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EFFECT OF AJMALOON ON THE BARORECEPTOR - HEART RATE REFLEX IN ANAESTHETIZED RABBITS AND MONKEYS

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Abstract: The effects of a herbal drug, Ajmaloon (Hamdard, India), on the arterial blood pressure, heart rate (HR) and baroreceptor-heart rate reflex were studied in anaesthetized rabbits and monkeys. Intravenously administered Ajmaloon produced a dose-dependent hypotensive response in both the species without any significant effect on the heart rate. Only in high doses (200 mg/kg or more), Ajmaloon produced a bradycardia response in rabbits. Even the highest dose (300 mg/kg) of Ajmaloon used in the present investigation did not cause arrhythmia or any other conduction disorder or respiratory distress. Baroreflex SAP-HR curve was shifted to the left of the control following treatment with 100 mg/kg intravenous Ajmaloon in both the species. Loss of tachycardia response to fall in arterial pressure in Ajmaloon treated animals indicated the drug induced suppression of normally existing sympathetic excitatory influence in response to hypotension. Baroreflex regulatory HR response to hypertension remains intact after intravenous administration of 100 mg/kg Ajmaloon, a dose much higher than the prescribed highest oral dose for humans.

Intact baroreflex regulation of arterial blood pressure in response to hypertension in Ajmaloon treated mammals suggests that in patients besides lowering the blood pressure, Ajmaloon might not interfere with the normal blood pressure regulatory mechanism through arterial baroreceptors during hypertension.

Key words: ajmaloon rauwolfia serpentina hypertension herbal drugs baroreflex

INTRODUCTION

Ajmaloon, a preparation from Rauwolfia serpentina with certain herbs reduces blood pressure (BP) in humans and animals (1). Use of this herbal drug for 3-6 months in hypertensive patients, lowers the BP with minimal side effects (2, 3). Hypertension is the most common cardiovascular disease with high morbidity all over the world and various factors are known to contribute to this disorder (4-9).

The arterial baroreceptors are known to play an important role in the regulation of BP (10-20). Increase in BP causes stimulation of arterial baroreceptors which leads to inhibition of sympathetic nerve activity and the relationship between the BP and HR changes and the resetting of the baroreflex for the resulting BP occurs. Since most of the modern drugs are in pure active form and cause certain side-effects, it is essential to look into the hypotensive efficacy of

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naturally occuring herbal drugs, with relatively less side effects, as an alternative to commonly used allopathic drugs. For standardization for such herbal drugs the information about the potency, toxicity and mechanism of action of the drugs is essential. However, many of the herbs have been used over decades for treatment of hypertension and other diseases without adequate knowledge of its mechanism of action and side-effects.

The present investigation was undertaken with a view to test the: (a) hypotensive effect of Ajmaloon on rabbits and monkeys, (b) dose response curve of Ajmaloon, and (c) baroreflex response in animals treated with Ajmaloon.

METHODS

Experiments were performed on seven rabbits weighing 1.5-2 kg and five monkeys weighing 4.5-5.2 kg of either sex. The animals were anaesthetized with 40 mg/kg sodium pentobarbital (Sagatal M & B) given intraperitoneally. Subsequent maintenance doses were given intravenously. A polyethylene catheter was placed into descending aorta through femoral artery for recording BP with a pressure transducer (Statham P-23 Db).

An increase or decrease in BP was achieved by bolus i.v. injection of phenylephrine (PE) or sodium nitroprusside (NP) respectively in varying doses in control as well as after Ajmaloon treatment. The corresponding changes in HR with increase or decrease in BP were recorded.

A rectal thermometer was used to record body temperature which was maintained at 37-38°C. Arterial blood samples were drawn anaerobically from femoral arterial catheter periodically and blood PO_2, PCO_2, and pH were measured with the help of radiometer (BMS-3 MK-2 blood microsystem in conjuction with PHM-73 pH/blood gas monitor). Adequate levels of PO_2 (>90 mmHg) were maintained by the addition of humidified oxygen to the inspired air. PCO_2 and pH were within the range of 30-40 mmHg and 7.3-7.4 respectively.

The data was subjected to analysis of variance in a randomized block animal arrangement after ascertaining the homogenity of variance and normality. The data from each series of experiments was analyzed separately. On evidence of significant effects, individual and other appropriate comparisons were done through linear contrasts (20). The variables have been expressed throughout as mean values and the variation between animals of the same group is indicated by standard error of mean (± SEM).

Ajmaloon administration: For intravenous administration of Ajmaloon standard tablets (500 mg) were dissolved in normal saline and the homogenous solution was filtered. The volume of Ajmaloon solution for intravenous injection was kept constant (2 ml). In order to inject varying doses of the drug appropriate dilution of the stock solution was done with normal saline. Equal volume (2 ml) of normal saline was injected for control records before Ajmaloon.

Each 500 mg Ajmaloon (Hamdard, India) tablet available commercially contains 50 mg Zea mays, 50 mg Cicer arietinum, 1 mg Juniper communis, 6.2 mg Rauwolfia serpentina, 25 mg Hordeum Volgare and 2 mg Shora Kalmi (1).

RESULTS

Hypotensive effect of Ajmaloon was tested in anaesthetized rabbits and monkeys. In both the species, Ajmaloon lowered the BP in dose-dependent manner (Fig.1 and Tables I, II).

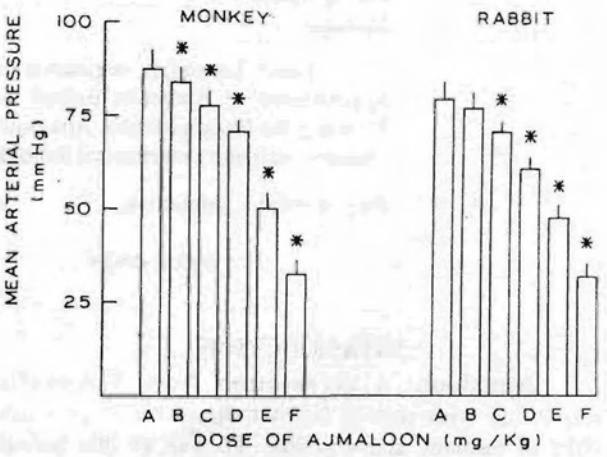

Fig. 1: Histograms showing the effect of varying doses of intravenous Ajmaloon on mean arterial pressure in anaesthetized monkeys and rabbits. In each set A: control before Ajmaloon, B, C, D, E, F: after intravenous administration of 25, 50, 100, 200, 300 mg/kg Ajmaloon respectively.

Effect of Ajmaloon on rabbits:

In rabbits 100 mg/kg Ajmaloon produced a significant ($P<0.05$) fall in systolic, diastolic and mean arterial pressure. The bradycardia was not found to be statistically significant ($P>0.05$). With half of the dose of Ajmaloon (50 mg/kg) only diastolic and mean arterial pressure showed statistically significant ($P<0.05$) fall (Table I and Fig.1). The drug in higher doses 200 mg/kg or more reduced the systolic and diastolic pressure to nearly fifty percent of the control and also produced a significant ($P<0.05$) fall in pulse pressure and the HR (Table I). Ajmaloon in intravenous doses higher than 300 mg/kg produced drastic fall in BP which caused subsequent death of the animal.

Effect of Ajmaloon on monkeys:

The effects of varying intravenous doses of Ajmaloon on arterial blood pressure and heart rate of anaesthetized monkeys are summarized in Table II and Fig.1.

Like in rabbits as well as in monkeys, Ajmaloon produced dose-dependent fall in the BP (Table II and Fig. 1). However, even with the highest dose of the drug, there was no significant ($P>0.05$) change in the HR of monkeys (Table II). 50 mg/kg or more intravenous Ajmaloon produced significant ($P<0.05$) fall in only diastolic and mean arterial pressure in higher doses (100 mg/kg or more) produced significant ($P<0.05$) fall in systolic pressure also (Table II). 300 mg/kg Ajmaloon reduced the systolic pressure more than fifty percent of the control and diastolic pressure to one third of the control with a significant fall in pulse pressure and no significant ($P>0.05$) fall in HR (Table II).

Effect of Ajmaloon on baroreflex response in rabbits:

Systolic arterial pressure (SAP)- heart rate (HR) curves were obtained by varying the arterial pressure (range 50-175 mm Hg) from the resting value with different doses of intravenous PE and NP and noting the resulting HR response. The procedure and the calculation of the curve parameters were same as described earlier (13,14). Tachycardia response to hypotension and a bradycardia response on increase in BP were consistently observed (Fig. 2). The SAP-HR curve was sigmoid in shape and following intravenous administration of 100 mg/kg Ajmaloon, it shifted to the left from its original control position (Fig. 2). Slopes of the curve for both the bradycardia and tachycardia responses were attenuated (Fig. 2). There was hardly any tachycardia response to hypotension following Ajmaloon treatment whereas, the decrease in the slope of the curve for bradycardia response to hypertension was small (Fig. 2).

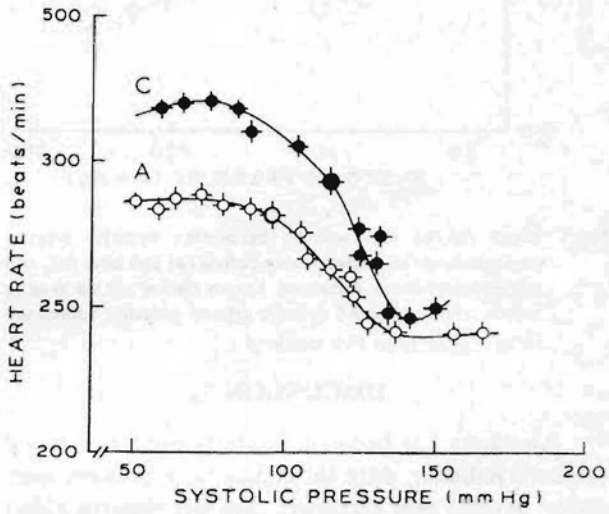

Fig. 2: Mean curves representing baroreflex systolic arterial pressure-heart rate relationship before (•) and after (o), 100 mg/kg intravenous Ajmaloon. Larger circles are the resting values. Heart rate and systolic arterial pressure values are mean ±SEM from seven rabbits.

Effect of Ajmaloon on baroreflex response in monkeys:

BP was varied over wide range with intravenous PE and NP and resulting HR response was recorded. The baroreflex SAP-HR curve was sigmoid in shape and with increase and decrease in SAP, the HR response was similar to that observed in case of rabbits. After treatment with 100 mg/kg intravenous Ajmaloon, the baroreflex SAP-HR curve shifted to the left from the control position (Fig. 3). Like in rabbits the tachycardia response to fall in SAP was drastically reduced by Ajmaloon and there was no significant change in the bradycardia response with increase in SAP (Fig. 3).

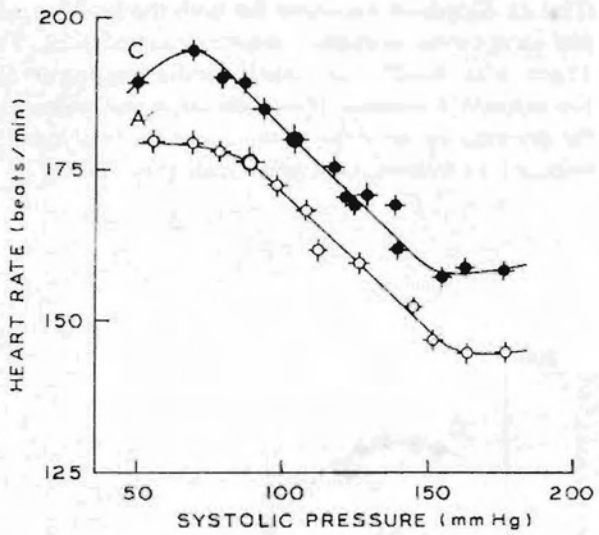

Fig.3: Mean curves representing baroreflex systolic arterial pressure-heart rate relationship before (•) and after (o), 100 mg/kg intravenous Ajmaloon. Larger circles are the resting values. Heart rate and systolic arterial pressure values are mean ±SEM from five monkeys.

DISCUSSION

Ajmaloon has been successfully used as a blood pressure reducing drug in hypertensive patients with minor adverse side effect (1). The hypotensive effect of Ajmaloon is reported to be reversible, the pressure starts coming back towards normal level after seven to ten days of stopping the drug (1). The dose of Ajmaloon generally prescribed for the treatment of essential hypertension ranges from 1-6 tablets daily depending on the severity of hypertension. Each tablet of Ajmaloon weighs 500 mg. The oral dose of Ajmaloon normally used in humans is much less than what we used in our experiments on monkeys and rabbits intravenously. The reason for using higher intravenous dose in our study was mainly because of acute experiments. Single bolus dose was given in order to test the potency of the drug and any damage to the cardiopulmonary system due to its toxic effects if any. Much higher dose (5 g/kg for three days) has been used in rats by other investigators (1), and has been found to have protective effects in isoprenaline induced cardiac necrosis in rats, rather than toxic.

The results of present investigation clearly demonstrate a definite and dose-dependent hypotensive effect of intravenous Ajmaloon in rabbits and monkeys. Extremely high doses of the drug were found to be fatal for both the species and the cause of death was probably the drastic fall in arterial blood pressure as other possible reasons for death e.g. arrhythmia and other conduction disorders and respiratory disorder were not observed.

The fall in the HR on intravenous bolus injection of 100 mg/kg, Ajmaloon was not found to be statistically significant ($P>0.05$) in rabbits and monkeys. The baroreflex mediated HR response to SAP change was reduced particularly in case of fall in SAP (Fig. 2 and 3). During fall in blood pressure, the resulting tachycardia response is known to be mainly due to increase in sympathetic and inhibition of parasympathetic activity (13). The reduction in the tachycardia response to fall in blood pressure in Ajmaloon treated animals can be attributed to the drug induced suppression of sympathetic excitatory or vagal inhibitory ability due to its influence on the autonomic nervous system, which is clearly reflected in the shift of SAP-HR curve to the left of the control curve, after Ajmaloon.

The type of shift in SAP-HR curve from its control position due to a drug depends on whether or not it acts on cardiac autonomic motoneurones with projections from cardiac baroreceptors (14). Since mean level of HR is not altered by the drug, it indicates that the drug influences mainly those motoneurones which receive baroreceptor afferents. However, the influence of drug on the baroreflex independent motoneurone pool can not be ruled out.

In conclusion, Ajmaloon is a potent antihypertensive drug which produces dose-dependent fall in blood pressure. Significant fall in diastolic pressure and no significant effect on HR by smaller dose (50 mg/kg) of Ajmaloon indicates its importance as an antihypertensive drug. The action of Ajmaloon on the SAP-HR curves indicates that during increase in SAP the sensitivity of baroreflex is only slightly reduced in rabbits and there was no change in monkeys. Loss of tachycardia response during fall in SAP after Ajmaloon indicates that the drug inhibits

the sympathetic activity and hence the baroreceptor mediated tachycardia response. Thus, in anaesthetized rabbits and monkeys, Ajmaloon acts as a potent antihypertensive agent in dose-dependent manner and it does not interfere with the normal baroreceptor mediated reflex regulatory mechanism in response to increase in BP.

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