

ditions, occasionally results in renal wasting of other substances, such as potassium (Sanderson, 1967) and amino-acids (Cusworth *et al.*, 1970), which may be reversible when the hypercalcaemia is corrected. The defective renal conservation of magnesium in our patients, which was often associated with slight urea retention, may be a similar and sometimes reversible effect of primary hyperparathyroidism.

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## Practolol in Treatment of Supraventricular Cardiac Dysrhythmias

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**S**ummary: Practolol (I.C.I. 50172) was used to treat supraventricular dysrhythmias in 32 patients with a rapid ventricular rate and with heart disease of varied aetiology. In 26 patients the average reduction in ventricular rate was 75 per minute, while immediate reversion to sinus rhythm occurred in three patients. The slowing effect was mainly due to a direct action on the atrioventricular node. The effectiveness of practolol was unrelated to the type of dysrhythmia or its aetiology. No serious adverse clinical effects were noted.

### Introduction

Practolol (I.C.I. 50172) is a cardioselective beta-adrenergic receptor blocking drug with weak sympathomimetic properties (Barrett *et al.*, 1967; Brick *et al.*, 1968). It lacks local anaesthetic and quinidine-like actions and therefore has no direct depressant effect on the myocardium. The use of the drug in the management of supraventricular dysrhythmias has been encouraging (Gibson *et al.*, 1968; Jewitt *et al.*, 1969). We report here our clinical experience with intravenous practolol given to patients with supraventricular dysrhythmias associated with a rapid ventricular rate.

### Patients Studied

Practolol was given to 32 patients (see Table) who had various cardiac lesions. Fifteen had rheumatic heart disease and four had undergone recent heart valve replacement—the mitral valve in three and both aortic and mitral valves in one. Three patients with calcific aortic stenosis had recently had aortic valve replacement. Ischaemic heart disease was the underlying cardiac lesion in seven patients, recent cardiac infarction having occurred in two. Six patients had prolonged attacks of paroxysmal tachycardia, associated with Wolff-Parkinson-White syndrome in four, and one patient had a fossa ovalis atrial septal defect. Clinical and radiological evidence of heart failure was present in 22 patients and in eight the failure was severe.

Practolol was injected intravenously with electrocardiographic control in a dose of 2 mg./minute until a therapeutic effect was noticed or a total of 20 mg. had been given.

### Results

The response of the ventricular rate to practolol and the dosages required are shown in the Table. The effect of the drug was apparent within a few minutes of administration. The maximum dosage was 12 mg. in the 26 who responded, but usually the effective dose was between 5 and 10 mg. In six cases there was no response to the drug, the ventricular rate being unchanged after 20 mg. of practolol.

*Atrial Fibrillation.*—Before administration of practolol the

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Details of Patients, Dysrhythmias, and Response to Practolol

Case No.	Age and Sex	Aetiology	Cardiac Failure	Heart Rate/min.		Dose of Practolol (mg.)	Rhythm Change
				Before	After		
<i>Atrial fibrillation</i>							
1	49 F	Aortic valve replacement	—	150	100	6	—
2	41 F	Mitral valve replacement	+++	180	100	6	Sinus rhythm
3	48 M	Mitral valve replacement	++	150	105	10	—
4	34 M	R.H.D.	+++	180	100	8	—
5	54 F	R.H.D.	+++	160	95	10	—
6	35 F	R.H.D.	+	200	100	8	—
7	52 F	R.H.D.	++	180	95	12	—
8	37 F	R.H.D.	—	160	160	20	—
9	61 M	I.H.D., C.I.	—	180	100	10	—
10	64 M	I.H.D., C.I.	+++	160	110	10	—
11	51 M	I.H.D.	—	150	90	8	—
<i>Atrial Flutter</i>							
12	55 M	R.H.D.	—	130	90	10	A.F.
13	53 M	R.H.D.	—	170	90	10	3:1 A/V block
14	67 M	R.H.D.	—	140	100	6	3:1 & 2:1 A/V block
15	55 F	R.H.D.	+++	160	80	10	A.F.
16	75 M	I.H.D.	+	140	90	8	3:1 A/V block
17	62 M	A.S.D.	+++	160	80	10	4:1 A/V block
18	48 M	P.T.	—	125	80	8	4:1 A/V block
19	51 M	Aortic valve replacement	+	160	80	12	4:1 A/V block
<i>Supraventricular tachycardia</i>							
20	56 F	Aortic and mitral valve replacement	++	180	65	12	Sinus rhythm
21	50 M	Aortic valve replacement	++	160	160	20	—
22	56 F	Mitral valve replacement. Digitalis overdosage	++	200	90	8	—
23	61 F	R.H.D.	+	180	100	10	2:1 A/V block
24	56 F	R.H.D.	—	160	80	8	2:1 A/V block
25	64 F	I.H.D. Ventricular aneurysm	+++	200	140	10	Varying A/V block
26	55 F	I.H.D. Digitalis overdosage	+++	180	90	12	A.F.
27	64 F	I.H.D. Digitalis overdosage	+	160	80	8	Sinus rhythm
28	70 F	P.T.	+	180	100	12	2:1 A/V block
29	60 F	W.P.W.	++	180	180	20	—
30	45 F	W.P.W.	+	180	180	20	—
31	40 F	W.P.W.	—	200	200	20	—
32	60 M	W.P.W.	+	250	250	20	—

R.H.D. = Rheumatic heart disease. I.H.D. = Ischaemic heart disease. C.I. = Cardiac infarction. A.S.D. = Atrial septal defect. W.P.W. = Wolff-Parkinson-White syndrome. P.T. = Paroxysmal tachycardia. A.F. = Atrial fibrillation

ventricular rate (averaged over 10 consecutive beats) was 150/minute or greater in all 11 patients. No effect on the rate was produced in one patient, and in the other 10 a mean reduction in ventricular rate of 70 beats per minute was induced, with reversion to sinus rhythm in one case. Six patients were already receiving digitalis. In two patients practolol was continued orally in a dose of 50 mg. twice daily in addition to digitalis to maintain control of the ventricular rate. While practolol was effective acutely in one patient increasing oral administration to

300 mg. a day failed to maintain control. In this latter patient a number of digitalis preparations used to toxic doses had failed to control the rate, as had propranolol; treatment with reserpine now appears to be controlling the ventricular rate.

**Atrial Flutter.**—Eight patients had atrial flutter and were receiving digitalis. In six with ventricular rates of 140 or more per minute 2/1 atrioventricular block was present; in the remaining two, with slightly slower rates, there was varying 2/1 and 3/1 atrioventricular block. In all eight patients an increase in the atrioventricular block resulted in a ventricular rate of 100/minute or less. In two patients a small decrease in the flutter rate was noted. In two cases the rhythm changed to atrial fibrillation with a controlled ventricular response. One patient reverted to sinus rhythm with subsequent oral administration of 100 mg. of practolol daily. Cessation of the drug led to atrial flutter returning, but on recommencing practolol sinus rhythm was regained. The higher atrioventricular ratio was maintained by oral therapy in two patients; reversion to sinus rhythm some hours later occurred in two patients; atrial fibrillation returned in one patient with further digitalis therapy.

**Supraventricular Tachycardia.**—There were 13 patients with other supraventricular tachycardias. The ventricular rate varied from 160 to 250/minute and in the eight patients who responded an average reduction of 90/minute was achieved. Seven were receiving digitalis, and in three it was considered that digitalis overdosage was the cause of the dysrhythmia. After treatment with practolol two patients reverted to sinus rhythm, and one patient returned to atrial fibrillation. In four patients the ventricular rate was controlled by inducing 2/1 atrioventricular block (see Figure). In one patient who appeared



Electrocardiogram, lead II. Top, showing supraventricular tachycardia, ventricular rate 160 per minute. Bottom, after 8 mg. practolol, 2:1 atrioventricular block, ventricular rate 80 per minute.

to have a nodal tachycardia the ventricular rate was slowed but the mechanism of slowing was uncertain. Reversion to sinus rhythm some hours later occurred in two patients, and atrial fibrillation developed in one other. The 2/1 atrioventricular block was maintained with digitalis in one patient and with oral practolol in another. No effect was seen in five patients. The four patients with Wolff-Parkinson-White syndrome showed no response to practolol.

### Clinical Response to Practolol

In 10 patients who were tolerating the rapid ventricular rate well no clinical deterioration occurred, and in 21 patients in heart failure there were no side-effects. The remaining patient in heart failure who had Wolff-Parkinson-White syndrome and a supraventricular tachycardia developed hypotension, systolic pressure less than 100 mm. Hg, after 20 mg. of practolol had no slowing effect. Sinus rhythm was restored after rapid intravenous digitalization with ouabain with correction of the hypotension. Six out of eight patients in the early postoperative period had shown deterioration with the development of a fast ventricular rate, and in the five who showed a

good response to practolol this deterioration was reversed. Controlling the ventricular rate in one patient with extensive cardiac infarction and heart failure did not result in improvement, and the patient died some days later with uncontrolled heart failure. The dysrhythmias were superimposed on chronic heart failure in 11 patients and the effect of controlling the ventricular rate was less impressive, but in all patients the failure was subsequently controlled with conventional therapy, except in the patient with an atrial septal defect and gross heart failure who required peritoneal dialysis to control the failure.

### Discussion

In the management of supraventricular dysrhythmias with a rapid ventricular rate digitalization remains the principal mode of therapy. Even with rapidly acting digitalis preparations, however, such as ouabain used intravenously, full digitalization may not be achieved safely unless the digitalizing dose is given over one to two hours. If direct-current shock is contemplated there are increased hazards in the fully digitalized patient. As the efficacy of practolol in this situation can be judged within minutes and alternative therapeutic possibilities are not influenced, practolol is a useful adjunct to antidysrhythmic drugs, and successful control of the ventricular rate is likely in most cases. Only six of the 32 patients failed to respond. Similar results have been reported principally in postoperative dysrhythmias and in patients with acute cardiac infarction. The use of practolol in the treatment of supraventricular tachycardias associated with Wolff-Parkinson-White syndrome has not previously been reported, and all four patients in this series failed to respond. This is in contrast to the effect of propranolol (Stock, 1966), suggesting that the antidysrhythmic effect of propranolol in this situation is related to its quinidine-like effect and not to its beta-adrenergic receptor blocking action.

As with other beta-adrenergic blocking drugs the possibility of provoking or aggravating heart failure must be considered (Stock and Dale, 1963; Stephen, 1966; Conway *et al.*, 1968). Haemodynamic studies (Shinebourne *et al.*, 1968; Sowton *et al.*, 1968) have shown that 5 mg. of practolol, while slowing the

heart, does not reduce the cardiac output, but in higher dosage a modest reduction in cardiac output results. Only one patient in this series showed clinical evidence of haemodynamic deterioration after 20 mg. of practolol had failed to produce a beneficial slowing effect. The risks are probably less with practolol than with other drugs such as propranolol, which in addition to its beta-adrenergic blocking action has a direct myocardial depressant effect.

The slowing effect of practolol was mediated through a direct action on the atrioventricular node in 22 of the 23 patients who responded without a return to sinus rhythm. In the remaining case the precise mechanism of slowing was not clearly established.

Our experience with long-term administration of practolol to maintain control of the ventricular rate is limited to six patients, in five of whom it was effective for periods extending up to nine months. We do not, however, consider the drug to be an alternative to digitalis, which has additional benefit other than control of rate. In some "resistant" patients practolol controls the heart rate when digitalis alone has been inadequate.

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Request for reprints to Dr. G. M. Gent.

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## Rate of Disappearance of Endogenous Insulin from the Circulation after Removal of Insulinomas

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**S**ummary: In two patients with insulinomas a rapid rate of disappearance of insulin from the circulation was found after the tumours had been removed. In a third case the rate of disappearance was slower but the insulin was not immunologically identical to normal human insulin standards, as it was in the other two cases.

### Introduction

It has been suggested in the past that the half-time of disappearance of insulin from the circulation might be about 35 minutes using radioiodine-labelled insulin (Berson *et al.*, 1956). Samols and Marks (1966) and Williams *et al.* (1968) measured the rate of fall of endogenous immunoreactive insulin in man at the cessation of prolonged glucose and glucagon infusions and found half-times of insulin disappearance of 7 to 15 minutes. As has been pointed out (Stimmler, 1966) there is no certainty that insulin secretion stops instantly in such studies, and if it did continue at all

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