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Original Article

Targeting the proinflammatory cytokines, oxidative stress, apoptosis and TGF-β1/STAT-3 signaling by irbesartan to ameliorate doxorubicin-induced hepatotoxicity☆

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ABSTRACT

Doxorubicin (DOX) is an anthracycline antibiotic that is used frequently for treatment of various types of malignancies. Hepatotoxicity is one of the serious complications of DOX. The aim of this study was to explore the effect of different doses of irbesartan on doxorubicin-induced hepatotoxicity in mice. Sixty male BALB/c mice were divided into six equal groups as follows: Control group; DOX group; Irbesartan (Small dose) group; Irbesartan (Large dose) group; DOX + Irbesartan (Small dose) group and DOX + Irbesartan (Large dose) group. Liver weight/body weight ratio, food intake, serum albumin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and total bilirubin were measured. Also, tissue antioxidant enzymes, transforming growth factor beta 1 (TGF-β1), nuclear factor (erythroid-derived 2)-like 2/heme oxygenase-1 (Nrf2/HO-1) content, tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) and signal transducer and activator of transcription-3 (STAT-3) were assessed. Parts of the hepatic tissues were subjected to histopathological examination. Irbesartan administration to DOX-treated mice induced significant decrease in serum ALT, AST, ALP, total bilirubin, tissue TGF-β1, TNF-α, IL-6 and liver weight/body weight ratio associated with significant increase in food intake, serum albumin, tissue Nrf2/HO-1 content, STAT-3 and antioxidant enzymes and significant improvement in the histopathological picture compared to DOX group. This improvement was significant with DOX + Irbesartan large dose compared to DOX + Irbesartan small dose. In conclusion, irbesartan – in a dose-dependent manner – might represent a promising hope for cancer patients to ameliorate DOX-induced hepatotoxicity.

1. Introduction

Doxorubicin (DOX) is one of anthracycline antibiotics that is used frequently for treatment of various types of malignancies including lung, breast, gastrointestinal and testicular cancers [1]. DOX reacts with DNA by intercalation and inhibits the synthesis of DNA macromolecular components. This inhibits the progression of topoisomerase II, an enzyme which is vitally important for DNA transcription. Moreover, DOX may increase the production of free radicals and reactive oxygen species, which in turn will contribute to its cytotoxic effects [2]. Also, it was suggested that DOX increases the production of ceramide which might be specifically involved in sensitizing cancer cells to the cytotoxic effects of DOX [3].

Hepatotoxicity is one of the serious complications of DOX [4]. Its mechanisms are still not fully understood but induction of oxidative stress, increased formation of the proinflammatory cytokines and affection of mitochondrial functions were proposed as

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potential causes [5]. So, it has become increasingly important to find pharmacological remedies to protect against this serious adverse effect. In an attempt to minimize DOX effective chemotherapeutic dose and thereby its side effects, a variety of approaches were investigated to be used in combination with DOX [1].

Irbesartan is an angiotensin II receptor blocker used frequently for management of hypertension [6]. Irbesartan was reported to have the highest oral bioavailability among the other angiotensin II receptor blockers [7]. Recent investigations suggested that drugs acting on the renin-angiotensin system such as irbesartan may have potential protective effects on various body organs including the heart, kidney and liver [8]. Irbesartan was proven to have anti-inflammatory effects on the vascular endothelium, possibly though inhibition of the expression of the proinflammatory cytokines such as tumor necrosis factor alpha and interleukin 6 [9]. Moreover, irbesartan was reported to have potent effects on the intracellular antioxidant enzymes expression and activity, hence ameliorating the deleterious effects of oxidative stress on various tissues of the body [10]. Also, other angiotensin receptor blockers such as losartan and valsartan were proven to have protective effects against hepatic toxicity, possibly through down-regulating the expression of type I and type III collagen and exerting potent antioxidant and anti-inflammatory effects on the hepatic tissues [8,11]. The aim of this study was to explore the effect of different doses of irbesartan on DOX-induced hepatotoxicity in mice.

2. Materials and methods

2.1. Drugs and reagents

DOX was obtained from Carlo Erba, Turkey. Irbesartan was obtained from Sigma Aldrich Co., Saint Louis, Missouri, USA. All other chemicals were obtained from Crescent Diagnostics Co., Jeddah, Saudi Arabia. All chemicals used were of analytical grade. DOX was dissolved in normal saline to reach a final concentration of 3 mg/ml. Irbesartan was suspended in distilled water.

2.2. Experimental animals

This study was carried out on 60 male BALB/c mice weighing about 20–25 g that were purchased from King Fahd Medical Research Center, King Abdul-Aziz University, Jeddah, Saudi Arabia. They were allowed to acclimatize for two weeks before starting the experiment. Mice were kept in a special room at a constant temperature of 25 ± 3 °C with relative humidity of 55 ± 5% and were exposed to 12 h light/dark cycle. They were fed with standard diet and distilled water provided ad libitum. Animal handling was followed according to Helsinki declaration of animal ethics. All the experiments were conducted according to the National Research Council's guidelines.

2.3. Groups

Animals were randomly divided into six equal groups of 10 mice each as follows:

Group 1: Control group; received daily intraperitoneal injection of normal saline (0.9% Sodium chloride solution) on alternate days for 7 doses.

Group 2: DOX-group; received intraperitoneal injection of DOX in a dose of 2.5 mg/kg on alternate days for 7 doses [12].

Group 3: Irbesartan small dose group; received irbesartan in a dose of 20 mg/kg/day by oral gavage for 3 weeks [13].

Group 4: Irbesartan large dose group; received irbesartan in a dose of 75 mg/kg/day by oral gavage for 3 weeks [14].

Group 5: DOX + Irbesartan small dose group; received irbesartan in a dose of 20 mg/kg/day by oral gavage for one week before starting DOX injection and continued for 2 weeks concurrently with DOX.

Group 6: DOX + Irbesartan large dose group; received irbesartan in a dose of 75 mg/kg/day by oral gavage for one week before starting DOX injection and continued for 2 weeks concurrently with DOX.

2.4. Assessment of food intake

The preweighed food was provided in standard stainless steel containers. After 24 h, mice were removed from cages and weighed. The weight of the remaining food, including any particles that had been spilled out under each cage or on the bottom of the cages was recorded. Food intake was calculated every three days throughout the whole study as the weight of the food provided less than the weight of the food recovered [15].

2.5. Assessment of serum biochemical parameters

At the end of the study (After two weeks from starting DOX injection), mice were fasted overnight, weighed and anaesthetized with thiopental sodium (60 mg/kg body weight, intraperitoneal). Blood was collected from the retro-orbital plexus, kept in glass tubes in a water bath for 30 min at 37 °C till blood clotting occurs. Then, serum was separated by centrifugation for 20 min and used for assessment of serum albumin, alanine transaminase (ALT), aspartate transaminase (AST) and total bilirubin using kits supplied by Crescent Diagnostics, Jeddah, Saudi Arabia according to the instructions of the manufacturer. Serum alkaline phosphatase (ALP) was assessed using kits obtained from Sigma Aldrich Co., USA, according to the manufacturer's protocol.

2.6. Assessment of liver weight/body weight ratio, hepatic tissue oxidative stress parameters, heme oxygenase-1 (HO-1) and nuclear factor (erythroid-derived 2)-like 2 (Nrf2) content

Mice were killed by decerebration and liver was removed and weighed for determination of liver weight/body weight ratio. Parts of the liver were homogenized for determination of tissue catalase (CAT) according to Sinha [16], tissue glutathione reductase (GR) activity using kits supplied by Sigma Aldrich Co., USA, according to the instructions of the manufacturer and thiobarbituric reactive acid substances (TBARS) levels according to Wright and Sutherland [17]. Tissue Nrf2 and HO-1 content were measured using ELISA kits supplied by Cloud clone, Uscn Life Science, INC. USA, according to the manufacturer's protocol.

2.7. Assessment of hepatic tissue signal transducer and activator of transcription-3 (STAT-3), transforming growth factor beta 1 (TGF-β1) and the proinflammatory cytokines

STAT-3 levels were assessed using ELISA kits purchased from RayBiotech, Inc., USA according to the instructions of the manufacturer. TGF-β1 levels were measured using ELISA kits obtained from Uscn Life Science Inc. Wuhan, according to the manufacturer's protocol. Tumor necrosis factor alpha (TNF-α) was assessed using mouse TNF-α ELISA kits supplied by Ray Biotech, Inc. according to the manufacturer's protocol. Interleukin 6 (IL-6) was assessed using ELISA kits purchased from Sigma Aldrich Co. according to the manufacturer's instructions.

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