Electrophysiological effects of acebutolol¹

JAY W. MASON, ROGER A. WINKLE, PETER J. MEFFIN, AND DONALD C. HARRISON

From the Cardiology Division, Stanford University School of Medicine, Stanford, California, U.S.A.

We administered acebutolol, a partially cardioselective beta-adrenergic blocking agent with membrane stabilising properties, to 11 patients with coronary artery disease but no evidence of conduction system disease. Electrophysiological studies and serial plasma concentration determinations were made before and after infusion of acebutolol, 1.0 mg/kg, over 15 minutes. At 25 minutes after initiation of the infusion, mean heart rate decreased from 77 ± 5 to 68 ± 3 (SEM) beats/min ($P < 0.005$). Systolic blood pressure fell by 10 mmHg ($P < 0.02$). AH interval rose from 110 ± 8 to 137 ± 15 ms ($P < 0.02$). The atrioventricular node functional refractory period increased from 447 ± 29 ms to 471 ± 30 ms ($P < 0.07$). The HV interval increase, from 46 ± 2 to 51 ± 2 ms, was not significant. The sinus node recovery time and atrial effective refractory period were inconsistently affected.

The mean plasma concentration of acebutolol at 25 minutes was 957 ± 92 ng/ml. Four patients (group 1) had concentrations above 1000 ng/ml (mean 1280 ± 113 ng/ml), and the other 7 (group 2) had concentrations below 1000 ng/ml (mean 774 ± 55 ng/ml). The mean HV interval increased in group 1 patients from 44 ± 2 ms to 52 ± 3 ms. This change was significantly different from the negligible change in HV interval in the group 2 patients. In addition, the increase in AH interval was much greater in group 1 patients.

We conclude that, like propranolol, acebutolol reduces heart rate and blood pressure, and slows conduction and increases refractoriness in the atrioventricular node. Acebutolol also slows His-Purkinje conduction at higher plasma concentrations.

We have examined the electrophysiological effects of acebutolol in 11 patients with coronary artery disease. Acebutolol is a new beta-adrenergic blocking agent which has a direct membrane stabilising effect. Acebutolol may exert a lesser effect upon the bronchial β_2 adrenergic receptors than does propranolol (Basil *et al.*, 1971; Leary *et al.*, 1973; Lewis *et al.*, 1973a; Kumana *et al.*, 1975) but is not otherwise cardioselective (Briant *et al.*, 1971; Cuthbert and Owusu-Ankomah, 1971). Acebutolol is effective in preventing angina pectoris in patients with coronary atherosclerosis (Lewis *et al.*, 1973b) and in reducing the frequency of premature ventricular contractions in man (Gradman *et al.*, 1975). It was the purpose of this investigation to determine the acute effects of intravenous acebutolol on the conduction system in man, by use of His bundle recording techniques.

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Subjects and methods

Eleven patients with chest pain caused by coronary artery disease were studied at the time of diagnostic cardiac catheterisation. The group consisted of 10 men, aged 32 to 67 (mean 49), and 1 woman, aged 55. All medications were discontinued at least 48 hours before study. No patients with overt congestive heart failure, electrocardiographic evidence of cardiac conduction system disease, or myocardial infarction within 6 months were accepted for study. The procedure was approved by the Stanford Human Subjects Committee, and all patients gave informed consent. The patients were studied in a postabsorptive state under light sedation with oral diazepam 10 mg.

At least 30 minutes after left ventriculography, a No. 7F quadripolar recording-stimulating electrode catheter was positioned in the high right atrium through a peripheral vein, and a No. 7F tripolar or a No. 5F bipolar His bundle recording catheter

was advanced across the tricuspid valve from the same or a separate peripheral vein. Surface electrocardiographic leads I, aVF, and V1 were recorded simultaneously with the atrial and His bundle electrograms. Intracardiac signals were filtered at frequencies of 40 to 500 Hz through the AC input of a Hewlett-Packard 88-11A electrocardiographic amplifier, and data were displayed on a switched-beam oscilloscope. Atrial pacing stimuli of 2 ms duration were delivered by a Tektronix pulse generator through an electrical isolation unit at twice the diastolic threshold. The spontaneous sinus cycle length and resting AH and HV intervals were determined from recordings on photographic paper at a speed of 100 mm/s. The sinus node recovery time was determined three times by measuring the length of the pause before re-emergence of a spontaneous sinoatrial depolarisation after abrupt termination of atrial pacing which had been continued for one minute at a cycle length of 430 ms. Basic atrial pacing at a cycle length of 25 to 50 ms shorter than the spontaneous sinus cycle length was then initiated and the AH and HV intervals recorded again. The atrial effective refractory period and the refractory period of the atrioventricular (AV) node were determined at the base pacing rate by the extrastimulus technique (Krayner *et al.*, 1951): after every eighth paced beat (S_1), a premature stimulus (S_2) was introduced; the timing of these stimuli was varied by a programmable digital stimulator (M. Bloom, Philadelphia). The S_1 - S_2 interval was then reduced by 10 ms decrements until the atrial refractory period was reached. The atrial effective refractory period is defined as the longest S_1 - S_2 interval at which S_2 consistently fails to depolarise the atrium. The shortest H_1 - H_2 interval conducted from the atrium is the AV nodal functional refractory period, and the longest A_1 - A_2 interval at which A_2 fails to conduct through the AV node is the effective refractory period. Central aortic blood pressure was measured through a 4F polyethylene catheter attached to a Statham P23Db transducer.

After completion of these measurements, acebutolol (1.0 mg/kg), was administered by constant intravenous infusion during a 15-minute period. The spontaneous heart rate, the AH and HV intervals, and the blood pressure during base-rate pacing were recorded 5, 15, and 25 minutes after initiation of acebutolol infusion. The sinus node recovery time and the atrial and AV nodal refractory periods were also re-measured at this time. Blood samples were obtained at 5, 15, 25, and 35 minutes for estimation of plasma acebutolol concentration by selective solvent extraction and gas chromatography (Meffin *et al.*, 1976).

Electrophysiological data before and after drug administration were compared by the two-tailed Student's *t* test for paired data, except for the changes in HV interval. These were studied by the Wilcoxon matched pair signed rank test, and the Wilcoxon two-sample statistic. This nonparametric method was chosen to analyse HV interval changes because of the probable asymmetry of distribution of HV interval values in man.

Results

HIS-PURKINJE SYSTEM

Electrophysiological and pharmacological data are summarised in the Table. The HV interval for the entire group of subjects was not significantly changed by acebutolol; the mean HV interval measured during base-rate atrial pacing before and 25 minutes after initiation of drug infusion increased from 46 ± 2 ms to 51 ± 2 ms (NS).¹ Four patients (group 1) had plasma concentrations of acebutolol above 1000 ng/ml, and the other 7 patients (group 2) had concentrations below 1000 ng/ml at 25 minutes (Fig. 1). Group 1 patients showed an increase in mean HV interval from 44 ± 2 ms to 56 ± 3 ms after acebutolol administration (Fig. 2). Group 2 patients showed a negligible change in HV interval; their mean HV time was 48 ± 2 ms before and 47 ± 2 ms after acebutolol. The mean change in HV time was +27 per cent for group 1 and -1 per cent for group 2 (Fig. 3). The HV inter-

¹Wilcoxon matched pair signed rank test, two-tailed.

Table Electrophysiological data*

	Control†	Acebutolol†	P value
HV interval (groups 1 and 2) (ms)	46 ± 2	51 ± 2	NS‡
(group 1)	44 ± 2	56 ± 3	
(group 2)	48 ± 2	47 ± 2	
AH interval (ms) (groups 1 and 2)	110 ± 8	137 ± 15	< 0.02
(group 1)	99 ± 17	139 ± 42	NS
(group 2)	116 ± 9	136 ± 11	< 0.001
AV nodal functional refractory period (ms)	447 ± 28	471 ± 30	< 0.07
Sinus node recovery time (ms)	1023 ± 69	1076 ± 82	NS
Atrial effective refractory period (ms)	277 ± 14	285 ± 14	NS
Heart rate (beats/min)	77 ± 13	67 ± 16	< 0.005
Systolic blood pressure (mmHg)	151 ± 6	141 ± 6	< 0.02
Diastolic blood pressure (mmHg)	85 ± 3	78 ± 3	< 0.005
Mean blood pressure (mmHg)	107 ± 4	101 ± 3	< 0.005
Acebutolol concentration* (ng/ml)			
(groups 1 and 2)		957 ± 92	
(group 1)		1280 ± 113	
(group 2)		774 ± 95	

*These measurements were obtained 25 minutes after start of acebutolol infusion.

†Mean ± standard error of the mean.

‡Wilcoxon matched pair signed rank test, two-tailed.

val change after acebutolol in group 1 was significantly different from the change in group 2 ($P < 0.006$).¹ Because the division of patients into groups 1 and 2 on the basis of plasma concentrations above or below 1000 ng/ml is arbitrary, we performed the same statistical analysis, first using the patients with the five highest plasma concentrations, and then the patients with the six highest plasma concentrations, to represent group 1, and obtained P values of < 0.03 and < 0.01 , respectively.² Though the method of grouping patients by plasma concentration remains arbitrary, this analysis suggests that higher plasma concentrations of acebutolol are associated with HV interval prolongation. His-Purkinje refractoriness was within the range of normal in all patients, though longer AV nodal refractory periods precluded determination of exact

ventricular specialised conduction system refractory periods in all but two patients, in whom there was no change.

ATRIOVENTRICULAR NODE

Acebutolol prolonged AV nodal conduction time, as judged by an increase in AH interval in 10 of 11 patients. The mean AH interval for the entire group of patients increased from 110 ± 8 ms to 137 ± 15 ms ($P < 0.02$) (Fig. 4). The AH interval in group 2 patients increased by 17 per cent (116 ± 9 ms to 137 ± 11 ms), and by 36 per cent in group 1 patients (99 ± 17 ms to 139 ± 42 ms).

Fig. 1 Group 1 is composed of the 4 patients whose plasma acebutolol concentrations were above 1000 ng/ml at 25 minutes. The other 7 patients made up group 2. The mean plasma concentrations of group 1 were significantly greater than in group 2 at each sampling time. The bars indicate standard errors of the means.

¹Wilcoxon matched pair signed rank test, two-tailed.

²Wilcoxon two-sample statistic, two-tailed.

Fig. 2 Group 1 patient (plasma acebutolol concentration 1468 ng/ml). Recordings (100 mm/s) of surface electrocardiographic leads I, aVF, and V1, atrial electrogram (AE), and His bundle electrogram (HBE). (A) before acebutolol infusion: HV interval 45 ms. (B) 25 minutes after the start of acebutolol infusion: HV interval 55 ms.

The AV nodal functional refractory period, which was measured in 10 of the 11 patients, increased in 8 patients and remained unchanged in 2 after acebutolol. The mean functional refractory period increased from 447 ± 28 ms to 471 ± 30 ms ($P < 0.07$) (Fig. 5).

ATRIUM AND SINUS NODE

Acebutolol had no consistent effect upon atrial effective refractory period, which increased insignificantly from a mean of 277 ± 14 ms to 285 ± 14 ms. Acebutolol exerted a definite depressant effect upon sinus node automaticity. Heart rate was reduced in 10 patients and unchanged in one. The mean heart rate for the group fell from 77 ± 5 beats/min to 68 ± 3 beats/min after acebutolol (i.e. the cycle length increased from 807 ± 47 ms to 898 ± 38 ms) (Fig. 6). The mean sinus node recovery time increased insignificantly from 1023 ± 69 ms to 1076 ± 82 ms.

ARTERIAL PRESSURE

Acebutolol produced a slight though statistically significant reduction in systolic blood pressure, measured during base-rate atrial pacing, from 151 ± 6 mmHg to 141 ± 6 mmHg ($P < 0.02$). Diastolic and mean arterial pressures also fell (85 ± 3 mmHg to 78 ± 3 mmHg, $P < 0.005$, and 107 ± 4 to 101 ± 3 mmHg, $P < 0.005$, respectively). In only 1 patient

was there a fall in systolic blood pressure greater than 12 mmHg, and in no patient did systolic pressure fall below 118 mmHg.

Discussion

We have found that acebutolol, administered intravenously in man, slows the heart rate, lowers the blood pressure, prolongs AV nodal conduction time, and increases AV nodal refractoriness. In addition, a high plasma concentration of acebutolol slows conduction through the His-Purkinje system.

A steady state plasma concentration was not achieved in this short investigation. In addition, we monitored plasma concentrations, which do not necessarily reflect myocardial levels. However, with propranolol, to which acebutolol is pharmacokinetically similar, the response of myocardial beta-receptors appears to depend upon plasma

Fig. 3 Change in HV interval in 4 patients in group 1 and 7 patients in group 2. The mean change was +27 per cent in group 1 and -1 per cent (not significant) in group 2.

Fig. 4 AH interval before and after acebutolol. Mean AH interval increased significantly from 110 ± 8 ms to 137 ± 15 ms. AH interval fell in only 1 patient. The means and standard errors of the means are indicated in this and subsequent figures.

levels; it has been shown that the chronotropic effect of propranolol is a nearly constant function of its plasma concentration (McDevitt and Shand, 1975).

Touboul *et al.* (1975) reported electrophysiological changes similar in direction and magnitude to those in our patients in 15 patients with suspected cardiac disease. Thirteen of their patients were studied because of syncope, and the other 2 were studied to differentiate between supraventricular and ventricular tachycardia. Thus, the majority of their patients had abnormal conduction systems: 10 of 15 patients had HV intervals 55 ms or more, 5 of 12 had AV nodal functional refractory periods 500 ms or more, and 5 of 15 had sinus node dysfunction with episodes of tachycardia and bradycardia. They administered 0.5 mg/kg of acebutolol, one-half the dose which we gave, over a 15-minute infusion period, and did not measure plasma concentrations. They made electrophysiological measurements at 30 minutes after the start of infusion (5 minutes later than our measurements). Despite differences from our procedure, their results were similar to ours, except that they reported no change in the HV interval in any of their subjects. The lower dose which they administered may account for the lack of an effect on

His-Purkinje conduction, as we found that only those patients with the highest plasma concentrations showed HV prolongation after acebutolol.

Acebutolol produces electrophysiological effects in man similar to those of propranolol. On the basis of the weight of drug required to produce a given degree of beta-blockade, the dosage of acebutolol used in this study is comparable to the propranolol dosage used in human studies (Berkowitz *et al.*, 1969; Smithen *et al.*, 1971; Seides *et al.*, 1974). However, these authors failed to show any effect of propranolol upon His-Purkinje conduction. The HV prolongation in our group 1 patients is of considerable importance, since use of beta-blocking agents has been considered safe in patients with abnormalities of the ventricular specialised conduction system (Seides *et al.*, 1974). Propranolol and acebutolol possess both beta-adrenergic blocking and membrane stabilising effects. The beta-blocking effect of propranolol is seen at the usual clinical doses, while some of its membrane actions, including slowing of Purkinje fibre conduction velocity, are seen only at much higher dose levels beyond the therapeutic range (Vaughan-Williams, 1966; Davis and Temte, 1968; Whitsitt and Lucchesi, 1968). Acebutolol appears to have greater membrane effects than propranolol; this may account for the HV prolongation

Fig. 5 AV nodal functional refractory period before and after acebutolol. AV nodal refractory period increased in 8 of 10 patients and was unchanged in 2; the mean increased from 446 ± 28 ms to 471 ± 30 ms.

Fig. 6 Spontaneous sinus cycle length before and after acebutolol. Cycle length increased in all but 1 patient whose heart rate was unchanged; mean increased from 807 ± 47 ms to 898 ± 38 ms.

in our patients with plasma acebutolol concentrations above 1000 ng/ml. Since plasma concentrations near or above 1000 ng/ml may be achieved with chronic oral administration of acebutolol,¹ we think that large intravenous and oral doses of acebutolol should be used with caution in patients with disease of the ventricular specialised conduction system. The observations reported by Touboul *et al.* (1975) in patients with initially increased HV intervals, given 0.5 mg/kg of acebutolol intravenously, suggest that lower doses should be safe in such patients. Though it seems unlikely that the HV prolongation by acebutolol, which we found solely in patients with high plasma concentrations, is coincidental or spurious, corroboration of this finding should be sought, as it may significantly affect clinical use of acebutolol.

¹The therapeutic oral dose of acebutolol for suppression of premature ventricular contractions ranges from 300 mg to 600 mg given two to four times daily. In patients given single 300 mg doses of acebutolol at Stanford Medical Center, acebutolol concentrations have ranged from 40 ng/ml to 1024 ng/ml (mean 827 ng/ml) at 2 hours in one group of patients, and from 599 ng/ml to 896 ng/ml (mean 745 ng/ml) at 4 hours after administration in another group.

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Requests for reprints to Dr. Jay W. Mason, Cardiology Division, Stanford University Medical Center, Stanford, California 94305, U.S.A.