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Research Article
Histopathological Changes Induced by Artesunate in Liver of Wistar Rat

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Abstract

Background: Artesunate, a potent and rapidly acting blood schizontocide generally used to treat chloroquine resistant malaria. Artesunate has been noted to produced hepatotoxicity, neurotoxicity and hematological abnormalities besides cause embryo, reduced reproductive capacity. **Material and Methods:** The present study reported sub-chronic safety profile of artesunate on the liver of Wistar rat after 7 days oral administration at 2, 4 and 8 mg kg^{-1} day^{-1}. **Results:** Treatment with artesunate at 4 and 8 mg kg^{-1} day^{-1} produced inflammatory changes in liver besides sinusoidal dilation, sinusoidal congestion, cytoplasmic vaculation and focal necrosis. **Conclusion:** Drugs may yield adverse effects instead of fight against illnesses, when administered inaccurately. It is right time that now all countries should issue proper guidelines. So, it is very important to aware certified drug sellers and medicine store keepers to regularly create awareness in drug users on how to use their prescribed drugs.

Key words: Artesunate, malaria, hepatotoxicity, Wistar rat

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

According to the WHO[1], there were 149-303 million new cases of malaria worldwide. The African region contributing 88% of total malaria cases, while 10% cases are coming from South-East Asia region and rest cases (2%) are coming from Eastern Mediterranean region. The 438000 malaria deaths (range 236 000-635 000) were reported worldwide in 2015. About 90% of these deaths occurred in the African region, while the South-East Asia region contribute 7% and the rest 2% from Eastern Mediterranean region. Mostly the children below 5 years age are particularly susceptible to malaria and then ultimately to the death[1].

Artesunate is used to treat complicated chloroquine resistant malaria. World Health Organization (WHO) preferred this drug over quinidine, the only other non-oral medication for severe malaria[1]. It is available as a solution both for intravenous or intramuscular injection and as in salt form for oral use[2]. Artesunate is semi-synthetic derivative from the sweet wormwood plan (*Artemisia annua*) and in the artemisinins medication class[2]. Artesunate has active metabolite dihydroartemisin which are potent blood schizonticides and awfully potent against complicated chloroquine resistant strain *Plasmodium falciparum*[3]. This drug is used in combination therapy and many studies on toxicity of this drug showed validation of toxicity on the brain stem[4-6], superior colliculus[7], stomach[8] and testis[9]. Serious questions have been raised about irrational use of artesunate because presently it is the last option to fight against resistant strains of *P. falciparum* malaria[10]. In furtherance to protect their effectiveness and to avoid emanation of new resistant strains of *Plasmodium*, these drugs should be used in controlled manner and their use should be restricted on proved multi-drug resistance strain of severe malaria[11]. The patient may have untoward toxic harmful effects[12]. Research on brain stem toxicity proved clinically in animals[13]. Bigoniya *et al.*[14] studied hematological and biochemical effects in rats after sub-chronic exposure of artesunate. Akpanyung *et al.*[15], Desai *et al.*[16] and Onovo *et al.*[17] also studied toxicological effects of artesunate in rats.

The largest metabolic organ and center of all metabolic activities is liver. The liver is susceptible to the toxicity because in liver all other foreign substances and drugs are metabolized and inactivated. Certain medicinal agents may cause injury to liver when popping in exuberance and even within suggested salutary ranges. Only few narrations are available regarding the sub abiding chattels of artesunate on the histopathology of the liver. In lieu of this, the current investigation was effectuated to investigate the response of this drug on the liver of Wistar rats.

MATERIALS AND METHODS

This study was conducted in Parasitology laboratory, Zoology Department, College of Science, King Saud University, during September, 2015. The experimental protocol was approved by the local animal experiment ethics committee.

Animals: Twenty four adult male Wistar rats weighing between 100-115 g and 7-8 weeks old were choosen for this study. The rats were kept in well-ventilated wire mesh cages measuring 45×35×28 cm and exposed to a 12 h light at a temperature of 25±2°C and food and water was provided.

Drug: Ulteria, the artesunate tablets were manufactured by Cipla limited, India. The drug solution was prepared in double distilled water (2 mg mL^{-1}) and administered to the rats orally for 7 days.

Experimental design: Four groups of 6 rats were made and drug administered; Group 0: Control (water), group 1: 2 mg kg^{-1}, group 2: 4 mg kg^{-1} and group 3: 8 mg kg^{-1}. The rats were sacrificed after 7 days.

Histopathology: Anesthetized animals sacrificed. Soon after dissection, the livers sections were kept in plastic containers and fixed by 10% formal saline for 24 h and then they were processed for histopathological examinations by using standard histopathological methods[14].

RESULTS

The results of histopathological changes in liver tissues are shown in Fig. 1-3. No fatality induced by this drug in the experimental animals. Figure 1 shows normal liver with no

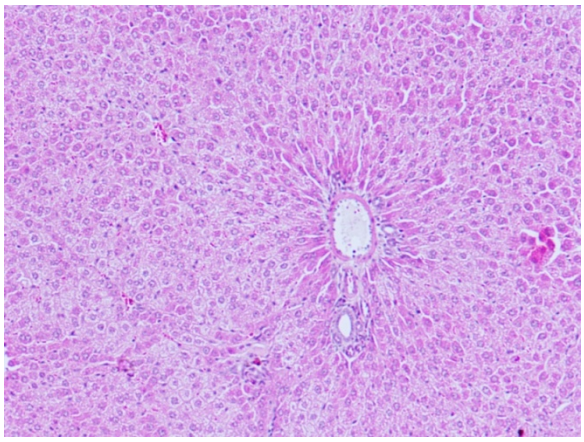

Fig. 1: TS of liver of control group

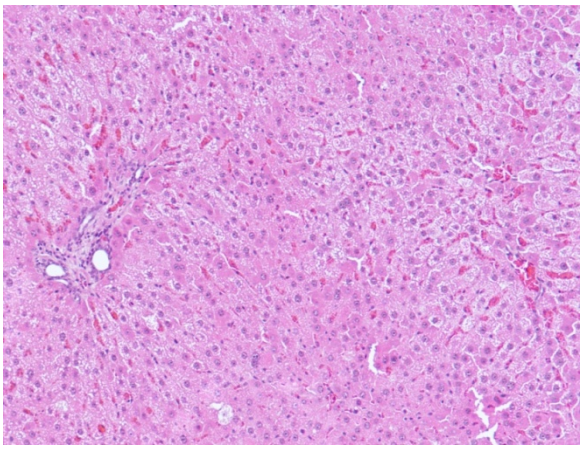

Fig. 2: TS liver of the group after treating with 2 mg kg^{-1} of oral artesunate, they showed normal hepatocyte, sinusoid and central vein

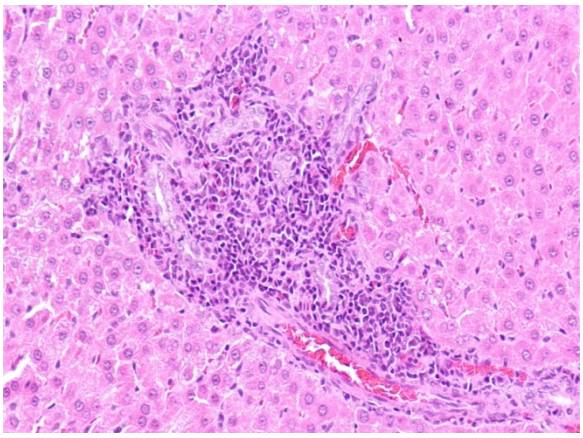

Fig. 3: TS liver of the group after treating with 4 mg kg^{-1} of oral artesunate induce liver damage and has led to pronounced morphological alterations and fibrosis

parenchyma damaged and normal central vein and tissue architecture. The animal groups which were given 2 mg kg^{-1} of oral artesunate, showed no form of distortion in the tissue architecture of the liver they showed normal hepatocyte, central vein and hepatic sinusoids (Fig. 2). Histological examination of the samples of liver revealed some abnormal morphology characteristics in group treated with 4 and 8 mg kg^{-1} for toxicity study, 4 mg kg^{-1} of oral artesunate produced liver damage and which ultimately led to preclinical morphological alterations and fibrosis, as proved by disrupt tissue architecture, formation of fibrosis septa, fibers accumulation and extension of fibers (Fig. 3). This drug induced loss of tissue architecture, sinusoidal congestion and

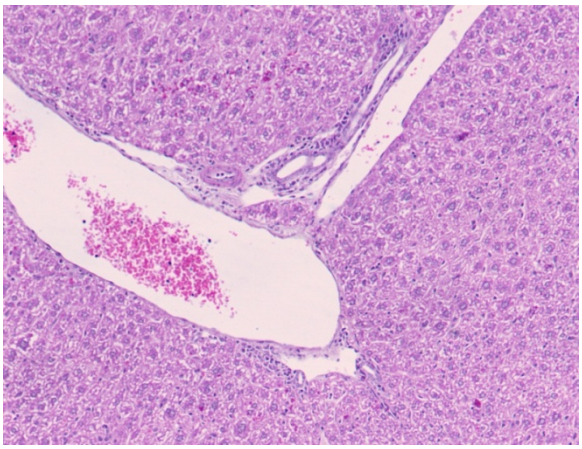

Fig. 4: TS liver of the group after treating with 8 mg kg^{-1} of oral artesunate caused sinusoidal congestion, infiltration of inflammatory cells and there was loss of tissue architecture in the liver

infiltration of inflammatory cells in the liver of the animals of group which were administered with 8 mg kg^{-1} (Fig. 4).

DISCUSSION

World Health Organization (WHO) introduced artesunate to combat against resistant starins of *P. falciparum* malaria[18]. It is most commonly and easily available artemisinin-related compounds, which is a semisynthetic hemisuccinate derivative of dihydroartemisinin[2]. It is potent antimalarial remarkably well tolerated drugs[16]. It can be administered parentally, intravenously, intramuscularly and can be given orally or rectally[17,19]. Usually, artesunate produced its anti-malarial exertion by the generating reactive oxygen species from its endoperoxide bond leading to lipid peroxidation. The reactive oxygen species cause macromolecular damage by alkylating heme and several other proteins. The recommended dose of artesunate is 2-10 mg kg^{-1} day^{-1} or maximum up to 200 mg day^{-1} in adult human body. Large clinical studies with malaria patients have shown that with insignificant side effects it can be well tolerated. However, some studies have suggested evidence of toxicity on the brainstem, superior colliculus, stomach, testis and liver in artesunate treated rats. Moreover, artesunate has been reported to destroy cancer cells and also reduces proliferation, interferes in DNA replication and cell cycle and enhance apoptosis through the intrinsic death pathway by ROS generation. It has been reported that artesunate is toxic at nanomolar concentration to malaria parasites, while micromolar concentration produced toxicity in mammalian

cells[20,21]. Evidences showed the neurotoxicity of artesunate at high doses (50-100 mg kg^{-1} day^{-1} oral and IM) in laboratory animals[13] including the cytotoxicity of artesunate on tumor cell lines have been reported[22,23].

Izunya *et al.*[24] reported that artesunate treatment at 4-8 mg kg^{-1} for 7 days has no effects on the histology of the heart in rats. Artesunate given at 16 mg kg^{-1}, orally for 7 days caused disturbance in liver function with damage to hepatocytes of guinea pig[25]. Hepatotoxicity and hemolytic effects of artesunate on rats at 4 mg kg^{-1}, oral for 5 days treatment are reported by Omotuyi *et al.*[26] Potential hepatotoxicity of artesunate is also reported by Izunya *et al.*[27] at 4-8 mg kg^{-1}, orally administered for 7 days on rats. Numerous research on artesunate exhibit deposition of toxicity on brain stem[4-6], superior colliculus[7], stomach[8] and testis[9]. Artemisinin derivatives showed male reproductive dysfunction and hematological abnormalities effecting liver blood cells and testis of guinea pigs at 2-8 mg kg^{-1} oral dosing for 7 days. Anyasor and Olorunsogo[28] reported alteration in biochemical parameters of liver and kidney of rats by artesunate at 2-5 mg kg^{-1}, oral dosing for 7 days. This study resemble with the investigation executed by Olurishe *et al.*[29] and Izunya *et al.*[24] where animals showed different degrees of haemosiderosis, cytoplasmic vacuolation, sinusoidal congestion and inflammation of the liver's portal tracts after receiving immunosuppressive remedy.

CONCLUSION

Drugs may yield adverse effects instead of fight against illnesses, when administered inaccurately. It is right time that now all countries should issue proper guidelines. So, it is very important to aware certified drug sellers and medicine store keepers to regularly crate awareness in drug users on how to use their prescribed drugs. The histopathological changes in liver of wister rats may occur humans. So, it is strongly proposed that the drug should be prescribed with all care in patients which were diagnosed with hepatic dysfunction.

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