Use of bundle of His potentials to assess changes in atrioventricular conduction produced by a series of beta-adrenergic blocking agents

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Changes in atrioventricular conduction produced by propranolol, practolol, and dextro-propranolol were studied in 10 patients using the technique of recording His bundle potentials. Increasing the heart rate alone using atrial pacing resulted in a progressive and significant increase in the P-His interval, representing atrial and atrioventricular nodal conduction, but no change in the His-S interval, representing total intraventricular conduction. Propranolol significantly increased the P-His interval by approximately 10 per cent with a dose of 0.02 mg/kg and by 17 per cent with a dose of 0.05 mg/kg, with no effect on His-S interval. Dextro-propranolol significantly increased atrioventricular nodal conduction by 6 per cent with a dose of 0.2 mg/kg and had no effect on intraventricular conduction. Practolol produced no significant prolongation in either interval in any of the doses given.

Beta-adrenergic blocking drugs are being used increasingly in the treatment of cardiac dysrhythmias. One of the advantages of some of these preparations has been their ability to slow the ventricular response to atrial fibrillation. It has been possible to separate conduction in the atrioventricular node from total intraventricular conduction since Scherlag *et al.* (1969) introduced the technique of recording His bundle potentials in man. It was the purpose of this study to determine the effect of certain beta-adrenergic blocking agents on atrioventricular conduction using bundle of His recordings. The technique of atrial pacing was used to control the heart rate to exclude changes due to slowing of the heart which usually occurs with these agents, and thus permit separation of this action from effects on atrioventricular conduction. We report here our findings with three of these drugs, propranolol, dextro-propranolol, and practolol.

Material and methods

Ten patients with ischaemic heart disease were studied during a routine atrial pacing investigation which formed part of their evaluation for possible

revascularization surgery (Balcon, Maloy, and Sowton, 1968). All were in sinus rhythm and had no evidence of other forms of heart disease or cardiac failure. The pertinent clinical data are summarized in Table 1. There were 8 men and 2 women ranging in age from 41 to 59 years. None was taking digitalis or a beta-blocking preparation. The diagnosis of ischaemic heart disease was based on a typical history of angina and an abnormal electrocardiogram at rest or on exercise in all patients. Four patients had previous myocardial infarctions and the coronary angiogram was abnormal in 3 other patients.

The patients were fasted but were not pre-medicated. They were studied in the supine position at rest. In order to record the His bundle potential, a bipolar electrode catheter was introduced percutaneously into the right femoral vein, and under fluoroscopic control positioned across the tricuspid valve as shown in Fig. 1. The proximal terminals of the electrode catheter were attached to an electrocardiogram amplifier and used either as a unipolar or bipolar system. The position of the catheter was adjusted slightly until a sharp biphasic deflection appeared between the P wave and the QRS complex. Simultaneous records were made of the intracardiac electrogram and standard lead II of the electrocardiogram on a Sanborn Direct Writer recorder at a paper speed of 100 mm/sec. A Zucker bipolar electrode catheter was introduced through an arm vein, advanced to the junction of the right atrium and superior vena cava, and used to pace the right atrium with an external battery powered pacemaker. A diagrammatic representation of the

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TABLE I *Clinical data in 10 patients with ischaemic heart disease*

Case No.	Age and sex		Medications	Propranolol	Practolol	Dextro-propranolol
1	48	M	NTG	*		
2	50	M	None	*		
3	51	M	NTG	*		
4	59	F	Cyclopenthiazine			*
			Clofibrate			
			Cyclopenthiazine			
5	42	F	NTG			*
6	48	M	NTG			*
7	49	M	NTG		*	
8	50	M	NTG and diazepam		*	
9	46	M	Cyclopenthiazine		*	
			Clofibrate			
10	41	M	Phenindione		*	
Total				3	4	3

NTG = Nitroglycerin.

FIG. 1 *x-ray showing position of catheter for recording His bundle potentials. The catheter is in the middle of the tricuspid valve area at the base of the atrial septum. The other catheter is situated at the junction of the superior vena cava and right atrium and is used for atrial pacing.*

FIG. 2 *Diagrammatic representation of measurements made and their relation to the conducting system.*

measurements made and their relation to the conducting system is shown in Fig. 2. The P-His interval represents conduction through the atrium and atrioventricular node and the His-S interval represents total intraventricular conduction. In this way it was possible to separate effects on the atrioventricular node from the remainder of the conduction system.

Fig. 3 shows an actual recording. The pacing stimulus is followed by the P wave, the bundle of His potential, and finally the QRS complex. The P-His interval was measured from the beginning of the pacing stimulus to the beginning of the His potential. The His-S interval was measured from the beginning of the His potential on the intracardiac electrogram to the end of the QRS complex in lead II. The His-Q interval was measured from the beginning of the His potential on the intracardiac electrogram to the beginning of the QRS in lead II. The mean values from 5 complexes were calculated. In this record the P-His interval was 105 msec and the His-S interval was 140 msec.

Control measurements were made at pacing rates of 90, 100, 110, and 120 beats/min. After 10 minutes the drug was administered into the right atrium at doses within the known therapeutic range and measurements repeated at the same pacing rates after a further 5 minutes. Propranolol was given to 3 patients in doses of 0.02 and 0.05 mg/kg, dextro-propranolol to 3 patients in doses of 0.02, 0.05, and 0.20 mg/kg, and practolol to 4 patients in doses of 0.02, 0.05, and 0.20 mg/kg.

Comparisons of the variables were then made before and after the drugs at the same heart rates. Statistical analysis was made by Student's paired 't' test.

Results

The results of all measurements made are shown in Table 2.

Fig. 4 shows the effect of the atrial pacing procedure alone on atrioventricular conduction in the 10 patients. In the left hand panel the P-His interval is plotted against the pacing rate. There was a progressive and significant increase with each pacing increment, the mean P-His interval being 153 msec at 90 beats/min, 166 msec at 100 beats/min, 180 msec at 110 beats/min, and 198 msec at 120 beats/min. In the right-hand panel the His-S interval was plotted similarly. As the pacing rate was increased there was no significant change in the His-S interval.

The effect of propranolol on atrioventricular conduction is shown in Fig. 5. The data shown are the mean values for the 3 patients given the drug. In all cases the P-His interval was prolonged progressively with increasing dosage at each heart rate. This increase in the P-His interval was significant at the 0.1 per cent level for the 0.02 mg/kg dose and at

FIG. 3 Actual recording of His potential in a patient. Paper speed 100 mm/sec.

FIG. 4 Effect of atrial pacing on atrioventricular conduction.

TABLE 2 *Measurements of atrioventricular conduction in 10 patients before and after drug administration*

Case No.		P-His interval (msec)				His-Q interval (msec)				His-S interval (msec)				QRS interval (msec)			
		90	100	110	120	90	100	110	120	90	100	110	120	90	100	110	120
1	Heart rate																
		90	100	110	120	90	100	110	120	90	100	110	120	90	100	110	120
1	Control	118	128	131	144	51	50	50	51	120	120	122	121	69	70	72	70
	Propranolol (0.02 mg/kg)	133	148	162	165	—	—	—	—	—	—	—	—	—	—	—	—
2	Control	116	115	129	134	46	45	47	42	104	105	105	102	58	60	58	60
	Propranolol {	126	137	137	146	46	45	48	48	101	100	100	100	55	55	52	52
		118	131	140	140	47	48	47	50	102	99	100	98	55	51	53	48
3	Control	202	208	213	223	29	30	29	30	121	120	121	118	92	90	92	88
	Propranolol {	210	215	235	240	30	31	30	30	126	123	123	125	96	92	93	95
		215	225	237	247	30	30	30	30	125	123	121	122	95	93	91	92
4	Control	186	202	212	216	32	35	30	33	83	84	79	81	51	49	49	48
	Dextro-propranolol {	186	201	211	220	34	35	35	33	82	82	85	83	49	47	50	50
		183	204	214	223	33	32	32	35	83	82	80	83	50	50	48	48
		192	204	218	226	35	35	35	34	84	85	80	82	49	50	46	48
5	Control	101	110	123	140	40	40	42	40	81	80	82	83	41	40	38	43
	Dextro-propranolol {	112	124	145	—	38	38	38	—	80	75	75	—	41	38	38	—
		109	125	145	—	38	38	35	—	79	80	78	—	41	42	43	—
		123	132	148	175	42	—	40	35	81	80	83	78	39	—	43	43
6	Control	158	183	214	262	38	33	35	—	125	128	120	125	90	95	85	—
	Dextro-propranolol {	152	170	234	264	40	38	38	39	128	130	128	133	88	92	90	94
		153	174	233	260	40	40	35	40	135	130	135	130	95	90	100	90
		150	175	238	—	35	35	40	—	130	130	130	—	95	95	90	—
7	Control	190	194	200	215	65	64	63	65	133	129	128	120	68	64	65	55
	Practolol {	190	198	209	218	61	60	64	62	126	125	125	130	65	65	60	68
		190	199	205	208	55	61	67	60	115	120	120	125	60	58	53	65
8	Control	137	159	180	186	43	44	43	45	90	94	95	91	47	50	52	50
	Practolol {	127	136	182	181	—	—	—	—	—	—	—	—	—	—	—	—
		121	152	166	175	44	47	46	43	94	95	95	93	50	48	49	50
		118	151	170	173	42	44	46	43	92	92	91	90	50	48	45	48
9	Control	143	163	188	223	62	60	65	65	107	102	105	105	45	42	40	40
	Practolol {	176	190	201	210	60	61	64	58	106	106	106	101	46	45	43	43
		170	177	207	216	59	55	58	61	102	103	102	108	42	48	43	46
		190	202	213	225	63	65	63	53	103	117	107	100	40	52	43	48
10	Control	132	146	158	173	35	38	42	38	122	122	123	123	87	84	83	83
	Practolol {	136	151	160	178	36	38	36	35	127	125	124	120	90	87	88	85
		142	151	165	178	38	36	35	34	126	121	125	120	88	85	90	85

the 1 per cent level for the higher dose when the data at the four heart rates were pooled. The difference between the two doses was also significant at the 1 per cent level. No significant change in the His-S interval was shown after propranolol.

The dextroisomer of propranolol had no significant effect on atrioventricular conduction at the same dosage levels as propranolol (Fig. 6). However, in the larger dose of 0.02 mg/kg the P-His interval was significantly prolonged when compared to the control values ($P < 0.01$). As with propranolol, the dextroisomer had no effect on the His-S interval.

The results with practolol on atrioventricu-

lar conduction are shown in Fig. 7. No significant effect could be shown on either the P-His or the His-S intervals at the doses used.

The observed changes were therefore only on the P-His interval representing atrial and atrioventricular nodal conduction. The histogram in Fig. 8 compares the effects of the 3 drugs on this interval. Propranolol significantly increased the P-His interval by approximately 10 per cent with a dose of 0.02 mg/kg and by 17 per cent with a dose of 0.05 mg/kg. This drug was not given in the higher dose because of possible side effects. Dextro-propranolol increased conduction only slightly in the lower doses but with a dose of

EFFECT of PROPRANOLOL on ATRIO-VENTRICULAR CONDUCTION

(3 patients)

FIG. 5 Effect of propranolol on atrioventricular conduction.

0.02 mg/kg there was a significant prolongation of the P-His interval by 6 per cent. Propranolol produced no significant prolongation in any of the doses given.

Discussion

The value of His bundle recordings in man has recently been shown by a number of investigators (Damato and Lau, 1970; Narula *et al.*, 1970b). The position of the monitoring electrode should be stable at the base of the atrial septum in the middle of the tricuspid valve area, and the His potential appears as a rapid biphasic or triphasic deflection between the P wave and the QRS complex; it should not vary significantly either in configuration or distance from the P wave in several successive cardiac cycles. The configuration and relations of the bundle of His deflection have been validated by direct placement of the electrode on the His bundle during cardiectomy under experimental conditions (Alanís, González, and López, 1958; Hoffman *et al.*, 1960). We have found the recording of the His potential to be a simple and safe procedure, and were able to record it quickly in all 10 patients studied.

It has been previously shown that increasing the heart rate by atrial pacing results in a

FIG. 6 Effect of dextro-propranolol on atrioventricular conduction.

EFFECT of DEXTRO-PROPRANOLOL on ATRIO-VENTRICULAR CONDUCTION (3 Patients)

progressive prolongation of the PR interval (Balcon and Sowton, 1970). In this study we have shown that this prolongation is due entirely to an increase of the P-His interval, the His-S interval remaining constant. Scherlag *et al.* (1969) and Narula *et al.* (1970a) reported similar findings.

Racemic propranolol is known to affect the rate of rise of the action-potential, (a 'membrane effect') in addition to blocking the beta-adrenergic effects of adrenaline. While the dextroisomer possesses only the membrane effect in normal clinical doses (Barrett, 1969). In doses within the known therapeutic range the racemic drug produced a significant increase in atrioventricular conduction of up to 17 per cent without affecting intraventricular conduction. This effect was anticipated since it has previously been shown that beta-adrenergic stimulation with isoprenaline conspicuously shortened the P-His interval without changing the His-S interval (Damato *et al.*, 1969). Since dextro-propranolol produced a much smaller but still statistically significant change in P-His interval, the racemic mixture appears to act by both beta blockade and by membrane action.

Assuming a similar level of sympathomimetic activity in all patients, practolol, a beta-blocker without significant membrane action in these doses, would be expected to have an effect somewhere between the other two in comparable doses, since the molecular weight of the three drugs is similar. However, its observed effect was negligible. Part of this discrepancy might be explained by the intrinsic sympathomimetic action of practolol which tends to counteract the slowing of conduction. Another possibility is that the dose of practolol used was not sufficient to produce any effect on atrioventricular conduction, and that a higher dose would have resulted in prolongation of the P-His interval. Finally, this difference may have been due to varying rates of diffusion of the drugs to the effector site in the atrioventricular node. This finding emphasizes the danger of assuming uniformity of action in intact man of different beta-adrenergic blocking agents. The effect on one variable such as conduction through the atrioventricular node cannot necessarily be predicted by knowledge of the action on any other variable that forms part of the beta-adrenergic system. Gibson, Hoy, and Sowton

FIG. 8 Effect of propranolol, dextro-propranolol, and practolol on the P-His interval.

EFFECT of PRACTOLOL on ATRIO-VENTRICULAR CONDUCTION

(4 patients)

FIG. 7 Effect of practolol on atrioventricular conduction.

Effect of Drugs on P-His Interval

(1970) have already shown with various drugs that they have quantitatively different actions with respect to their chronotropic effect compared with their action on ventricular function.

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