SOME LOCAL ANAESTHETICS IN EXPERIMENTAL CARDIAC ARRHYTHMIAS

By

B.R. Madan, V.K. Khanna And V. Madan

Department of Pharmacology, S.P. Medical College, Bikaner.

Procaine and some of its congeners have been reported to be effective in the suppression or prevention of cardiac arrhythmias arising from various experimental and natural causes (1, 3, 5, 8). These compounds were originally synthesised and used as local anaesthetics. It was, therefore, considered worthwhile to determine if such an anti-arrythmic property is also shared by other local anaesthetics which have either been in use for long, *viz.*, *Piperocaine* (dl-(2-methylpiperidino) propyl benzoate hydrochloride) and Cyclomethycaine (3(2-methyl-piperidino) propyl-p-cyclohexyloxybenzoate hydrochloride) or have been introduced recently *viz.*, Baycain (3-methyl-2-diethylaminoacetylamino-benzoic acid methyl ester-hydrochloride) and QX-572**(N,N-bis (phenyl carbamoyl methyl)d—imethyl ammonium chloride). The purpose of this communication is to report the results of these investigations.

MATERIALS AND METHODS

Freshly prepared aqueous solutions of the drugs under study were used throughout. Quinidine sulphate was used as a standard for comparison of the antiarrhythmic activity.

Acetylcholine induced auricular fibrillation: Mongrel dogs of both sexes, weighing between 8 and 13 Kg. were anaesthetised with pentobarbital, 30 *mg/kg* given intravenously. Acetylcholine-induced auricular fibrillation was produced according to the method of Scherf and Chick (10) which was followed in all essential details as described in a previous communication (6).

Auricular flutter : Mongrel dogs of both sexes weighing between 12 and 18 *Kg.* were anaesthetised with sodium pentobarbital, 30 *mg/kg* intravenously. According to the method of Rosenblueth and Garcia Ramos (9), a self-perpetuating type of auricular flutter was produced. Details of this procedure have been previously described (1). The dosage scheme used was the "titration procedure" employed by Winbury and Hemmer (13), that is, 1 *mg/kg/min* of the drug was injected intravenously until reversion to normal sinus rhythm occurred. In addition to the bipolar Lead II, electro-cardiogram directly from the auricle was recorded by a 2-channel Galileo Electrocardiograph.

Ventricular arrhythmia : The technique of two-stage ligation of anterior descending branch of the left coronary artery was used (2, 7). Mongrel dogs of both sexes weighing between 12 and 18 **kg.** were anaesthetised with sodium pentobarbital, 30 *mg/kg*. After tracheal intubation,

*Baycain is the trade name of the drug synthesied by Farbenfabriken Bayer A.G.
**Qx-572 is the code name of the drug synthesied by Astra Pharmaceutical Products.

artificial respiration was instituted. A small incision was made at the left fourth interc space and the anterior descending branch of the left coronary artery was exposed. It dissected free from the connective tissue at a level between 2 and 5 mm distal to the free of the left atrial appendage. A double ligature was passed under the artery and cut to pro two ligatures. One was tied snugly but not too tightly around the artery along with a No hypodermic needle, the needle was withdrawn immediately leaving the artery constricted not totally occluded. After 30 minutes., the second ligature was tied. The chest wound closed in layers and natural respiration restored.

The animals were studied in the unanaesthetised state 18 to 24 hours after the operat when their electrocardiograms showed the development of ectopic ventricular tachycar The drugs, diluted in 20 ml of 5 per cent glucose in normal saline, were administered intraveno ly over a period of 10 minutes. The dose was repeated after 30 minutes if necessary. Lead of the electrocadriogram was recorded.

RESULTS

Auricular arrhythmias : In acetyl choline-induced fibrillation, all the drugs brought ab a significant reduction in the duration of fibrillation as shown in Table I. In the arrhythm

TABLE I

Drugs in Acetylcholine-Induced Auricular Fibrillation

No. of experiments	Drug	Dose *mg/kg*	Mean percentage reduction in duration of fibrillation	S.
6	Quinidine	2.5	52.8	±
4	Baycain	2.5	72.5	±
5	Piperocaine	2.5	65.0	±
6	Cyclomethycaine	2.5	64.6	±
6	QX-572	5.0	62.0	±

induced by injury-stimulation procedure, the initial effect of these compounds was to decrea the rate of auricular flutter. The ventricular rate followed no definite pattern. It usual registered a rise at the time auricular rate was declining. As typified in Fig. 1, increasing t dose caused abrupt reversion to normal sinus rhythm. However, restoration to normal sin rhythm did not occur in all the experiments as shown in Table II.

Ventricular arrhythmia : Only those animals were selected for drug administrati which had more than 75 per cent beats ventricular in origin with complete dissociation

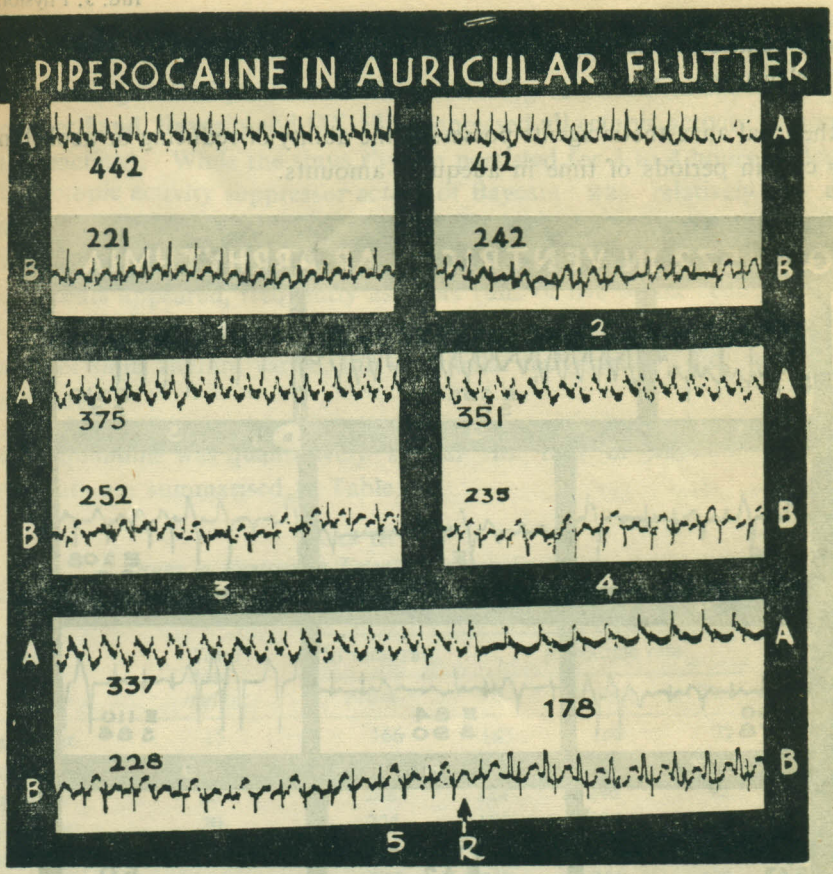

Fig. 1

TABLE II

Drugs in Auricular Flutter

No. of experiments	Drug	Mean dose (*mg/kg*) causing reversion	S.E.
8	Quinidine;	5.6	±0.36
8	Baycain*	2.6	±0·33
6	Piperocaine**	3.0	±1.30
8	Cyclomethycaine**	5.0	±1.06
7	QX-572**	6.0	±0.77

*In one experiment, reversion to normal sinus rhythm did not occur.
**In two experiments, reversion to normal sinus rhythm did not occur.
1 to 5 are excerpts from electrocardiographic tracing.
A : Electrocardiagram recorded directly from auricle :
B : Lead II;
1 : After the production of auriecular flutter; 2 to 5 illustrates the effect of increasing doses of piperocaine. After administration of 4 *mg/kg* of the drug there is abrupt reversion (R) to Sinus rhythm at the arrow-head.

auricular and ventricular activity and little evidence of atrial activity as characterised by absence of 'P' waves.

All the local anaesthetic agents possessed the ability of reducing or abolishing the ect activity for certain periods of time in adequate amounts.

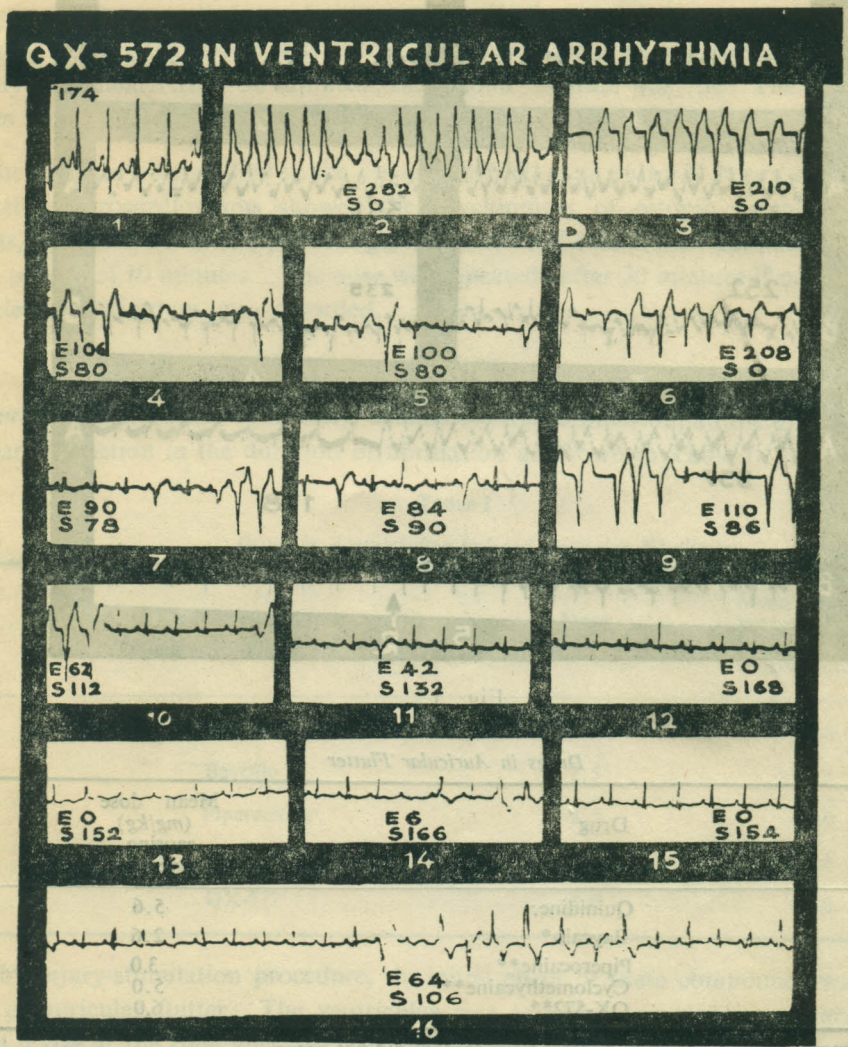

Fig. 2

1 to 16 are excerpt of electrocardiographic tracinigs.

E and S represent ectopic and sinus beats per minute respectively. 1 : Before coronary ligation; 2 : A coronary ligation (First postoperative day), at D, Qx-572 has been administered. 3 to 12 are recordings take intervals of 5 minutes and 13 to 16 at interals of 30 minutes.

Piperocaine and Cyclomethycaine caused a severe degree of excitement in some experiments. On the other hand, Baycain and QX-572 suppressed all ectopic activity without causing any serious toxic reactions. While the sinus rhythm persisted for 3 to 4 hours in dogs treated with QX-572, the ectopic activity suppressor action of Baycain was relatively of a shorter duration, lasting for 10 to 30 minutes. A typical response to the administration of QX-572 is illustrated in Fig 2. At first there was reduction in total heart rate. As the action progressed, sinus beats appeared, frequently as short runs of five or six beats. The rhythm then fluctuated between sinus and ventricular and shifted to nearly continuous sinus rhythm. Although duration of sinus rhythm varied, the ventricular tachycardia did not fully return to the pre-injection level.

The effect of quinidine was qualitatively similar to that of Baycain. The results of individual experiments are summarised in Table III.

TABLE III
Drugs in Ventricular Ectopic Tachycardia

Exp. No.	Drug	Total dose *mg/kg*	Peak Effect Changes				Side Effects
			In total rate		In ectopic rate		
			From	To	From	To	
1	Quinidine	15	166	145	160	32	Nil
2	Quinidine	20	172	152	138	0	Nil
3	Quinidine	20	246	224	246	92	Excitement
4	Quinidine	20	224	182	224	94	Nil
5	Quinidine	20	240	200	220	58	Nil
6	Quinidine	20	264	240	264	130	Vomiting
7	Baycain	10	202	162	170	52	Nil
8	Baycain	10	210	184	198	8	Nil
9	Baycain	25	184	128	164	42	Excitement.
10	Baycain	30	196	184	190	0	Excitement.
11	Baycain	30	170	138	170	0	Nil
12	Baycain	40	172	138	154	8	Excitement.
13	Piperocaine	5	175	146	135	10	Nil
14	Piperocaine	10	184	230	156	114	Convulsions
15	Piperocaine	10	252	182	230	136	Convulsions
16	Cyclomethycaine	10	208	178	174	8	Excitement.
17	Cyclomethycaine	20	268	142	268	116	Excitement & tremors
18	Cyclomethycaine	20	172	144	168	0	Excitement & Vomiting
19	QX-572	10	202	148	190	0	Nil
20	QX-572	10	146	134	120	12	Nil
21	QX-572	15	212	170	208	0	Nil
22	QX-572	20	168	134	168	0	Excitement
23	QX-572	20	282	152	282	0	Nil
24	QX-572	20	186	40	180	0	Nil

DISCUSSION

As the results obtained in the present study indicate, Baycain, Piperocaine, Cyclomet caine and QX-572 possess the quinidine-like ability of suppressing both auricular and ven cular arrhythmias. When these findings are coupled with the results obtained by other inve gators (4, 8, 10, 11, 12), it appears that antiarrhythmic activity is the common property of local anaesthetic agents. However, the therapeutic usefulness of such drugs is subject the limitation imposed by toxic effects produced in the intact unanaesthetised animals by relatively large doses that are required to abolish the ectopic pacemakers. In this connecti another factor to be taken into account is the duration of control of arrhythmia after restorat to normal sinus rhythm and after cessation of drug therapy. When cognizance is taken the severity of the toxic reactions, Piperocaine and Cyclomethycaine do not merit any con deration from the point of being used clinically. However, Baycain and QX-572 do not exh any signs of severe toxicity in doses which suppress all ectopic activity. Also no signific changes in the conduction are discernible in the electrocardiogram when the arrhythmias suppressed by these drugs, nor is there any evidence of initiation of abnormal rhythms. Wh thc absence of severity of toxic reactions and duration of control are considered together, resu with QX-572 compare very favourably with findings obtained with quinidine. Baycain m also deserve more extensive trial, though its duration of effect is relatively brief.

SUMMARY

Four local anaesthetic agents, namely, Baycain, Piperocaine, Cyclomethycaine and Q 572, have been compared with quinidine for their actions in acetylcholine-induced auricul fibrillation, auricular flutter produced by injury-stimulation procedure and ventricular ecto tachycadria resulting from two-stage cornonary ligation. All these drugs are effective in a lishing the various arrhythmias or in reducing their severity. The toxic responses elicited Piperocaine and Cyclomethycaine in the unanaesthetised intact dog preclude the possibi of their being therapeutically useful in the disorders of the rate and rhythm of heart. Howev QX-572 and Baycain are devoid of any serious effects in doses in which the ectopic activity completely suppressed.

ACKNOWLEDGEMENT

Grateful acknowledgement is made to Farbenfabriken Bayer AG for the generous sup of Baycain, to Eli Lilly and Company for Piperocaine and Cyclomethycaine and to Astra Ph maceutical Products for QX-572.

REFERENCES

1. Arora, R.B., V.N. Sharma and B.R. Madan. Ortho substituted benzoic acid e

of dialkyl aminoalkanol in experimental cardiac arrhythmias. *J. Pharm.* **8** : 323, 1956.

2. Harris, A.S. Delayed development of ventricular ectopic rhythms following experimental coronary occlusion. *Circulation.* **1** : 1318, 1950.
3. Harris, A.S., A. Estandia, T.J. Ford Jr., H.T. Smith, R.W. Olsen and R.F. Tillostson. The effects of intravenous procaine and procaineamide (Pronestyl) upon ectopic ventricular teachycardia accompanying acute myocardial infarction. *Circulation.* **5** : 551, 1952.
4. Harris, A.S., C.A. Guerra, A.R. Liptac and J.C. Brigham. Effects of certain local anaesthetic drugs upon ventricular tachycardia resulting from myocardial infarction. *J. appl. Physiol.* **8** : 499, 1956.
5. Hitchcock, P. and K.K. Keown. Lidocaine in the control of cardiac arrhythmias. *Fed. Proc.* **17** : 378, 1958.
6. Madan, B.R., R.B. Arora and K. Kapila. Anticonvulsant, antiveratrine and antiarrhythmic action of Acorus calamus Linn—an Indian Indigenous drug. *Arch. int. Pharmacodyn.* **124** : 201, 1960.
7. Madan, B.R. and V.K. Pendse. Antiarrhythmic activity of Thioridazine hydrochloride (Mellaril). *Am. J. Cardiol.* **11** : 78, 1963.
8. Miller, G., S.L. Weinberg and A. Pick. The effects of procaineamide in clinical auricular fibrillation and flutter. *Circulation.* **6** : 41, 1952.
9. Rosenblueth, A. and J. Garcia Ramos. Studies on flutter and fibrillation. *Am. Heart J.* **33** : 677, 1947.
10. Scherf, D. and F.B. Chick. Abnormal cardiac rhythms caused by acetylcholine. *Circulation.* **3** : 764, 1951.
11. Sharma, V.N. Quinidine-like activity of eight local anaesthetics. *Indian J. Physiol. Pharmacol.* **6** : 47, 1962.
12. Singh, K.P. and V.N. Sharma, Arrhythmia-combating properties of some local anaesthetics. *Arch. int. Pharmacodyn.* **131** : 1, 1961.
13. Winbury, M.M. and M.L. Hemmer. Action of quinidine, procaineamide and other compounds in experimental atrial and ventricular arrhythmias in the dog. J. *Pharmacol.* **113** : 402, 1955.