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THE EFFECT OF POTASSIUM ON OUABAIN TOXICITY IN RESERPINIZED GUINEA PIGS

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ABSTRACT

The antagonistic activity of reserpine pretreatment on ouabain toxicity was investigated in the guinea pig, with attention paid to the water and potassium unbalance caused by diarrhea.

Reserpine pretreament alone exhibited no protective action against ouabain toxicity, but it was manifested by the administration of potassium chloride. On the other hand, glucose water was ineffective. There was no significant decrease of potassium concentration in the serum in reserpinized animals.

The possible role of potassium in the antagonistic action of reserpine on ouabain toxicity was discussed.

INTRODUCTION

It has been reported that the procedure to reduce the heart rate causes an antagonizing effect on digitalis glycoside toxicity[1)2)3)]. In an earlier communication[4)], propranolol, quinidine and hexamethonium were shown to possess both heart rate reducing action and antagonizing effect on ouabain toxicity in the guinea pig. Reserpine pretreatment also produced marked reduction in heart rate, but the lethal dose of ouabain never increased beyond that of the control. Reserpinized guinea pigs usually exhibit severe diarrhea. Therefore, it would be natural to consider that there is a loss of water and electrolytes, especially potassium, from the animal body. Potassium is well known to be contained in the gastrointestinal tract in much higher concentration than in other extracellular fluids[5)].

The present study was conducted to determine the role of heart rate reduction on ouabain toxicity in the reserpinized guinea pig supplied with glucose water or potassium chloride.

MATERIALS AND METHODS

Guinea pigs of either sex, weighing between 400 to 800 g, were used. Pretreatment with reserpine was performed by a single intraperitoneal injection

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of reserpine 5 mg/kg body weight, 18 hours before the experiments. Guinea pigs were anesthetized by subcutaneous injection of urethan 1.5 g/kg body weight. 20 μg/kg ouabain was cumulatively administered by intravenous injections at 3-minute intervals. The electrocardiogram (Lead II) was monitored for the detection of ventricular arrhythmia and fibrillation and cardiac arrest. Total dose of ouabain administered until no electrical activity was observed for 3 minutes, was determined as the lethal dose of ouabain. The guinea pigs were divided into the following five groups.

1) Control group.

2) Group with reserpine pretreatment.

3) Group with the administration of potassium chloride solution. 20 ml/kg of 1% potassium chloride was administered intraperitoneally 30 minutes before the experiments.

4) Group with reserpine pretreatment and with administration of potassium chloride in the same dose as described above.

5) Group with reserpine pretreatment and with the intraperitoneal administration of 20 ml/kg of glucose water (5% w/v) 30 minutes before the experiments.

Blood was collected by heart puncture in normal and reserpine pretreated animals to measure serum potassium by the flame-photometer.

RESULTS

Data of the five groups are shown in Table 1. Data of control group (group 1) are based on 26 animals. 25 showed ventricular arrhythmia and 25 terminated in ventricular fibrillation. The average lethal dose of ouabain

TABLE 1. Influence of Various Treatments on Ouabain Toxicity in Guinea Pigs

Treatment	No. of experiments	Incidence of ventricular arrhythmia	Incidence of ventricular fibrillation	Lethal dose of ouabain (mean±S.D. μg/kg)
None (group 1)	26	25	25	464±48.6
Reserpine (group 2)	8	7	7	480±23.8
Potassium (group 3)	13	10	8	477±31.9
Reserpine and potassium (group 4)	13	4	2	619±49.3*
Reserpine and glucose water (group 5)	7	6	6	447±40.7

* Asterisk shows that the difference from the control value is significant ($P<0,01$).

in this group was 464±48.6 μg/kg (mean±S.D.). Reserpine pretreatment (group 2) did not affect the incidence of ventricular arrhythmia and fibrillation. Among 8 animals, 7 showed ventricular arrhythmia and 7 terminated in cardiac arrest following ventricular fibrillation. The average lethal dose of ouabain was 480±28.3 μg/kg. No differences were found in the parameters examined between the control group and group pretreated with reserpine. Administration of potassium chloride (group 3) affected neither the incidence of ventricular arrhythmia, nor the lethal dose of ouabain. Of 13 animals, 10 showed arrhythmia and 8 terminated in ventricular fibrillation. The average lethal dose of ouabain was 477±31.9 μg/kg in this group. The protective action against ouabain toxicity was marked in the reserpine pretreated and potassium administered animal group (group 4). Sinus arrhythmia or ventricular extrasystole was observed in 4 of the 13 animals. Most of the animals terminated in cardiac standstill without showing ventricular fibrillation. The average lethal dose was 619±49.3 μg/kg. These data suggested that the protective action of reserpine pretreatment against ouabain toxicity was manifested by the addition of potassium ion. In order to clarify if the water supply was responsible for the protective action mentioned above, the following experiments (group 5) were carried out. Of 7 animals given 20 ml/kg of 20% glucose solution, 6 produced arrhythmias and 6 terminated in cardiac standstill following fibrillation. The average lethal dose of ouabain was 447±40.7 μg/kg. The data revealed that the protective action was not due to water addition but to potassium supply.

TABLE 2. Concentration of Serum Potassium in Control and Reserpine Treated Guinea Pigs

	No. of experiments	Serum potassium (mEq/l)
Control	8	7.28±0.9
Reserpine pretreatment	9	7.16±1.1

Serum potassium of control and reserpine treated guinea pigs was 7.28±0.9 and 7.16±1.1 mEq/l respectively, and a difference was not found between them (Table 2).

DISCUSSION

Reserpine treatment, in spite of the presence of heart rate reducing action, did not inhibit ouabain toxicity, while propranolol, quinidine or hexamethonium which reduce the heart rate, possessed antagonizing effect on ouabain toxicity[4]. It is conceivable that reserpine pretreatment could not display its protective action against the ouabain toxicity on account of the loss of potassium in cardiac muscle.

Reserpine treatment produces usually a diarrhea which would cause dehydration and electrolytes loss in the animal. Administration of glucose water or potassium chloride just before ouabain injection was performed in reser-

pinized animals in these experiments. Although water supply could not prevent ouabain toxicity in reserpinized animals, the lethal dose of ouabain was increased by potassium supplied in doses which were ineffective in normal animals. There was no significant decrease of the potassium concentration in serum. It was reported that reserpinized rat show cardiac decompensation accompanied by a depletion of myocardial potassium[6]. Potassium which had been lost and supplied in this experiment may be considered to be contained mainly in the tissue cell.

There have been several reports of studies made on the effect of reserpinization on ouabain toxicity. Some[7)-11)] reported the antagonizing effect of reserpine pretreatment on ouabain toxicity, while others[12)-15)] showed that this treatment did not influence ouabain toxicity. In the present study, an antagonizing effect was observed if potassium chloride was supplied to reserpinized animals. Thus it could be suggested that the heart rate reducing effect antagonizes ouabain toxicity also in case of reserpine pretreatment just as in propranolol, quinidine or hexamethonium administration. The problem whether catecholamine deficiency in the heart induced by reserpine participates in the antagonizing effect on ouabain toxicity still requires further elucidation.

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