ANTIARRHYTHMIC ACTIVITY OF ETHOSUXIMIDE AND GALLAMINE TRIETHIODIDE IN EXPERIMENTALLY INDUCED ARRHYTHMIAS

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Summary: Antiarrhythmic action of ethosuximide and gallamine triethiodide was studied by Dawes' method and against amodiaquine induced ventricular arrhythmias in dog. Both ethosuximide and gallamine triethiodide reduced maximum driving frequency in Dawes' method. In addition gallamine triethiodide was effective against amodiaquine induced ventricular arrhythmias in dog.

Key words: ethosuximide gallamine triethiodide experimental cardiac arrhythmias

INTRODUCTION

Diphenyhydantoin, a well-known anticonvulsant has established its status as an antiarrhythmic agent (6.). However after anticonvulsants have received only scant attention so for as their antiarrhythmic potential is concerned. It was therefore decided to investigate ethosuximide and gallamine triethiodide for their antiarrhythmic activity.

MATERIALS AND METHODS

Antiarrhythmic action was studied by Dawes' method (3) and against amodiaquine induced ventricular arrhythmias in dog as per the method of Arora and Arora (1).

Dawes' Method: 9 Albino rabbits weighing between 1 and 1.5 *kg* and of either sex were used. After killing the animal, its atria were dissected out and suspended in strongly oxygenated Ringer-Locke solution, the temperature of which was maintained at 29°C. The maximum driving frequency (MDF) of isolated atria before and after the addition of a drug was found out. The concentrations of drugs were adjusted in such a way that the percentage reduction in MDF would lie approximately between 10 and 30. Three doses each of quinidine sulphate, gallamine triethodide and ethosuximide were tested to compare their potencies. Electrical stimulation from square wave electronic stimulator was given 10 min after the addition of drugs to bath. Six readings were taken for each dose and six readings were taken on each pair of atria.

Method of Arora and Arora: 11 dogs of both sexes weighing between 9 and 13 *kg* were anesthetised with phenobarbitone, 150 *mg/kg* given intraperitoneally. Ventricular arrhythmias were induced by 2% aqueous solution of amodiaquine hydrochloride given through femoral vein which was canulated beforehand. Blood pressure was recorded from carotid artery and electrocardiogram (ECG) was recorded in standard limb lead II. Amodiaquine hydrochloride was

injected rapidly in the dose of 6 *mg/kg* to produce ventricular extrasystoles and other less serious arrhythmias and in the dose of 10 *mg/kg* to produce ventricular tachycardia and fibrillation. ECG was recorded every two minutes. Two to three control readings were taken giving a gap of 20 min between two amodiaquine injections to determine the onset and duration of arrhythmias. Preventive and curative action of ethosuximide and gallamine triethiodide were tested. To study preventive antiarrhythmic action ethosuximide or gallamine triethiodide were injected slowly and challenging doses of amodiaquine hydrochloride were given after 5, 25 and 45 min and ECG records were taken in between every 2 min. To study curative antiarrhythmic action, arrhythmia was produced first by giving a challenging dose of amodiaquine with ECG monitoring. As soon as the arrhythmia appeared ethosuximide or gallamine triethiodide was injected.

RESULTS

Dawes' Methods: All the three drugs tested i.e. quinidine sulphate, ethosuximide and gallamine triethiodide reduced the MDF. Quinidine sulphate was found to be most effective in reducing the MDF, followed by gallamine triethiodide and ethosuximide. (Table I).

TABLE I: Reduction in maximum driving frequency of rabbit atria.

Drug	*Dose in mcg/ml. (No. of observations)*	*Mean % reduction in MDF ± S.E.*
Quinidine	1 (6)	15 ± 0.84
Sulphate	1.25 (6)	25 ± 1.02
	1.5 (6)	36 ± 1.29
Gallamine	3 (6)	16.5 ± 1.02
Triethiodide	4 (6)	25 ± 1.09
	5 (6)	31.25 ± 1.59
Ethosuximide	4 (6)	18.75 ± 1.08
	5 (6)	25 ± 1.008
	6 (6)	30 ± 1.26

Method of Arora and Arora: In one set of experiments amodiaquine hydrochloride was used in the dose of 6 *mg/kg*. It produced various types of ventricular arrhythmias excepting ventricular tachycardia and fibrillation. Widening of QRS complexes, depression of ST segments and ventricular extrasystoles were noted. The arrhythmias appeared within two minutes and lasted for about 8 min and were reproduceable every time amodiaquine was injected. Amodiaquine itself caused a transient fall of blood pressure of about 20 mm. Hg. The blood pressure however returned to normal quickly. Ethosuximide and gallamine triethiodide which were injected slowly did not produce any fall of blood pressure. Also, these drugs by themselves did not produce any ECG abnormality.

In another set of experiments amodiaquine hydrochloride was injected in the dose of 10 *mg/kg*. It produced ventricular tachycardia or fibrillation within 2 minutes every time. If ventricular tachycardia appeared first it would soon progress to fibrillation.

Ethosuximide in 5,10,15,20,25 and 30 *mg/kg* doses proved disappointing both in preventing and arresting ventricular arrhythmias produced by this method. The dog in which ventricular tachycardia or fibrillation was produced would die unless gallamine triethiodide was injected within seconds of appearance of the arrhythmia.

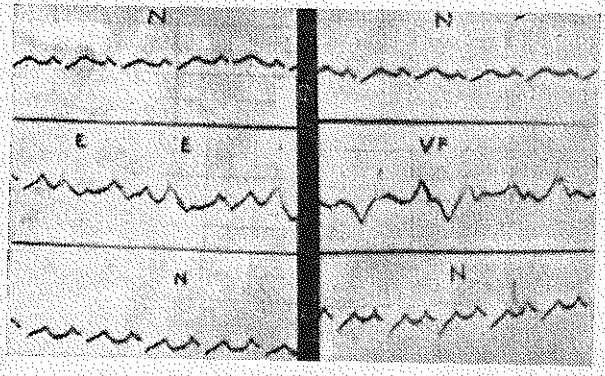

Fig 1: ECG : Limb lead II showing effect of gallamine triethiodide against amodiaquine induced ventricular arrhythmias in dog.

Left panel shows normal (N) ECG recorded in upper tracing, amodiaquine induced ventricular extrasystoles(E) in middle tracing and preventive antiarrhythmic action of gallamine triethoiodide in lower tracing. Right panel shows antiarrhythmic action of gallamine triethiodide in ventricular fibrillation (VF).

Gallamine triethiodide was effective in controlling all ventricular arrhythmias produced by this method. It has both preventive and curative antiarrhythmic action. The dose employed was 0.6 *mg/kg*. The antiarrhythmic effect lasted for about 20 minutes after which time challenging dose of amodiaquine hydrochloride could again produce ventricular arrhythmias. (Fig. 1).

DISCUSSION

Both ethosuximide and gallamine triethiodide reduce MDF as tested by Dawes' method in this study. This shows their ability to increase the effective refractory period of atria (3). Thus they are likely to interrupt the circus movement or re-entry phenomenon e.g. auricular firbrillation (3,5).

Gallamine triethiodide is effective against amodiaquine induced ventricular arrhythmias in dog. This may be due to its ability to decrease the rate of phase — 4 depolarisation and thus abolish the ectopic foci. This requires confirmation by electrophysiological studies. Ethosuximide seems to lack this property in the doses used in this study.

Quinidine, the presently available drug for auricular flutter and fibrillation, is quite toxic (7). Ethosuximide which is comparatively a safe antiepileptic in clinical practice (8), may offer a therapeutic promise in these conditions.

The efficacy of gallamine triethiodide in experimental arrhythmias points to the antiarrhythmic potentiality of neuromuscular blocking agents which is a new group to be explored in this respect. Gallamine triethiodide is comparatively a safe muscle relaxant in clinical practice (2). It too, therefore appears to deserve clinical trials in auricular and ventricular arrhythmias. If it fulfills this therapeutic promise it will offer an additional advantage of its antiarrhythmic action, during its use as an adjuvant to general anaesthetics.

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