Veterinary Parasitology 203 (2014) 80–86

Contents lists available at ScienceDirect

Veterinary Parasitology

journal homepage: www.elsevier.com/locate/vetpar

Enhanced chemoprophylactic and clinical efficacy of albendazole formulated as solid dispersions in experimental cystic echinococcosis

Patricia E. Pensel[a,d], Silvina Castro[b,d], Daniel Allemandi[b,d], Sergio Sánchez Bruni[c,d], Santiago D. Palma[b,d], María Celina Elissondo[a,d,*]

[a] Laboratorio de Zoonosis Parasitarias, Facultad de Ciencias Exactas y Naturales, Universidad Nacional de Mar del Plata, Argentina
[b] Laboratorio de Farmacotecnia, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, UNITEFA, Argentina
[c] Laboratorio de Farmacología, Departamento de Fisiopatología, Facultad de Ciencias Veterinarias, Universidad Nacional del Centro de la Provincia de Buenos Aires, CIVETAN, Argentina
[d] Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina

ARTICLE INFO

Article history:
Received 3 September 2013
Received in revised form 23 January 2014
Accepted 28 January 2014

Keywords:
Cystic echinococcosis
Echinococcus granulosus
Albendazole
Solid dispersions

ABSTRACT

Cystic echinococcosis is a chronic, complex, and still neglected disease. Although albendazole has demonstrated efficacy, only about one-third of patients experience complete remission or cure and 30–50% of treated patients develop some evidence of a therapeutic response. Different strategies have been developed in order to improve the albendazole water solubility and dissolution rate. The aim of the current work was to investigate the chemoprophylactic and clinical efficacy of an albendazole:poloxamer 188 solid dispersion formulation on mice infected with *Echinococcus granulosus* metacestodes. Albendazole formulated as solid dispersion had greater chemoprophylactic and clinical efficacy than albendazole alone. The improved in therapeutic efficacy could be a consequence of the increase in the systemic availability of albendazole sulfoxide. The work reported here demonstrates that in vivo treatment with albendazole:poloxamer 188 impairs the development of the hydatid cysts. This new pharmacotechnically based strategy could be a suitable alternative for treating cystic echinococcosis in humans.

1. Introduction

Cystic echinococcosis (CE), a zoonosis caused by the larval stage of *Echinococcus granulosus*, is characterized by long term growth of hydatid cysts in humans and mammalian intermediate hosts (McManus et al., 2012). This parasitic infection is a chronic, complex, and still neglected disease (Brunetti et al., 2011).

Currently four treatment approaches are in use: surgery, PAIR (puncture, aspiration, injection of protoscolicidal agent, reaspiration), chemotherapy with benzimidazoles (BZ), and watch and wait for inactive, clinically silent cysts (Stojkovic et al., 2009). The appropriate treatment depends on cyst characteristics (for hepatic cysts, size and stage are the most important criteria), the therapeutic resources available, and the physician's preference. The level of evidence supporting one therapeutic modality over the other is low because only few prospective, randomized studies comparing different treatments are available (Brunetti and White, 2012).

* Corresponding author at: Laboratorio de Zoonosis Parasitarias, Facultad de Ciencias Exactas y Naturales, Universidad Nacional de Mar del Plata (UNMdP), Funes 3250, 7600 Mar del Plata, Argentina.
Tel.: +54 223 475 2426; fax: +54 223 475 3150.
E-mail addresses: c.elissondo@gmail.com, mceliss@mdp.edu.ar (M.C. Elissondo).

0304-4017/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.vetpar.2014.01.027

Surgery is usually complemented by antiparasitic drugs, and in inoperable cases, chemotherapy is the only option. The drugs commonly used for anti-hydatid cysts treatment are BZ, such albendazole (ABZ) and mebendazole (McManus et al., 2012). ABZ belongs to type II biopharmaceutical classification system, with low aqueous solubility (0.01 mg/ml in water at 25 °C) and high permeability (Jung et al., 1998). Consequently, this compound has to be administrated at higher doses or as multiple doses in order to provide therapeutic concentrations and acceptable anthelmintic efficacy (Cook, 1990). According to WHO recommendations, ABZ is given in daily doses of 10–15 mg/kg of body weight in two divided doses postprandially for 3–6 month (WHO, 2001). Although albendazole has demonstrated efficacy, only about one-third of patients experience complete remission or cure and 30–50% of treated patients develop some evidence of a therapeutic response. Furthermore, between 20 and 40% of patients with hydatid cysts do not respond to medical management with ABZ (Moro and Schantz, 2009).

Therapeutic failures following oral administration with ABZ have been primarily linked to the poor drug absorption rate resulting in low drug level in plasma and hydatid cysts (Daniel-Mwambete et al., 2004). It is well known that the slow dissolution rate of ABZ leads generally to a poor and erratic absorption from the gastro-intestinal tract (Castro et al., 2012). Moreover, the low solubility drugs offer only few formulation alternatives, limiting the administration routes available (Alanazi et al., 2007; Vogt et al., 2008; Castro et al., 2012). Therefore, the increasing of aqueous solubility and dissolution rate of ABZ is a relevant goal to optimize the chemotherapeutic treatment of CE.

Different strategies have been developed in order to improve to ABZ water solubility and dissolution rate such as preparation of oil in water emulsion (Shuhua et al., 2002), incorporation into liposomes (Wen et al., 1996) and complexation with cyclodextrins (Kata and Schauer, 1991). Increased systemic bioavailability of albendazole was also reported when drug co-administered with a fatty meal (Lange et al., 1988), fruit juice (Nagy et al., 2002), cosolvent (Torrado et al., 1997), or with surfactants (del Estal et al., 1994). In addition, several clinical studies have demonstrated that enhanced systemic availability of the parent drug/active metabolite obtained by increased drug absorption correlates with an improved antiparasitic effect (Torrado et al., 1997; Wen et al., 1996; Mingjie et al., 2002; Shuhua et al., 2002; García et al., 2003; Ceballos et al., 2006, 2008, 2009; Liu et al., 2012).

Solid dispersions (SDs) are one of the most successful strategies to improve drug dissolution rate of poorly soluble drugs. SDs are molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties (Vasconcelos et al., 2007). Different materials have been evaluated as carriers. The first SDs generation involved the use of crystalline carries (Levy, 1963; Sekiguchi et al., 1964) and sugars (Kanig, 1964), while for the second generation several types of hydrophilic polymers such as polyethylene glycols (Wang et al., 2004; Janssens et al., 2008), polyvinylpyrrolidone (Marín et al., 2002; Konno et al., 2008) among others, have been evaluated. Recently, some studies evidenced that the dissolution rate may be improved using carriers, which possess surface activity or self-emulsifying properties. This third generation of SDs were more efficient at enhancing bioavailability of poorly soluble drugs and SDs thus obtained were more stable owing mainly to a reduction of drug recrystallization (Vasconcelos et al., 2007).

Poloxamers are polyoxyethylene–polyoxypropylene block copolymer nonionic surfactants that have been widely used as wetting and solubilizing agents. Furthermore, these compounds are used in a variety of oral, parenteral, and topical pharmaceutical formulations and are generally regarded as nontoxic and nonirritant materials (Castro et al., 2012). Poloxamers are not metabolized in the body (Collett and Popli, 2000). Previous works have demonstrated a significant increase on dissolution rate of ABZ using Poloxamer 188 (P 188) as carrier in SDs or physical mixtures (Castro et al., 2010, 2012). Moreover, the in vitro dissolution rate of ABZ formulated as SDs showed an acceptable correlation with the in vivo pharmacokinetic studies. Increased systemic availability was obtained when ABZ was administered as ABZ:P 188 SDs, with a 50% enhancement in systemic exposure (AUC values) compared to treatment with a simple ABZ suspension. Consistently, the Cmax increased 130% following treatment with P 188 based SDs ABZ formulation. The enhanced bioavailability of ABZ in SDs containing P 188 as carrier could be attributed to the improved dissolution rate and the surfactant effects of this carrier (Castro et al., 2012).

The aim of the current work was to investigate the chemoprophylactic and clinical efficacy of an ABZ:P 188 solid dispersion formulation on mice infected with *E. granulosus* metacestodes.

2. Materials and methods

2.1. Chemicals

For the preparation of SDs the following materials were used: ABZ (Pharmaceutical grade, Parafarm, Buenos Aires, Argentina), and POLOXAMER 188 (BASF, Germany). All other reagents were of analytical grade.

2.2. ABZ formulations

SDs were prepared by melting of ABZ and poloxamer (1:1) in a water bath at 63 °C. The mixtures were homogenized by stirring. The resulting homogenous preparations were rapidly cooled and pulverized. The 212-micron particle size fraction was obtained by sieving and kept in a screw-capped glass vial until use.

ABZ suspension (2.1 mg/ml) was prepared by dissolution of ABZ pure standard in deionized water (pH = 7.0) under shaking (12 h). The ABZ:P188 (4.2 μg/ml) was prepared by dissolution of ABZ:P 188 (1:1) in deionized water (pH = 7.0) under shaking (24 h). ABZ suspension and ABZ:P 188 were vigorously shaken before its intragastric administration to mice.