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

CHRISTINE ROBINSON1, 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 It has recently been withdrawn from general use because of serious side effects (Felix et al., 1974; Wright, 1975).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 Schaanning, 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.
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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 minigraph 81 eight-channel direct-writing recorder at a paper speed of 100 mm/s. Electrophysiological measurements included determination of (1) sinus node function; (2) atrioventricular 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.

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

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QTc = \frac{QT \sqrt{R-R}}{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 atrioventricular 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 S1–S2 interval at which S2 fails to depolarise the atrium.

The functional refractory period (FRP) of the atrium is defined as the shortest A1–A2 interval recorded.

The effective refractory period of the atrioventricular node is defined as the longest A1–A2 interval at which A2 fails to propagate to the His Purkinje system.

The functional refractory period of the atrioventricular node is defined as the shortest H1–H2 interval recorded.

The effective refractory period of the His Purkinje system is defined as the longest H1–H2 interval at which H2 fails to conduct to the ventricles.

The relative refractory period of the His Purkinje system is defined as the longest H1–H2 interval at which H2 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 S1–S2 interval at which S2 fails to depolarise the ventricle.
atenolol dose levels was (Fig. 2). Atrial pacing during the three dose levels of atenolol.}(P<0.05).

Significant change in HV at any of the three dose levels of atenolol.

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
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Fig. 3  Effect of atenolol 0.12 mg/kg on sinus node recovery time.
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.
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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 Schaning, 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 1 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.

References


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Requests for reprints to Dr. D. E. Jewitt, Cardiac Department, King's College Hospital, Denmark Hill, London SE5 9RS.
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C Robinson, J Birkhead, B Crook, K Jennings and D Jewitt

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