

## SHORT COMMUNICATION

### A PRELIMINARY REPORT ON THE ANTIARRHYTHMIC ACTION OF SOME NEWLY SYNTHESIZED GLUTARIMIDE COMPOUNDS\*

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**Summary:** The effects of a new series of glutarimide compounds have been studied in acetylcholine induced auricular fibrillation in anaesthetized cats and epinephrine induced ventricular arrhythmias in conscious pigeons. Some of the compounds showed varying degree of protective action against experimental arrhythmias. However these compounds were found to be less potent than quinidine. The mechanism of antiarrhythmic action has been discussed.

**Key words:** glutarimide compounds antiarrhythmic action

#### INTRODUCTION

Glutarimide compounds have been shown to have several interesting pharmacological actions ranging from CNS depression (4,14) to convulsant (6,7,11,12) action. Recently Devani and Shishoo (1970) synthesized a series of glutarimide analogues whose pharmacology was investigated in this laboratory (8). During the course of this study, it was observed that the amphibian hearts showing ectopic beats and an irregular rhythm were immediately brought to normal following administration of some of these compounds which indicated antiarrhythmic activity.

The present report deals with our preliminary experiments designed to evaluate the effect of some of these compounds on the normal E.C.G. recordings and against experimentally induced arrhythmias in the intact heart of pigeon and cat.

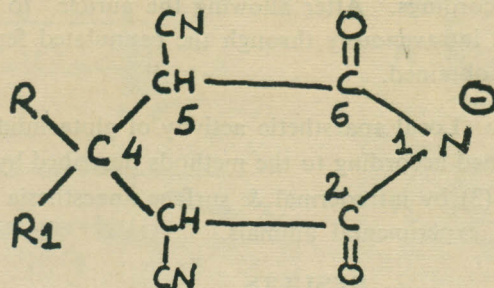
#### MATERIALS AND METHODS

*Epinephrine induced fibrillation in conscious pigeons:* Experimental procedure was essentially similar to the one described by Viiu V. Klein *et al.* (13). Unanaesthetized pigeons (either sex, 250-350 G) were immobilized with the vagi intact. Platinum electrodes were inserted into the right wing base, the left wing base and the left leg of the pigeon. Standard lead II E.C.G. were taken using special cardiopan. 10  $\mu\text{g}/\text{kg}$  of U-0882 was injected i.v. for sensitizing the heart. After 2 minutes epinephrine (40  $\mu\text{g}/\text{kg}$ ) was administered through an indwelling polythelene catheter into an alar vein. Glutarimide compounds (Table I) were tested for their antifibrillatory effect if any against the experimentally produced arrhythmias in conscious pigeons. The compounds were administered in graded doses and the  $\text{ED}_{100}$  was determined.

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TABLE I: Showing the code number, code name, chemical structure and LD<sub>50</sub> of various glutarimide compounds investigated.



Basic structure  
3,5-dicyano glutarimide

Code No.	Code name	R	R1	N	LD <sub>50</sub> in mice (mg/kg; I.P.)
1	CJ <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	+ C <sub>5</sub> H <sub>10</sub> NH <sub>2</sub>	152
2	CJ <sub>4</sub>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>5</sub> H <sub>10</sub> NH <sub>2</sub>	158
8	MB <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	+ (C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> NH <sub>2</sub>	251
9	MB <sub>3</sub>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> NH <sub>2</sub>	265
10	MB <sub>1</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub> NC <sub>4</sub> H <sub>8</sub> O	240
11	MB <sub>4</sub>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> NC <sub>4</sub> H <sub>8</sub> O	286
12	MG <sub>1</sub>	CH <sub>3</sub>	CH <sub>3</sub>	+ NH <sub>2</sub> C <sub>4</sub> H <sub>8</sub> O	215
13	MG <sub>2</sub>	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	NH <sub>2</sub> C <sub>4</sub> H <sub>8</sub> O	232
	PIP	C <sub>5</sub> H <sub>10</sub> NH	—	— (B.P.)	oral 485 mg/kg
	DEA	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> NH	—	— (B.P.)	oral 500 mg/kg
	MOR	C <sub>4</sub> H <sub>8</sub> O.NH	—	— (B.P.)	oral 525 mg/kg

TABLE II: Antiarrhythmic effect of glutarimide compounds in conscious pigeons, against epinephrine induced ventricular fibrillation.

Drug. Code No.	Drug Code name	No of observations	Mean Ed <sub>100</sub> mg/kg; i.v.	95% confidence limit
1	CJ <sub>2</sub>	4	14.65	(12.2 — 16.1)
2	CJ <sub>4</sub>	4	14.98	(11.9 — 16.2)
8	MB <sub>2</sub>	4	13.88	(9.49 — 14.1)
9	MB <sub>3</sub>	4	14.60	(10.2 — 14.9)
10	MB <sub>1</sub>	4	10.00	(8.4 — 11.9)
11	MB <sub>4</sub>	4	11.50	(9.9 — 12.8)
12	MG <sub>1</sub>	4	15.75	(13.92 — 16.8)
13	MG <sub>2</sub>	4	16.20	(14.7 — 17.3)
	Quinidine	4	8.00	(7.2 — 9.3)

*Acetylcholine induced auricular fibrillation in cats:* The method employed to induce auricular fibrillation was similar to the one described by Scherf and Chick (10). Adult healthy cats (either sex, 4-6 kg) were anaesthetized with pentobarbitone sodium (30 mg/kg i.v.) and artificially ventilated. E.C.G. (Cardiopan, Philips) was recorded by using standard lead II.

A small pledget of cotton wool soaked in 5% acetylcholine was placed over the region of S-A node for 1 minute. The auricle was then pinched and fibrillation was induced almost immediately as confirmed by E.C.G. recordings. After allowing the auricle to fibrillate for about 1 minute, the drugs were injected intravenously through the cannulated femoral vein and continuous record of E.C.G. was obtained.

*Local anaesthetic activity:* Local anaesthetic activity of glutarimide compounds (0.5 to 2.0%) under study was determined according to the methods described by Bulbring and Wajda (1) and Chance and Lobstein (3) by intradermal & surface anaesthesia respectively by using either guineapigs or rabbits as experimental animals.

## RESULTS

*Effect of glutarimide compounds against epinephrine induced ventricular fibrillation in conscious pigeons:* Compounds 1, 2 and 8 to 13 (8 mg/kg; i.v.) showed slight reduction in heart rate (mean % reduction being 8.5 to 19.5; n=4) without any marked change in rhythm, P wave, S and T wave and ST segment (Fig. 1) on normal E.C.G. recordings. However, these drugs showed protection against epinephrine induced fibrillation (Fig. 1 & 2). Hence ED<sub>100</sub> for each compound was determined and compared with the reference drug quinidine (Table II). The relative potencies were also determined. Compound 10 was found to be the most potent although it was less potent than quinidine.

*Effect of glutarimide compounds against acetylcholine induced auricular fibrillation in anaesthetized cats:* Compounds 1, 2 and 8 to 13 (8 mg/kg; i.v., n=3) exhibited some reduction in normal heart rate (mean % reduction being 8.76 to 14.8) without causing any significant change in rhythm, P, QRS, T waves and PR, ST, QT interval (Fig. 2) on normal E.C.G. recordings. During fibrillation induced by acetylcholine, ventricular rate varied between 252 to 300/min, with an average of 276 /min. Following administration of the compounds under test the rate was significantly reduced varying from 121 to 178/min with a mean of 149/min. Irregularities of rate, rhythm, P wave, PR interval, Q wave, RS waves, QT interval, T wave and ST segment seen during fibrillation were restored to almost normal level after administration of the compounds (Fig. 2). Quantitative differences existed between various compounds.

*Local anaesthetic activity:* All the compounds tested showed varying degree of local anaesthesia. Compounds 8 to 13 were found to be more potent both as intradermal as well as surface anaesthetic agents. The relative potency of compounds 8 to 13 was found to be almost similar. Compounds 1 and 2 exhibited moderate local anaesthetic activity by both the tests. Compound 1 was found to be more potent than compound 2.

## DISCUSSION

Chemically the glutarimide compounds investigated in the present study can be divided into three principal groups. Firstly, compounds 1 and 2 having piperidine moiety; secondly, compound 8 and 9 having diethylamine moiety, thirdly, compounds 10 to 13 having morpholine grouping.

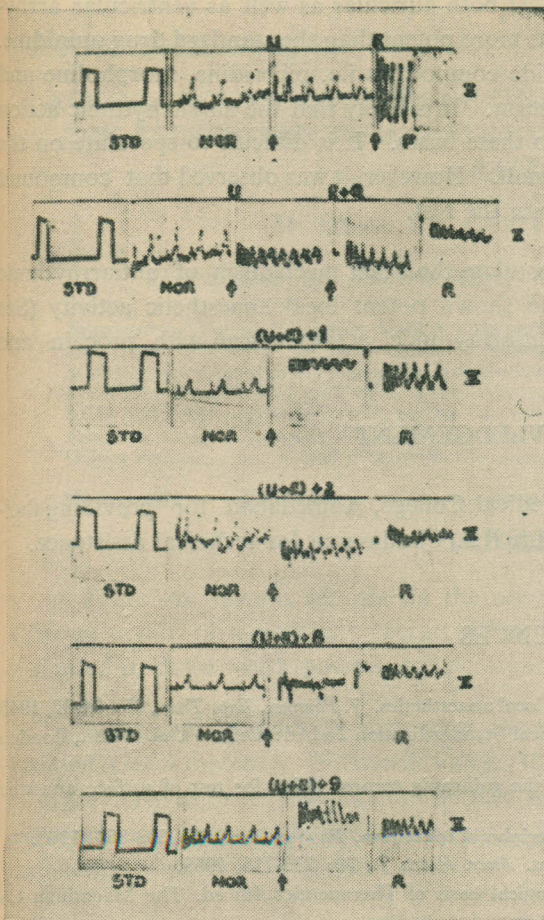


Fig. 1: Antifibrillatory effect in conscious pigeons: Electrocardiographic record of antifibrillatory effect of glutarimide compounds (16 mg/kg; code numbers as mentioned in parenthesis) and quinidine (8 mg/kg) administered intravenously in conscious pigeons.  
Key Words: STD—Standardization, NOR—Normal E.C.G., II—Lead two, U—Alpha-phenoxy-alpha-dimethyl-aminomethyl propiophenone hydrochloride (U-0882), E—Epinephrine hydrochloride, Q—Quinidine hydrochloride, F—Fibrillation/arrhythmias, R—Recovery.

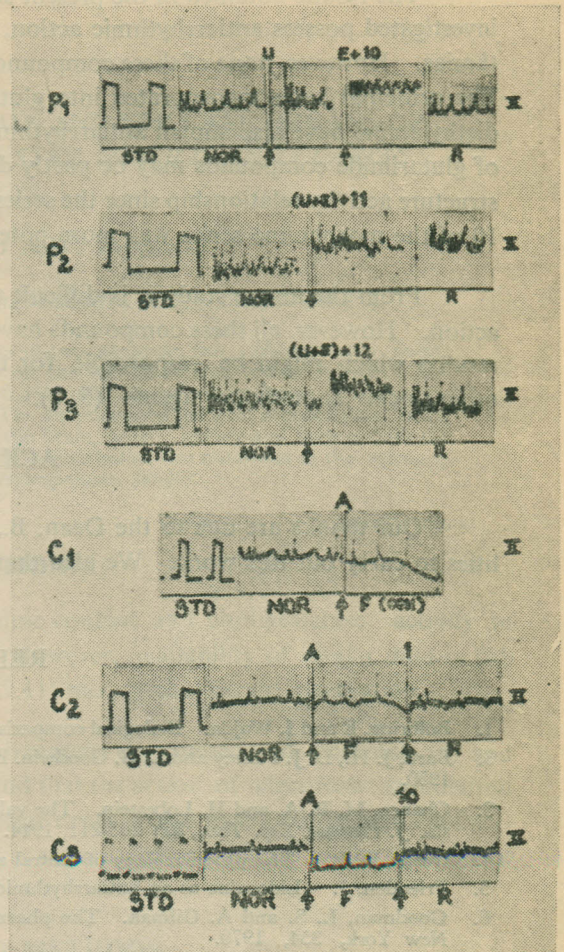


Fig. 2: Antifibrillatory effect in conscious pigeons and anaesthetized cats: Electrocardiographic record of antifibrillatory effect of glutarimide compounds (code numbers as mentioned in parenthesis) administered intravenously in a fixed dose 16 mg/kg in conscious pigeons and anaesthetized cats.  
Key words: STD—Standardization, NOR—Normal E.C.G., U—Alpha-phenoxy-alpha-dimethyl-aminomethyl propiophenone hydrochloride (U-0882), E—Epinephrine hydrochloride, A—Acetylcholine, F—Fibrillation/arrhythmia, R—Recovery, II—Lead two. Panels —P<sub>1</sub>, P<sub>2</sub> and P<sub>3</sub> of Pigeons E.C.G. Panels —C<sub>1</sub>, C<sub>2</sub> and C<sub>3</sub> of Cats E.C.G.

The results obtained in the present study have shown that all the glutarimide compounds investigated possess antiarrhythmic action, against both auricular as well as ventricular arrhythmias. However, none of these compounds was more potent than the standard drug quinidine. The principal bases incorporated into glutarimide compounds i.e. piperidine, morpholine and diethylamine have also shown antiarrhythmic action. It is likely that the antiarrhythmic action of glutarimide compounds may be partly due to these bases. It is difficult to speculate on the structure activity relationship since the series is small. However, it was observed that compound 10 of the morpholine series was more potent than the rest.

From the above study it is difficult to postulate the exact mechanism of antiarrhythmic action. However, all these compounds have also shown potent local anaesthetic activity (See results) which might be responsible for the antiarrhythmic action as seen with procain and other local anaesthetic agents (5, 8).

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