including:

**Timing.** Used during the incubation period the subsequent course of the disease may be altered completely resulting in a complete blocking with no subsequent febrile or other clinical response, or a temporary febrile response without any symptoms developing. In sheep and goats treatment during the incubation period may result in a retarded febrile reaction as long as 20–25 days after infection. This reaction may be of such severity that treatment may be required.

When used during the early febrile stage a favourable

response can be obtained using a single, small dose. Weiss *et al.* (1952) reported the successful use of chlortetracycline (aureomycin) when employed at a dose rate of 2 mg/kg using a single injection.

During the advanced stages of heartwater larger dosages and/or multiple injections become necessary.

**Dose rate.** Dosages employed have varied from 2–40 mg/kg. Both Weiss *et al.* (1952) and Haig *et al.* (1954) concluded that the minimum therapeutic dose of tetracyclines for heartwater is 5 mg/kg given as a single dose or in divided doses over a 24 h period. Although Weiss *et al.* (1952) reported the successful use of chlortetracycline at 5 mg/kg in advanced cases, the pharmacokinetics of tetracyclines can be subjected to many changes under such conditions. For example, the drop in blood pressure observed in advanced cases may interfere with absorption from the injection site; less available binding protein in the vascular compartment may allow more "free" tetracycline which will result in a more rapid excretion; an increased capillary permeability could facilitate penetration of the blood-brain barrier resulting in higher concentrations in the central nervous system. Interpretation of effective therapeutic dose rates will also be influenced by pathophysiological changes in the body. This probably explains the variation in response to a specific dose rate seen in advanced cases. *In vitro* testing of minimum inhibitory concentrations (MIC) of tetracyclines against the various important strains of *Cowdria ruminantium* will facilitate calculation of dosage rates to be used in heartwater.

**Formulations.** These may have a significant influence on the clinical efficacy of the tetracyclines against heartwater. In two articles comparing several different formulations of tetracyclines including chlortetracycline, oxytetracycline and rolitetracycline, Poole (1961b), found that the number of treatments to effect a clinical cure for heartwater was smallest when a chlortetracycline hydrochloride suspension in oil was used. Carriers used, water solubility and tissue irritation can play important roles in the absorption and disposition of tetracyclines (Black, Claxton & Robinson, 1982). Uilenberg (1983) did not find superior results when using a long-acting oxytetracycline formulation compared to normal formulations in clinical cases of heartwater. Immelman & Dreyer (1982), used doxycycline<sup>1</sup>, a synthetic derivative of methacycline in experimentally-induced heartwater in sheep. This formulation is more lipid soluble than oxytetracycline and because of a longer serum half life, smaller therapeutic doses and longer intervals between treatments can be used (Immelman & Dreyer, 1982). In this trial, 12 sheep were given a single administration of doxycycline<sup>1</sup>, at a dose rate of 2 mg/kg, 24 h after the rectal temperature had gone up to above 40 °C. All 12 sheep recovered, the rectal temperatures remaining above 40 °C for an average of 3.2 days after the single treatment. Of the control group, 9 out of 10 animals died.

**Route of administration.** Beside the intramuscular and intravenous routes, Karrar & El Hag Ali (1965) have also shown that the use of the oral route for tetracyclines is effective in both experimental and natural cases of heartwater. Minimum therapeutic doses quoted were 400 mg/50 kg for sheep and 500 mg/200 kg for cattle given daily until recovery.

In a recent trial using oxytetracycline<sup>2</sup>, in experimentally-induced cases of heartwater in sheep, the persistence of fever was noticed despite two to three daily treatments

<sup>1</sup> Doxyvet, Samvet Laboratories

<sup>2</sup> Curamycin 123 Injectable solution (Reg. No. G 1337 Act 36/1947), Agrihold

at a dose rate of 10 mg/kg. When either phenylbutazone<sup>3</sup> or DMSO<sup>4</sup> were incorporated in the treatment neither the rate of clinical improvement nor the persistence of the temperature reaction was changed (Oberem, unpublished data, 1986).

#### 4. Chloramphenicol

Haig (1952) and Syngé & Scott (1976) reported that chloramphenicol at doses up to 40 mg/kg was ineffective in the treatment of clinical cases of heartwater. This was confirmed by Oberem (unpublished data, 1986). However numerous reports from veterinarians in South Africa suggest that a combination of chloramphenicol with tetracyclines may be superior to using tetracycline alone in the treatment of heartwater. In a recent trial on experimentally-induced heartwater in sheep and mice the combination of oxytetracycline with chloramphenicol did not seem to improve the recovery rate (Oberem unpublished data, 1986).

#### 5. Macrolides

##### Tylosin

Syngé & Scott (1976) found tylosin to be ineffective in clinical cases of heartwater.

#### 6. Polymixins

##### Polymixin E (colistin)

Du Plessis (unpublished data, 1984) found in both *in vivo* and *in vitro* trials that polymixin is ineffective against *C. ruminantium*.

The addition of polymixin to preparations of bacterial lipopolysaccharides (LPS) has been shown to drastically alter many of the *in vivo* deleterious pathophysiological effects of LPS (Morrison & Jacobs, 1976). Since it was speculated that a toxin may play a role in the pathogenesis of heartwater (Camus & Barré, 1982), polymixin E was used in the treatment of experimentally-induced heartwater in sheep and mice but was found to be completely ineffective either on its own or in combination with the aminoglycosides (Oberem, unpublished data, 1986).

#### Antimicrobials—Sulphonamides

Uleron, a short-acting sulphonamide, was the first agent to be used successfully in the specific treatment of heartwater (Neitz, 1940a). Neitz had a recovery rate of 39 out of 41 experimentally-infected sheep treated with uleron whereas 26 out of 37 untreated sheep died. He pointed out that the best results were obtained when treatment was applied during the early part of the reaction. Alexander, Neitz & Adelaar (1946) used both uleron and sulphapyradine, a medium-acting sulphonamide, in natural cases of heartwater. They also stressed the necessity of early treatment and further pointed out that early cases of the disease could easily be confused with babesiosis. They recommended that repeat injections of these sulphonamides be used every 12–24 h until improvement sets in, but that it was seldom necessary to repeat the injections more than three times.

Haig (1952) stated that the use of sulphadimidine, a medium acting sulphonamide, gave good results. Weiss *et al.* (1952) stated that a wide variety of sulphonamides, including sulphanilamide, sulphathiazole, sulphadiazine and sulphaguanidine, had been used in the treatment of heartwater but give no details. Syngé & Scott (1976) reported that a potentiated sulpha combination (trimethoprim and sulphadoxine) was ineffective in the treatment of heartwater. This was confirmed by Oberem (unpublished data, 1986).

#### Biologicals—Hyperimmune serum

Alexander (1931) and Du Plessis (1970) stated that hyperimmune serum has no value as a curative for heartwater.

#### SUPPORTIVE TREATMENT

Soga (1896) recommended the use of lime and salt on an empirical basis. Alexander (1931) suggested that the foregoing treatment was sound as a drop in inorganic calcium both during the incubation period and during the febrile state occurred and he also found a beneficial effect when calcium, magnesium and formalin were used. Measurement of total inorganic calcium may be misleading as its fluctuations may follow fluctuations in protein content. Leakage of protein as occurs in heartwater (Clark, 1962) may result in lowered total calcium levels whereas the ionised calcium levels may remain unaffected, the latter being the physiologically active fraction (Ganong, 1975).

Clark (1962) suggested treatments directed at maintaining intravascular volume by fluid expansion of the vascular compartment through administration of whole blood or packed cells and counteracting the peripheral vasodilation by means of adrenaline, noradrenaline or methylamphetamine (also a sympathomimetic). In one experimental sheep showing peripheral vasocollapse, Clark (1962) was able to raise the diastolic arterial pressure from 0 to 80 mm Hg within 5 min using 30 mg methylamphetamine given subcutaneously. The effect lasted 2 h.

Oberem (unpublished data, 1986) observed a beneficial effect when animals were bled even when they were showing quite severe clinical signs of heartwater. The exact physiological mechanisms involved bringing about this change is not known.

Treatment for brain oedema is suggested (Camus & Barré, 1982, quoting Bezuidenhout, 1982). Several agents could be employed in this regard including diuretics, corticosteroids and other anti-inflammatory agents e.g. non-steroidal anti-inflammatory drugs and dimethyl sulfoxide (DMSO).

Of the diuretics, furosemide<sup>5</sup> (high-ceiling diuretic) and the osmotic diuretics mannitol<sup>6</sup> and 50 % dextrose<sup>7</sup>, have been employed most commonly in field cases of heartwater. Furosemide acts primarily to inhibit chloride and sodium reabsorption in the ascending limb of the loop of Henle (Mudge, 1980). This results in the excretion of an accompanying volume of water. An increase in potassium excretion also results from its secretion in the distal segment and is approximately proportional to the increased rate of flow in this segment (Mudge, 1980). Abnormalities of fluid and electrolyte imbalance are the most common forms of clinical toxicity seen (Mudge, 1980). Mudge also warns that in cases of acute pulmonary oedema, the prompt and significant diuretic effect of furosemide following intravenous or intramuscular administration, may cause a reduction in venous return and right ventricular output. This effect of furosemide in clinical cases of heartwater has not been examined.

Of the osmotic diuretics, mannitol is the agent most extensively employed (Mudge, 1980). Mannitol undergoes very little reabsorption in the kidney tubules and this unreabsorbed solute limits the back diffusion of water. Mannitol is distributed in the extracellular fluid and, consequently, its administration may lead to an acute expansion of the extracellular fluid volume which

<sup>3</sup> Tomanol, Byk Gulden

<sup>4</sup> DMSO, Centaur

<sup>5</sup> Lasix, Hoechst

<sup>6</sup> Mannitol Injection B.P. 20 % (m/v), Sabax (Pty) Ltd

<sup>7</sup> Dextrose Injection B.P. 50 % (m/v), Sabax (Pty) Ltd

may aggravate the interstitial lung oedema seen in cases of heartwater.

The effectiveness of 50 % dextrose as a diuretic in clinical cases of heartwater is untested.

Dimethyl sulfoxide (DMSO) causes diuresis after topical, oral or parenteral administration (Brayton, 1986). The mechanism of action is probably the rapid renal excretion of DMSO in combination with its hygroscopic nature, resulting in water being drawn with it into the urine (Brayton, 1986). The therapeutic intravenous (i.v.) dose is about 1.0 g/kg, in a 10–45 % solution, given slowly. This dose has been employed in humans, cats, dogs and horses (Brayton, 1986). Near lethal, single i.v. doses of DMSO in laboratory animals produce sedation, diuresis, intravascular hemolysis and hematuria. Van Amstel (unpublished results, 1984) used DMSO in field cases of heartwater in calves in a similar manner to that outlined above. Treated calves developed a halitosis and dark coloured urine. No improvement in recovery rates in these calves was observed. However, further work in this regard needs to be done.

Another possible reason for the use of DMSO in clinical cases of heartwater is its anti-inflammatory effect, the mechanism of which is probably its radical scavenging property (Brayton, 1986). In clinical situations, an anti-inflammatory benefit has been reported with acute, traumatic and inflammatory disorders of the central nervous system (Brayton, 1986). As preliminary findings by Du Plessis & Malan (1987) indicate that certain inflammatory products may play a role in the pathogenesis of heartwater, the use of anti-inflammatory agents may be well indicated. The nonsteroidal anti-inflammatory drugs (NSAID's) inhibit prostaglandin cyclo-oxygenase which converts arachidonic acid derived from cell membrane phospholipids to thromboxane and prostaglandins (Jenkins, 1984). The NSAID's include, among others, the salicylates (e.g. aspirin), indole acetates (e.g. indomethacin), the pyrazolidinediones (e.g. phenylbutazone) and a nicotinic acid derivative, flunixin meglumine.

Corticosteroids may also be indicated in clinical cases of heartwater because of their anti-inflammatory action. Results of preliminary studies in experimentally-induced heartwater in calves show the absence of high levels of endogenous cortisone during the course of the disease (Van Amstel *et al.*, unpublished results, 1986). The mechanisms of the anti-inflammatory action, although not entirely understood, include the following: decreased release of arachidonic acid from membrane phospholipids and depressed prostaglandin synthesis, inhibition of the kinin cascade and plasminogen activation; decreased lysosomal release from neutrophils and neutrophil chemotaxis is inhibited by large doses; inhibition of monocyte-macrophage activities and suppression of T-lymphocyte functions (Jenkins, 1984). Prednisolone, a medium acting corticosteroid, can be used at a dose rate of 1 mg/kg intramuscularly and repeated 12 hourly if necessary.

Administration of parenteral antacids for the presence of a metabolic acidosis as suggested by Ilemobade (1976) should be investigated.

References to the effects of heartwater on the forestomachs were made by several authors. Haig *et al.* (1954) suggest soluble carbohydrate and acidification for cases with atony as a complication. Alexander *et al.* (1946) refer to the use of raw linseed oil and magnesium sulphate as purgatives.

#### CONCLUSIONS

It would seem that treatment of heartwater during the early febrile stages presents very few problems and that recovery can be expected when either sulphonamides or

tetracyclines are used at generally accepted dose rates. It was felt that tetracyclines are more effective than sulphonamides. There seems still to be some uncertainty as to the optimum dose rate for tetracyclines in clinical cases of heartwater. This is of importance as tetracyclines are generally accepted as causing stasis of growth of pathogens by means of inhibition of protein synthesis. For a bacteriostatic or rickettsiastatic drug to be effective, both optimal and persistent blood levels and, in this case blood-brain levels, are required. Bacteriocidal (rickettsiacidal) drugs are less dependent on persistent optimal levels but such drugs could interfere with the immunity to heartwater as in the case of gloxazone (Du Plessis, 1981). The possible resistance to either sulphonamides or tetracyclines has not been investigated. Camus & Barré (1982) quoting Da Graça (1966) mention the possibility of *Cowdria ruminantium* developing resistance to tetracyclines. Investigations directed at the possible determinations of both resistance and minimum inhibitory concentrations should be undertaken. The search for alternative effective drugs should be continued.

Treatment of heartwater once neurological signs have developed becomes much more difficult. Pathophysiological changes associated with the disease must obviously play a major role in the variation of success in treating field cases, which are usually presented only when clinical signs become apparent. Not enough is known about the pathophysiology to make supportive treatment really effective. Both the exact causes of the peripheral vasocollapse and of the increased capillary permeability remain largely unknown. Drugs active in reducing oedema (diuretics), stabilisation of membranes [corticosteroids, dimethylsulphoxide (DMSO)] and blocking the effect of vasoactive compounds released with cellular death (corticosteroids, non-steroidal anti-inflammatory agents) should be investigated.

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