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Bretylium tosylate in treatment of refractory ventricular arrhythmias complicating myocardial infarction

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In 10 patients with severe myocardial infarction and left ventricular failure, bretylium tosylate was used in the treatment of ventricular arrhythmias which had proved refractory to lignocaine and procainamide; 6 cases had also failed to respond to phenytoin. In 7 patients stable sinus rhythm was achieved and 5 of these survived to leave hospital. For the period during which bretylium was used, the only observed side-effect was sinus bradycardia.

The anti-arrhythmic effect of bretylium tosylate was first described in 1965 when Leveque reported its protective effect in experimentally-induced atrial fibrillation in dogs. In the following year, Bacaner (1966) showed that bretylium protected the dog heart against ventricular fibrillation by raising the fibrillation threshold, and later demonstrated (Bacaner, 1968a) that it was more effective in this respect than lignocaine, procainamide, quinidine, phenytoin, and propranolol. Since then, the use of bretylium for the treatment and prophylaxis of cardiac arrhythmias in man following myocardial infarction and cardiac surgery has been reported in the United States (Bacaner, 1968b; Richards and Jerde, 1969; Castaneda and Bacaner, 1969).

Over the past 12 months we have encountered 10 patients with ventricular arrhythmias complicating severe myocardial infarction in whom conventional anti-arrhythmic therapy was either ineffective or only of temporary benefit. In this report we describe our experience of bretylium in the treatment of these patients.

Patients and Methods

The patients were treated in the Coronary Care Unit of the Royal Infirmary of Edinburgh. Clinical details are summarized in Table 1. Myocardial infarction was confirmed in every case by serum enzyme changes and in 9 by the electrocardiogram. The ventricular arrhythmias and treatment before bretylium therapy are shown in Table 2 and in the Figure. Also present in Cases 4, 6, and 10, were multiple 'R on T' ventricular extrasystoles beginning at the apex of the preceding T wave.

All patients were given lignocaine and procainamide, 6 had phenytoin, and 1 also received propranolol. Lignocaine is used routinely in the treatment and prophylaxis of ventricular arrhythmias in doses of 100–200 mg. intravenously followed by the infusion of 1–2 g. over 24 hours. In patients who fail to respond to lignocaine, procainamide is given intravenously up to 1 g.; if this is unsuccessful phenytoin is injected intravenously, the maximal dose being 250 mg. Following successful conversion to sinus rhythm prophylactic therapy consists of procainamide, 2–3 g. daily given by mouth for 6 weeks.

Bretylium was administered after this regimen of suppressive therapy had failed to prevent recurrent episodes of ventricular arrhythmias, the loading dose being 5 mg. per kg. body weight intramuscularly; in three cases the initial dose was given by slow intravenous injection. The maintenance dose of bretylium was 3 mg. per kg. body weight intramuscularly every 8 to 12 hours. The electrocardiogram was monitored continuously, the blood pressure was recorded hourly, and chest *x*-ray was taken daily.

Results

The results of bretylium administration in the prophylaxis of refractory recurrent ventricular arrhythmias are summarized in Table 3. Five patients survived to leave hospital and 5 died in the Coronary Care Unit.

Survivors In Cases 1 and 3 the ventricular arrhythmias were abolished 90 and 30 minutes, respectively, after the first dose of bretylium; in Case 1 the coexisting supraventricular arrhythmias persisted for 5 days

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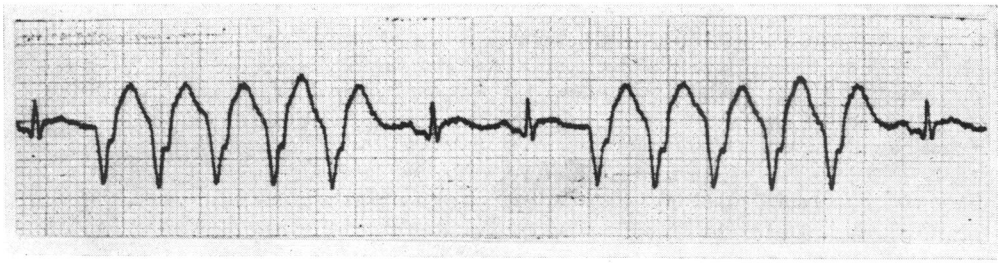
TABLE 1 *Clinical details*

Case No.	*Age (yr.) and sex*		*No. of previous myocardial infarctions*	*Site of recent myocardial infarction*	*Maximum recorded serum creatine phosphokinase* (i.u./litre)*	*Complications before onset of ventricular arrhythmia*	*Chest x-ray at onset of ventricular arrhythmia*
1	51	M	0	Inferior	608	Atrial arrhythmias Complete heart block	Pulmonary oedema
2	61	M	0	Anterior	1400	—	Pulmonary oedema
3	60	M	1	Anterior	504	Right bundle-branch block Complete heart block	Pulmonary venous congestion
4	65	M	1	Anterior	†	Atrial arrhythmias	Pulmonary oedema
5	54	M	2	Anterior	> 500	—	Pulmonary oedema
6	57	M	0	Anterior	1060	Right bundle-branch block	Pulmonary oedema
7	40	M	0	Inferior	1260	—	Pulmonary oedema
8	65	F	1	Anterior	‡	—	Pulmonary oedema
9	54	F	1	Anterior	1300	Right bundle-branch block Complete heart block	Pulmonary oedema
10	58	M	3	Not known	1560	Intraventricular block	Pulmonary venous congestion

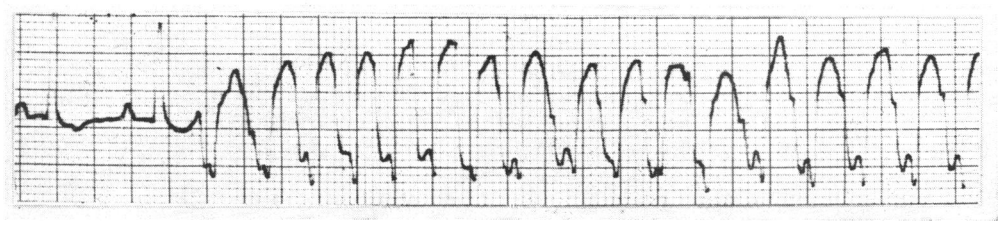
* Normal value < 80 i.u./litre.
† Serum aspartate aminotransferase, 110 units/ml. (normal value < 40 units/ml.).
‡ Serum aspartate aminotransferase, 145 units/ml.

TABLE 2 *Ventricular arrhythmias and treatment before bretylium therapy*

Case No.	*Arrhythmia*	*Day of onset*	*No. of episodes of ventricular fibrillation*	*Duration (hr.)*	*Treatment*	*Maximal single I.V. dose (g.)*	*Effect*	*Maximal dose in 24 hours (g.)*
1	Ventricular tachycardia	9	0	72	Lignocaine; procainamide; phenytoin	0·2 0·5 0·25	Temporary suppression	2·25 3·0 —
2	Ventricular tachycardia; ventricular fibrillation	5	6	24	Lignocaine; procainamide	0·1 0·5	None	2·0 2·5
3	Ventricular tachycardia	8	0	20	Lignocaine; procainamide	0·2 0·3	Temporary suppression	2·0 3·0
4	Ventricular tachycardia; 'R on T' ventricular extrasystoles	11	0	24	Lignocaine; procainamide	0·2 0·5	Temporary suppression	2·0 3·0
5	Ventricular tachycardia; ventricular fibrillation	19	53	140	Lignocaine; procainamide; phenytoin	0·2 1·0 0·25	Terminated ventricular tachycardia	2·6 4·5 —
6	Ventricular tachycardia; ventricular fibrillation; 'R on T' ventricular extrasystoles	9	3	24	Lignocaine; procainamide; phenytoin; propranolol	0·2 0·5 0·25 —	None	1·5 4·5 0·4 0·08
7	Ventricular tachycardia	7	0	120	Lignocaine; procainamide; phenytoin	0·2 0·85 0·25	Temporary suppression	4·0 4·5 —
8	Ventricular tachycardia; ventricular fibrillation	12	13	150	Lignocaine; procainamide	0·15 0·3	Terminated ventricular tachycardia	2·0 4·5
9	Ventricular tachycardia; ventricular fibrillation	6	8	72	Lignocaine; procainamide; phenytoin	0·2 0·5 0·15	Temporary suppression	2·0 3·0 —
10	Ventricular tachycardia; ventricular fibrillation; 'R on T' ventricular extrasystoles	1	11	48	Lignocaine; procainamide; phenytoin	0·2 — 0·25	See text	2·0 2·0 —



(*a*)



(*b*)

FIG. (*a*) *Case 7: paroxysmal ventricular tachycardia. Similar episodes occurred in Cases 1, 3, 4, 6, and 9.* (*b*) *Case 8: prolonged ventricular tachycardia. Similar tracing obtained in Cases 2, 5, and 10.*

TABLE 3 *Results of bretylium administration on prophylaxis of refractory recurrent ventricular arrhythmias*

Case No.	*Dosage of bretylium (intramuscular)*		*Interval between initial dose and anti-arrhythmic effect (min.)*	*Duration of treatment (dy.)*	*Prophylactic effect on recurrent ventricular arrhythmias*	*Blood pressure (mm. Hg)*		*Outcome*
	Loading (mg.)	*Maintenance (mg./24 hr.)*				*Before bretylium*	*After total dose of bretylium*	
1	400	400	90	5	Recurrent ventricular tachycardia abolished	110/60	120/70	Discharged home
2	400*	—	—	< 1	None in 90 min.	90/60	90/60	Died (asystole)
3	400	400	30	3	Sinus rhythm	100/70	100/60	Discharged home
4	300 200	See text 400	20	1	Sinus rhythm for 18 hr.; ventricular fibrillation; sinus rhythm for 11 hr.	110/60	120/70	Died (ventricular fibrillation)
5	300*	—	—	< 1	None in 15 min.	95/60	†	Died (ventricular fibrillation
6	200*	400 600	20	4	Sinus rhythm for 36 hr.; 'R on T' ventricular extrasystoles; sinus rhythm for 60 hr.	90/60	85/60	Died (ventricular fibrillation)
7	300	400	See text	3	Sinus rhythm	90/60	105/60	Discharged home
8	300	400 600	—	5	Continuation of ventricular extrasystoles; ventricular fibrillation; sinus rhythm	100/60	90/60	Discharged home
9	300	—	—	< 1	None in 20 min.	95/60	—	Died (ventricular fibrillation)
10	350	400	40	9	Sinus rhythm for 4 days; ventricular fibrillation (see text); sinus rhythm	100/70	130/80	Discharged home

* Dose given intravenously. † Recurrent ventricular fibrillation prevented recording.

before sinus rhythm was restored. Case 7 had paroxysms of ventricular tachycardia which were abolished for periods of up to 20 minutes by lignocaine, procainamide, and phenytoin, but relapse was not prevented by lignocaine infusion and procainamide given orally. Thirty minutes after the initial dose of bretylium, an injection of 100 mg. lignocaine resulted in stable sinus rhythm. Case 8 continued to have ventricular ectopic beats followed by ventricular fibrillation 20 hours after the loading dose of bretylium; after resuscitation and an increase in the maintenance dose of bretylium stable sinus rhythm was achieved.

Case 10 differed from the others in that numerous 'R on T' extrasystoles occurred within 12 hours of the onset of symptoms. Lignocaine produced nystagmus and dysarthria without decreasing the frequency of ectopic beats. Procainamide given orally was also ineffective and was discontinued after the sixth dose; the first 3 episodes of ventricular fibrillation occurred within 1½ to 2 hours after the second, fourth, and sixth doses of this drug. Recurrent ventricular fibrillation was unaffected by phenytoin, and bretylium was substituted. Stable sinus rhythm was achieved 40 minutes after the loading dose of bretylium and was maintained for 4 days. Prophylaxis was started with procainamide, but 30 minutes after the first oral dose of 500 mg. there was gross lengthening of the QT interval and T wave distortion, 'R on T' ventricular extrasystoles recurred and ventricular fibrillation developed 30 minutes later. Bretylium was continued for a further 5 days without recurrence of the arrhythmia and further successful prophylaxis was achieved with quinidine.

Deaths Case 4 reverted to sinus rhythm 20 minutes after the first dose of bretylium. The second injection was inadvertently omitted and 18 hours later he had ventricular tachycardia which progressed to fibrillation. After successful defibrillation a maintenance dose of bretylium was given every 12 hours. Eleven hours after the second injection there was repeated ventricular fibrillation with a fatal outcome 24 hours later. Case 6 returned to sinus rhythm 20 minutes after the first injection of bretylium. Thirty-six hours later frequent 'R on T' extrasystoles reappeared and the dose of bretylium was increased to 200 mg., 8 hourly. Thereafter sinus rhythm was maintained for a further 60 hours when ventricular fibrillation recurred, terminating in death.

Cases 5 and 9 died of recurrent ventricular fibrillation within 20 minutes of the initial dose of bretylium. Case 2 was given bretylium intravenously to terminate prolonged ventricular tachycardia refractory to lignocaine and procainamide but this had no effect in 90 minutes. DC shock restored sinus rhythm which was followed in 2 hours by asystole.

Discussion

The results observed in 10 patients suggest that bretylium tosylate can be effective in restoring and maintaining sinus rhythm in some patients with acute myocardial infarction who develop ventricular arrhythmias refractory to conventional treatment. It is not suggested that bretylium should be the first drug for these cases, since lignocaine, procainamide, and phenytoin are satisfactory and effective in the majority.

The 5 survivors all maintained a striking stability of sinus rhythm after the use of bretylium; it is unlikely that this effect was coincidental in view of the duration of the arrhythmias before the drug was introduced. Of those who died, Cases 4 and 6 had paroxysmal ventricular tachycardia for 24 hours which ceased 20 minutes after the first injection of bretylium; the maintenance of sinus rhythm for 18 and 36 hours, respectively, suggests that the drug was temporarily beneficial. The variable delay in onset of the anti-arrhythmic effect of bretylium (Bacaner, 1966, 1968b) may have accounted for the lack of response in Cases 5 and 9, both of whom died within 20 minutes of administration of the loading dose. In Case 2, bretylium given intravenously was unsuccessful in terminating a prolonged episode of ventricular tachycardia.

In 9 of our patients the ventricular arrhythmias were of late onset, occurring 5 to 19 days after myocardial infarction; it is recognized that arrhythmias of this type associated with left ventricular failure are often difficult to suppress and carry a poor prognosis (Lawrie, 1968). Though such arrhythmias may result from further infarction (Spracklen *et al.*, 1968), there was no clinical, biochemical, or electrocardiographic evidence of recurrence in any of our patients. All patients were treated for cardiac failure, and received digoxin and diuretic therapy with supplements of potassium chloride; in each case plasma potassium levels remained normal throughout treatment. Though digitalis toxicity cannot be excluded as a causative factor in these ventricular arrhythmias, the amount of digoxin administered was not considered excessive and there were no other features of toxicity. In Case 10 it is probable that procainamide predisposed to ventricular fibrillation by prolonging the QT interval (Cohen, 1966).

Bretylium tosylate is an adrenergic neuronal blocking agent. It was introduced in

1959 as a hypotensive drug but was unsatisfactory because of unreliable absorption from the gastro-intestinal tract and tolerance to its hypotensive effect. Significant lowering of blood pressure was not observed after bretylium administration in any of our patients (Table 3) but sinus bradycardia occurred in Cases 3 and 10. The patients were treated in bed and the effect of posture on the blood pressure was not determined. The antifibrillatory properties of bretylium may be related to hyperpolarization and improved conduction velocity (Watanabe, Josipovic, and Dreifus, 1968). Bretylium differs from quinidine-like compounds both in its electrophysiological effect and in its lack of local anaesthetic properties (Papp and Vaughan Williams, 1969).

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