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ORIGINAL ARTICLE

The possible antianginal effect of allopurinol in vasopressin-induced ischemic model in rats

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Abstract The anti-anginal effects of allopurinol were assessed in experimental model rats of angina and their effects were evaluated with amlodipine. In the vasopressin-induced angina model, oral administration of allopurinol in dose of 10 mg/kg revealed remarkably analogous effects in comparison with amlodipine such as dose-dependent suppression of vasopressin-triggered time, duration and severity of ST depression. In addition, allopurinol produced dose dependent suppression of plasma Malondialdehyde (MDA) level, systolic blood pressure, cardiac contractility and cardiac oxygen consumption; while in contrast, amlodipine minimally suppressed the elevation of plasma MDA level. Endothelial NO synthase (eNOS) expression, serum nitrate were strikingly increased, however lipid profile was significantly reduced. Seemingly, allopurinol was found to be more potent than amlodipine – a calcium channel antagonist. To conclude, it was explicitly observed and verified that on the ischemic electrocardiography (ECG) changes in angina pectoris model in rats, allopurinol exerts a significant protective effects, reminiscent of enhancement of vascular oxidative stress, function of endothelial cells, improved coronary blood flow in addition to the potential enhancement in myocardial stress. Moreover, our findings were in conformity with several human studies.

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1. Introduction

In majority of the epidemiological studies, a striking correlation of escalating levels of uric acid in serum was observed in addition to augmented cardiovascular event rate, furthermore the rise in the serum levels of uric acid was also found to be associated with increase in the mortality in individuals with recognized hazards of vascular disorders as well as normal healthy volunteers. Nevertheless, antioxidant properties

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of uric acid are well known, and few preclinical and clinical studies proposed the protective effects of uric acid in neurodegenerative disorders. In contrast, considerable data exhibit to sustain the harmful and prothrombotic effects of xanthine oxidase, and this enzyme is well recognized as a significant cause of oxidative stress in the blood vessels, in addition to the implication of high levels of serum uric acid in the progress of cardiovascular disorders. Basically, xanthine oxidase is a group of enzymes, predominantly present in the liver, gastrointestinal tract, kidney and brain. Nevertheless, its presence is revealed all through the cardiovascular system (George and Struthers, 2008). Increased levels of proinflammatory cytokines and augmentation of ischemia were revealed by expression of xanthine oxidase and uric acid, Berry and Hare (2004) suggestive of their implication in the inflammatory response which is a distinctive feature of atherosclerosis. Moreover, increased oxygenation of LDL (De scheerder et al., 1991), and augmented release of the thrombolytic components such as 5HT, ATP and ADP were also observed with uric acid (Ginsberg et al., 1977). Xanthine oxidase enzymes can stimulate or initiate oxidative stress by virtue of their property to release free radicals of hydrogen oxide and hydrogen peroxide (Hille and Massey, 1981). The significant role of uric acid to enhance in vitro production was observed in rat vascular smooth muscle (Barberi and Mene, 2006). In addition to its correlation with endothelial dysfunction in hypertensive patients by means of its enhanced impact on nitric oxide formation in the macula densa (Mazzali et al., 2002; Saito et al., 1978; Dyer et al., 1999).

Fundamentally, allopurinol has a structural resemblance with hypoxanthine and is rapid metabolism to oxypurinol, and both of them work in a similar fashion. Their preferential binding to xanthine oxidase inhibits its activity (Elion, 1966). This in turn leads to lowering of both uric acid and xanthine oxidase mediated free radical formation. All these motivating findings have focused recent clinical research on the utilization of the xanthine oxidase inhibitors allopurinol and oxypurinol in the prevention of cardiovascular disorders.

Different studies of the inhibitory effects of xanthine have revealed that, inhibition of xanthine oxidase significantly reduced the levels of oxidative stress in the circulation in individuals with heart failure (Doehner et al., 2002), diabetes (Desco et al., 2002), metabolic syndrome (Yiginer et al., 2008), obstructive sleep apnea (El Solh et al., 2006), coronary artery disease (Eskurza et al., 2006), and liver disease (Vuppalanchi et al., 2011). Furthermore, blood pressure was improved in hypertensive individuals in response to xanthine oxidase inhibition (Feig et al., 2008). A noteworthy finding on reduction of "infarct size extension" was revealed in acute coronary syndrome on treatment with allopurinol, nevertheless explanation of this finding seems to be complex in view of methodological consideration (Parmley et al., 1992). Finally, a large retrospective study recommended a protective effect of high-dose allopurinol in comparison with low-dose treatment; interestingly this study revealed that low-dose treatment is as good as no treatment (Struthers et al., 2002). Therefore, the intention of this paper is to examine the possible antianginal effects of allopurinol compared with standard antianginal drug, amlodipine, on the ST segment depression of ECG, blood pressure, myocardial function, oxidative stress, eNOS expression, serum uric acid and lipid profile using ischemic rats' model with vasopressin.

2. Materials and methods

2.1. Animal

89 Male Wistar strain rats (8–10 week old) were purchased from the faculty of pharmacy, king Abdul Aziz University, Jeddah, Saudi Arabia. The animals were housed in animal house of King Fahd Medical Research Center, King AbdulAziz University at a controlled temperature of 23–26 °C under a 12 h light–dark cycle with free access to food and water. All animals received humane care in compliance with the ethical standards.

2.2. Drugs

Allopurinol and vasopressin (VP) were purchased from Sigma (St. Louis, MO, USA). Amlodipine Tablets 5 mg were purchased from Pfizer (Norvasc®; USA). For the oral administration allopurinol and amlodipine were dissolved in sterile water to a concentration of 10 mg/ml solution. For the intravenous administration vasopressin was diluted in saline 0.9% to 1 IU/ml solution. The dose of amlodipine was 10 mg/kg selected on the basis of a study conducted by (Sasaki et al., 2005). Vasopressin dose was 2 IU/kg depended on the result of pilot study. The doses of allopurinol were 35, 70, 105 mg/kg selected according to the human therapeutic dose by using conversion formula by (Freireich et al., 1966). Rats were weighed weekly and the dose adjusted accordingly.

2.3. Induction of myocardial ischemia

Induction of ischemia was conducted based on a method of (Hirata et al., 2005). Albino male rats were anesthetized using pentobarbital (60 mg/kg), and then placed on a heating pad to maintain temperature at 37 °C with backs down. Polyethylene I.V. cannula (26G × 19 mm) was inserted in the right lateral vein of the tail. After stabilization period following the completion of the cannulation of polyethylene I.V. cannula, vasopressin (VP) was intravenously injected at a dosage of 2 IU/kg through the same cannula. The ST-segment depression $\geqslant$ 1 μv was considered as an index of myocardial angina (Ikeda et al., 2006), as shown in which recorded by the Powerlab system (Model Figure). The recorded signals should be free of electrical interference and noise. When the recording is over, the rats were given time to wake up and then returned to their cages.

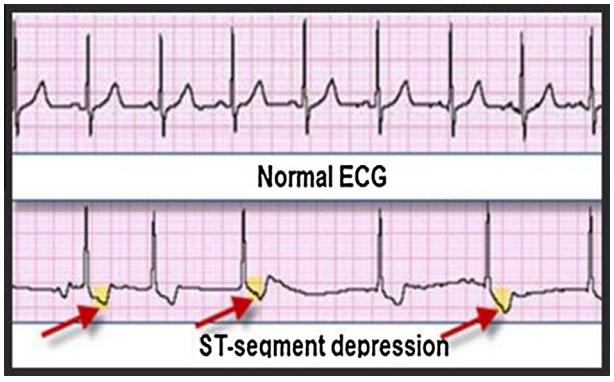

Figure 1 Induction of stable angina in rats.