Saudi Pharmaceutical Journal (2016) **24**, 635–644

King Saud University

Saudi Pharmaceutical Journal

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ORIGINAL ARTICLE

Effect of amlodipine, lisinopril and allopurinol on acetaminophen-induced hepatotoxicity in rats

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Received 28 March 2015; accepted 30 April 2015
Available online 19 May 2015

KEYWORDS

Acetaminophen;
Allopurinol;
Amlodipine;
Hepatotoxicity;
Lisinopril;
Rat

Abstract *Background:* Exposure to chemotherapeutic agents such as acetaminophen may lead to serious liver injury. Calcium deregulation, angiotensin II production and xanthine oxidase activity are suggested to play mechanistic roles in such injury.

Objective: This study evaluates the possible protective effects of the calcium channel blocker amlodipine, the angiotensin converting enzyme inhibitor lisinopril, and the xanthine oxidase inhibitor allopurinol against experimental acetaminophen-induced hepatotoxicity, aiming to understand its underlying hepatotoxic mechanisms.

Material and methods: Animals were allocated into a normal control group, a acetaminophen hepatotoxicity control group (receiving a single oral dose of acetaminophen; 750 mg/kg/day), and four treatment groups receive N-acetylcysteine (300 mg/kg/day; a reference standard), amlodipine (10 mg/kg/day), lisinopril (20 mg/kg/day) and allopurinol (50 mg/kg/day) orally for 14 consecutive days prior to acetaminophen administration. Evaluation of hepatotoxicity was performed by the assessment of hepatocyte integrity markers (serum transaminases), oxidative stress markers (hepatic malondialdehyde, glutathione and catalase), and inflammatory markers (hepatic myeloperoxidase and nitrate/nitrite), in addition to a histopathological study.

Results: Rats pre-treated with amlodipine, lisinopril or allopurinol showed significantly lower serum transaminases, significantly lower hepatic malondialdehyde, myeloperoxidase and nitrate/nitrite, as well as significantly higher hepatic glutathione and catalase levels, compared with acetaminophen control rats. Serum transaminases were normalized in the lisinopril treatment group, while hepatic myeloperoxidase was normalized in the all treatment groups. Histopathological evaluation strongly supported the results of biochemical estimations.

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jsps.2015.04.004

Conclusion: Amlodipine, lisinopril or allopurinol can protect against acetaminophen-induced hepatotoxicity, showing mechanistic roles of calcium channels, angiotensin converting enzyme and xanthine oxidase enzyme in the pathogenesis of hepatotoxicity induced by acetaminophen.

1. Introduction

Liver is the main detoxifying organ in the body. However, continuous exposure to certain chemotherapeutic agents, drugs, environmental toxins, viral infections or bacterial invasion can trigger liver injury and eventually lead to various liver diseases (Stephens et al., 2014). Susceptibility of the liver to injury by such agents is much higher than any other organ because of its central role in metabolism as well as its ability to concentrate and biotransform xenobiotics (Kumar et al., 2015).

Acetaminophen is an over-the-counter drug commonly used for its analgesic and antipyretic properties. Although considered a safe drug, it is the most frequent cause of severe liver failure in the world, having a mortality rate of about 90% (Zyoud et al., 2010). In therapeutic levels, most of the administered dose is normally metabolized via phase II reactions and excreted as glucuronide and sulfate conjugates, while only a small portion is metabolized via phase I pathway to yield the highly toxic intermediate N-acetyl-*p*-benzoquinoneimine (NAPQI), which is normally detoxified by interaction with cellular glutathione (GSH). When GSH becomes depleted by the overproduction of NAPQI caused by saturation of the conjugation pathways at high doses, NAPQI binds to cellular macromolecules, leading to oxidative stress, cellular necrosis and finally cell death (Coen, 2014).

N-acetylcysteine (NAC) is a thiol containing antioxidant which acts as a direct scavenger of free radicals and a precursor for GSH biosynthesis (Tobwala et al., 2015). It can inhibit the induction of pro-inflammatory cytokines and can also block the tumor necrosis factor-α (TNF-α)-induced apoptotic cell death (Sen et al., 2014). It is old known as the standard antidote of acetaminophen poisoning (Bateman et al., 2014).

Amlodipine is a third generation dihydropyridine-type calcium channel blocker commonly used for the treatment of hypertension. Calcium channel blockers were reported to possess hepatoprotective activities in previous studies (Kamal, 2013) based on the mechanistic role of calcium deregulation in the progression of hepatotoxicity (Kheradpezhouh et al., 2014). In addition, the antioxidant activity of amlodipine was reported. This was attributed to its physicochemical properties where its high lipophilicity and chemical structure could facilitate proton-donating and resonance-stabilization mechanisms that quench free radicals (Mason et al., 2014). The anti-inflammatory potential of amlodipine was also reported (Zhang et al., 2012).

Lisinopril is a lipophilic non-sulfhydryl angiotensin converting enzyme (ACE) inhibitor reported to have the ability to enhance endogenous antioxidant enzyme activities (Velayutham et al., 2013). Inhibition of the rennin-angiotensin-aldosterone system may have beneficial effects on oxidative injury as angiotensin II was recently reported to cause mitochondrial oxidative injury (Li et al., 2014b). Additionally, lisinopril was reported to have anti-inflammatory effects via suppression of the pro-inflammatory cytokines such as TNF-α production (Morsy, 2011).

The prototypical xanthine oxidase inhibitor allopurinol has been applied in different models of tissue injury, based on its reported ability to inhibit the production of reactive oxygen species (ROS), and the release of inflammatory mediators such as TNF-α (Rachmat et al., 2013; Prieto-Moure et al., 2014).

Based on the aforementioned background, the present study aims to investigate the possible protective effects of three agents acting through different mechanisms, namely amlodipine as a calcium channel blocker, lisinopril as an ACE inhibitor, and allopurinol as a xanthine oxidase inhibitor, on acetaminophen-induced hepatotoxicity in experimental rats, using NAC as a reference standard agent, aiming also to declare the role of calcium channels, ACE enzyme and xanthine oxidase enzyme in the pathogenesis of acetaminophen-induced hepatotoxicity.

2. Materials and methods

2.1. Chemicals and diagnostic kits

N-acetylcysteine powder was obtained as a kind gift from SEDICO Pharmaceutical Company, Egypt. Amlodipine was obtained as a kind gift from Pfizer Pharmaceutical Company, Egypt. Lisinopril was obtained as a kind gift from AstraZeneca Pharmaceutical Company, Egypt. Allopurinol was obtained as a kind gift from GlaxoSmithKline pharmaceutical company, Egypt. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) reagent kits were purchased from Spinreact (Spain). 1,1-3,3-tetramethoxypropane, 5,5′-Dithiobis-2-nitrobenzoicacid (DTNB), GSH powder, Horseradish peroxidase, N-(1-Naphthyl) ethylenediamine dihydrochloride, *o*-dianisidine hydrochloride, thiobarbituric acid (TBA), malondialdehyde (MDA), Tris-hydroxymethyl-amino methane, hexadecyltrimethylammonium bromide (HTAB) and sulfanilamide were purchased from Sigma–Aldrich (USA). Vanadium chloride was obtained from Acros (Belgium). All other chemicals used were of analytical grade.

2.2. Animals

Adult male Wistar rats, purchased from the Modern Veterinary Office for Laboratory Animals, Cairo, Egypt, were fed with standard laboratory rat diet (Modern Veterinary Office) and water *ad libitum* until reaching weights of 180–200 g. Animals were housed in a room kept at 22–25 °C with 12-h light/12-h dark cycles, in individual stainless steel wire-bottomed cages having an upper water supply to avoid coprophagy. All animal housing and handling were conducted in compliance with the Beni-Sueif University guidelines and in