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Research Article

ANTIDYSRHYTHMIC EFFECTS OF GALLIC ACID ON $CACl_2$-INDUCED ARRHYTHMIA IN RAT

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ABSTRACT

In many cases, myocardial infarction leads to arrhythmia. Since antioxidant agents play an important protective role in heart disease, therefore, many of them are used as medicinal plants in traditional medicine. Gallic acid, as a potent antioxidant agent, was shown many preventive effects on diseases; therefore, the aim of this study was the evaluation of antidysrhythmic effects of gallic acid on $CaCl_2$-induced arrhythmia in rat. Forty male Sprague-dawley rats (200-250 gr) were divided into 5 groups included: control (N/S, 1ml/kg, gavage, 10 days), GA (10, 30, 50 mg/kg, gavage, for 10 days), quinidine (50mg/kg, iv). In all chronic groups before experiments and 10 days later, lead II electrocardiogram was recorded for calculating HR. The arrhythmia was produced by i.v. injection of a solution $CaCl_2$ (140 mg/kg) at time effect peak chemical antiarrhythmias drugs. Then percentage of Ventricular premature beats (VPB), Ventricular fibrillation (VF) and Ventricular tachycardia (V.tach) were recorded. Results were analyzed by using t-test, one-way ANOVA and FISHER exact test. $P<0.05$ was considered as significant level. The chronotropic effect was not significant with GA after 10 days. GA displayed antidysrhythmic effects on $CaCl_2$-induced arrhythmia with the highest activity at the medium dose of 50 mg/kg, compared to Control group by significant reduction of VPB, VF and V.tach comparable to that of quinidine as a chemical anti arrhythmias drug. GA considered as an antiarrhythmic agent because of reduces the incidence of VPB, Vtac and VF. Results suggest a protective role of GA against heart disease.

Keywords: Gallic Acid, CaCl2-induced arrhythmia, antiarrhythmic effects, chronotropic effect.

INTRODUCTION

Arrhythmias or dysrhythmia is any type of rhythm, except normal sinus rhythm (NSR). Arrhythmias resulted from irregularly at impulse generation, impulse conduction in heart or combination of both them (1). The most important causes of cardiac arrhythmias are congenital heart diseases, myocardial ischemia, cardiac valvular diseases, electrolyte imbalances, metabolic disturbances, acidosis or alkalosis and drugs toxicity (2). The most important ventricular arrhythmias including ventricular fibrillation (VF), premature ventricular beat (PVB) and ventricular tachycardia (V.Tach) is the most important causes of mortality rate at industrial communities. VF and V.tach are two causes of sudden cardiac death (SCD) (3). VF is arrhythmias life-threatening and characterized by undistinguished rhythm but V.tach is organized arrhythmias and manifested with further than 3- 4 beats/min PVB (4).

There are three methods for induced arrhythmias including, ischemia-reperfusion, electrical and chemical (such as $CaCl_2$) (5, 6). Direct action of $CaCl_2$ on myocardium is mainly manner of $CaCl_2$ induced arrhythmias, but it possibly acts an indirect manner, that may be mediated sympathetic nervous system (6). Chemical drugs in according of the Vaughan-williams are classified into four classes. Sodium channel

blockers, such as quinidine which is classified in Class-1(1-7) The most significant complication of quinidine is torsade de pointe (8).

Herbal medicines or traditional medicines which have preventive and therapeutic effects in multiple diseases are specially valuable and important. Herbal remedies with respect to the availability, low cost and their side effects, as an alternative to chemical drugs have been considered by researchers (9).Grape seed (Vitis vinifera) has 5-8% polyphenole which mainly, have gallic acid, catechine and epicatechine. The antioxidant effect of these phenols is 20 folds vitamin E and 50 folds vitamin C. These are improving circulation in vessels (10). Phenols with potent antioxidant properties, could reduce intracellular ionized calcium and eventually abate apoptosis (11). Gallic acid (GA)(3,4,5-trihydroxy benzoic acid), as an organic acid, are found in some plants such as, grape seed, tea leaves, oak bark, walnut and sumac, that has various properties includes anti-microbial, anti- fungal and anti-viral (12) and has trait of cytotoxic against cancer cells, without effect on normal cells (13). GA inhibits mast cell by blocking histamine release and pro-inflammatory cytokines. Therefore, it can be advantage for anaphylaxis reactions (14). GA is an effective factor for weight-loss, due to that attenuated percent of plasma lipid, visceral fat and abate insulin-resistance (15).

Cardio protective effect of GA was shown in isopretrenolol-induced myocardial infarction, which was resulted from its antilipoperoxidative and antioxidant property (16).

In according to previous study, gallic acid, as an antioxidant, was shown many preventive effects on diseases; therefore, the aim of this study was the evaluation of antidysrhythmic effects of gallic acid on CaCl2-induced arrhythmia in rat.

MATERIALS AND METHODS

Chemicals

Gallic acid (sigma), quinidine (sigma), $CaCl_2$ 2.5% solution (merk), normal saline (N/S), ketamine hydrochloride and xylazine (Alfasan Co, Woderen- Holland).

Animals

Forty adult male Sprague-dawley rats (200-250 gr) were purchased from animal house of Ahvaz Jundishapur University of Medical Sciences. Animals were housed for 10 days in polyethylene cages at a room under the same conditions such as temperature controlled room 22±2°C, adequate ventilation, with a 12 h dark- light cycle supplied with food and water ad libitum (16). The animals were divided into 5 groups (8 animals at each group) included: control (N/S, 1ml/kg, gavage, 10 days), GA (10, 30, 50 mg/kg, gavage, for 10 days), quinidine (50mg/kg, iv). This study was approved by the animal care and ethical committee of the Ahvaz Jundishapur University of Medical Sciences.

Preparation of animals

The animals were operated under anesthesia with combination of ketamine (50mg/kg) and xylazine (10mg/kg) via intraperitoneal (ip) route. After anesthesia (at groups which need to injection of iv) prep & drep with betadine were done. Then, a longitudinal incision was created in area of groin; a poly ethylene catheter was inserted in femoral vein, and fixed around it, for later injections (6). Lead II electrocardiogram (ECG) was recorded by Bio Amp and monitored continuously by a Power Lab system (ADInstruments, Australia) for calculating and interpretation of electrophysiological parameters.

The manner of induced and recording of arrhythmias

ECG was obtained in all groups for 15 min, before the induction of chemical- arrhythmia to allow hemodynamic equilibration. Heart rate (HR) was calculated from ECG recording in first day and 10 days after administration of GA or normal saline. In quinidine group, Heart rate (HR) was obtained before and 5 min after injection of quinidine. In this study, arrhythmia was induced by intravenously injection of $CaCl_2$ (140mg/kg), and Percentage of incidence of Ventricular premature beats (VPB), Ventricular tachycardia (V.tach) and Ventricular fibrillation (VF) were calculated after injection of $CaCl_2$.

Statistical methods

Results were analyzed using SPSS and expressed as Mean ± SEM. Comparisons among groups were performed using t-test, one way ANOVA or FISHER exact test. P-values of less than 0.05 were considered significant statistically.

RESULTS

Evaluation of antiarrhythmic effects of chronic doses of gallic acid (10, 30, 50 mg/kg), has shown that incidence of Ventricular premature beat, Ventricular tachycardia and Ventricular fibrillation significantly were reduced in GA

groups with the highest activity at the medium dose of 50 mg/kg, compared to control group. Significantly reduction effects on CaCl2-induced arrhythmia were displayed by acute injection of quinidine (5 mg/kg). Comparison of the GA and quinidine reduction effects on CaCl2-induced arrhythmia showed that GA at the medium dose of 50 mg/kg was more effective than quinidine (5 mg/kg) (Table 1).

In control and GA groups, chronotropic effect was not shown before and after treating animals by chronic doses of gallic acid (10, 30, 50 mg/kg) or saline. Significantly decrease in heart rate was observed 5 min after injection of quinidine ($P<0.05$) (Fig. 1).

DISCUSSION

In this study, gallic acid was shown antidysrhythmic effects on $CaCl_2$-induced arrhythmia by decreased VF, PVB and V.tach but has not affected heart rate in intact rats.

In according to previous investigations, gallic acid binds to lipid membrane, acts as an antioxidant factor and attenuated the level of cardiac enzymes that impaired both structure and function of cardiac. Considerably, previous study was shown that gallic acid increased activation of non-enzymatic materials such as vitamins C and E as well as glutathione (17) which act as a potent agent to scavenging reactive oxygen species (ROS), superoxide anions and hydroxyl radicals (17). These effects may be related to polyphenolic traits of gallic acid that eliminated harmful materials such as free radicals and no permission that ROS release. Pretreatment with gallic acid decreased the levels of lipid peroxidase in the plasma. This shows the antilipoperoxidative effect of gallic acid (16). In the present study, pretreatment with GA showed preventive effects on cardiac dysrhythmia and suggests that GA has effects similar to other antioxidants.

According to previous researches, decrease PLT aggregation may be one of the mechanisms for preventive effect against arrhythmias (18) which suggests similar mechanism for GA preventive effect in $CaCl_2$-induced arrhythmia.

The GA protective effects were similar to the effect of the quinidine and sometimes were shown the more effective properties.

CONCLUSION

In conclusion, on the basis of $CaCl_2$-induced arrhythmia studies, the present results approve our hypothesis that gallic acid pretreatment improved the dysrhythmia and is comparable with quinidine, but has not affected chronotropic effect in intact rats. Herbal remedies with respect to low side effects, as an alternative to chemical drugs have been considered by this study.

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