The Journal of Basic & Applied Zoology (2014) **67**, 40–47

The Egyptian German Society for Zoology

The Journal of Basic & Applied Zoology

www.egsz.org
www.sciencedirect.com

The potential role of mefloquine against *Schistosoma mansoni* infection by prohibition of hepatic oxidative stress in mice

Sohair R. Fahmy [a], Ibrahim Rabia [b], Eman M. Mansour [a,*]

[a] *Department of Zoology, Faculty of Science, Cairo University, Egypt*
[b] *Department of Parasitology, Theodor Bilharz Research Institute, Giza, Egypt*

Received 9 June 2014; revised 10 September 2014; accepted 15 September 2014
Available online 7 October 2014

KEYWORDS

Schistosoma mansoni;
Mefloquine;
Antioxidant;
Oxidative stress

Abstract The present study was designed to assess the relationship between anti-schistosomal effect of the antimalarial drug mefloquine (Mef) and the oxidative stress status of *Schistosoma mansoni* infected mice. Forty mice were divided into eight groups (5 mice/group); control (I, II), infected (III, IV), Mef low dosage (200 mg/kg) (V, VI), and Mef high dosage (400 mg/kg) (VII, VIII). Mef (200 and 400 mg/kg) was administered orally as a single dose at days 14 and 35 post infection (PI). All mice were sacrificed after 8 weeks PI. Oral administration of Mef (200 or 400 mg/kg) at day 14 or 35 PI reduced the total worm burden by 84%, 78% and 94%, 85.7% respectively. Meanwhile, Mef treatment reduced egg load in the intestine and the liver. Following Mef (200 and 400 mg/kg) treatment to mice at day 14 or 35 PI, the oogram pattern showed complete disappearance of all immature and mature ova. Treatment of mice with Mef at the two tested doses significantly decreased the activities of ALT, AST, ALP and GGT enzymes as compared to infected untreated group. However, administration of Mef (200 and 400 mg/kg) at day 14 or 35 PI significantly ($P < 0.05$) decreased the MDA level and increased the levels of GSH and CAT as compared to infected untreated group. In conclusion, Mef is an effective curative anti-schistosomal and anti-oxidative drug as it alleviates the biochemical and the oxidative stress alterations. Also, Mef has schistosomicidal and ovicidal effects.

* Corresponding author at: Zoology Department, Faculty of Science, Cairo University, Giza 12613, Egypt. Tel.: +20 01226667020.
E-mail address: eman.mansour@hotmail.com (E.M. Mansour).

Peer review under responsibility of The Egyptian German Society for Zoology.

ELSEVIER Production and hosting by Elsevier

Introduction

Schistosomiasis is a prevalent parasitic disease in tropical and sub-tropical areas, which accounts for the second place in terms of socioeconomic and public health burden (Cardoso et al., 2013; Kadry et al., 2013). Each year schistosomiasis afflicts up to 600 million people in 74 tropical and sub-tropical

2090-9896
http://dx.doi.org/10.1016/j.jobaz.2014.09.002

countries, predominantly in the developing world (El Ridi et al., 2014).

Schistosomiasis is associated with many complications; the most important of these are liver damage (WHO, 2010). Among the five different schistosome species, *Schistosoma mansoni* is the most abundant one in Egypt (Helmy et al., 2009). Pathology associated with *S. mansoni* results primarily from the accumulation of parasite eggs, giving rise to hepatomegaly that may be superseded by extensive liver fibrosis (Gryseels et al., 2006). It has also been shown that the granulomatous inflammatory response to *S. mansoni* eggs entrapped in the liver induces oxidative stress.

Oxidative stress is one of the most frequent problems in patients with chronic liver diseases as schistosomiasis (Heidelbaugh and Sherbondy, 2006). It was previously reported that during schistosome infestation, the parasite tends to switch from Krebs cycle to lactate production in the host which results in a surplus supply of O_2 which subjects the infected host to a state of oxidative stress or increased free radical formation (Tielens, 1994). Moreover, the parasite is exposed to ROS generated by the host effector cells as macrophages, eosinophils, neutrophils, and platelets (McDermott et al., 1997). ROS leads to the release of toxic oxygen radicals principally O_2 and H_2O_2 during the respiratory burst. These two radicals may interact to produce hydroxyl radical, which is even more reactive.

Several medications are used in the treatment of schistosomiasis including praziquantel and oxamniquine, metrifonate, antimonials, hycanthone and niridazole. Current treatment relies on praziquantel (PZQ) (Zhang and Coultas, 2013). Unfortunately, PZQ has stage-dependent susceptibility, showing only poor efficacy against immature schistosome stages (Keiser et al., 2009). In addition, many lines of evidence indicate to increasing the emergence of strains of *S. mansoni* resistant to praziquantel (Zhang and Coultas, 2013). So for controlling schistosomiasis, there is an urgent need to develop a new effective drug.

In recent years, antimalarial drug mefloquine (Mef) has been found to exhibit potential effects against schistosomes (Xiao and Xue, 2012). The drug presented remarkable *in vitro* and *in vivo* activities against major schistosome species (El-Lakkany et al., 2011; Ingram et al., 2012; Zhang and Xiao, 2012). Based on the previous information, the present study was designed to assess the relationship between anti-schistosomal effect of the antimalarial drug mefloquine and the oxidative stress status of *S. mansoni* infected mice.

Material and methods

Drug and dose

Mefloquine (Larium, 250 mg tablet) was provided by F. Hoffmann-La Roche (Basel, Switzerland). Mefloquine was suspended in vehicle (7% (v/v) Tween-80 and 3% (v/v) ethanol) and administered orally as a single low dosage of 200 mg/kg or high dosage of 400 mg/kg (Keiser et al., 2009).

Animals

Male Swiss albino mice (CD-1 strain) weighing 18–20 g were used in all experiments. The animals were obtained from a closed random bred colony at the Schistosome Biological Supply Center (SBSC) at Theodor Bilharz Research Institute (TBRI), Giza, Egypt. Animals were housed in polycarbonate boxes with steel-wire tops (not more than six animals per cage) and bedded with wood shavings. Ambient temperature was controlled at 22 ± 3 °C with a relative humidity of 50 ± 15% and a 12-h light/dark photoperiod. Food and water were provided *ad libitum*. This study was conducted in accordance with legal ethical guidelines of the Medical Ethics Committee of the Theodor Bilharz Research Institute (TBRI), Giza, Egypt (Approval No. 4018/2011).

Schistosome infection

S. mansoni cercariae (Egyptian strain) were obtained from infected intermediate host snails (*Biomphalaria alexandrina*) maintained at the SBSC. Mice were infected subcutaneously with freshly shed 60 ± 10 cercariae/mouse (Liang et al., 1987).

Experimental design

Forty mice were divided into eight groups (5 mice/group), as follows: Two normal, non-infected control groups received vehicle at days 14 and 35. Two infected non treated groups received vehicle at days 14 and 35. Two treated groups received a single low dosage of Mef (200 mg/kg) at days 14 and 35. Two treated groups received a single high dosage of Mef (400 mg/kg) at days 14 and 35. Mice of all experimental groups were euthanized by exsanguination at 8 weeks post-infection.

Study of parasitological criteria

Immediately after mice euthanization, blood was collected from the neck blood vessels in centrifuge tubes. Hepatic and portomesenteric vessels were perfused for worms' recovery and subsequent counting (Duvall and De Witt, 1967). After perfusion, a piece of liver and the middle part of the small intestine were used for the determination of the number of ova per gram liver or intestinal tissues after digestion overnight in 5% KOH (Cheever, 1968; Kamel et al., 1977). The percentage of eggs at various developmental stages was examined in three samples from each mouse and the mean number of eggs at each stage/animal was determined (Pellegrino et al., 1962). Perfused liver, was stored at −80 °C for assessing oxidative stress parameters.

Sample preparation

Serum preparation

Blood samples collected in centrifuge tubes were centrifuged at 3000 rpm for 20 min. Serum was stored at −20 °C until used for biochemical assays.

Tissue homogenate preparation

Liver tissue was homogenized (10% w/v) in ice-cold 0.1 M Tris–HCl buffer (pH 7.4). The homogenate was centrifuged at 3000 rpm for 15 min. at 4 °C and the resultant supernatant was used for biochemical analysis.