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ORIGINAL ARTICLE

Protective effect of berberine chloride on *Plasmodium chabaudi*-induced hepatic tissue injury in mice

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Abstract The present study aimed to investigate the protective role of berberine (BER) against *Plasmodium chabaudi*-induced infection in mice. Animals were divided into three groups. Group I served as a vehicle control. Group II and group III were infected with 1000 *P. chabaudi* infected erythrocytes. Group III was gavaged with 100 µl of 10 mg/kg berberine chloride for 10 days. All mice were sacrificed at day 10 post-infection. The percentage of parasitemia was significantly reduced more than 30%, after treatment of mice with BER. Infection caused marked hepatic injuries as indicated by histopathological alterations as evidenced by the presence of hepatic lobular inflammatory cellular infiltrations, dilated sinusoids, vacuolated hepatocytes, increased number of Kupffer cells and the malaria pigment, hemozoin. These changes in livers led to the increased histological score. Also, infection induced a significant increase in liver alanine aminotransferase and aspartate aminotransferase and a significant increase in the total leucocytic count. Moreover, mice became anemic as proved by the significant decrease in erythrocyte number and haemoglobin content. BER showed a significant protective potential by improving the above mentioned

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parameters. Based on these results, it is concluded that berberine could offer protection against hepatic tissue damage.

1. Introduction

Malaria was recognized as a human disease more than 5000 years ago (Sherman, 1999). It continues to be a major health threat in tropic countries. Malaria infects 225 million people and kills 781,000 people, mainly African children, worldwide per annum (Garcia, 2010; WHO, 2010). An estimated 5.1 billion dollars is required to control malaria each year (WHO, 2012).

The liver is known as the site of preerythrocytic development of *Plasmodium* parasites and it is also an important effector against malarial blood stages (Frevert and Nardin, 2008). In particular, the reticular endothelial system of the liver is able to eliminate parasite-derived hemozoin and even *Plasmodium*-infected erythrocytes through phagocytosis (Krücken et al., 2009).

Phillips et al. (1997) reported that, a convenient model to study the role of the liver in malaria is the murine malaria *Plasmodium chabaudi*, which shares several common characteristics with the most dangerous human parasite *Plasmodium falciparum*, causing malaria tropica.

Recently, attention has been focused on the protective role of naturally occurring antioxidants, generally in biological systems (Van Wyk and Wink, 2004; Wunderlich et al., 2014a,b) and specifically against malaria (Mubaraki et al., 2014).

Berberine is a plant alkaloid with a long history of medicinal use in both Ayurvedic and Chinese medicine (Kulkarni and Dhir, 2008; Bhutada et al., 2010). Previous studies have shown that BER has a wide ranging pharmacological and biological activities including anti-protozoal infection (Malik et al., 2014). Also, Dkhil (2014) reported the antischistosomal activity of berberine as well as its ameliorative effect on the induced liver injury due to infection with *Schistosoma mansoni*. The present study aimed to investigate the protective role of berberine against *P. chabaudi*-induced infection in mice.

2. Materials and methods

2.1. Animals

Thirty male Swiss albino mice were bred under specified pathogen-free conditions and fed a standard diet and water *ad libitum*. The experiments were performed only on mice at an age of 10–12 weeks and were approved by state authorities and followed Saudi Arabian rules for animal protection.

2.2. Infection of mice

The strain of *P. chabaudi* was kindly provided by Prof. Wunderlich (Heinrich Heine University, Dusseldorf, Germany). Blood stages of *P. chabaudi* were weekly passaged in Swiss albino mice. Experimental animals were challenged with 1000 *P. chabaudi*-parasitized erythrocytes. Parasitemia was evaluated in Giemsa stained blood smears, and total erythrocytes were counted in a Neubauer chamber.

2.3. Experimental design

Animals were divided into three groups. The first group served as a vehicle control. The second and the third group were infected with 1000 *P. chabaudi*-parasitized erythrocytes. The third group was gavaged with 100 µl of 10 mg/kg berberine chloride for 10 days (Jahnke et al., 2006). All mice were sacrificed at day 10 post-infection.

2.4. Liver histology

Pieces of the liver were fixed in 10% buffered formalin at room temperature overnight and embedded in paraffin, and 5 µm sections were stained with hematoxylin and eosin.

For the liver, the extent of histological changes was scored according to Jamshidzadeh et al. (2008) as follows: 0: absent; +: mild; ++; moderate; and +++: severe. The liver activity index was estimated using a modified quantitative Ishak scoring system (Ishak et al., 1995); scores of 1–3 were assigned to cases of minimal liver damage, scores of 4–8 to mild, scores of 9–12 to moderate, and scores of 13–18 to severe cases.

2.5. Hematological studies

Blood was collected into tubes containing ethylene diamine tetra acetic acid for the determination of some important hematological parameters (total erythrocyte count, total leucocytic count and haemoglobin content) using an automatic counter (VET-530 CA Medonic; Medonic, Stockholm, Sweden).

2.6. Biochemical studies

Blood plasma was separated and kept at −20 °C until use. Plasma was then analyzed using commercial kits (Biomerieux, Marcy l'Etoil, France) for alanine amino transferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP).

2.7. Statistical analysis

One-way ANOVA was carried out. The data were analyzed by using Excel 2007 (Microsoft, USA), and SigmaPlot 2001 (SPSS, USA). $P \leqslant 0.05$ is considered to be statistically significant. The obtained data were presented as means ± standard deviation.

3. Results

Parasitemia reached about 40% at day 10 p.i. with *P. chabaudi* (Fig. 1). The percentage of parasitemia was significantly reduced more than 50%, after treatment of mice with berberine (Fig. 1).