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Effect of Arq Gauzaban a Unanipathy product on the isolated Frog Heart

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Abstract

Arq gauzaban (a clear aqueous distillate of the plant *Onosma bracteatum*) a unanipathy product recommended by the unanipathy practioners to strengthen the sick heart both pre and post operatively was studied. Despite its extensive use in unanipathy health care system, no systematic study has been reported so far. Hence, in the present study an effort was made to screen the product for its cardiac effects on isolated frog heart. Arq guazaban exhibited a positive inotropic effect on the isolated perfused frog heart. The main mechanism behind this pharmacological response appears to be through the calcium channels. The study thus further supports the use of arq guazaban as a myocardial strengthening agent in unanipathy health care practice.

Key words: Arq gauzaban, Positive inotropic effect, Beta blocker, Calcium channel blocker, Isolated frog heart

Introduction

Arqs are liquid preparations, obtained by the distillation of macerated crude drugs in aqueous medium (Mohmad , 2001). Different types of arqs like arq gulab, arq guazaban, arq kewra etc. are used by the unanipathy practitioners for the management of various cardiac and related problems. However, the arq gauzaban is the widely used.

Arq gauzaban is a clear, non viscous liquid preparation, obtained by the distillation of the plant *Onosma bracteatum* wall (family *Boraginaceae*) duly macerated in water (Vaidya, 1982). The leaves of this plant have the shape like that of tongue of a cow, which is hirsute and rough. Hence in Sanskrit it is called as gojivha (Go=cow, Jivha=tongue) and in Arabic gauzaban (Gau=cow, Zaban=Tongue).

In unanipathy system of medicine, it has been advocated for varieties of disease conditions like chest, lungs and throat troubles, gingivitis, stomatitis, insanity, gonorrhea, lumbago, leprosy, allay thirst, diuretic, aphrodisiac and tonic (Kirtikar *et al.,* 1935). In addition, gauzaban is one of the ingredients in many unanipathy formulations.

Phytochemical literature reveals the presence of tannins, glycosides, resins, alkaloids, carbohydrates and saponins in the plant. However, the qualitative analysis of the arq gauzaban revealed the presence of flavonoids, tannins and saponins. The tranquilizing activity of the plant has been reported (Tandale *et al.*, 1986).

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Though the arq gauzaban is extensively used to manage a variety of cardiac and related problems, no systematic pharmacological evaluation on cardiovascular system has been reported prior to this study. Hence, in the present study, an effort was made to conduct preliminary investigations on isolated frog heart, especially on the parameters that is force of contraction and the heart rate.

Materials and Methods

Drugs: Arq gauzaban (M/s.Hamdard laboratories, Gaziabad, India) was purchased from the retail unanipathy pharmacy. Drugs like propranolol and nifedipine of Sigma chemicals were used. All other required chemicals of analytical grade were procured from the central store of the institution.

Experimental procedure: The study was conducted on 10 frogs (*Rana tigrina*) weighing between 200-260 g. The experimental protocols were approved by the Institutional Animals Ethical Committee and the experiment was conducted in an institution approved by the CPCSEA*.

The frogs were pithed so as to destroy the central nervous system but without causing any injury to their heart and associated blood vessels. The sternum was completely removed and the pericardium was cut open exposing the heart. The liver was pushed aside from the inferior vena cava as far as the hepatic veins. A small cut was made into the venous sinuses; Syme's cannula was inserted towards the heart and isolated. A steady flow of the perfusion fluid (Frog ringer) having the following composition (Burn *et al.*, 1952), was perfused through this cannula.

Ingredients	**Quantity in mM/litre**
Sodium chloride	111.11
Potassium chloride	1.88
Calcium chloride	1.08
Sodium bi carbonate	2.38
Sodium dihydrogen phosphate	0.07
Glucose	11.11

Through the opening of the cannula drugs/Arq could be injected by pushing a capillary tube attached to a syringe through an injection needle. A small hook was attached to the tip of beating heart which was tied with a thread. The other end of the thread was attached to the Starling's heart lever so that the movements of the beating heart could be recorded on a kymographic paper. The force of contraction was recorded and the rate of contraction was counted and tabulated (Hardman *et al.*, 1996).

The entire experimental study was carried out in the following stages:

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* CPCSEA=Committee for the Purpose of Control and Supervision of Experiments on Animals

Stage-I: A stabilizing period of 15 minutes was allowed. After basal recording, 0.1ml of adrenaline ($2.5x10^{-5}M$) was administered to identify the sensitivity of the myocardium and then the effect of Arq gauzaban (0.4ml, undiluted) on the heart rate and the force of contraction was studied. Sufficient time was allowed to the preparation to return to base line after every dose. This served as control for comparing the effect of other drugs.

Stage-II: In this stage, in order to understand the possible mechanism of action of the Arq under study, the hearts were perfused with Ringer solution containing ß-blocker (Propranolol). First the antagonizing effect of the ß-blocker on the adrenaline induced positive inotropic and positive chronotropic effect was studied. The Arq gauzaban (0.4ml, undiluted) was then added through the opening of the cannulas as usual.

Stage-III: The isolated hearts were then perfused with a calcium channel blocker (Nifedipine) and its antagonizing effect on the digoxin induced positive inotropic effect was studied. The Arq was then administered as usual.

Data Analysis: The cardiac effects of arq gauzaban before and after perfusion with β-blocker and calcium antagonists were compared with that of basal values. The data are presented as mean±SEM. The data was analysed by using one way analysis of varience (ANOVA) followed by Dunnett's test. A value of $P<0.05$ was considered statistically significant.

Control values HR: 43.4± 1.70 (100%), FOC: 17.2± 0.25 (100%). Values are mean ± SEM and n=10. 'a' represents significant at *P<0.001,* HR= Heart Rate, FOC= Force of Contraction, UD=Un- Diluted and NS= Non-Significant.

Results and Discussion

From the results compiled in theTable-1, the following was deduced. The mean basal value of amplitude of contraction was 17.2 ± 0.25mm (100%) and heart rate was 43.4±1.70 beats (100%) per minute respectively.

Effect of Arq gauzaban: Administration of arq gauzaban showed a significant increase in the mean force of contraction (141.86±2.48%) of the heart ($P<0.001$); however, there was no much influence on the heart rate (99.54±4.02%).

Interaction with β-blocker: The positive inotropic and chronotropic effect of adrenaline was antagonized by the β-blocker indicating the involvement of β-receptor in its mechanism of action. However, when Arq gauzaban was added there was no significant change either in rate of contraction (97.69±3.17%) or force of contraction (134.30±2.52%) of the heart, this clearly rules out the involvement of β-receptor in the positive inotropic action of Arq gauzaban.

Interaction with calcium channel blocker: The positive inotropic effect of digoxin was antagonized by the calcium channel blocker indicating the involvement of Ca^{2+} channels in its mechanism of action. Similarly, when arq gauzaban was administered, its positive inotropic effect was blocked by the nifedipine (50.00±2.48%) ($P<0.001$) and also the heart rate was reduced significantly (53.22±0.87) ($P<0.001$).

Formulation/Drugs	Frog Ringer		Frog Ringer + propranolol ($3x10^{-5}$ M)		Frog Ringer + nifedipine ($2.88x10^{-5}$ M)	
	HR%	FOC%	HR%	FOC%	HR%	FOC%
Digoxin ($1.28x10^{-5}$M)	59.91±0.97 [a]	304.65±4.26[a]	---	---	33.41±1.20[a]	130.81±4.18[a]
Adrenaline ($2.5x10^{-5}$M)	126.96±5.96[a]	268.60±2.26[a]	62.90±5.80[a]	193.6±3.01[a]	---	---
Arq Gauzaban (UD)	99.54±4.02[NS]	141.86±2.48[a]	97.69±3.17[NS]	134.30±2.52[NS]	53.22±0.87[a]	50.00±2.48[a]
One-way ANOVA F	44.86	122.48	28.89	574.7	159.44	949.80
df	3, 36	3, 36	3, 36	3, 36	3, 36	3, 36
P	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*

Table-1. Effect of *arq gauzaban* on isolated frog heart.

Discussion

Unanipathy authoritative text "Baiz-kabir" quotes a number of therapeutic indications for arq gauzaban. However, no pharmacological evaluation on cardiovascular system has been reported prior to this study. In the present investigation the arq gauzaban has been found to increase the force of contraction of isolated frog heart perfused with normal Ringer solution.

When myocardium is excited, action potential is generated followed by contraction of myocardium. In the process one electrical and other mechanical event occurs coupled together, and the coupling agent is calcium. It is evident that, catecholamine like adrenaline show cardiac excitatory action, which is responsible for increase in heart rate and force of contraction (Gaddum, 1953). Adrenergic beta-receptor blocking agents like propranolol block this effect. In the present investigation inability of propranolol to block the positive inotropic effect of arq gauzaban rules out the possibility of action of arq gauzaban via β-receptors.

$Na^+ K^+$ ATPase inhibition by cardiac glycosides leads ultimately to increase intracellular Ca^{2+} concentrations through Na^+/Ca^{2+} exchange and an associated increase in slow inward Ca^{2+} current (Wang *et al.*,2001) as well as in transient Ca^{2+} current (Mc Garry and Williams 1993). Ca^{2+} induced Ca^{2+} release is a general mechanism that most cells use to amplify Ca^{2+} signals (Wang *et al.*, 2001). In heart cells, this mechanism is operated between voltage-gated L-type calcium channels in the plasma membrane and calcium release channel, generally known as ryanodine receptors in the sarcoplasmic reticulum (Fabiato 1985). Nifedipine is a L-type calcium channel antagonist (Wang *et al.*, 2001). In the present investigation, nifedipine antagonized the positive inotropic effect of Arq gauzaban significantly and there was also decrease in the heart rate significantly. All these imply that, the arq might have produced its action by opening the voltage sensitive slow Ca^{2+} channel. It is thus apparent that, the cardiac stimulant effects of arq gauzaban on the isolated frog heart involve calcium channels.

Further, the documented reports indicate that, the saponin glycosides might be responsible for the positive inotropic effect, while the tannins and flavonoids provide free radical antioxidant activity and vascular strengthening (Chaterjee *et al.*, 1997). The presence of saponins offers cardioprotective effects (Dwivedi and Agarwal 1994). The Arq under study contains all afore mentioned phytoconstituents. Hence, it may be concluded that, the Arq gauzaban is endowed with significant positive inotropic effect with antioxidant, cardioprotective and vascular strengthening beneficial properties. Hence, the present study thus further encourages the use of Arq gauzaban in unanipathy health care practice for the management of sick hearts.

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