REVISTA CONTRIBUCIONES A LAS CIENCIAS SOCIALES

Albendazole-praziquantel association in experimental neurocysticercosis induces metabolic stress in energy pathways

Associação de albendazol-praziquantel na neurocisticercose experimental induz estresse metabólico nas vias energéticas

Asociación de albendazol-praziquantel en la neurocisticercosis experimental induce estrés metabólico en las vías energéticas

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ABSTRACT
Neurocysticercosis (NCC) is a serious public health problem, with high incidence in countries where sanitary conditions are poor. The disease is caused by infection of the central nervous system by cysticerci of *Taenia solium*, the larval form of the parasite, and can lead to severe neurological symptoms such as seizures, headaches, and cognitive deficits. The intracranial inoculation of *Taenia crassiceps* in mice is an experimental model used for NCC studies. NCC treatment may vary and is primarily carried out using the drugs albendazole (ABZ) and praziquantel (PZQ), either alone or in combination. This study aimed to determine and evaluate the metabolic impact of ABZ-PZQ combination therapy in mice intracranially infected with *T. crassiceps* cysticerci. The combined use of ABZ and PZQ showed a significant impact on glycolysis, fatty acid oxidation, propionate production, and protein catabolism compared to the control group (treated with 0.9% NaCl). The combined mode of action of ABZ-PZQ induced metabolic stress and increased the use of alternative energy pathways by the cysticerci. Therefore, both anthelmintics demonstrated a significant impact on the metabolism of *T. crassiceps* cysticerci.

Keywords: neurocysticercosis, drug association, experimental infection, *Taenia crassiceps*, albendazole, praziquantel.

RESUMO
A neurocisticercose (NCC) é um grave problema de saúde pública, com alta incidência em países onde as condições higiênicas são precárias. A doença é causada pela infecção do sistema nervoso central por cisticercos da *Taenia solium*, a forma larval do parasito, e pode provocar sintomas neurológicos graves, como convulsões, cefaleia e déficits cognitivos. A inoculação intracraniana de *Taenia crassiceps* em camundongos é um modelo experimental utilizado para estudos de NCC. O tratamento da NCC pode variar e é realizado principalmente com os fármacos albendazol (ABZ) e praziquantel (PZQ), seja isoladamente ou em associação. Este estudo teve como objetivo determinar e avaliar o impacto metabólico da associação ABZ-PZQ em camundongos infectados intracranianamente com cisticercos de *T. crassiceps*. O uso em associação de ABZ e PZQ apresentou impacto significativo na glicólise, na oxidação de ácidos graxos, na produção de propionato e no catabolismo proteico em comparação ao grupo controle (tratado com NaCl 0,9%). O modo de ação combinado de ABZ-PZQ induziu estresse metabólico e aumentou o uso de vias energéticas alternativas pelos cisticercos. Portanto, ambos os anti-helmínticos demonstraram impacto significativo no metabolismo dos cisticercos de *T. crassiceps*.

Palavras-chave: neurocisticercose, associação de fármacos, infecção experimental, *Taenia crassiceps*, albendazol, praziquantel.

RESUMEN
La neurocisticercosis (NCC) es un grave problema de salud pública, con alta incidencia en países donde las condiciones higiénicas son precarias. La enfermedad es causada por la infección del sistema nervioso central por cisticercos de *Taenia solium*, la forma larval del parásito, y puede provocar síntomas neurológicos graves, como convulsiones, cefaleas y déficits cognitivos. La inoculación intracraneal de *Taenia crassiceps* en ratones es un modelo experimental utilizado para estudios de la NCC. El tratamiento de la NCC puede variar y se realiza principalmente con los fármacos albendazol (ABZ) y prazicuantel (PZQ), ya sea de forma individual o combinada. Este estudio tuvo como objetivo determinar y evaluar el impacto metabólico de la combinación ABZ-PZQ en ratones infectados intracranealmente con cisticercos de *T. crassiceps*. El uso combinado de ABZ y PZQ mostró un impacto significativo en la glucólisis, la oxidación de ácidos grasos, la producción de propionato y el catabolismo proteico en comparación con el grupo control (tratado con NaCl al 0,9%). El modo de acción combinado de ABZ-PZQ indujo estrés metabólico y aumentó el uso de vías energéticas alternativas por parte de los cisticercos. Por lo tanto, ambos antihelmínticos demostraron un impacto significativo en el metabolismo de los cisticercos de *T. crassiceps.*

Palabras clave: neurocisticercosis, asociación de fármacos, infección experimental, *Taenia crassiceps*, albendazol, praziquantel.

1 INTRODUCTION

Neurocysticercosis (NCC) is a parasitic infection caused by the presence of *Taenia solium* cysticerci in the central nervous system (CNS). NCC may be asymptomatic or it may present varied symptoms such as seizures, headaches, focal neurologic deficits, cognitive decline, intracranial hypertension, and others. The symptoms are directly correlated to the location, quantity, and viability of the cysticerci (Fogang et al., 2015; White et al., 2018). It is estimated that 2.5 to 8.9 million people are affected by NCC globally (World Health Organization, 2019). It is the main cause of acquired epilepsy reaching up to 29% of epilepsy cases in endemic regions such as Africa, Asia, Latin America, and the Caribbean (Carpio; Romo, 2014; World Health Organization, 2015).

Antiparasitic treatment in NCC is recommended when there are viable cysticerci located within the CNS. Albendazole (ABZ) monotherapy is indicated when there are one or two viable cysticerci in a maximum dose of 1,200 mg/day, up to 14 days of treatment. The albendazole – praziquantel (ABZ-PZQ) association is indicated when there are more than two viable

parenchymal cysticerci for up to 14 days (White et al., 2018).

The mode of action of albendazole and praziquantel leads to a great metabolic impact on cysticerci. ABZ is a benzimidazole derivative that affects tubulin polymerization leading to a disruption of microtubule-based processes. While praziquantel (PZQ) which is a pyrazinoisoquinoline induces tegumental damage, targeting calcium homeostasis and impairment of the aerobic metabolism (Vinaud; Ambrosio, 2020; Vinaud; Junior, 2017).

The metabolic impact of the isolated administration of ABZ and PZQ has been described *in vivo* NCC models using *Taenia crassiceps* cysticerci, which is the most common parasite used for this purpose (Vinaud; Ambrosio, 2020). The ABZ-PZQ combination has induced greater ultrastructural changes and cysticidal efficacy than the isolated drugs *in vivo* exposure of *T. crassiceps* cysticerci (Palomares et al., 2006). Therefore, this study aimed to evaluate the metabolism of *T. crassiceps* cysticerci experimentally intracranially inoculated in mice after treatment with the albendazole-praziquantel association.

2 METHODOLOGY

2.1 ETHICAL APPROVAL

This study is on the ethical principles determined by the National Council of Animal Experimentation and Control (CONCEA) and was approved by the Ethics Committee in Animal Use of the Federal University of Goiás, protocol number 001/18.

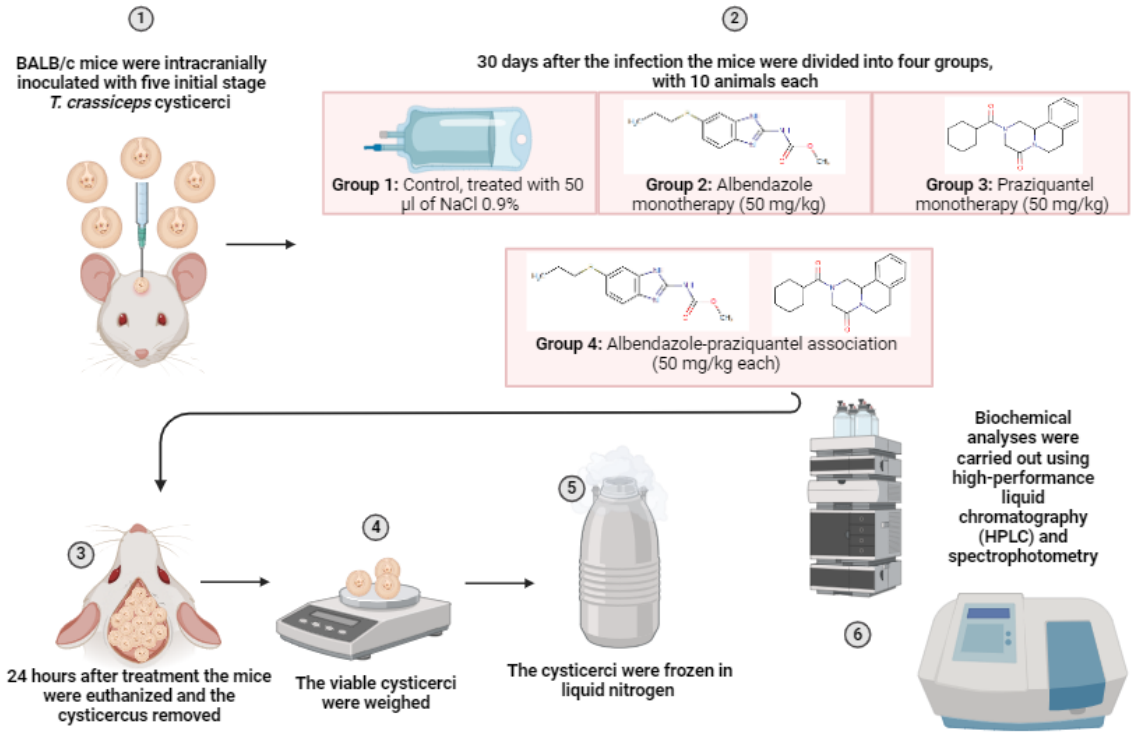
2.2 MAINTENCE OF *Taenia crassiceps*

Taenia crassiceps cysticerci Ontario Research Facilities (ORF strain) have been maintained in the animal facilities of the Tropical Pathology and Public Health Institute of the Federal University of Goiás through intraperitoneal passages in mice since 2002 as described previously (Vaz et al., 1997).

2.3 CYSTICERCI INTRACRANIAL INOCULATION AND *in vivo* TREATMENT

BALB/c mice 8 to 12 weeks old were intracranially inoculated with five initial stage *T. crassiceps* cysticerci as described previously (Figure 1) (Matos-Silva et al., 2012). Thirty days after the infection the mice were divided into four groups as follows: 1. Control group (treated with 50 µl of NaCl 0.9%), 2. Group treated with albendazole monotherapy (50 mg/kg); 3. Group treated with praziquantel monotherapy (50 mg/kg); 4. Group treated with albendazole-praziquantel association (50 mg/kg each). All groups had 10 animals each. The animals received treatment through gavage in a single dose. Since the experiment intended to determine the metabolic effects of the drug's association treatment, the dosages of the drugs were chosen to be standardized (equal dosages of both drugs) and not kill the parasite in a single dose treatment. Also, the dosages were chosen based on the guidelines for NCC treatment (World Health Organization, 2015). The animals were euthanized 24 hours after treatment. The cysticerci were removed from the mice, and washed with NaCl 0.9%. The viability of the cysticerci was visually determined according to the contraction movements of the parasite`s vesicle. Only viable cysticerci were selected for the biochemical analysis. The selected cysticerci were weighed, and frozen in liquid nitrogen for posterior biochemical analysis (Fraga et al., 2012; Vinaud et al., 2009).

Figure 1: A schematic representation of the infection and treatment of the mice during the experiment.



Prepared by the authors.

2.4 BIOCHEMICAL ANALYSIS

The cysticerci were defrosted and homogenized in tris-HCl buffer supplemented with protease inhibitor (SigmaFast, Sigma®) pH 7.6. The resulting extract was centrifuged at approximately 15,000 g / 10 min / 4ºC and, then, the organic metabolites were extracted through an ionic exchange solid phase extraction column (Bond Elut ®) followed by a chromatographic analysis (HPLC) through an organic acid's exclusion column BIORAD-Aminex HPX-87H®. The solid phase eluent was sulfuric acid 5mM, flow 0.6 ml/min, with spectrophotometric reading at 210nm (Fraga et al., 2012; Vinaud et al., 2009).

The results were analyzed through the Star Chromatography Workstation software (Agilent®), previously calibrated for the following organic acids identification: phosphoenolpyruvate (PEP), pyruvate and lactate (glycolytic pathway), oxaloacetate, citrate, alpha-ketoglutarate, succinate, fumarate and malate (tricarboxylic acid cycle), fatty acids oxidation (acetate, acetoacetate, beta-hydroxybutyrate). The quantification of the organic metabolites was adjusted per gram of cysticerci.

Quantification of glucose, lactate dehydrogenase (LDH), urea, and creatinine were performed through an Architec C8000 Plus device with commercial kits (ABBOT®) that employed the enzymatic method for quantification.

2.5 STATISTICAL ANALYSIS

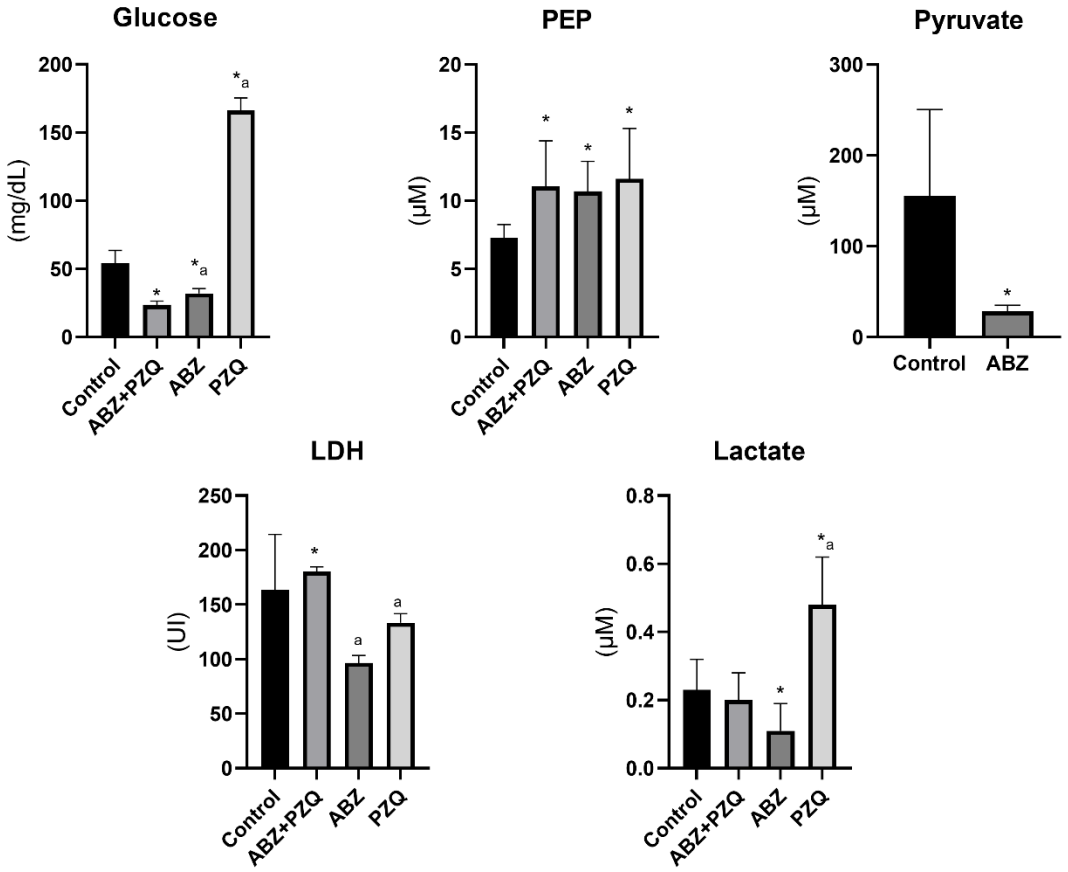
The statistical analysis was performed using the Prisma 7.0 software. The descriptive analysis determined the normal distribution, mean, and standard deviation. The differences between groups were determined through two-way ANOVA followed by Tukey post-test. The differences were considered significant when $p \leq 0.05$.

3 RESULTS AND DISCUSSIONS

This study is the first description of the metabolic impact of the albendazole-praziquantel association on the energetic pathways of *T. crassiceps* experimentally inoculated in Balb/C mice brains. It was possible to evaluate the glycolysis, homolactic fermentation, tricarboxylic acid (TCA) cycle, fatty acids oxidation, protein catabolism, and propionate fermentation in the cysticerci extract post-*in vivo* treatment with the ABZ+PZQ association.

The ABZ+PZQ association induced a significative impairment in glycolysis due to decreased concentrations of glucose and pyruvate in comparison to the control group $(p \leq 0.05)$. The increase in gluconeogenesis or glycogenolyses was observed after the PZQ treatment due to higher concentrations of glucose and PEP followed by higher homolatic fermentation compared to the control group $(p \leq 0.05)$. The ABZ treatment induced a decrease in the glycolytic pathway due to lower concentrations of glucose, pyruvate LDH, and lactate in comparison to the control group $(p \leq 0.05)$ (Figure 2).

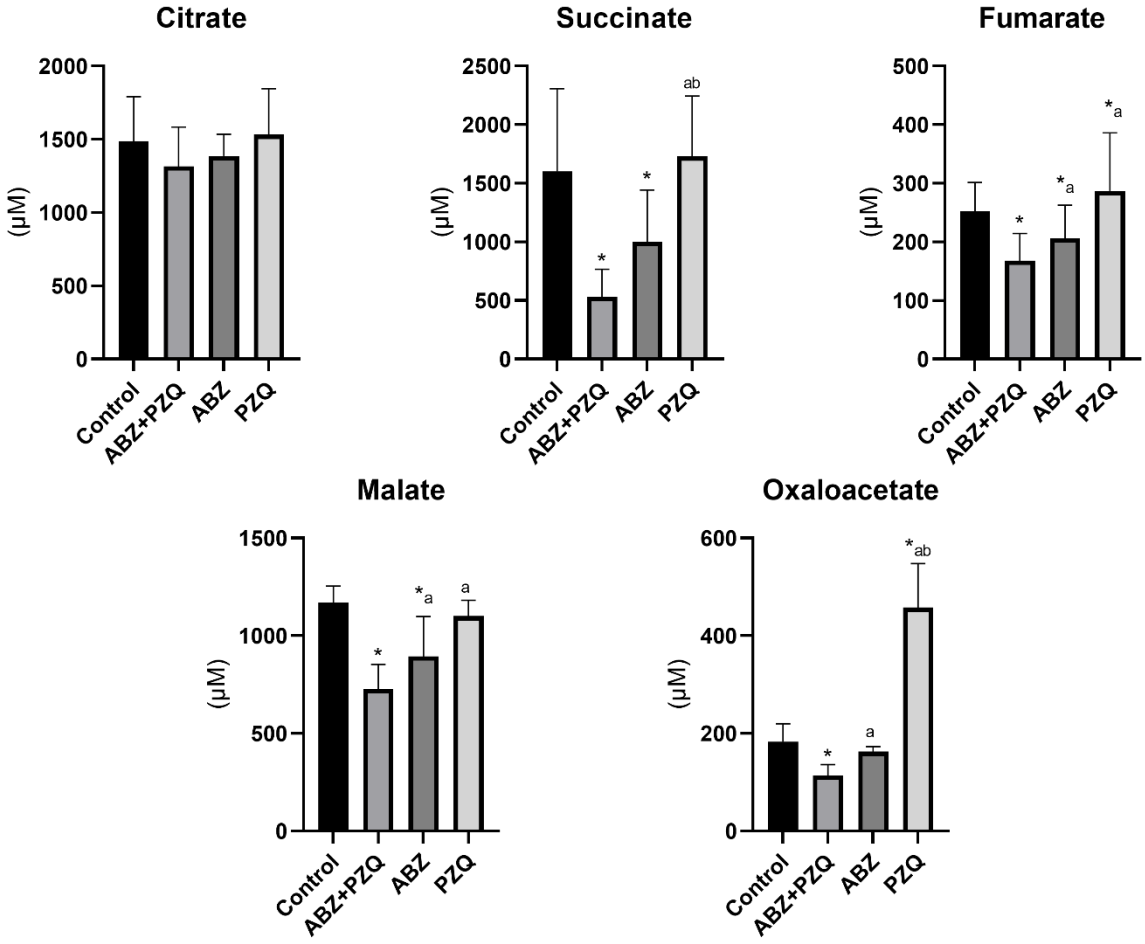
Figure 2. Mean concentrations of metabolites related to the glycolytic and homolactic fermentation pathways detected in *Taenia crassiceps* cysticerci intracranially inoculated in mice after *in vivo* treatment with the association of albendazole and praziquantel.



LDH= Lactate dehydrogenase; PEP= Phosphoenolpyruvate; Control= group treated with 50 µl of NaCl 0.9%; ABZ+PZQ= group treated with the albendazole and praziquantel association, ABZ= group treated with albendazole; PZQ = group treated with praziquantel. * $p \leq 0.05$ in comparison to control group; [a] $p \leq 0.05$ in comparison to the albendazole + praziquantel treated group (ABZ + PZQ). Statistical analysis: two-way ANOVA followed by Tukey post-test.
Source: Prepared by the authors.

Regarding the TCA cycle, it was possible to observe that the ABZ+PZQ association induced a significant decrease in most of its metabolites – succinate, fumarate, malate, and oxaloacetate- compared to the control group *(p≤0.05).* A similar impact was observed after the ABZ treatment while the PZQ treatment induced an increase in fumarate and oxaloacetate (p≤0.05) (Figure 3).

Figure 3. Mean concentrations of metabolites related to the tricarboxylic acid cycle detected in *Taenia crassiceps* cysticerci intracranially inoculated in mice after *in vivo* treatment with the association of albendazole and praziquantel.

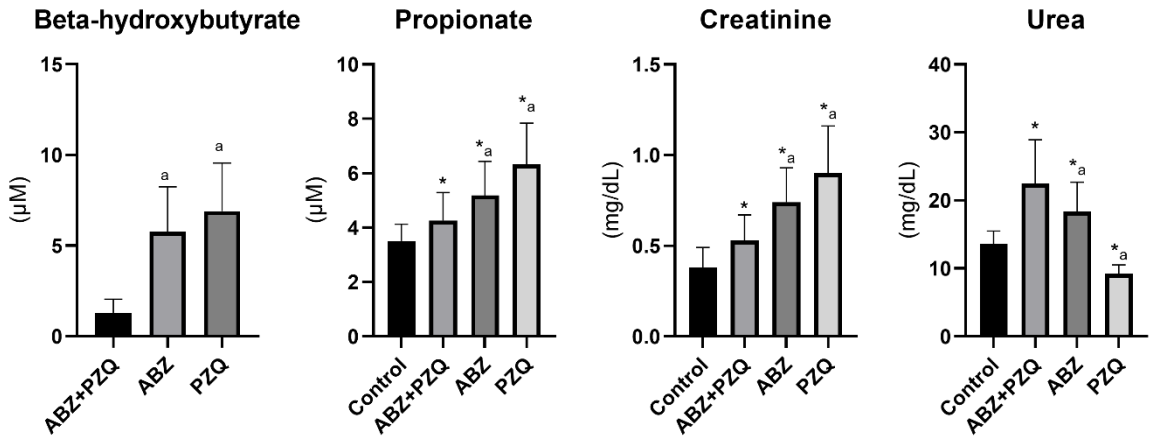


Control= group treated with 50 µl of NaCl 0.9%; ABZ+PZQ= group treated with the albendazole and praziquantel association, ABZ= group treated with albendazole; PZQ= group treated with praziquantel. * $p \leq 0.05$ in comparison to control group; [a] $p \leq 0.05$ in comparison to the albendazole + Praziquantel treated group (ABZ + PZQ), [b] $p \leq 0.05$ in comparison to the albendazole treated group. Statistical analysis: two-way ANOVA followed by Tukey post-test.
Source: Prepared by the authors.

Considering the alternative energetic pathways, it was possible to detect that the ABZ+PZQ association and the monotherapies induced an increase in fatty acids oxidation due to the detection of beta-hydroxybutyrate compared to its non-detection in the control group. Furthermore, the protein catabolism presented significant augmentation in creatinine and urea concentrations after the ABZ+PZQ association treatment and ABZ treatment in comparison to the control group ($p \leq 0.05$), while the PZQ treatment induced a decrease in urea concentrations.

Another alternative energetic product, propionate, was increased after the treatments ($p \leq 0.05$) (Figure 4).

Figure 4. Mean concentrations of metabolites related to the fatty acids oxidation, protein catabolism, and propionate fermentation detected in *Taenia crassiceps* cysticerci intracranially inoculated in mice after *in vivo* treatment with the association of albendazole and praziquantel



Control= group treated with 50 µl of NaCl 0.9%; ABZ+PZQ = group treated with the albendazole and praziquantel association, ABZ = group treated with albendazole; PZQ = group treated with praziquantel. * $p \leq 0.05$ in comparison to control group; [a] $p \leq 0.05$ in comparison to the Albendazole + Praziquantel treated group (ABZ + PZQ). Statistical analysis: two-way ANOVA followed by Tukey post-test.
Source: Prepared by the authors.

This study determined the metabolic impact of the association of the most commonly used anthelminthic drugs, albendazole, and praziquantel, on *T. crassiceps* cysticerci intracranially inoculated in mice. The use of experimental models in NCC studies has helped to determine several aspects of the host-parasite relationship as well as the mechanisms used by the parasite to ensure survival in different habitats and its adaptations to stressful environments (Lange; Mahanty; Raimondo, 2013).

T. crassiceps is a good experimental model to mimic the *T. solium* infection and also as a model for drug screening (Mahanty; Madrid; Nash, 2013). Biochemical approaches represent important evaluations to determine the responses of the parasite to the drugs used as well as a predictor of the parasite`s death due to the extension of the metabolic damage (Vinaud; Ambrosio, 2020).

Albendazole and praziquantel have been used in NCC treatment for over 40 years without a standardized protocol and with diverse information regarding side effects, better dosage for different clinical presentations, and duration of treatment. Several aspects influence the treatment

outcome, some linked to the host such as age and immunological status, and others linked to the parasite such as location, quantity, and evolutive stage of cysticerci within the central nervous system (Garcia et al., 2014). Both drugs are effective, although albendazole presents more significant efficacy regarding clinical outcomes in NCC patients (Matthaiou et al., 2008). Garcia et al. (2014) have demonstrated that the ABZ-PZQ association increased the parasiticidal effect when used in NCC treatment and also that increased ABZ dosages lead to complete cyst clearance.

The ABZ-PZQ association induced an impairment in glycolysis within the parasites. Glycolysis is the main energetic pathway and when followed by the TCA cycle is the most rentable one in terms of ATP generation (Saz, 1981). The drug's modes of action are capable of inducing tegument damage and impairment of the tubulin polymerization which alters the glucose uptake forcing the parasite to use the energetic reserves such as glycogen stored in tegument vesicles and other alternative energetic pathways (Vinaud; Ambrosio, 2020).

The PZQ monotherapy exposure probably induced greater consumption of the carbohydrate reserves stored in the parasite`s tegument which can be observed by the increase in glucose, PEP, and LDH concentrations, or induced gluconeogenic pathways when the concentrations of glucose, oxaloacetate, and malate are considered. The pyruvate non-detection in the drug association and the PZQ monotherapy treatments may have occurred due to its consumption to form lactate or oxaloacetate.

The TCA cycle was inhibited by the ABZ-PZQ association in comparison to the control group due to the significant decrease in succinate, fumarate, malate, and oxaloacetate concentrations. A similar effect was observed after the ABZ monotherapy which is following previous studies performed by our group (Leandro et al., 2014; Picanço et al., 2019). The PZQ monotherapy induced the fumarate reductase pathway due to the enhancement of succinate and fumarate concentrations which has also been described as a particular response of intracranially inoculated cysticerci to the hostile presence of this drug (Leandro et al., 2014; Silva et al., 2018). The fumarate reductase pathway is an important one to ensure aerobic mitochondrial metabolism and it is commonly used by the parasite whether under the presence of drugs or not. Alterations in the fumarate-reductase pathway have been described to be linked to benzimidazole derivatives resistance in helminths (Bryant; Bennet, 1983).

It was possible to observe an increase in the propionate fermentation after the ABZ-PZQ association treatment. Propionate is an end product of a series of catabolic reactions that occur inside mitochondrion. These reactions take place when there is an excess of lactate, pyruvate, and succinate through the propionyl-CoA enzyme activity (Zhuge et al., 2013). This increase in propionate concentrations may explain the lower lactate concentrations found in the ABZ-PZQ association treatment group in comparison to PZQ monotherapy treated one. The detection of the propionyl-CoA and methylmalonyl CoA pathway in cestodes has been described in *Spirometra mansonoides* (Meyer; Mueller; Meyer, 1978; Tkachuck et al., 1997) and two species of *Echinococcus* (McMannus; Smyth, 1978). Therefore, the main end products of the carbohydrate energetic metabolism of cestodes are lactate, succinate, acetate, malate, pyruvate, and propionate which are affected by the presence of drugs as determined in our study.

It is interesting to highlight the induction of alternative energetic pathways such as fatty acids oxidation and protein catabolism after the ABZ-PZQ association. These alternative energetic pathways are increased when there is an impairment of energy production by the main routes such as glycolysis and TCA cycle. It is an important indication that the parasite is metabolically suffering and is adapting to ensure survival (Vinaud; Ambrosio, 2020). The influence of anthelminthic drugs on alternative energetic pathways of *T. crassiceps* cysticerci has been described previously and is following the findings in this study (Fraga et al., 2012; Vinaud et al., 2009).

4 CONCLUSION

As reported in the literature the ABZ-PZQ association has been demonstrated to present clinical advantages in NCC treatment (Dominik et al., 2023). In addition, as described in this study, it also presented important metabolic impacts on the parasite regarding glycolysis, TCA cycle, propionate fermentation, and protein catabolism which are important indicators of metabolic stress in the parasite. The *in vivo* treatment with ABZ-PZQ association in experimental NCC was responsible for a harmful environment for the parasite detected by the increase in alternative energetic pathways. Accordingly, the single drug treatment also induced important metabolic alterations in glycolysis, homolactic fermentation, TCA cycle, fumarate reductase cycle, and alternative energetic pathways. Thus, the metabolic impact of albendazole and

praziquantel association is greater than the ones observed after the monotherapies and should be considered as an alternative therapeutic approach in NCC cases.

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