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Comparative efficacy assessment of pentamidine isethionate and diminazene aceturate in the chemotherapy of *Trypanosoma brucei brucei* infection in dogs

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Abstract

The chemotherapeutic efficacy of diminazene aceturate (Berenil®) – a standard veterinary trypanocide and pentamidine isethionate (PMI) – a human trypanocide was compared in dogs experimentally infected with *Trypanosoma brucei brucei*. Also, the activities of the drugs on some serum liver enzymes were evaluated before and after treatment to ascertain the relative safety of the drugs.

Fifteen local dogs (mongrels) were used for the study. Three of the dogs were uninfected controls, and twelve were infected with a stock of *T. brucei brucei*. Three of the infected dogs were untreated controls, three were given diminazene aceturate (DA) at 7 mg/kg body weight intramuscularly (i/m), another three received pentamidine isethionate (PMI) at 4 mg/kg i/m on days 14, 17, 19, 27, 29, and 31 post infection (PI) and the remaining three dogs were also given same dose of PMI on days 14, 16, 18, 20, 22, 24 and 26 PI.

Both trypanocides effectively cleared the parasites from the blood of the infected treated dogs. However, the infection subsequently relapsed at day 42 PI in one of the dogs in the DA treated group which later died at day 70 PI. Relapse infection was not recorded with the PMI treated groups although two dogs died in the PMI treated group II (treatment at days 14, 17, 19, 27, 29, and 31 PI) without showing relapsed parasitaemia. The packed cell volume (PCV), red blood cell (RBC) count, and haemoglobin (Hb) level which decreased significantly following infection, were reversed by the trypanocidal treatment. The reversal in the red cell values was faster in the PMI treated groups than in the DA treated group. The serum alkaline phosphate (SAP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels increased following infection and drug administration. The increase in the enzyme levels was greater in the DA treated groups than PMI treated groups.

It was thus concluded that PMI given at 4 mg/kg i/m at days 14, 16, 18, 20, 22, 24, and 26 PI constituted a safe and efficient trypanocide and exhibited a superior trypanocidal action than DA in *T. brucei brucei* infected dogs.

Keywords: Comparative efficacy; Pentamidine isethionate; Diminazene aceturate; *Trypanosoma brucei*; Dogs

1. Introduction

Trypanosomosis consists of a group of important animal and human diseases caused by parasitic protozoa of the genus *Trypanosoma* (Barret et al., 2003). In the course of the infection, the parasite may be restricted to

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the small vessel for example *Trypanosoma congolense* and *T. vivax,* or they may occur primarily in the connective tissue, for example as with *Trypanosoma brucei* (Mulligan and Potts, 1970). Pathogenic trypanosomes are transmitted by tsetse flies (*Diptera*) in the genus *Glossina* in which cyclical development takes place.

Trypanosomosis is a serious threat to profitable livestock production and a major health hazard for dogs and other companion animals in the South Eastern Nigeria (Anene and Omamegbe, 1987). The socio-economic problems inherent with the disease was observed by Asuamah (1977) who saw the disease as being partly responsible for nomadism and transhumance being practiced in Nigeria. Also Ilemobade (1981) identified it as being a major hindrance to the efforts to settle the nomadic grazers.

FAO (1987) put the direct losses in meat production and milk yield, and the cost of programmes that attempt to control trypanosomosis at between US$ 600 million and US$ 1.26 billion each year. The report also stated that over US$ 20 million are spent per year on trypanocides accounting for over 44% of the total expenditure on veterinary drugs.

Of all the strategies used in the control of trypanosomosis, chemotherapy is the most widely used, more effective, and more accepted means of control. The three trypanocides namely diminazene aceturate, isometamidium chloride, and homidium chloride (novidium) commonly used in the control of trypanosomosis in animals in Africa have been in use for over 40 years and not surprisingly resistance has emerged (Geerts et al., 2001). Delay in commencement of treatment, under-dosing and improper and inefficient monitoring of drug efficacy in the field have been identified as the causes of relapses and drug resistance in trypanosomosis (Blood et al., 1994).

Consequently, the use of the available trypanocides require careful management in order to minimize the incidence of resistance (Brown et al., 1990) and prolong their usefulness. This is necessary because the relatively limited market for trypanocides in Africa and high cost of developing and patenting new trypanocides have discouraged international pharmaceutical companies in the development of new trypanocides for use in either animals or humans. This has posed a great challenge to both veterinary and medical practitioners and therefore the current trend is to achieve optimum use of the existing trypanocides (Geerts et al., 2001).

Pentamidine isethionate is a human trypanocide developed in the 1930s. It is remarkably effective in patients with early stage *T. brucei gambiense* infection (Pepin and Milord, 1994). Its use in humans is presently not encumbered by the problems of resistance (Fairlamb et al., 1992; Bacchi, 1993; Bray et al., 2003) whereas resistance to the few available veterinary trypanocides is a rapidly growing problem (Kalu, 1995; Anene et al., 2001).

Among animal trypanosomosis, *T. brucei brucei* infection of dogs is highly pathogenic and responds poorly to treatment with the available veterinary trypanocides and commonly encounters relapses of infection (Sayer et al., 1979; Anene and Omamegbe, 1987; Kaggwa et al., 1984, 1988; Chukwu et al., 1990) thus posing a major challenge to veterinary clinicians.

As part of the concerted effort to find a better and lasting treatment for canine trypanososmosis, we have thus investigated the comparative efficacy of PMI, a human trypanocide, and DA, a standard animal trypanocide, in dogs experimentally infected with an isolate of *T. brucei brucei*. Furthermore we have tried to determine the toxicity, if any, of the Pentamidine isethionate protocols used in this study in comparison with that of diminazene aceturate. Finally, we tried to ascertain the possibility of recommending Pentamidine isethionate as an alternative remedy in the treatment of clinical cases of trypanosomosis due to *T. brucei brucei* in dogs.

2. Materials and methods

2.1. Experimental animals

Fifteen local dogs of both sexes weighing between 5.7 and 6.2 kg were used for the study. They were kept in metal cages in a fly-proof house. They were fed once daily and were given clean drinking water *ad libitum*. The dogs were acclimatized for 2 weeks during which time they were dewormed and deticked with ivermectin (Ivomec Merck Sharp and Dohme B.V. Haarlem, Holland) at a dose of 0.2 mg/kg given subcutaneously (s/c). The dogs were confirmed parasitologically negative for trypanosomes by wet blood film and buffy coat technique (Murray et al., 1977) before commencement of the experiment.

2.2. Drugs

DA (Berenil, Hoechst Roussel Vet. Limited Cookstown, Tallaght, Dublin) and PMI (May and Baker Limited, Dagenham, England, RM10 7XS) were reconstituted in distilled water according to the manufacturer's recommendation and given i/m in the thigh muscle.