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Influence of treatment with 3′-deoxyadenosine associated deoxycoformycin on hematological parameters and activity of adenosine deaminase in infected mice with *Trypanosoma evansi*

Luciana Dalla Rosa [a,*], Aleksandro S. Da Silva [b], Jader B. Ruchel [a], Lucas T. Gressler [a], Camila B. Oliveira [a], Raqueli T. França [c], Sonia T.A. Lopes [c], Daniela B.R. Leal [a], Silvia G. Monteiro [a]

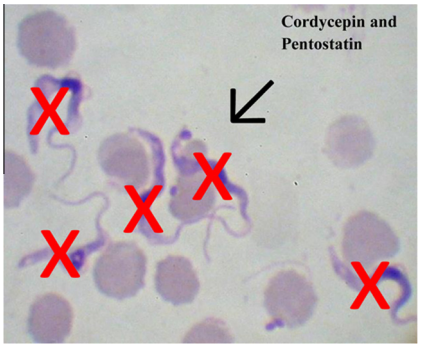
[a] Departamento de Microbiologia e Parasitologia, Universidade Federal de Santa Maria, Brazil
[b] Departamento de Ciência Animal, Universidade do Estado de Santa Catarina, Chapecó, Brazil
[c] Departamento de Pequenos Animais, Universidade Federal de Santa Maria, Brazil

HIGHLIGHTS

- The treatment in the doses used caused no alterations in hematological parameters.
- The plasma total protein levels can be reduced as a consequence of this treatment.
- The activity of ADA had inhibition in plasma of animals treated with pentostatin.
- The activity of ADA had inhibition in brain of animals treated with pentostatin.

GRAPHICAL ABSTRACT

The treatment influence in activity of adenosine deaminase in plasma and brain of infected mice with *Trypanosoma evansi*.



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ABSTRACT

This study aimed to verify the effect of 3′-deoxyadenosine and deoxycoformycin on hematologic parameters and adenosine deaminase (ADA) activity in plasma and brain of mice infected with *Trypanosoma evansi*. Seventy animals were divided into seven groups, which were divided into two subgroups each for sampling on days 4 and 8 post-infection (PI). The groups were composed of three uninfected groups (A–C), namely, not-treated (A), treated with 3′-deoxyadenosine (B), and treated with deoxycoformycin (C) and four infected groups, mice with *T. evansi* (D–G), namely, not-treated (D), treated with 3′-deoxyadenosine (E), treated with deoxycoformycin (F), and treated with a combination 3′-deoxyadenosine and deoxycoformycin (G). Hematological parameters and ADA activity were evaluated in plasma and brain. Animals in groups B and C exhibited a reduction in the levels of plasma total protein compared group A. Animals in groups D and F showed changes in the hematological parameters. The ADA activity significantly reduced in the animals of groups C, D, F and G. Mice in the group E presented increased ADA activity in plasma. Therefore, we conclude that the treatment interferes significantly in the hematologic parameters in mice infected with *T. evansi*. On the other hand, when the ADA inhibitor was used we

* Corresponding author at: Departamento de Microbiologia e Parasitologia, Universidade Federal de Santa Maria, Av. Roraima no 1000, Camobi, Santa Maria, RS, CEP 97105-900, Brazil. Fax: +55 55 3220 8242.
E-mail addresses: lucianadallarosa@gmail.com, ludallarosa@hotmail.com (L. Dalla Rosa).

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observed a significant decrease in the values of hematocrit, total erythrocytes, and hemoglobin concentration. The deoxycoformycin was able to inhibit the ADA activity of parasite thus it may be one of the mechanisms of efficacy of this treatment.

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1. Introduction

The *Trypanosoma evansi* is the etiologic agent of trypanosomosis, a disease with broad distribution in Africa, Asia, and Latin America (Lun and Desser, 1995) which may result in immeasurable economic losses (Luckins and Dwinger, 2004; Dobson et al., 2009). The parasite is transmitted mechanically by blood-sucking insects during feeding such as *Tabanus* spp. and *Stomoxys* spp. and/or vampire bats (Hoare, 1972). A large number of species may be parasitized by *T. evansi* including horses (in which the disease is called "*Mal das cadeiras*" or "*Surra*"), camels, dogs, and in rare cases, humans (Powar et al., 2006). Trypanosome-infected animals present clinical signs such as fever, poor body condition, weakness, subcutaneous edema, petechiae of the serous membranes, and instability of the hind limbs (Silva et al., 1995). An accurate diagnosis of this disease is possible during its acute and chronic stage, but chronic clinical signs are more evident and the animal condition is more severely affected (Silva et al., 2002).

In Brazil, the therapy for trypanosomosis relies on the use of diminazene aceturate, which is effective for the treatment in cattle, buffalo, sheep, pigs and camels (Peregrine and Mamman, 1993; Sirivan et al., 1994). However, when only one dose is used the treatment is not effective for horses, mules or dogs (Tuntasuvan et al., 2003; Colpo et al., 2005), which results in lack of efficacy of this drug as a consequence (Tuntasuvan et al., 2003; Da Silva et al., 2008). Thus, it is important to investigate alternatives to improve the success of the treatment using new drugs, anti-protozoa associations, and other components that could increase the curative efficacy as occurred when diminazene aceturate is associated with selenium in the therapy of infected rats with *T. evansi* (Tonin et al., 2011). Based on this idea, some studies have emerged suggesting new options for the treatment of trypanosomosis.

The effective treatment in the cure of infected mice with *Trypanosoma brucei* was observed when an analogue product of purine, 3-deoxyadenosine was used (Rottenberg et al., 2005; Vodnala et al., 2008, 2009). The efficacy of the treatment is related to the protection of 3-deoxyadenosine against the enzyme adenosine deaminase (ADA), which is responsible for the deamination of this adenosine analogue (Rottenberg et al., 2005; Vodnala et al., 2008, 2009). However, the administration of 3-deoxyadenosine alone did not result in a complete cure from the infection (Aiyedun et al., 1973; Da Silva et al., 2011d). Therefore, this treatment requires the combination of 3-deoxyadenosine with an inhibitor of ADA_1 and ADA_2, known as deoxycoformycin (Rottenberg et al., 2005).

In addition to the treatment of trypanosomosis, 3-deoxyadenosine combination with deoxycoformycin has been used for the treatment of certain malignant tumors in humans, e.g., leukemia and melanoma (Adamson et al., 1977). This adenosine analogue can perform similar functions to adenosine that is present in all tissues of mammals, demonstrating important functions related to cell signaling, neuroprotection, thromboregulation, and immune processes (Burnstock, 2006; Desrosiers et al., 2007). In addition, adenosine has an anti-inflammatory action playing a central role in inflammation and immunomodulation (Di Virgilio et al., 1998; Luttikhuizen et al., 2004). The concentration of extracellular adenosine is regulated by the ADA activity, which is considered an enzyme in the purine metabolism, catalyzing the irreversible deamination of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively (Franco et al., 1997). The observation that ADA deficiency leads to a severe combined immunodeficiency syndrome points to the physiological importance of controlling extracellular adenosine levels (Aldrich et al., 2000).

A recent study showed that the combination of 3′-deoxyadenosine with deoxycoformycin was effective in treating mice infected with *T. evansi*, but the cured animals showed histological lesions in their liver and kidneys (Dalla Rosa et al., 2013). Thus, this study has as objective to verify the effect of 3′-deoxyadenosine and deoxycoformycin on hematologic parameters and ADA activity in plasma and brain of mice infected with *T. evansi* and to check the effect of deoxycoformycin on the ADA activity of parasite.

2. Materials and methods

2.1. Drugs

3′-Deoxyadenosine (Cordycepin®) was obtained from Sigma Chemical Co (St. Louis, MO, USA). Deoxycoformycin (Pentostatin®) was obtained from Tocris Bioscience (Minneapolis, MN, USA). Unless otherwise indicated, all reagents were diluted in PBS, aliquoted and stored at −20 °C until further use.

2.2. T. evansi isolate

To reactivate the isolated and obtain a large amount of blood parasites for the subsequent infection of mice that formed the experimental groups, in this study, two Wistar rats (R_1 and R_2) were intraperitoneally infected with blood cryopreserved in liquid nitrogen containing 1.3×10^6 trypanosomes.

2.3. Animal groups and T. evansi infection

Seventy adult female mice with a mean age of 60 days and weighing average 23.2 ± 1.9 g were used in this study. The animals were housed in cages, ten in each cage, in a room with controlled temperature and humidity (25 °C; 70%) on a 12 h light/dark cycle with free access to food and water. All animals were submitted to an adaptation period of 15 days before the beginning of the experimental period.

Mice were divided into seven groups (A, B, C, D, E, F and G) with 10 animals each. The groups A, B and C were formed by uninfected animals with the parasite. Animals of groups D–G were intraperitoneally infected with 0.1 mL of blood from rat (R_1) containing 1.1×10^6 trypanosomes (Day 0). Subsequently, the parasitemia was estimated daily by microscopic examination of smears. Each slide was mounted with blood collected from the tail vein, Romanowsky stain, and visualized at a magnification of 1000×.

2.4. Experimental design

Group A was composed of uninfected and untreated animals (negative control), group B consisted of uninfected and treated with 1 mg/kg/day of 3′-deoxyadenosine and the animals of group C were uninfected and treated with 1 mg/kg/day of deoxycoformycin. Group D was composed of infected and untreated animals (positive control). Animals of groups E, F and G were infected with *T. evansi* and treated with 1 mg/kg/day of 3′-deoxyadenosine, 1 mg/kg/day of deoxycoformycin and treated with combination 1 mg/kg/day of 3′-deoxyadenosine with 1 mg/kg/day of

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