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The Effects of Acebutolol and Carbamazepine on the Ouabain-Induced Arrhythmias in Rabbits

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ABSTRACT

The effects of acebutolol and carbamazepine on ouabain-induced arrhythmias were investigated in rabbits. Ouabain produced ventricular arrhythmias which persisted for 7-8 min at the mean dose of 69±1.3 μg/kg. Ouabain arrhythmias were converted to normal sinus rhythm by administration of acebutolol or carbamazepine singly but lower dosages increased the recovery time. And then, ouabain arrhythmias were effectively converted to normal sinus rhythm and prevented by combined administration of carbamazepine and acebutolol. Each of the combined doses was ineffective when given singly.

From the above results, it may be concluded that carbamazepine and acebutolol inhibited the ouabain-induced arrhythmias depending on the level of dosage and showed synergistic interaction.

Key Words: acebutolol, carbamazepine, ouabain-induced arrhythmias, synergistic interaction

INTRODUCTION

Antiepileptic drugs, such as phenytoin, are known to affect ventricular tachycardia in experimental acute myocardial infarction in dogs (Harris and Kohernot, 1950) and widely used clinically for the treatment of ventricular arrhythmia, particularly those produced by digitalis toxicity (Bigger and Hoffman, 1985). Carbamazepine is related chemically to the tricyclic antidepressants and has been known effective in the treatment of epilepsy (Theodore and Leonard, 1985). The effects of carbamazepine on the heart has been studied without any clear result.

Steiner *et al.* (1970) reported that carbamazepine in dogs effectively converted ventricular tachycardia from digitalis intoxication to normal sinus rhythm in vivo. Benaim and Chiche (1973) observed that premature beats and ventricular fibrillation of patient with chronic premature ventricular contraction could be prevented by administering carbamazepine. But many clinical case reports showed the side effects of carbamazepine during the course of carbamazepine treatment: ventricular stand still and Adams-Stokes attack (Beermann *et al.*, 1975), sinus bradycardia (Herzberg, 1978), complete heart block (Hamilton, 1978) and decreased A-V conduction and automaticity of heart (Beerman and Edhag, 1978). Recently Kim *et al.* (1986) reported prolonged durations of antiarrhythmic effect of carbamazepine in rabbits depending on the applied doses. The toxic effect on heart in high dosage was found to be dangerous.

Meanwhile, recently many reports showed the beta 1 selective antagonist, acebutolol, was effective in the premature ventricular contraction (Arnow *et al.*, 1979; Arnow *et al.*, 1980; Soyza *et al.*, 1985), supraventricular arrhythmias (Willams *et al.*, 1979) and ventricular arrhythmias (Ahumada *et al.*, 1979; Glasser *et al.*, 1983; Lui *et al.*, 1983; Platia *et al.*, 1985; Soyza *et al.*, 1982). Basil *et al.* (1974) also reported acebutolol in dogs effectively converted arrhythmias from ouabain intoxication to normal sinus

rhythm in vivo. Some of the reports supported that acebutolol and carbamazepine had antiarrhythmic effects, but the interaction of both drugs is not yet clear.

It was, therefore, attempted in the present study to investigate the effects of carbamazepine and acebutolol administered singly or in combination on the ouabain-induced arrhythmias in rabbits.

MATERIALS AND METHODS

The rabbits of either sex, weighing from 1.6 to 3.2 kg, were anesthesized with urethane. After the trachea was cannulated, the rabbits were ventilated with room air using a respirator (Narcobiosystem V5KG). Drugs were given into polyethylene cannula in the femoral vein. Blood pressure was recorded by physiograph (Narcobiosystem MK-IV P) attached to pressure transducer (Narcobiosystem RP-1500) connected with cannula in the femoral artery. ECG was also recorded by physiograph (Narcobiosystem MK-IV P) connected with the electrode implanted in both axillars.

Measurements of arrhythmic dose of ouabain were made by continous infusion of 0.04% ouabain solution at a rate of 0.194 ml/min using an infusion pump (Havard 940). The duration of persistent arrhythmia at single injection of ouabain was also observed.

Experimental groups were as follows

1) Treatment of ouabain-induced arrhythmias with acebutolol or carbamazepine administered singly: Ventricular arrhythmias were produced with the administration of 69 μg/kg of ouabain in 48 rabbits. 24 rabbits were then given carbamazepine 15, 10, 5, 2.5 mg/kg i.v., whereas remaining 24 rabbits were given a acebutolol 8, 4, 2, 1 mg/kg.

2) Treatment of the ouabain-induced arrhythmias with combined administration of acebutolol and carbamazepine: After ventricular arrhythmias were produced by ouabain, 4 groups, each consisting of 6 of the 24 rabbits were given combined drugs of acebutolol 1 mg/kg and carbamazepine 2.5 mg/kg, acebutolol 0.5 mg/kg and carbamazepine 1.3 mg/kg, acebutolol 0.25 mg/kg and carbamazepine 0.6 mg/kg and acebutolol 0.13 mg/kg and carbamazepine 0.3 mg/kg. Each of the combined doses was ineffective when given singly.

3) Pretreated group with acebutolol and carbamazepine: 24 rabbits were pretreated with acebutolol 1 mg/kg and carbamazepine 2.5 mg/kg, and acebutolol 0.5 mg/kg and carbamazepine 1.3 mg/kg, followed by the i.v. administration of 0.04% ouabain 10 minutes later at a rate of 0.194 ml/min. until ventricular arrhythmia was produced.

Drugs used in this study were; Strophanthin-G (Ouabain) crystal (Merck) in 5% dextrose and sodium, acebutolol (Korean Rhone-Poulenc) in 5% dextrose and sodium and carbamazepine (Han-Su) in propylene glycol.

RESULT

Ouabain produced ventricular arrhythmias at mean dose of 69±1.3μg/kg (Table 1) and the developed arrhythmias persisted for 7-8 min (Table 2). At the time of ouabain arrhythmia, there was over 30 beats/min. of premature ventricular contraction with variable curve of blood pressure. Table 3 and Figure 1 show the effects of acebutolol and carbamazepine on the ouabain-induced arrhythmias administered singly. Given 8 mg/kg of acebutolol, arrhythmia was converted to sinus rhythm approximately within 40 sec. In lower dosage, the recovery

Table 1. Toxic effects of ouabain on the electrocardiogram of rabbits

Toxic effect	Dose (μg/kg)
Appearance of ventricular contraction	55±1.4
Development of ventricular tachyarrhythmia	69±1.3
Cardiac arrest	119±1.5

The values are shown as Mean ± S.E.

Table 2. Durations of persistence of ventricular tachyarrhythmias induced by ouabain in rabbits

No.	BW (kg)	Ouabain (69 μg/kg) Injection	
		D_1 (sec)	D_2 (sec)
1	2.5	400	350
2	2.4	660	1390
3	2.0	450	2060
4	2.3	370	no recovery
5	2.5	400	no recovery
6	2.5	690	no recovery
Mean ± S.E.		495±5.3	

D_1, D_2; Durations of persistence of arrhythmias
Repeated treatment (D_2) applied i.v. injection after 20 minutes of cessation of arhythmia (D_1) for each rabbit

time increased and more rabbits showed no recovery. ECG of no recovery showed severe bradycardia. 5 mg/kg of carbamazepine also converted arrhythmia to sinus rhythm approximately within 30 sec. In a dosage less or more than 5 mg/kg, the recovery time increased and more rabbits did not recover. ECG findings of no recovery were severe bradycardia or A-V block.

From the above result, antiarrhythmic action was not shown by 1 mg/kg of acebutolol (recovery time was 1535 sec) or 2.5 mg/kg of carbamazepine (recovery time was 820 sec) when given singly. But the combined administration of above mentioned dosages (1 mg/kg of acebutolol and 2.5 mg/kg of carbamazepine) converted arrhythmia to sinus rhythm within 35 sec and similar effects were shown in half the dosage (Table 4). Moreover, the arrhythmic dose of ouabian significantly increased in the pretreated group with above mentioned combination as compared with control (Table 5, Fig. 2).

Table 3. Effects of acebutolol and carbamazepine on the ouabain induced arrhythmias when given singly

Dose (mg/kg)	Time for recovery (sec)	No. of no recovery
Acebutolol		
1	1535±21.3	3
2	245±3.7	2
4	240±5.9	3
8	40±1.9	1
Carbamazepine		
2.5	820±4.6	2
5	23±1.8	0
10	30±1.9	2
15	108±6.3	3

The values are shown as Mean ± S.E.

Table 4. The effects of combined administration of acebutolol and carbamazepine on the ouabain-induced arrhythmias in rabbits

Dose (mg/kg) Acebutolol & Carbamazepine		Time for recovery (sec)	No. of no recovery
1	2.5	35±2.4	0
0.5	1.25	134±2.6	1
0.25	0.625	348±8.1	1
0.125	0.313	768±7.2	2

The values are shown as Mean ± S.E.
no recovery: The cases ouabain-induced arrhythmias were not converted to sinus rhythm
time for recovery: Time required for ouabain-induced arrhythmias to convert to sinus rhythm after treatment

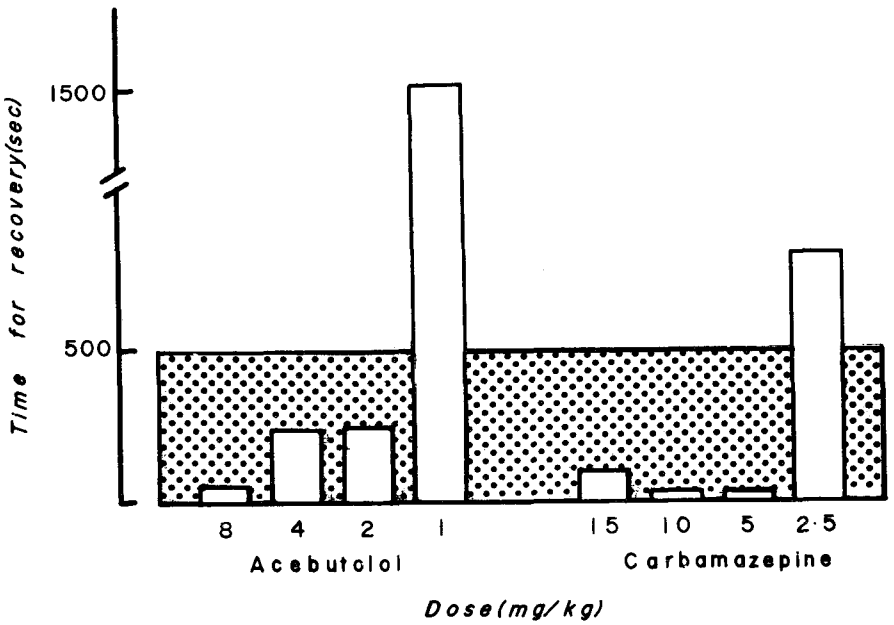

Fig 1. Antiarrhythmic effects of acebutolol and carbamazepine given singly
▨; Duration of persistence of arrhythmias due to 69 μg/kg of ouabain

Table 5. Effects of acebutolol and carbamazepine on the prevention of ouabain-induced arrhythmias

Toxic effect	Arrhythmic dose of ouabain (μg/kg)		
	Control	ACB (1 mg/kg) & CBZ (2.5 mg/kg)	ACB (0.5 mg/kg) & CBZ (1.25mg/kg)
Appearance of ventricular contraction	55 ± 1.4	97 ± 1.8*	108 ± 2.2*
Development of ventricular arrhythmia	69 ± 1.3	113 ± 1.9*	113 ± 1.8*
Cardiac arrest	119 ± 1.5	166 ± 1.7*	193 ± 2.3*

The values are shown as Mean ± S.E.
ACB; acebutolol
CBZ; carbamazepine
* $p<0.01$

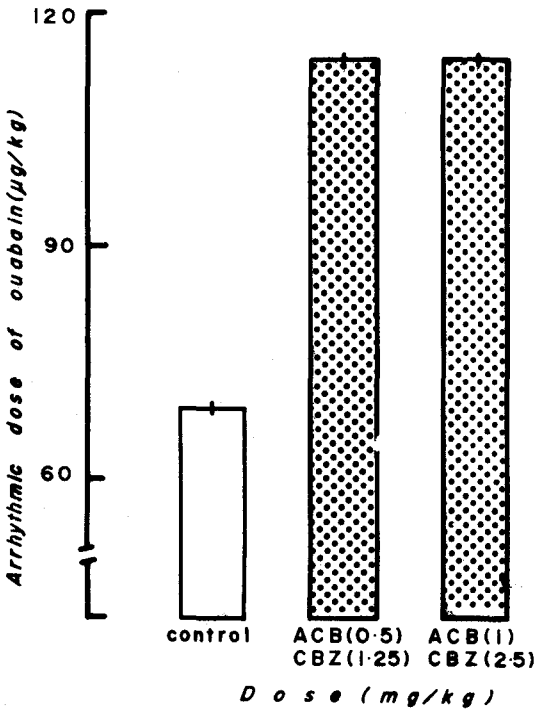

Fig 2. Effects of acebutolol and carbamazepine on the prevention of ouabain-induced arrhythmias
ACB; acebutolol
CBZ; carbamazepine

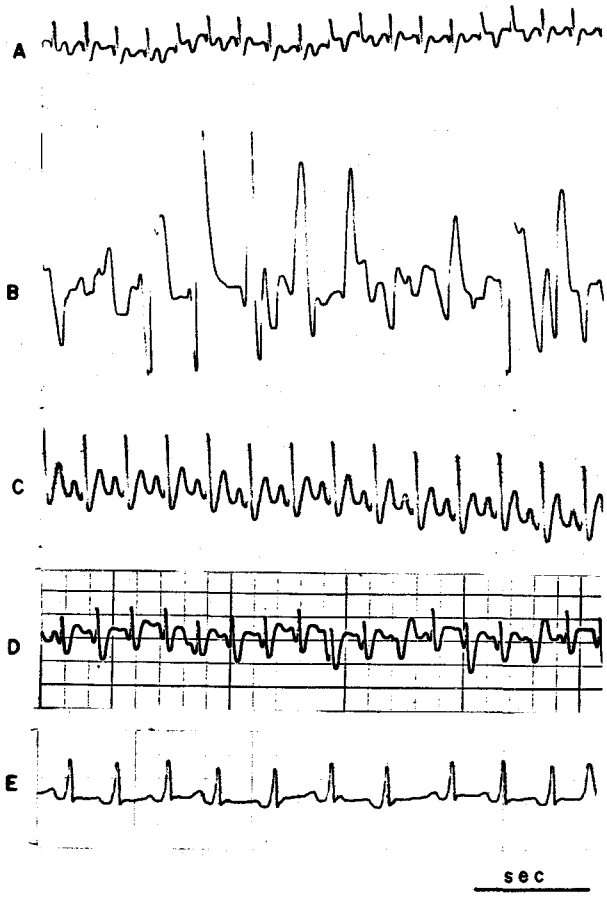

Fig 3. ECG findings in the states of arrhythmias induced by ouabain during acebutolol and carbamazepine treatment administered singly or in combination
A; Normal sinus rhythm
B; Ventricular arrhythmia induced by 69 μg/kg of ouabain
C; Converted sinus rhythm by i.v. injection of acebutolol
D; Converted sinus rhythm by i.v. injection of carbamazepine
E; Converted sinus rhythm by combined administration of acebutolol and carbamazepine

DISCUSSION

Tiula *et al.* (1982) reported the serum levels of alpha 1-acid glycoprotein (α-AGP) of patients received phenytoin or carbamazepine treatment were

significantly higher than the control and the serum level and pharmacological action of cationic drugs such as propranolol might be associated with these enzyme inducing drugs such as phenytoin or carbamazepine. But it is only theoretical, the interaction of acebutolol and carbamazepine was not well documented (Philip, 1985). In the present study, carbamazepine and acebutolol were found to be very effective in converting ventricular arrhythmia from ouabain toxicity to sinus rhythm. Moreover, the combined administration of carbamazepine and acebutolol, which had no antiarrhythmic action when given singly, was found to be effective in abolishing and preventing this arrhythmia. And this antiarrhythmic action was greater than arithmetic summation of antiarrythmatic action when administered singly. The recovery time of 1mg/kg of acebutolol and 2.5 mg/kg of carbamazepine was 35 sec and this record is equivalent to 8 mg/kg of acebutolol or 5 mg/kg of carbamazepine when given singly. Similar effects were shown in half the dosage of combination. These results do not seem to corresponding to the ideas of Tiula *et al.* (1982).

Meanwhile, in the group treated with acebutolol, the cases without recovery were 9 of 24 rabbits, and ECG findings are severe bradycardia. These results are supported by following reports.: Watt *et al.* (1968) observed highly dangerous progressive bradycardia might be induced by administration of propranolol in the patients with digoxin intoxication, and Orelly *et al.* (1974) and Philip (1985) also reported bradycardia due to digitalis might be aggravated by propranolol. Especially in the group treated with carbamazepine, the cases of no recovery were 7 of 24 rabbits and ECG findigs were severe bradycardia and heart block. These results might be explained by cardiac toxicity of carbamazepine (Beerman *et al.*, 1975; Beerman and Edhag., 1978; Hamilton, 1978; Herzberg, 1978; Kim *et al.*, 1986) But in the group treated with combined acebutolol and carbamazepine, only 4 of 24 rabbits did not recover. From this result we could assume the side effects of these drugs might be reduced by combined treatment.

In summary, the present study indicates as follows: because carbamazepine and acebutolol have synergistic interaction on antiarrhythmic effect, this arrhythmia may disappear or be prevented by combined therapy of acebutolol and carbamazepine. Cardiac toxicity of carbamazepine may also be reduced.

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=국문초록=

가토의 ouabain 유발 부정맥에 미치는 acebuolol 및 carbamazepine의 영향

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Adrenergic beta 1 수용체 봉쇄 약물인 acebutolol과 항 경련제로 사용되고 있는 carbamazepine은 실험적으로 ouabain유발 부정맥을 정상 심박동으로 환원시키는데 유효하다고 보고되었으나 그 상호 작용에 대해서는 밝혀진바가 없다. 이에 본 실험에서는 가토에 ouabain 투여로 부정맥을 유발시킨 후 acebutolol과 carbamazepine을 단독 혹은 병용 투여하여 이 두 약물이 ouabain 유발 부정맥에 미치는 영향과 그 상호 작용을 규명하고자 하였다.

실험 결과 ouabain 유발 부정맥은 acebutolol 혹은 carbamazepine 단독 투여로 정상 심박동으로 환원되었으며 용량이 감소함에 따라 정상 심박동으로 회복하는데 요하는 시간이 연장되었다. 또 단독 투여시 항 부정맥 효과를 볼 수 없었던 용량을 병용 투여하였을 때 ouabain 유발 부정맥은 즉시 정상 심박동으로 환원되었으며 상기 용량의 두약물을 병용하여 전처치함으로써 ouabain의 부정맥 유발 용량이 의의있게 증가되었다($P < 0.01$). 이상의 결과로 acebutolol과 carbamazepine은 ouabain 유발 부정맥을 용량 의존적으로 억제시키며 상협적인 상호 작용(synergistic interaction)을 나타낸다고 사료된다.