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Historic of therapeutic efficacy of albendazol sulphoxide administered in different routes, dosages and treatment schemes, against *Taenia saginata* cysticercus in cattle experimentally infected

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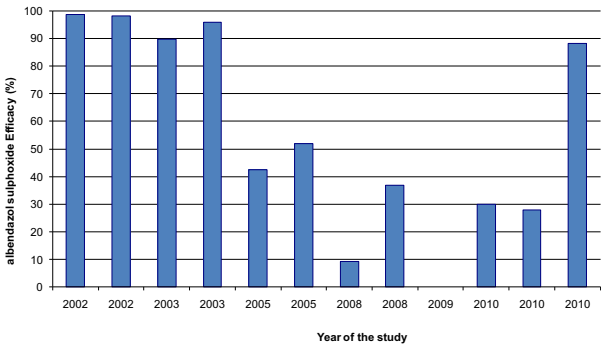
HIGHLIGHTS

- We compare the effects of ALB-SO against *Taenia saginata* cysticercus.
- The active of ALB-SO show low efficacy during studies performed 2008–2010.
- ALBZ had insignificant efficacy against *T. saginata* larvae parasitizing bovines.

GRAPHICAL ABSTRACT



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ABSTRACT

The present study aimed to notify the history of albendazole sulphoxide (ALB-SO) and albendazole (ALBZ) efficacy against *Taenia saginata* cysticercus (*Cysticercus bovis*) parasitizing experimentally infected bovines. A total of 11 efficacy trials were performed between the years of 2002 and 2010. In order to perform these trials, animals were individually inoculated with 2×10^4 eggs of *T. saginata* in each study's day zero (D0). For every trial, a positive control group (untreated infected animals) and a negative control group (animals that were neither infected nor treated) were used. ALB-SO or ALB were administered in the different dosages, in different days of treatments. In a last study with this formulation, this active principle was administered orally, mixed with the mineral supplement, on the 60th DPI, in a dosage of 30 mg/kg. In all trials, on the 100th DPI, all animals were euthanized and submitted to the sequenced slicing of 26 anatomical segments (fragments of approximately five millimeters) for the survey of *T. saginata* cysticercus. With the obtained results it is possible to verify that in the first trials, conducted in 2002, ALB-SO reached, independently of dosage and treatment scheme, efficacies superior to 98% (arithmetic means). The trials conducted in 2005 (2.5 mg/kg on the 30th, 60th, and 90th DPI) obtained values of efficacy all inferior to 60%. In 2008, the trials with 2.5 and 7.7 mg/kg demonstrated efficacy values inferior to 40%, for both dosages and treatment schemes (30th/60th/90th DPI and 60th DPI). When this formulation was administered orally on the dosage of 30 mg/kg on the 60th DPI, the efficacy against *T. saginata* cysticercus reached 88.28%. ALB administered orally showed efficacy values of 0.0%, 29.88% and 28.64% in

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the dosages of 5, 10 and 15 mg/kg, respectively, using the treatment schemes described above for each dosage. Based on the results of these trials, conducted in an eight year period (2002–2010) using the sequenced slicing method for evaluating the efficacy of the aforementioned formulations against *T. saginata* cysticercus, it is possible to observe that, amongst the few molecules used in the chemotherapic treatment against *T. saginata* larvae, ALB-SO, administered in varied routes, dosages and treatment schemes, the studies conducted in 2008, 2009, and 2010, have a low therapeutic efficacy against *C. bovis* in Brazil, while ALBZ had insignificant efficacy values against *T. saginata* larvae parasitizing experimentally infected bovines. However, future studies using molecular biology will be necessary to assess whether the difference on the efficacy of the ALB-SO can be related to strain or another specific factor.

1. Introduction

Taeniosis and cysticercosis involve the same parasite with different denominations. For its dissemination and survival in nature, this parasite depends on the participation of two host species, human and animal (Plancarte et al., 2005). Thus, *Taenia saginata* has humans as its definitive host, developing the adult form in the small intestine, while the larvae of this cestode, the cysticerci, is found in animal tissues, amongst which bovines stand out, being their intermediate hosts (Costa et al., 2012).

Lopes et al. (2011) affirm that bovine cysticercosis does not present, in economical terms, high zootechnical importance for production of beef and milk, since the animals generally present moderate infections with absence of clinical signs. On the other hand, these authors emphasize that the prejudice for the producers is in slaughterhouses, resulting mainly on the discount and condemnation of the carcasses possessing live cysticerci diagnosed in the process. Schantz et al. (1994) state that, in Latin America, the annual economic losses due to bovine cysticercosis is of approximately US$ 164 million, while in Africa they are estimated around US$ 1000 and 2000 million. Acha and Szyfres (1986) say that the loss can be around US$ 25 per infected animal in developing countries.

Other than the aforementioned losses, it is necessary to consider the importance of contaminated beef as an infection source for teniasis in humans, even though they are the main responsible for causing this infirmity in animals (Flavigna-Guilherme et al., 2006).

Even though sanitary authorities contribute to significant advances in the epidemiological control of bovine and swine cysticercosis, few studies have been conducted in an attempt to establish prophylactic and therapeutic measures against this infection. This is probably a result of the low occurrence of clinical signs of parasitism by these metacestodes in infected animals (Barbosa et al., 2003).

Representing therapeutic products against *T. saginata* cysticercus (*Cysticercus bovis*) is albendazole (Lloyd et al., 1978). However, the search for a formulation that presents administration practicality in bovines allied with an elevated efficacy against this evolutionary stage of the parasite lead to the discovery of albendazole sulphoxide (ALB-SO), a synthetic injectable product derived from albendazole (ALBZ) (Soares et al., 2011). Efficacy studies conducted with these two principles in animals demonstrated satisfying results (Barbosa et al., 2003; Geerts and Kumar, 1981; Kaur et al., 1995; Lloyd et al., 1978). On the other hand, after this period, few trials were conducted aiming to evaluate the efficacy of such formulations against the larval stage (cysticerci) of this important zoonosis.

In this context, the present study had the objective of notifying the history of therapeutic efficacy of ALB-SO and ALBZ, administered in different dosages, routes and treatment schemes, against *T. saginata* cysticercus in cattle experimentally infected in Brazil, through sequenced slicing of the carcasses. In order to achieve this, 11 trials were conducted between the years of 2002 and 2012, comprising ten experiments with ALB-SO and one with ALBZ.

2. Materials and methods

2.1. Local and selection of bovines

All 11 trials were conducted in the "Center of Research in Animal Health", CPPAR, located in the Jaboticabal campus of the Universidade Estadual Paulista "Júlio de Mesquita Filho", in the state of São Paulo, Brazil, were the animals were kept throughout all the experimental period. The laboratorial activities were conducted in CPPAR and in the "Department of Basic Pathology" of the Universidade Federal do Paraná, UFPR, in the state of Paraná, Brazil.

Sera of bovines with ages ranging from 6 to 8 months, belonging to the city of Jaboticabal, São Paulo, Brazil, were submitted to ELISA indirect test (Minozzo et al., 1997; Wanzala et al., 2002). In short, the test was performed using microtiter plates coated overnight with 2.5 μg/mL of crude cyst antigen in 0.05 M Coating Buffer (pH 9.6). The wells were washed with 0.05% Tween 20 in saline, blocked by incubation at 37 °C for 1 h with 2% casein in PBS pH 7.4 and washed. Sera (1:100) were diluted in incubation buffer (0.25% casein, 0.05% Tween 20, PBS 7.4), distributed into the wells and incubated at 37 °C for 1 h; then the plate was washed and bound cattle IgG were detected by using an anti-cattle IgG peroxidase-conjugated (Sigma) diluted 1:400. Incubation and washing were repeated as above. The enzymatic reaction was revealed by the addition of 0.04 mg/mL OPD, 0.02% (v/v) H_2O_2 in 0.1 M citrate buffer (pH 5.2) for 15 min. The reaction was stopped by adding 2 N sulphuric acid to each well. The absorbance read at 492 nm. The cut off was determined using known negative control samples. To minimize the risk of false negative animals in the study only animals with absorbance values below the cut off value were selected. The selected animals had not received any cestodicide treatment and they were transported to CPPAR/FCAV/UNESP, Brazil, with water, feed and mineral salts provided *ad libitum*.

2.2. Experimental infection and treatment of animals

Several *T. saginata* proglottids were obtained from non-anthelminth-treated human patients, whose feces were screened and acquired from the Parasitology Laboratory of the Curitiba Municipal Health Office Paraná State, Brazil. The proglottids were gathered during a two-week period and they were maintained in saline buffer at 4 °C. Species identification was done by compressing the proglottids between glass slides and observing the number of uterine ramifications under an optical microscope. After identification, proglottids were dissected for the isolation of eggs. The egg count was determined by using a Neubauer chamber. For inoculum standardization, 2×10^4 *T. saginata* eggs were diluted in 20 mL of 0.09% NaCl solution, as previously described by Minozzo et al. (2002).