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Clinical electrophysiological effects of atenolol—a new cardioselective beta-blocking agent

CHRISTINE ROBINSON[1], JOHN BIRKHEAD, BERESFORD CROOK, KEVIN JENNINGS, AND DAVID JEWITT

From the Cardiac Department, King's College Hospital, London

Atenolol, a cardioselective beta-blocking agent, at dose levels of 0·03, 0·06, and 0·12 mg/kg intravenously, produced prolongation of atrioventricular nodal conduction in 22 patients with suspected coronary artery disease.

In a dose of 0·12 mg/kg body weight atenolol produced significant prolongation of sinus cycle length, sinus node recovery time, atrioventricular node conduction, and the effective and functional refractory periods of the atrium and the atrioventricular node.

No significant effects were observed on the His Purkinje system or the effective refractory periods of the ventricle.

In these actions atenolol closely resembles propranolol. However, because in contrast to propranolol it increases atrial refractoriness, it may have advantages in the treatment of atrial arrhythmias.

Beta-adrenergic blocking agents are widely used in the treatment of arrhythmias, particularly those of supraventricular origin.

Practolol was introduced as a cardioselective beta-blocking agent with the advantage over propranolol that it was less prone to causing bronchoconstriction or cardiac depression (Gibson, 1971; McNeill, 1971). Practolol differs from propranolol electrophysiologically in that it produces less pronounced depression of atrioventricular conduction, possibly because of its intrinsic sympathomimetic action (Smithen *et al.*, 1971). It has recently been withdrawn from general use because of serious side effects (Felix *et al.*, 1974; Wright, 1975).

Atenolol is a new beta-adrenergic blocking agent which appears to possess a degree of cardioselectivity, equivalent to that of practolol (Vilsvik and Schaaning, 1976). Its structural formula is illustrated in Fig. 1. However, it lacks intrinsic sympathomimetic properties and unlike propranolol has no membrane stabilising action (Barrett *et al.*, 1973).

The aim of the present investigation was to evaluate the effects of atenolol on the specialised conduction system of the heart, particular attention being paid to conduction times and refractoriness at all levels of the conduction system.

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Methods

Twenty-two patients with suspected coronary artery disease were studied 45 minutes after diagnostic cardiac catheterisation. Informed consent was obtained. Before investigation each patient had been premedicated with diazepam 10 mg intramuscularly. No patient had received cardioactive drugs, e.g. beta-blocking agents, digoxin, or sympathomimetic agents for 48 hours before study. Two electrodes, a number 6 USCI quadripolar and a number 6 USCI bipolar, were inserted percutaneously via the femoral vein. The quadripolar electrode was positioned in the right atrium so that the distal pair of electrodes could be used to stimulate the atrium, while a high right atrial electrogram was recorded from the proximal pair of electrodes. The bipolar

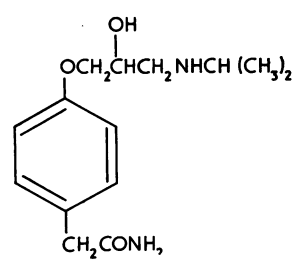

Fig. 1 *Structural formula of atenolol.*

electrode was positioned across the tricuspid valve and used to record a His bundle electrogram. Surface electrocardiograph leads I, II, V2 were simultaneously displayed on an SE labs. eight-channel oscilloscope and were recorded on an Elema Schonander mingograph 81 eight-channel direct-writing recorder at a paper speed of 100 mm/s. Electrophysiological measurements included determination of (1) sinus node function; (2) atrio-ventricular node conduction time; and (3) refractoriness at each level of the specialised conduction system and also of atrial and ventricular muscle using the extrastimulus technique (Goldreyer and Bigger, 1969).

The atrium was paced at a constant rate higher than the spontaneous sinus rate and a premature extrastimulus was introduced after every eighth beat followed by an appropriate delay to avoid repetitive firing. By increasing the prematurity of the extrastimulus the refractory periods of the different cardiac tissues could be determined. Impulses of 2 milliseconds duration at twice diastolic threshold were used.

After control measurements had been taken the effects of intravenous atenolol were studied. The first part of the study was carried out to investigate the response to three graded doses of atenolol, 0·03, 0·06, and 0·12 mg/kg body weight on the specialised conducting system in 6 patients. In the second part of the study the electrophysiological effects of atenolol on the sinus node, atrium, specialised conducting system, and the ventricle were recorded at the highest dose level, 0·12 mg/kg body weight.

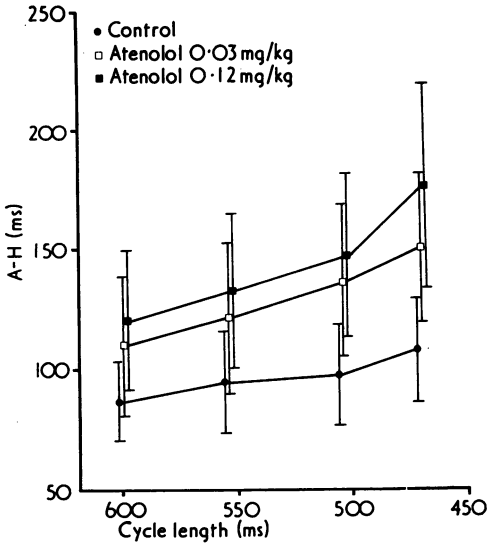

Fig. 2 *Effect of different doses of atenolol on atrioventricular nodal conduction.*

Definition of terms

Sinus node recovery time in the interval between the last paced beat and the first spontaneous sinus beat after two minutes of overdrive suppression of the sinus node at a rate faster than the sinus rate.

A is the right atrial electrogram.

H is the His bundle potential recorded with bipolar electrodes 1 cm apart.

V is the earliest recorded ventricular activity taken from the surface leads or the intracardiac electrogram.

S refers to the pacing stimulus.

QTc is the QT interval corrected to a cycle length of 1000 ms

$$QTc = QT\sqrt{R\text{-}R}$$

This is taken as a measure of duration of ventricular repolarisation.

The AH interval as measured in the His bundle electrogram recording is taken as a measure of atrio-ventricular nodal conduction time (normal range 60 to 140 ms).

The HV interval is a measure of the His Purkinje conduction time (normal range 35 to 55 ms).

The effective refractory period (ERP) of the atrium is defined as the longest S_1–S_2 interval at which S_2 fails to depolarise the atrium.

The functional refractory period (FRP) of the atrium is defined as the shortest A_1–A_2 interval recorded.

The effective refractory period of the atrioventricular node is defined as the longest A_1–A_2 interval at which A_2 fails to propagate to the His Purkinje system.

The functional refractory period of the atrio-ventricular node is defined as the shortest H_1–H_2 interval recorded.

The effective refractory period of the His Purkinje system is defined as the longest H_1–H_2 interval at which H_2 fails to conduct to the ventricles.

The relative refractory period of the His Purkinje system is defined as the longest H_1–H_2 interval at which H_2 is conducted to the ventricles with a longer HV time than that of the basic driving beat, or with a QRS complex of aberrant configuration.

The effective refractory period of the ventricle is defined as the longest S_1–S_2 interval at which S_2 fails to depolarise the ventricle.

Table 1 *Effect of atenolol 0·12 mg/kg body weight on sinus node function, atrioventricular nodal, and His Purkinje conduction, and Q-Tc: all values expressed in milliseconds*

Case No.	*Sinus cycle length*		*Sinus node recovery time*		*AH*		*HV*		*Q–Tc*	
	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	850	1080	1065	1110	100	110	30	40	400	365
2	1020	1125	—	—	105	115	35	40	390	390
3	860	1048	980	1200	140	140	35	40	400	366
4	690	790	1065	1110	85	100	50	50	430	380
5	623	886	720	970	120	180	55	60	426	375
6	883	990	1110	1130	95	105	50	50	372	348
7	1050	1067	1380	1470	150	150	40	40	445	438
8	802	871	1090	1370	75	100	70	73	404	375
9	753	833	560	830	108	125	40	40	460	425
10	600	790	710	1000	80	100	45	45	500	470
11	700	840	—	—	60	65	45	45	—	—
12	710	985	—	—	60	65	55	60	—	—
13	710	840	—	—	70	95	50	40	—	—
14	700	860	—	—	65	70	50	50	—	—
15	655	920	—	—	80	85	65	55	—	—
16	870	880	—	—	110	120	45	45	—	—
Mean	781	925	964	1132	94	108	48	48	423	393
SE	29·9	27·2	84·8	65·8	6·8	7·8	2·7	2·4	12	12
P value	< 0·001		< 0·01		< 0·001		NS		< 0·001	

Table 2 *Effect of atenolol 0·12 mg/kg body weight on refractoriness of atrium, atrioventricular node, and His Purkinje system: all values expressed in milliseconds*

Case No.	*Cycle length*	*Atrium ERP*		*FRP*		*AV node ERP*		*FRP*		*HPS RRP*	
		Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	790	274	314	290	320	—	—	380	390	380	400
2	770	276	288	300	310	305	360	448	480	448	
3	730	210	215	240	270	360	375	490	490	—	—
4	660	185	195	190	200	190	200	410	460	—	—
5	620	195	202	220	230	250	300	330	490	385	
	510	195	202	230	245	250	310	360	480	380	480
	430	195		230		240					
6	740	225	292	240	310	405	540	580	600	—	—
	660	225	295	240	310	410	540	—	590	—	—
7	760	188	220	200	250	330	330	440	460	485	—
	675	180	215	190	250	315	330	420	440	470	—
	560	160	210	195	250	325	260	400	380	430	430
8	740	—	185	—	240	—	260	—	470	—	—
	620	160	185	200	230	200	310	340	420	380	—
	510	160	172	230	240	200	300	360	420		—
9	460	270	335	290	340	—	—	350	370	380	430
10	500	237	270	270	290	—	—	365	390	—	—
	360	220	250	240	270	—	300	335	375	—	—
Mean		210	241	235	270	295	346	401	443	393	435
SE		12·7	5·6	9·1	9·9	22·2	29·2	17·6	15·9	13	17
P value		< 0·001		< 0·001		< 0·02		< 0·01			NS

Results

GRADED DOSE STUDY

During atrial pacing at cycle lengths ranging from 470 to 680 ms atenolol consistently caused AH prolongation. There was a trend towards greater AH prolongation at each higher dose level of atenolol (Fig. 2). The difference at each paced cycle length was statistically significant between the lowest (0·03 mg/kg) and the highest (0·12 mg/kg) atenolol dose levels ($P < 0·05$). There was no significant change in HV at any of the three dose levels of atenolol.

EFFECTS OF MAXIMUM DOSE OF ATENOLOL

The results are summarised in Tables 1 and 2. Mean values shown in these tables were calculated from patients with paired data only.

Sinus node function (Table 1)

Sinus cycle length was increased in all 16 patients in whom it was measured, with an overall

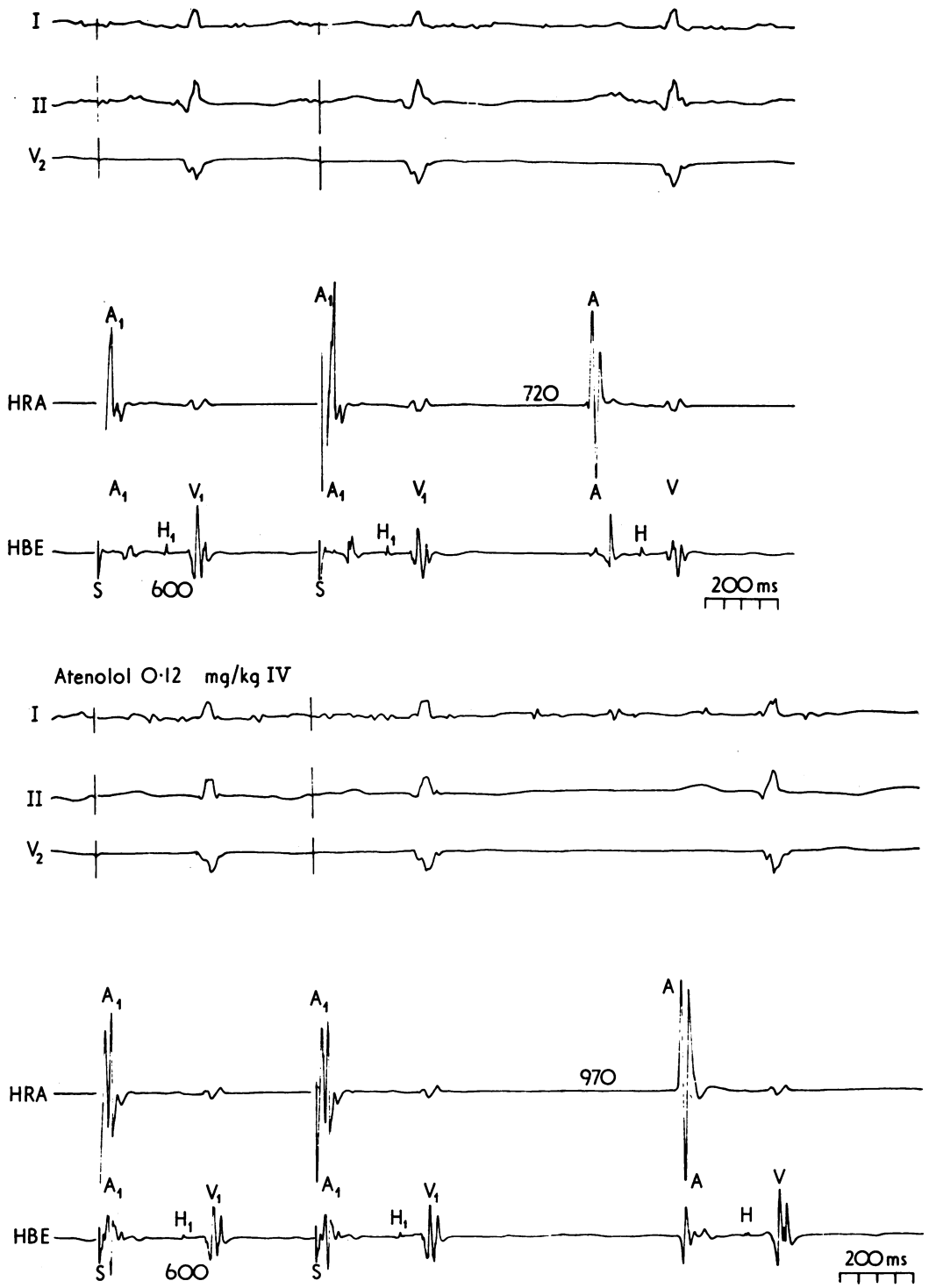

Fig. 3 *Effect of atenolol 0·12 mg/kg on sinus node recovery time.*

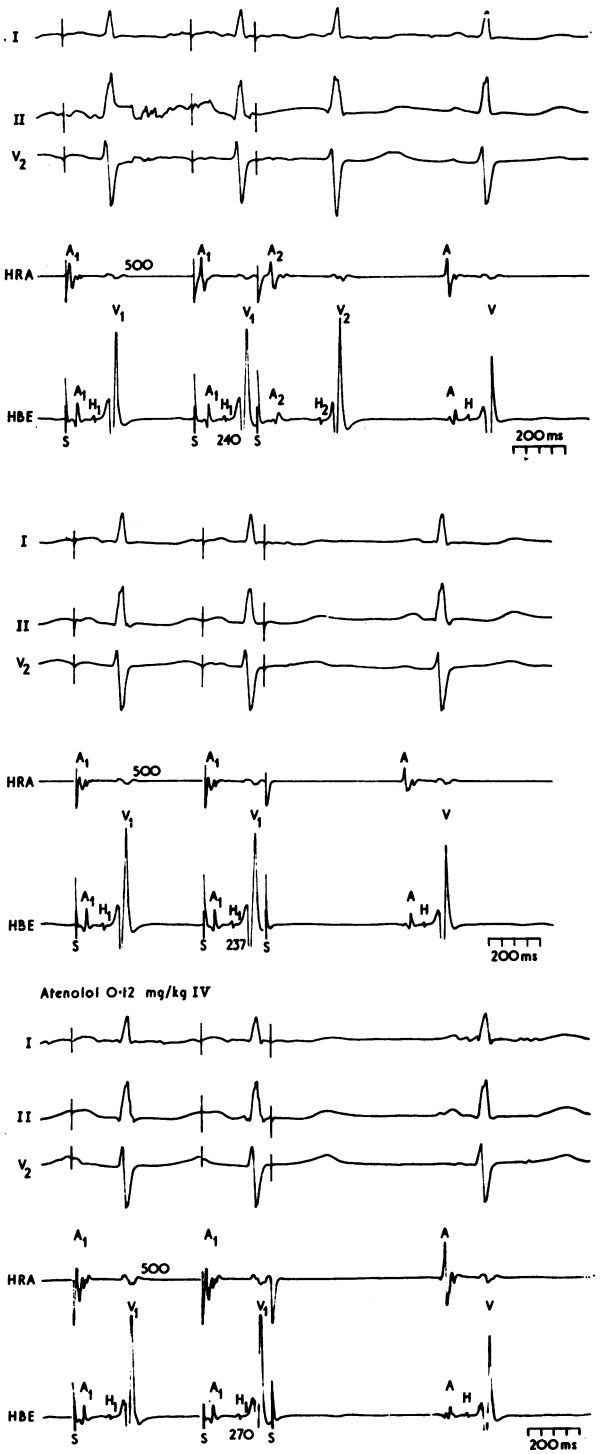

Fig. 4 *Effect of atenolol 0·12 mg/kg on the effective refractory period of the atrium.*

mean increase of 146 ±21 ms ($P < 0.001$), equivalent to a decrease in mean heart rate from 79 ±3 to 66 ±2 beats/minute.

The sinus node recovery time was increased in all 9 patients in whom it was measured with a mean rise of 168 ±38 ms ($P < 0.01$) and an example is shown in Fig. 3.

Atrioventricular nodal conduction (Table 1)
During spontaneous sinus rhythm AH was increased in 14 out of 16 patients after atenolol and unchanged in 2 patients with an overall mean increase of 14 ±4 ms ($P < 0.001$). During atrial pacing at cycle lengths ranging from 360 to 790 ms atenolol consistently caused AH prolongation. Atenolol produced no significant change in HV during sinus rhythm or during atrial pacing.

Q–Tc (Table 1) was shortened in 9 out of 10 patients in whom it was measured and unchanged in 1 patient, with an overall mean decrease of 30 ±5 ms ($P < 0.001$).

Atrial refractoriness (Table 2)
The effective refractory period of the atrium was increased by atenolol in all 10 patients in whom it was measured at paced cycle lengths ranging from 360 to 730 ms. The mean increase was 31 ±6 ms ($P < 0.001$). An example is shown in Fig. 4. There was a similar increase in the functional refractory period of the atrium with a mean change of 34 ±6 ms ($P < 0.001$).

Atrioventricular nodal refractory periods (Table 2)
The effective refractory period of the atrioventricular node was increased by atenolol in 6 of the 7 patients in whom it could be measured at paced cycle lengths ranging from 430 to 770 ms. An example is shown in Fig. 5. There was an overall mean increase of 51 ±17 ms ($P < 0.02$).

The functional refractory period of the atrioventricular node was increased in 10 out of 10 patients with a mean increase of 42 ±12 ms ($P < 0.01$).

His Purkinje refractoriness (Table 2)
The effective refractory period of the His Purkinje system could not be measured in any of the patients studied, because the functional refractory periods of either the atrioventricular node or the atrium were longer at the paced cycle lengths used, ranging from 360 to 790 ms.

The relative refractory period of the His Purkinje system could be measured in 6 out of 10 patients and showed no consistent change after administration of atenolol.

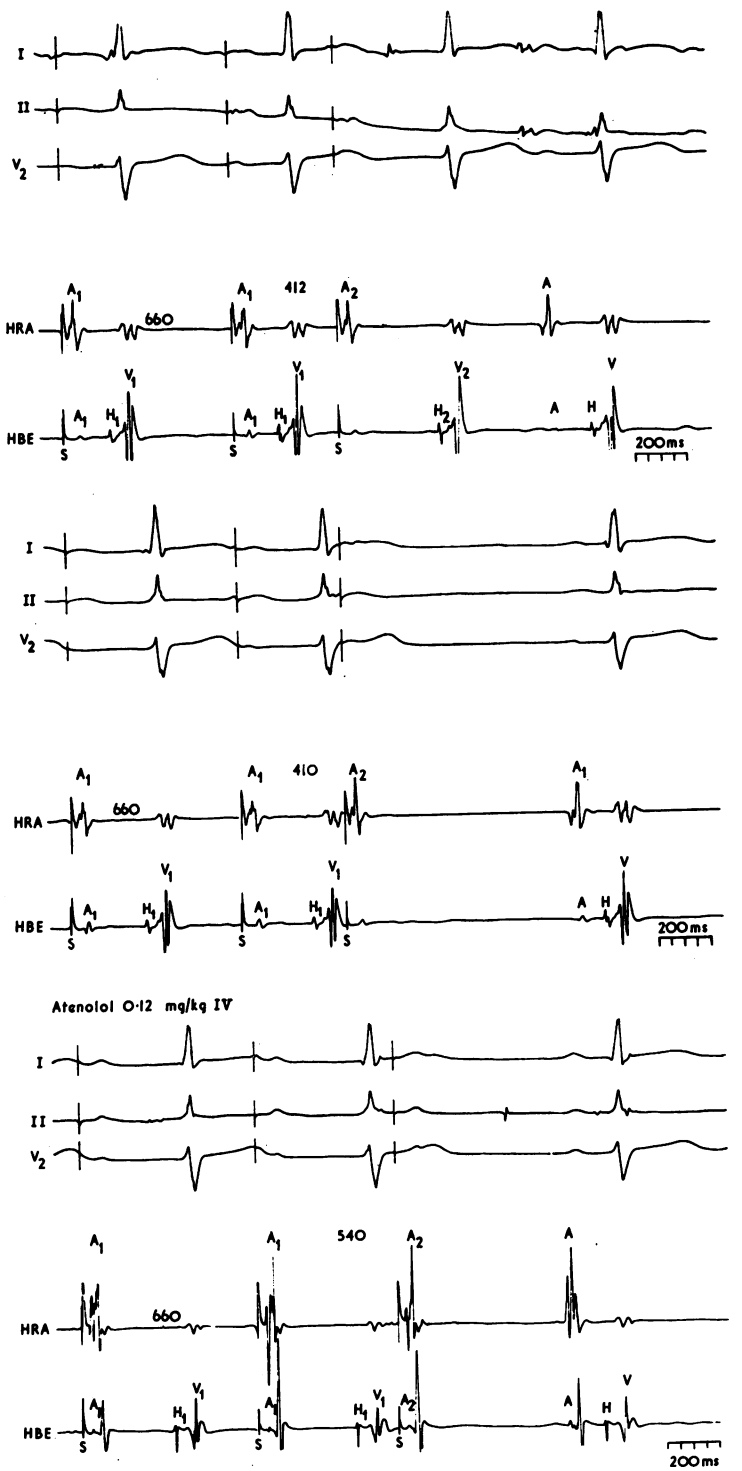

Fig. 5 *Effect of atenolol 0·12 mg/kg on the effective refractory period of the atrioventricular node.*

Effective refractory period of the ventricle
Atenolol produced no significant change in the effective refractory period of the right ventricle in the 6 patients in whom it was studied.

Arrhythmias
(1) *Supraventricular* One patient had a short run of supraventricular tachycardia induced during atrial pacing at a cycle length of 660 ms by a premature extrastimulus at an S_1–S_2 interval of 205 ms. After atenolol 0·12 mg/kg premature extrastimuli, including ones presented at the same coupling interval, failed to produce tachycardia.
(2) *Ventricular* Two patients had frequent ventricular extrasystoles which were abolished by atenolol and one of these patients had in addition spontaneous self-limiting episodes of ventricular tachycardia which were abolished by the drug.

Discussion

Atenolol causes significant prolongation of the sinus cycle length, sinus node recovery time, atrioventricular node conduction, and the effective and functional refractory periods of the atrium and atrioventricular node. No significant effect was observed on the His Purkinje system or the effective refractory period of the ventricle.

In these actions atenolol clearly resembles propranolol (Seides *et al.*, 1974) which also prolongs sinus cycle length, atrioventricular node conduction, and the refractory periods of the atrioventricular node. Propranolol, however, has not been shown to cause significant prolongation of atrial refractoriness. Theoretically, this difference should give atenolol an advantage over propranolol in the treatment of arrhythmias involving the atrium.

Atenolol differs from practolol in its prolongation of atrioventricular node conduction (Smithen *et al.*, 1971). Presumably this is because like propranolol it lacks intrinsic sympathomimetic properties. Atenolol has been shown to be as cardioselective as practolol on the bronchial tree (Vilsvik and Schaaning, 1976) but not on the peripheral circulatory system (Robinson *et al.*, 1978). It, therefore, resembles propranolol haemodynamically as well as electrophysiologically.

Like other beta-blocking agents which are classified as possessing Class 2 actions by Vaughan Williams (1970), atenolol differs from drugs with mainly Class I actions. Thus it differs from quinidine (Josephson *et al.*, 1974b) and procainamide (Josephson *et al.*, 1974a) which prolong His Purkinje conduction and refractoriness and decrease the effective refractory period of the atrioventricular node. The actions of these two agents are classified as subgroup 1a. Atenolol also differs from mexiletine (McComish *et al.*, 1975), lignocaine (Josephson *et al.*, 1972), and diphenylhydantoin (Caracta *et al.*, 1973) which all shorten the refractory period of the His Purkinje system and their actions are classified as subgroup 1b. Atenolol does not prolong action potential duration experimentally (Barrett *et al.*, 1973) as does amiodarone (Singh and Vaughan Williams, 1970), i.e. it possesses no class III actions.

Although atenolol has not been shown to affect the His Purkinje system in our patients with normal conducting systems, it should not be assumed that it is, therefore, safe to use in patients with conducting system disease.

In conclusion, atenolol is a new cardioselective beta-adrenergic blocking agent which, like other beta-blockers, would be a suitable agent in the treatment of supraventricular arrhythmias in particular. Though relatively selective on the bronchial tree its action electrophysiologically differs from practolol. Electrophysiologically it closely resembles propranolol and because of its action in increasing atrial refractoriness may prove to be more effective than propranolol in the treatment of supraventricular arrhythmias.

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Requests for reprints to Dr. D. E. Jewitt, Cardiac Department, King's College Hospital, Denmark Hill, London SE5 9RS.