Effect of intravenous propranolol on QT interval

A new method of assessment

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SUMMARY Changes in the QT and QTc intervals were studied in 16 patients by atrial pacing at rates of 100, 130, and 150 beats/minute. In all patients the measured QT shortened when the atrial paced rate was increased, but when corrected for heart rate the QTc lengthened. Intravenously administered propranolol produced a bradycardia and a lengthening of the QT interval in 15 of the 16 patients studied. When the QT interval was corrected for heart rate using Bazett's formula the QTc was shortened in 13 patients, unchanged in one, and lengthened in two. However, when the QT interval was measured at identical atrial paced rates the QT of the 15 patients studied was lengthened in 10 and unchanged in five. In none was the QT interval shortened. These results show firstly that Bazett's formula is unsuitable for correction of QT interval changes induced by atrial pacing, and secondly that, though intravenously administered propranolol usually produces a shortening of the QTc, when its effect is assessed directly by using an identical atrial paced rate the QT interval usually lengthens, or may remain unchanged, but never shortens. It is suggested that the formal assessment of drug induced QT interval changes should be made at identical atrial paced rates.

Prolongation of the QT interval may occur after the administration of drugs such as quinidine,¹ amiodarone,² disopyramide,³ the tricyclics,⁴ and the phenothiazines.⁵ The effect of propranolol on the QT interval remains controversial. Previous studies suggest that though it lengthens the measured QT, correction for heart rate by Bazett's hyperbolic correction factor⁶ shows that the QTc is usually shortened.^{7,8}

As such drugs may also cause changes in the heart rate, when assessing their effect on the QT interval the use of a correction factor for heart rate becomes necessary. Of the many formulae available Bazett's hyperbolic correction factor which corrects to a rate of 60 beats/min has been most readily accepted for use because it is simple to apply. In order to overcome the necessity for rate correction a new method has been devised for the assessment of drug induced QT changes using atrial pacing at identical rates before and after the administration of propranolol. This allows a direct comparison of these changes to be made and precludes the need for a correction factor. The purpose of this study was twofold. Firstly, to test the validity of Bazett's hyperbolic correction factor for QT changes induced by atrial pacing, and, secondly, to assess the

effect of intravenously administered propranolol on the QT interval both during sinus rhythm and at identical atrial paced rates.

Patients and methods

Sixteen patients were studied, all of whom were undergoing routine catheterisation. The age, sex, diagnosis, electrocardiogram, and chest x-ray findings are recorded in Table 1. They were volunteers who had been informed that this study was not a necessary part of their investigations. All the patients had a normal QT interval, were in sinus rhythm at the time of the study, and had been so for at least 24 hours before the study was undertaken. Each was capable of 1:1 atrioventricular conduction at a rate of 150 beats/min. The QRS complexes were normal and in no instance was there evidence of either a partial or complete bundle-branch block pattern. Patients with prominent U waves were excluded.

The patients had undergone cardiac catheterisation at least 24 hours before this investigation and at the time of catheterisation a bipolar pacing electrode was left high in the right atrium. All cardio-active drugs were stopped at least 24 hours before the study was performed. The investigation was

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Table 1 *Clinical data*

Case no.	Age (y)	Sex	Diagnosis	Electrocardiogram	Chest x-ray
1	37	M	Coronary artery disease	Non-specific T wave changes	Normal
2	39	M	Angina, normal coronary arteries	Non-specific T wave changes	Normal
1	37	M	Coronary artery disease	Non-specific T wave changes	Normal
3	57	M	Coronary artery disease	Normal	Normal
4	58	M	Coronary artery disease	Normal	Normal
5	45	M	Coronary artery disease	Old inferior infarct	Normal
6	15	F	Re-entry nodal tachycardia	Normal	Normal
7	39	M	Re-entry nodal tachycardia	Normal	Normal
8	39	M	Lown-Ganong-Levine syndrome	Short PR interval	Normal
9	47	M	Lown-Ganong-Levine syndrome	Short PR interval	Normal
10	50	M	Asystolic episodes, uncertain aetiology	Normal	Normal
11	65	M	Mitral regurgitation, coronary artery disease	Normal	Cardiomegaly
12	41	M	Concealed VA tract, ventricular tachyarrhythmias	Short PR interval	Normal
13	31	M	Spontaneous ventricular fibrillation	Normal	Normal
14	44	M	Sinuatrial disease	Normal	Normal
15	17	M	Hyperkinetic heart syndrome	Normal	Normal
16	31	F	Hyperadrenergic syndrome	Sinus tachycardia	Normal

undertaken on the open ward, with the patient in a semi-recumbent position lying at approximately 30° to the horizontal. A butterfly needle was inserted into an arm vein several minutes before the recordings were made. The electrocardiographic recordings were taken on a four-channel Elema mingograf with time markings at one second intervals, at a paper speed of 100 mm/s. As changes in the T wave vector may masquerade as changes in the QT interval three more-or-less orthogonal leads were recorded, as suggested by Pipberger and Tanenbaum.⁹ The QT interval was measured from the earliest QRS deflection to the terminal T wave deflection on any lead, and the cycle length was taken as the interval between the peaks of the two preceding R waves. When the end of the T wave was indistinct either because of a poor baseline, or other artefact, the trace was discarded. At high atrial paced rates the pacing stimulus artefact or the P wave fused with the preceding T wave rendering the measurement of the QT interval impossible. This was overcome by switching off the pacemaker and measuring the QT interval of the last of a sequence of atrial paced beats. Atrial pacing was undertaken for approximately 20 seconds before the pacemaker was switched off. The QT interval was measured during sinus rhythm and, when possible, at atrial paced rates of 100, 130, and 150 beats/min. An intravenous injection of propranolol 0.1 mg/kg body weight was given over three minutes and the QT interval was again measured during sinus rhythm and at the same atrial paced rates between five and 10 minutes later. The measured QT interval was then corrected to a heart rate of 60 beats/min using Bazett's formula, with which the corrected QTc is derived by

dividing the measured QT by the square root of the RR interval in seconds, that is

$$QTc = \frac{\text{measured QT}}{\sqrt{\text{RR interval (s)}}}$$

Results

Atrial pacing at higher rates shortened the measured QT and lengthened the rate corrected QT. The results are displayed graphically in Fig. 1. Five of the 16 patients studied were not included as two

Fig. 1 Mean measured QT and rate corrected QT intervals for atrial paced rates of 100, 130, and 150 beats/minute.

Propranolol and QT interval

had a sinus rate of greater than 100 beats/min, and in three the end of the T wave was not clearly delineated. Intravenous propranolol produced a relative bradycardia and a lengthening of the measured QT in 15 patients. One patient had a relative tachycardia and a shortening of the measured QT (Fig. 2). When the measured QT was corrected for heart rate intravenous propranolol produced a shortening of the QTc in 13 patients, no change in one, and a slight lengthening in two. Fig. 3 shows the effect of intravenous propranolol

Fig. 2 Effect of intravenous propranolol on sinus cycle length and measured QT interval.

Fig 3 Superimposed pre- and postpropranolol electrocardiograms for three approximately orthogonal leads recorded during sinus rhythm. The upper trace of each pair was recorded before propranolol and the lower after. The tracings are aligned at the onset of second QRS deflection. The end of the T waves in the control state and postpropranolol state are represented by the vertical interrupted line and the thin vertical continuous line, respectively. Propranolol has produced a relative bradycardia and increased the measured QT, though the QTc is shortened.

on the sinus rate and measured QT of an individual patient. The sinus cycle length increased from 545 to 645 ms, and the measured QT from 320 to 345 ms. However, the QTc using Bazett's formula shortened from 433 to 429 ms. When fixed atrial pacing with a cycle length of 375 ms was used (Fig. 4) intravenous propranolol lengthened the measured QT from 300 to 325 ms. The effect of intravenous propranolol on the measured QT and rate corrected QT during sinus rhythm and at various atrial paced rates for the same patient are shown in Fig. 5.

Fig. 4 Format of this illustration is similar to Fig. 3. However, atrial pacing with a cycle length of 375 ms has been employed. Propranolol has increased the QT interval from 300 to 325 ms.

Fig. 5 Measured QT and QTc of an individual patient are shown against the cycle length both during sinus rhythm and at atrially paced rates before and after the administration of propranolol. During sinus rhythm and at each atrially paced rate the QT interval has been lengthened by intravenous propranolol.

With atrial pacing the measured QT shortened linearly as the rate increased but when corrected for rate the QT lengthened both before and after the administration of propranolol. However, at each identical atrial paced rate both the measured QT and rate corrected QT were similarly lengthened by the administration of propranolol.

At identical atrial paced rates 10 patients showed a prolongation of the QT and five showed no change after the administration of propranolol. In no instance was the QT shortened by propranolol (Fig. 6). These results include 13 patients who were paced at 100 beats/minute, and one each at 120 and 130 beats/minute because their resting sinus rates were greater than 100 beats/minute. The results discussed above are set out in Table 2.

Discussion

The QT interval of the standard electrocardiogram is a clinical measurement of ventricular depolarisation and repolarisation. As the acute administration of intravenous propranolol has no effect on the QRS complex width,⁸ any change of this variable reflects a change in the duration of ventricular repolarisation. Many conditions in which a long QT interval occur are associated with syncope and sudden death.¹⁰⁻¹² Lengthening of the QT interval may increase the vulnerable period of the ventricular myocardium, during which ventricular arrhythmias may be precipitated by a ventricular premature beat.^{13 14} Therefore, drugs which shorten the QT interval may, theoretically, have therapeutic advantages in these conditions. Propranolol is one such

drug which shortens the QTc though this effect is variable. Stern and Eisenberg⁷ found that though the measured QT increased in 11 patients, decreased

Fig. 6 Effect of intravenous propranolol on the measured QT at identical paced rates. Thirteen patients were paced at 100 beats/minute and one each at 120 and 130 beats/minute as their sinus rates were greater than 100 beats/minute.

Table 2 Cycle length, measured QT, QTc in sinus rhythm, and atrially paced QT before and after propranolol

Case no.	Cycle length (ms)		Measured QT		QTc (sinus rhythm)		Atrially paced QT	
	Before	After	Before	After	Before	After	Before	After
1	490	605	275	300	393	385	275	275
2	1060	980	400	360	388	364	340	340
3	720	880	360	370	424	405	350	350
4	710	900	370	380	439	400	360	375
5	750	900	340	360	393	379	330	340
6	545	645	320	345	433	429	315	335
7	965	1170	435	460	443	434	395	395
8	740	960	350	360	407	367	330	340
9	710	940	370	390	421	402	355	360
10	1030	1080	400	410	396	392	380	400
11	760	820	380	400	436	442	360	380
12	720	800	360	380	425	425	360	360
13	640	800	320	360	400	403	320	340
14	620	775	325	340	413	386	320	330
15	610	775	320	350	410	398	Unable to measure	
16	885	1075	405	420	430	405	355	365

in four, and did not change in six after acutely administered propranolol, when corrected for rate the QT shortened in 20 and was unchanged in one. Seides *et al.*⁸ found that the QTc shortened in nine of 16 patients and was unchanged in seven. In this study the QTc was similarly shortened in 13 of 16 patients. In the light of the effect on the QTc interval propranolol has been recommended as treatment for the long QT syndrome, with some success,¹⁵⁻¹⁷ but its efficacy is by no means universal.¹⁸

Though it is important to assess accurately the effect of drugs on the QT interval, all previous comparisons have been made by applying a rate correction factor.

Many correction factors have been suggested.^{6,19-23} Of these Bazett's formula⁶ has been most widely used. In Bazett's formula the relation of the measured QT to cycle length is curvilinear rather than linear and though this is marginally less accurate for resting physiological heart rates it is more accurate at higher heart rates where a curvilinear relation applies.²³ Thus, Bazett's formula may appear to be relevant to our study where high rates of atrial pacing have been used. But our results show that at atrial paced rates Bazett's hyperbolic correction factor overcorrects for QT changes resulting in a spuriously long rate corrected QT interval. In defence of Bazett's formula, his conclusions were drawn from data taken from patients studied under physiological conditions at rest and after exercise unlike our patients who were atrially paced, which may not reflect the same haemodynamic and physiological state. It has been shown for instance that during exercise and the infusion of intravenous isoprenaline the PR interval shortens as the heart rate increases²⁴⁻²⁶ whereas when the heart rate is artificially increased by atrial pacing the PR interval lengthens.²⁷ It is possible that atrial pacing may have a similar unphysiological effect on the QT interval and that Bazett's formula, though applicable to physiological changes in heart rate, is unsuitable for correcting the measured QT for changes in heart rate induced by atrial pacing.

This study was designed to circumvent the use of a correction factor by directly comparing the measured QT before and after the administration of propranolol at identical atrial paced rates. The change in the measured QT interval induced by atrial pacing is not necessarily equivalent to the change seen after spontaneous or drug-induced rate changes. After the administration of a drug which produces sinus bradycardia it is necessary to overpace the atria by a proportionately greater increment in order to achieve the same paced rate for comparison. This may itself introduce artefac-

tual error which cannot be avoided by this new method.

Our results show that when propranolol produced a bradycardia the measured QT interval lengthened. One patient had a relative tachycardia after intravenous propranolol. Reflex sympathetic activity has been described after acutely administered beta-adrenergic blocking drugs and exercise,²⁸ and it is possible that this was the overriding effect in this patient. In the 15 patients who had bradycardia, though the QTc tended to shorten, the QT interval measured at identical atrial paced rates usually lengthened or remained unchanged but in no instance was it shortened. When comparing drug induced changes on cardiac conduction intervals it has become customary to make comparison between measurements made at identical paced rates in order to exclude changes resulting from alterations in heart rate after drug administration. This principle has been applied in this study to QT changes and has produced results consistent with those reported by Raine²⁹ on the QT changes secondary to long-term beta-blockade with propranolol. Comparable results have also been found by Bertil Olsson (1978, personal communication) using similar methods and acutely administered metoprolol.

These results suggest that it may not be the effect of propranolol on the QT interval, which it usually prolongs, that makes this drug a useful therapeutic agent in the long QT syndromes: direct anti-sympathetic activity, and its ability to increase the threshold for ventricular fibrillation,³⁰ may be more important. Using our technique, the effect of intravenously administered propranolol on the QT interval, in patients with the long QT syndrome, is not yet known; findings under such circumstances may be different from those in our study.

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