Acebutolol in Cardiac Arrhythmias

B. S. LEWIS, A. S. MITHA, M. S. GOTSMAN

SUMMARY

Acebutolol (Sectral), a new beta-adrenoceptor antagonist, was used in 44 patients with cardiac arrhythmias (53 episodes). It was used intravenously (12,5 and 25 mg), orally (100 mg every 8 hours) or in combination with quinidine. Acebutolol was most effective in supraventricular tachyarrhythmias, to control the ventricular response when digitalis was ineffective, as a synergist with quinidine to convert patients to sinus rhythm, or prophylactically to prevent relapse to atrial fibrillation. It also terminated ventricular tachycardia in two patients.

Side-effects occurred in three ill patients.

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Beta-adrenergic blocking agents are used in the management of cardiac arrhythmias.[1-7] Acebutolol (M&B 17803A; Sectral; DL - 1 - (2 acetyl - 4 - butyramidophenoxy) - 2 - hydroxy - 3 - isopropylaminopropane hydrochloride) is a new cardioselective beta-adrenoceptor antagonist with great affinity for, but low efficacy in, the beta receptor sites. It also has membrane stabilising properties which may make it a useful anti-arrhythmic agent.[8] In normal subjects, the cardiac output at rest and on exercise is not altered by the administration of acebutolol, and in patients with coronary artery disease, intravenous acebutolol produces a small fall in cardiac index, stroke index and in the parameters which are used to measure left ventricular contractility.[9,10]

We have used acebutolol in 44 patients (53 episodes) with cardiac arrhythmias to assess its value in therapy. This is the initial report of the anti-arrhythmic use of the drug in man.

PATIENTS AND METHODS

Acebutolol was used in 44 patients. The clinical data relating to each patient, the nature of the arrhythmia, route of administration of acebutolol and clinical outcome, are shown in Table I, and summarised in Table II.

The patients were hospitalised for acute rhythm disturbances or followed carefully in an outpatient clinic for long-term management. The drug was administered intravenously to 14 patients while heart rate, the electrocardiogram, blood pressure and clinical status were monitored. It was given orally to 39 patients.

The drug was given in 4 different dosage regimens:

Intravenous administration in a dose of 12,5 or 25 mg to terminate an arrhythmia.

Oral administration in a dose of 100 - 200 mg every 8 or 12 hours to control a tachycardia, to abolish an arrhythmia or to maintain sinus rhythm.

Combination therapy with quinidine after failure of attempted conversion of a supraventricular arrhythmia to sinus rhythm with quinidine or electroconversion, so that each patient served as his own control. In these patients quinidine was given in a dose of 400 mg every 6 hours for 4 doses; if sinus rhythm did not appear electroconversion was attempted. If this failed or the patient relapsed to atrial fibrillation on a prophylactic dose of quinidine (200 mg every 8 hours), pharmacological conversion to sinus rhythm was again attempted using quinidine (400 mg every 6 hours) with the addition of oral acebutolol (100 mg every 8 hours). If this regimen did not restore sinus rhythm after 24 hours, DC countershock was given again.

Synergistic therapy of quinidine and acebutolol to maintain sinus rhythm in patients with atrial fibrillation or flutter, in whom additional acebutolol was needed to achieve cardioversion (quinidine 200 mg every 8 hours + acebutolol 100 mg every 8 hours).

RESULTS

The results are summarised in Table II.

Ventricular Arrhythmias

Ventricular premature systoles (VPS). The drug was given intravenously to 3 patients; it reduced the number of VPSs in 1 patient with digitalis excess, and was ineffective in the other 2. It was given orally in another 3 patients; it reduced the number of VPSs per minute in one, was effective for a short period in another, and was ineffective in the third.

Ventricular tachycardia (VT). Acebutolol was given intravenously to 3 patients; it terminated the tachycardia in 2 and failed in a third, who became more hypotensive after administration of the drug. Prophylactic oral administration of 200 mg acebutolol *t.d.s.* reduced the number of paroxysms of VT in 1 of these patients; she can terminate an episode of arrhythmia at home with a small additional dose of the drug.

Cardiac Unit, Wentworth Hospital and University of Natal, Durban
B. S. LEWIS, M.B. B.CH.
A. S. MITHA, M.R.C.P.
M. S. GOTSMAN, M.D., F.R.C.P.

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Reprint requests to: Dr B. S. Lewis, Wentworth Hospital, P.B. Jacobs, Natal.

TABLE I. THE PATIENTS

	Patients	Age (yrs)	Diagnosis	Dose of acebutolol (mg)	Route of administration	Result +	Result −	Result ±	Side-effects
Ventricular (9 patients)	**Ventricular premature systoles**								
	1	34	Post-MVR	12,5	IV		−		
	2	18	AI; Dig. excess	12,5	IV	+			
	3	59	CAD	25	IV		−		
	4	58	DVR; myopathy	100 every 8 h	Oral			±	
	5	73	Pacemaker	100 every 8 h	Oral		−		
	6	41	CAD	100 every 8 h	Oral	+			
	Ventricular tachycardia								
	7	27	Idiopathic	25 + 200 every 8 h	IV + oral	+			
	8	17	Idiopathic	25	IV	+			
	9	53	Post-DVR	12,5	IV		−		Hypotension
Supraventricular (44 patients)	**Atrial premature systoles or atrial echoes**								
	10	61	Pacemaker	25	IV	+			
	11	35	MVD	100 every 8 h	Oral	+			
	12*	26	WPW	100 every 8 h	Oral		−		
	WPW + PAT								
	13	37	CAD	100 (single dose)	Oral	+			Hypotension
	14*	26	Idiopathic	25	IV		−		
	Nodal tachycardia								
	15	12	Post-MVR	15	IV		−		
	16	40	CAD	12,5	IV	+			
	Atrial flutter/fibrillation								
	(a) Control rate								
	17	40	Post-MVR	12,5	IV	+			Hypotension
	18	45	MS	25	IV	+			
	19	40	MVD	25	IV	+			
	20	9	Post-MVR	50 every 8 h	Oral	+			
	21	25	Post-MVR	100 every 6 h	Oral	+			
	22	39	MVD	100 every 8 h	Oral	+			
	23	48	MVD	100 every 12 h	Oral	+			
	24	42	Postmitral valvulotomy	100 every 12 h	Oral	+			
	(b) Cardioversion—without DC countershock								
	25	9	Post-MVR	50 every 8 h	Oral	+			
	26	29	Postmitral valvulotomy	100 every 12 h	Oral				
	27	25	Postmitral valvulotomy	100 every 8 h	Oral	+			
	28	51	Post-MVR	100 every 8 h	Oral	+			
	29	58	Idiopathic	100 every 8 h	Oral	+			
	30	63	Hypertension	100 every 8 h	Oral	+			
	31	38	Post-MVR	100 every 8 h	Oral	+			
	32	63	Pacemaker	12,5	IV	+			
	Cardioversion with DC countershock								
	33	42	Post-DVR	100 every 8 h	Oral		−		
	34	34	Postmitral valvulotomy	100 every 8 h	Oral		−		
	35	25	Post-MVR	100 every 8 h	Oral		−		
	36	52	Post-DVR	100 every 8 h	Oral	+			
	37	19	Post-MVR	100 every 8 h	Oral	+			
	38	39	Post-pulmonary-valvulotomy	100 every 8 h	Oral	+			
	39	31	Post-MVR	100 every 8 h	Oral	+			
	(c) Long-term maintenance of sinus rhythm								
	40	44	MS	100 every 12 h	Oral	+			
	41	51	MS	100 every 8 h	Oral	+			
	42	41	MVD	100 every 8 h	Oral	+			
	43	47	CAD	100 every 8 h	Oral	+			
	8 patients from group (b)*				8 Oral	4+	4−		
	Tachycardia/bradycardia syndrome (+ pacing)								
	52	63	CAD	100 every 8 h	Oral	+			
	53	86	Sick sinus syndrome	100 every 8 h	Oral	+			

AI = aortic incompetence; CAD = coronary artery disease; DVR = double valve (aortic + mitral) replacement; MS = mitral stenosis; MVD = mixed mitral valve disease; MVR = mitral valve replacement; IV = intravenous; * = patients fall into 2 groups; WPW = Wolff-Parkinson-White syndrome; PAT = paroxysmal atrial tachycardia.

TABLE II. EFFECTS OF ACEBUTOLOL (44 PATIENTS)

Arrhythmia	No. of patients	Route of administration		Result		
		IV	Oral	+	−	±
Ventricular	9					
VPS	6	3		1	2	
			3	1	1	1
Ventricular tachycardia	3	3	(1)	2	1	
Supraventricular	44					
APS	3	1	2	2	1	
WPW + PAT	2	1	1	1	1	
Nodal tachycardia	2	2		1	1	
Atrial flutter/fibrillation						
(a) Control rate	8	3	5	8		
(b) Cardioversion	15		15			
— without DC countershock				8		
— with DC countershock				4	3	
(c) Long-term maintenance of sinus rhythm	12		12	8	4	
Tachycardia-bradycardia syndrome (+ pacing)	2		2	2		
Total	—	—	—	—	—	—
	53 (9 patients fall into 2 groups)	14	39	38	14	1

TABLE III. ACEBUTOLOL IN CARDIOVERSION

Quinidine and/or electroversion				Addition of acebutolol (100 mg every 8 h)			
No. of patients	No.	Success then relapse	Failure	No.	Sinus rhythm on drugs alone	Sinus rhythm after electroversion	Failure
15	13	5	8	13	6	4	3
				2	2	—	—

2 patients were treated with acebutolol alone.

Supraventricular Arrhythmias

Atrial premature systoles (APS). The drug reduced the number of APSs in 2 patients and was ineffective in one.

Wolff-Parkinson-White syndrome and paroxysmal atrial tachycardia (PAT). The drug reduced the number of episodes in one patient although it induced a period of hypotension. It was ineffective in the second patient.

Nodal tachycardia. Acebutolol was given intravenously to 2 patients with nodal tachycardia; it abolished the arrhythmia in 1 and was ineffective in the other.

Atrial flutter or fibrillation. The drug was always effective in controlling the ventricular response in digitalised subjects when digitalis alone was inadequate.

Acebutolol was used for cardioversion in 15 patients (Table III). Each patient was used as his own control, and in 13 patients quinidine alone followed by electroconversion had been unsuccessful or the patient had immediately relapsed into atrial fibrillation after successful cardioversion. In 8 of the 15 patients sinus rhythm was restored within 24 hours on a combination of quinidine 400 mg every 6 hours and acebutolol 100 mg every 8 hours. In the other 7 patients electroconversion was applied after 24 hours and was successful in 4.

Eight patients of this group were maintained on quinidine and acebutolol to prevent recurrence of atrial fibrillation over a period of 3 months or longer; 4 relapsed into atrial fibrillation and 4 remained in sinus rhythm. Another group of 4 patients with intermittent atrial fibrillation were treated with oral acebutolol alone in a dose of 100 mg every 8 or 12 hours; atrial fibrillation did not recur in one patient and the number of episodes was reduced in the other 3.

Tachycardia-bradycardia syndrome. Both patients in this group had intermittent complete heart block and paroxysms of atrial flutter with rapid ventricular response. A demand pacemaker was inserted to control the bradycardia, and acebutolol prevented further episodes of supraventricular tachycardia.

Side-Effects

Ventricular tachycardia with hypotension after aortic and mitral valve replacement. Aortic and mitral valve replacement was undertaken in a 53-year-old woman. Ventricular tachycardia developed 12 hours after operation. The patient was hypotensive and hypovolaemic. Intraven-

ous acebutolol (12,5 mg) did not abolish the tachycardia and the patient's hypotension increased. This was corrected by administration of isoprenaline and intravenous fluids.

Rapid ventricular response to atrial fibrillation after mitral valve replacement (MVR). A 40-year-old woman developed rapid atrial fibrillation 24 hours after MVR. Acebutolol 12,5 mg intravenously reduced the ventricular rate from 150 to 110 beats/min, but the patient became cold and sweaty and the systolic pressure fell to less than 50 mmHg. The patient responded to intravenous isoprenaline, the systolic blood pressure increased to 100 - 110 mmHg and the ventricular rate to 130 beats/min.

Recurrent atrial tachycardia in the Wolff-Parkinson-White syndrome (WPW) and coronary artery disease. A 37-year-old man who had had two episodes of acute myocardial infarction was shown at cardiac catheterisation and cine-angiocardiography to have triple vessel coronary artery disease and extensive ventricular asynergy. His left ventricular end-diastolic pressure was 26 mmHg and the ejection fraction 31%. He also had the WPW syndrome and 10—30 episodes of paroxysmal atrial tachycardia (PAT) per day. Each episode of tachycardia was associated with hypotension and precipitated pulmonary oedema. A single oral dose of 100 mg acebutolol was given: this abolished the episodes of tachycardia but the patient became hypotensive within 3 hours and required isoprenaline assistance for the following 12 hours.

Chronic side-effects were not observed.

DISCUSSION

Beta-adrenoceptor antagonists appear to have a specific mode of action in the management of arrhythmias.[11] They may act by antagonising the action of catecholamines, by a local anaesthetic action, or by a quinidine-like effect in which phase O of the action potential may be altered. Acebutolol has all these effects, but extensive studies with other drugs suggest that in the dosage used in clinical practice, the beta-adrenoceptor effects are more important than the other two.[6] There are numerous reports of the efficacy of propranolol, practolol, sotalol and alprenolol: these drugs have been used to suppress atrial and ventricular premature systoles and to terminate supraventricular tachyarrhythmias.[5,6,12,13] The combination therapy of quinidine and beta blockade is effective in converting atrial fibrillation to sinus rhythm.[14,15]

In our study, acebutolol was most effective in supraventricular arrhythmias: it was a good drug to control a rapid ventricular response when digitalis alone was ineffective, it was a powerful synergist with quinidine in converting patients to sinus rhythm (with or without DC countershock) and was useful as an adjunct to quinidine in the maintenance of sinus rhythm after this had been restored. It compares favourably with other beta-blocking agents used in similar circumstances, but we do not know how to compare individual drugs with each other. Acebutolol was also capable of terminating ventricular tachycardia and of preventing recurrences of this arrhythmia. Its value in the suppression of different kinds of ventricular premature systoles needs further study. We did not have the opportunity to use acebutolol in the circumstance of acute myocardial infarction.

Serious side-effects were encountered in only 3 patients. In 2 patients intravenous acebutolol was administered within 24 hours of cardiopulmonary bypass, while the third patient had severe left ventricular dysfunction; he was critically dependent on sympathetic drive for maintenance of an adequate cardiac output, and administration of a single dose of the beta-blocking drug produced profound hypotension and cardiac failure. Prolonged oral administration was not associated with untoward effects.

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