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ORIGINAL ARTICLE

Effect of nitazoxanide on albendazole pharmacokinetics in cerebrospinal fluid and plasma in rats

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Abstract *Background:* Although albendazole is the drug-of-choice for the treatment of neurocysticercosis, its efficacy is limited due to its low bioavailability. An alternative for optimizing pharmacological treatment is through drug combinations. *In vitro* studies have shown that nitazoxanide and tizoxanide (the active metabolite of nitazoxanide) exhibit cysticidal activity and that the combination of tizoxanide with albendazole sulfoxide (the active metabolite of albendazole) produced an additive effect. *Objectives:* (1) To assess the concentration profile of tizoxanide in plasma and in cerebrospinal fluid; and (2) to evaluate the influence of nitazoxanide on the pharmacokinetics of albendazole in plasma and in cerebrospinal fluid. *Methods:* Two different studies were conducted. In study 1, 10 male Sprague-Dawley rats received a single oral dose of 7.5 mg/kg of nitazoxanide and serial blood and cerebrospinal fluid samples were collected over a period of 4 h. In study 2, 38 healthy male Sprague-Dawley rats were randomly divided into two groups: one of these received a single dose of albendazole (15 mg/kg) and, in the other group, albendazole (15 mg/kg) was co-administered with nitazoxanide (7.5 mg/kg). Plasma and cerebrospinal fluid samples were collected from 0 to 16 h after administration. Albendazole sulfoxide and tizoxanide levels were assayed by

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using HPLC or LC/MS techniques. *Results:* In study 1, tizoxanide reached a maximum plasma concentration of 244.42 ± 31.98 ng/mL at 0.25 h; however, in cerebrospinal fluid, this could be detected only at 0.5 h, and levels were below the quantification limit (10 ng/mL). These data indicate low permeation of tizoxanide into the blood brain barrier. In study 2, Cmax, the area under the curve, and the mean residence time of albendazole sulfoxide in plasma and cerebrospinal fluid were not affected by co-administration with nitazoxanide. *Conclusion:* The results of the present study indicate that in rats at the applied doses, tizoxanide does not permeate into the cerebrospinal fluid. Furthermore, nitazoxanide does not appear to alter significantly the pharmacokinetics of albendazole in plasma or in cerebrospinal fluid.

1. Introduction

Neurocysticercosis (NCC) is the most important parasitic infection of the nervous system caused by the larval form of the tapeworm *Taenia solium*. The infection is acquired when a human ingests oncospheres of *Taenia*, which permeate into the small blood vessels and migrate to muscles, brain, and other tissues (Nash and Garcia, 2011). NCC is the major cause of seizures and a public health problem in many countries of the Indian subcontinent and Latin America, including Mexico (Fleury et al., 2012; Ndimubanzi et al., 2010). Pharmacological treatment of NCC is based on two cysticidal drugs: praziquantel (PZQ) and albendazole (ABZ). Given its efficacy, to date ABZ is preferred over PZQ (Del Brutto et al., 2006). ABZ binds to the β-subunit of tubulin, inhibiting its polymerization, thus preventing microtubule formation (Lacey, 1990; Martin, 1997).

ABZ is rapidly and extensively metabolized to albendazole sulfoxide (ABZ-SO), an active metabolite. In humans, the metabolite permeates into the cerebrospinal fluid (CSF); however, due to the low solubility of ABZ, its bioavailability is low and variable, and therefore plasma and CSF levels of ABZ-SO are also highly variable among individuals (Jung-Cook, 2012).

In order to increase ABZ bioavailability, different strategies have been proposed during the last 10 years: for example, administration of ABZ with a fatty meal (Mares et al., 2005), use of surfactants in solid dispersions (Castro et al., 2013), the development of binary and ternary formulation systems with cyclodextrins, as well as the use of water soluble polymers or hydroxyacids (Casulli et al., 2006; Kalaiselvan et al., 2006, 2007; Palomares-Alonso et al., 2010). Recently, a novel intranasal microemulsion has been evaluated for the delivery of ABZ-SO to the brain (Shinde et al., 2015). Despite the positive results reported, none of them is available in the market.

The combination with existing drugs offers another alternative for increasing ABZ effectiveness. Little research has been performed in this area, and the majority of the studies are related to the ABZ–PZQ combination. For example, an *in vitro* additive interaction between PZQ and ABZ-SO was reported by our group (Palomares et al., 2006). It has also been demonstrated that plasma levels of ABZ-SO increased when the combined treatment was administered in patients with NCC (Garcia et al., 2011). Recently, the same authors documented that this combination was more effective than ABZ alone in patients with parenchymal NCC (Garcia et al., 2016).

Another drug that has demonstrated activity against different nematodes and trematodes is nitazoxanide (NTZ) (Anderson and Curran, 2007; van den Enden, 2009). This drug is used as a broad-spectrum antiparasitic drug in adults and children in many areas of the world (Somvanshi et al., 2014). Also, this drug has demonstrated cysticidal efficacy against *Taenia crassiceps* cysts (Palomares-Alonso et al., 2007). After its oral administration, NTZ is partially absorbed from the gastrointestinal tract and is rapidly hydrolyzed by plasma esterases into its desacetyl derivative, tizoxanide (desacetylnitazoxanide, TZO) which is the active metabolite (Stockis et al., 1996). Although its mechanism of action is not well known, it has been postulated that in helminths, NTZ is a non-competitive inhibitor of the pyruvate ferredoxin oxidoreductase enzyme, altering anaerobic metabolism (Romero et al., 1997; Walker et al., 2004).

Considering that the mechanisms of action of NTZ and ABZ are different, this combination has been evaluated for the treatment of echinococcosis and cysticercosis. Thus, Stettler et al. (2004) found that the use of NTZ in combination with ABZ improved the ABZ pharmacokinetics as well as efficacy in the echinococcosis murine model. In the case of cysticercosis, Palomares-Alonso et al. (2007) reported that the combination of NTZ and ABZ, as well as ABZ-SO and TZO, resulted in an additive effect against *Taenia crassiceps* cysts *in vitro*.

Taking into account that one of the major obstacles to successful pharmacological management of NCC is the presence of the blood brain barrier (BBB) (Nau et al., 2010), the present study attempted to determine whether TZO is capable of crossing the BBB and to evaluate the influence of NTZ on the pharmacokinetics of ABZ in plasma and in CSF.

2. Materials and methods

2.1. Chemicals and reagents

ABZ-SO and TZO standards used for the analytical methodology were synthesized by Drs. Rafael Castillo-Bocanegra and Alicia Hernández Campos at the Facultad de Química, UNAM, Mexico. Chemical identity was confirmed by NMR, MS analysis, and melting point determination. ABZ, mebendazole (MBZ), and nifuroxazide (NFZ), used as internal standards (IS) for plasma ABZ-SO and plasma TZO analysis, respectively, were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Methanol, acetonitrile, ether, dichloromethane, and chloroform were of HPLC grade (Mallinckrodt