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The role of minocycline in alleviating aluminum phosphide-induced cardiac hemodynamic and renal toxicity

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ABSTRACT

Poisoning with aluminum phosphide (AlP) has been attributed to the high rate of mortality among many Asian countries. It affects several organs, mainly heart and kidney. Numerous literature demonstrated the valuable effect of minocycline in mitigating pathological symptoms of heart and kidney disease. The aim of the present study was to evaluate the probable protective effect of minocycline on cardiac hemodynamic parameters abnormalities and renal toxicity induced by AlP-poisoning in the rat model. AlP was administered by gavage at 12 mg/kg body weight followed by injection of minocycline for two interval times of 12 and 24 h, at 40, 80, 120 mg/kg body weight. Electrocardiographic (ECG) parameters were monitored, 30 min after AlP gavage for 6 h using an electronic cardiovascular monitoring device. Kidney tissue and serum were collected for the study of histology, mitochondrial complexes I, II, IV, lactate dehydrogenase (LDH) and myeloperoxidase (MPO) activity, ADP/ATP ratio, mitochondrial cytochrome c release, apoptosis, lactate, BUN, and Cr levels. The results demonstrated that AlP induces ECG abnormalities, and failure of heart rate and blood pressure, which improved significantly by minocycline. Minocycline treatment significantly improved complexes I, IV, MPO and LDH activities, and also reduced the ADP/ATP ratio, lactate level, release of cytochrome c, and apoptosis in the kidney following AlP-poisoning. Also, the histological results showed an improvement of kidney injury in minocycline treated groups. In conclusion, the findings of this study showed that minocycline could improve cardiac hemodynamic abnormalities and kidney injury following AlP-poisoning, suggesting minocycline might be a possible candidate for the treatment of AlP-poisoning.

1. Introduction

Aluminum phosphide (AlP) in the form of tablets is commonly used as a pesticide to protect food products during storage and transportation processes (Goharbari et al., 2018; Mehrpour et al., 2008). Ease of use, cost-efficiency, no effect on the seeds viability, minimum remaining on stored food and high efficiency for insects control are the important reasons for frequent use of AlP in agriculture (Anand et al., 2011; Mehrpour et al., 2012). Despite its well-established high toxicity for human and other non-target species (Anand et al., 2011; Mostafalou et al., 2013), its usage has been increased among farmers, leading to the high availability of AlP in the market (Asghari et al., 2017). Due to the ease of access and free availability of this pesticide, AlP has emerged as a popular agent for suicide and unintentional poisoning mortality (Baeeri et al., 2013; Shadnia et al., 2008). Based on recent evidence, AlP is a common suicide agent among Indians, and there is an increasing tendency among Iranians (Mehrpour et al., 2012; Moghadamnia, 2012). The literature has emphasized that the poisoning by AlP is fatal, and 70% of individuals poisoned by AlP dies from multi-organ dysfunction (Anand et al., 2011; Bogle et al., 2006). Numerous studies have

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reported that heart, kidney, and liver are the most vulnerable organs affected by this pesticide that could contribute to death in poisoned individuals (Gupta and Ahlawat, 1995; Gurjar et al., 2011; Mehrpour et al., 2012). The most reported outcomes in AlP cardio-poisoning manifestations include profound and refractory hypotension, congestive heart failure, electrocardiographic (ECG) abnormalities responsible for death during the initial 24 h of poisoning (Bogle et al., 2006; Chugh et al., 1991). In addition, the most finding in renal injury is acute tubular necrosis, which is usually responsible for deaths after 24 h (Hsu et al., 2002; Misra et al., 1988). In human, the most common exposure route is through ingestion of AlP while inhalation of phosphine gas or absorption through the skin are among the rare conditions (Gurjar et al., 2011; Sudakin, 2005). There is also much evidence that through ingestion way, AlP reacts with water or hydrochloric acid available in the stomach leading to the release of lethal phosphine gas (Shadnia et al., 2009; Tehrani et al., 2013). Although many investigations have been carried out on the mechanisms of AlP-poisoning, further data collection is required to determine the whole and exact mechanisms. Several recent studies have reported the impairment of the electron transfer chain (ETC), especially mitochondrial complex IV, and mitochondrial dysfunction as the possible molecular mechanisms of AlP-poisoning (Anand et al., 2011; Moghadamnia, 2012). Other possible mechanisms, including oxidative stress, apoptosis, and inflammation were frequently reported in the previous literature (Asghari et al., 2017; Baghaei et al., 2016; Misra et al., 1988).

Although the protective effects of some drugs on AlP-cardiotoxicity including triiodothyronine (Abdolghaffari et al., 2015), iron sucrose (Solgi et al., 2015), vasopressin and milrinone (Jafari et al., 2015), acetyl-L-carnitine (Baghaei et al., 2016), coconut oil (Shadnia et al., 2005), etc. have been investigated, yet there is no specific antidote available to manage the AlP-cardiotoxicity. Also, there are limited reports of AlP-induced kidney injury and further investigations are needed to find a specific antidote for treatment of kidney injury (Hsu et al., 2002). Numbers of studies repeatedly reporting the protective effects of minocycline on cardiac and renal injury due to its radical scavenging activity, and its key regulatory role in apoptosis and inflammatory pathways, as well as improving mitochondrial dysfunction (Abbaszadeh et al., 2018; Haghi-Aminjan et al., 2017). Indeed, minocycline compared to other members of its family has more antioxidant properties (Kraus et al., 2005). It can reduce oxidative stress directly through its phenolic rings and indirectly through modulating of cellular antioxidant agents (Haghi-Aminjan et al., 2017; Schildknecht et al., 2011). Also, it is reported that minocycline improves mitochondrial function. In this content, minocycline through affecting the mitochondrial permeability transition pores and preventing the release of mitochondrial agents precedes the cellular oxidative stress and apoptosis (Zhu et al., 2002). Also, it is apparent that minocycline has protective effect against apoptosis via modulating mitochondrial function (Fernandez-Gomez et al., 2005; Jiang and Wang, 2000). On the other hand, the preservative property of minocycline on heart and kidney dysfunction have been previously reported in many pathological situations (Garrido-Mesa et al., 2013; Haghi-Aminjan et al., 2017). Numerous reports have provided evidence for the toxicity of exposure to pesticides and the association with many disorders in multi organs (Mostafalou and Abdollahi, 2017). The results of previous studies on the cytoprotective, and antiarrhythmic actions, as well as modulating mitochondrial function by minocycline bring the idea that it may have potential to counteract with the mechanisms of AlP-induced heart and kidney dysfunction (Haghi-Aminjan et al., 2017; Mousavi et al., 2016; Teng et al., 2004). As such, the purpose of this study attempts to show the optimistic effects of minocycline on the cardiac hemodynamic and renal AlP-poisoning in a rat model at two-time intervals. To our best knowledge, this is the first study on analysis the effect of minocycline on cardiac hemodynamic/renal toxicity induced by AlP.

2. Materials and methods

2.1. Ethics

All animal procedures were approved by the protocols of the Animal Care and Use in Research Committee at Tehran University of Medical Science (code number: IR.TUMS.REC.1395.2417).

2.2. Chemicals

ELISA kits for evaluation of mitochondrial cytochrome c release as well as lactate dehydrogenase (LDH) were obtained from Abcam (USA). Mitochondria isolation kit and lactate were purchased from BioChain Inc (USA), and ZellBio (Germany), respectively. ApoFlowEx® fluorescein isothiocyanate (FITC) kit was purchased from Exbio (Vestec, Czech Republic). AlP was obtained from Samiran Pesticide Formulating Co. (Iran). All the other chemicals and minocycline were obtained from Sigma-Aldrich (GmbH, Munich, Germany).

2.3. Animals

The pathogen-free adult male Albino Wistar rats, weighing 230–250 g were used and housed in standard polycarbonate cages in a room with 50–55% humidity, at 20–25 °C temperature, and a light-dark 12:12 photoperiod under conditions in which standard rat diet was available ad libitum. All procedures were done in accordance with guidelines for animal care and use, authorized by the Animal Care and Use in Research Committee at Tehran University of medical science.

2.4. Determination of AlP LD_{50}

The LD_{50} of AlP as was reported in the previous studies ranged from 8.7 to 12.5 mg/kg (Abdolghaffari et al., 2015; Jafari et al., 2015). On that basis, in the present study, AlP LD_{50} was determined by examining relevant doses of AlP including 10, 11, 12, and 13 mg/kg. To this aim, AlP tablets were powdered, dissolved in almond oil and the prepared doses were given to the animals by gavage. The control group received solely almond oil. Six rats were placed in each group and followed up until 24 h post exposure. All deaths during that time were recorded and LD_{50} of AlP was calculated as 12 mg/kg using the probit test.

2.5. Treatment strategy

The animals studies were divided into the two following steps:

In step one, the cardiac hemodynamic parameters were evaluated for which 6 groups each containing six rats were selected as follows: Group 1 (control) received almond oil alone; Group 2 received minocycline in dose of 120 mg/kg (MIN120); Group 3 received AlP (AlP); Group 4 received AlP + 40 mg/kg of minocycline (AM40); Group 5 received AlP + 80 mg/kg of minocycline (AM80), and Group 6 received AlP + 120 mg/kg of minocycline (AM120).

In step two, the biochemical and histological parameters were evaluated for which twelve rats were randomized into the 9 groups as follows: Group 1 received normal saline (NOS-T12); Group 2 (control) received almond oil (CON-T12); Group 3 received minocycline in dose of 40 mg/kg (MIN40-T12); Group 4 received minocycline in dose of 80 mg/kg (MIN80-T12); Group 5 received minocycline in dose of 120 mg/kg (MIN120-T12); Group 6 received AlP (AlP-T12); Group 7 received AlP + 40 mg/kg of minocycline (AM40-T12); Group 8 received AlP + 80 mg/kg of minocycline (AM80-T12), and Group 9 received AlP + 120 mg/kg of minocycline (AM120-T12). All were followed for 12 h. In addition, for 24 h follow-up, twelve rats were placed in groups similar to the abovementioned groups including NOS-T24, CON-T24, MIN40-T24, MIN80-T24, MIN120-T24, AlP-T24, AM40-T24, AM80-T24 and AM120-T24. In this step, six alive rats were chosen for analysis.