Effects of tocainide on left ventricular performance at rest and during acute alterations in heart rate and systemic arterial pressure

An echocardiographic study¹

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SUMMARY To determine if the new antiarrhythmic agent tocainide depresses left ventricular function we performed a double-blind cross-over trial of tocainide and placebo in 10 patients with valvular heart disease and recorded echocardiograms (a) in the basal state, (b) during atropine-induced increases in heart rate, and (c) during acute pressure loading with phenylephrine. The drug doses were 400 mg every 8 hours for 3 days, and the mean tocainide plasma concentration in the tocainide group was $5.3 \mu\text{g/ml}$.

Except after atropine when there was a slightly higher mean systolic blood pressure in the tocainide group than in the placebo group (mean blood pressure difference 7 mmHg, $P < 0.02$) heart rates and systolic blood pressures for both groups were closely matched during these pharmacological interventions. For the placebo and tocainide groups mean heart rates increased after atropine by 27 and 26 beats/minute, respectively, and during infusion of phenylephrine (when no significant heart rate slowing occurred) mean blood pressures rose by 51 mmHg in the placebo group (to 175 ± 6 mmHg) and by 45 mmHg in the tocainide group (to 176 ± 6 mmHg). During tocainide administration mean velocity of circumferential fibre shortening (mean VCF) in the basal state averaged 1.29 ± 0.06 diam/s. This increased to 1.39 ± 0.08 diam/s with atropine (NS) and then declined to 1.17 ± 0.09 diam/s during infusion of phenylephrine ($P < 0.01$ vs atropine). No significant differences were found when the corresponding values during placebo were compared with these values. Similar directional changes occurred in the average mean posterior wall velocity (mean VPW) during tocainide administration when the corresponding values were 0.75 ± 0.05 , 0.87 ± 0.07 ($P < 0.05$), and 0.71 ± 0.05 ($P < 0.01$ vs atropine) s^{-1} , respectively. Again placebo values did not differ significantly from tocainide values.

Thus, in patients with valvular heart disease tocainide in the dose employed has no significant depressant effect on left ventricular function either in the basal state or during acute alterations in heart rate or blood pressure. These data suggest that tocainide can be used safely for antiarrhythmic therapy in patients with mild to moderate left ventricular dysfunction.

Recent reports of animal (Duce *et al.*, 1973; Coltart *et al.*, 1974) and human studies (McDevitt *et al.*, 1976; Winkle *et al.*, 1976; Woosley *et al.*, 1977; Ryan *et al.*, 1978) indicate that an oral analogue of lignocaine, tocainide, is effective in suppressing ventricular arrhythmias and is a promising new antiarrhythmic agent. However, high doses of tocainide

in anaesthetised dogs have been shown to depress left ventricular function (Coltart *et al.*, 1974). To determine whether tocainide similarly depresses myocardial function in man we administered typical therapeutic doses of the drug to patients with organic heart disease, and using ultrasound assessed left ventricular function at rest and during acute alterations in heart rate and systemic arterial pressure.

Patients and methods

Ten patients without clinical evidence of coronary artery disease but with known heart disease formed

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Table 1 Clinical data

Case no.	Age (y) and sex	Diagnosis	Functional class (NYHA classification)	Treatment
1	52F	MR	II	Digoxin
2	40M	Prolapsing mitral leaflet	I	—
3	32F	Prosthetic aortic valve	II	Warfarin, oral contraceptives
4	62M	AR, mild MR	II	Digoxin
5	43F	MR, MS	II	Digoxin, propranolol
6	32F	AS, AR	I	—
7	54F	MR	I	—
8	68M	AR	II	Triamterene, hydrochlorothiazide, glyceryl trinitrate
9	24M	PS	I	—
10	23M	AR	I	—

MS, mitral stenosis; MR, mitral regurgitation; AS, aortic stenosis; AR, aortic regurgitation; PS, pulmonary stenosis.

the study group (Table 1). Their ages ranged from 23 to 68 years, with a mean of 43 years. All were in sinus rhythm. Control echocardiograms were first performed to familiarise the patients with the procedure, the personnel, and the surroundings. Each patient then underwent two echocardiographic studies one week apart. One study followed treatment with tocainide, the other treatment with placebo, and the order was double-blind. The drugs were administered in a dose of 400 mg every 8 hours for the 3 days before each study and all routine medications were continued. The code was not broken until the study was completed and the echocardiograms had been analysed.

An identical procedure was followed during both studies. Initial inquiry was made regarding possible drug-related sensitivity, a 12-lead electrocardiogram was recorded, urine was collected for analysis, an intravenous infusion of 5 per cent dextrose and water was begun, and a blood sample was obtained to evaluate haematological, hepatic, and renal function as well as plasma tocainide concentration and, thus, patient compliance. When the pulse rate and blood pressure (cuff sphygmomanometer) were stable for at least 30 minutes an echocardiogram was recorded. Subsequently atropine was administered intravenously in a quantity sufficient to raise the heart rate approximately 30 beats/minute or until 1.5 mg had been given. When the heart rate and systemic arterial pressure were stable for at least 5 minutes another echocardiogram was obtained. As previously described (Hirshleifer *et al.*, 1975; Crawford *et al.*, 1976), a solution of phenylephrine (40 mg/l) was then infused over 5 to 10 minutes in a quantity sufficient to raise the systolic arterial pressure approximately 40 to 50 mmHg.

With the heart rate response to increased arterial pressure blocked by atropine a final echocardiogram was obtained. The infusion was then terminated. The total volume of fluid used in a study was never more than 70 ml. During the second study a deliberate attempt was made to match the heart rate and blood pressure responses with those of the first study.

All patients gave informed written consent to the study procedure which was approved by the Committee on Investigations/Activities Involving Human Subjects, University of California, San Diego. Three of the 10 patients experienced mild adverse reactions while taking tocainide. These symptoms consisted of nausea in one, dizziness in one, and a brief cold sweating episode in one. Two additional patients with withdrawn from the study because of more severe side effects caused by tocainide. One experienced severe nausea and vomiting, and the other rigors. No patient had side effects while taking placebo.

Patients with coronary artery disease or congestive cardiomyopathy were not included in the study because of the concern that raising their heart rates and systemic arterial pressures might be deleterious. We recognise that the choice of patients with valvular heart disease, especially those with mitral and aortic regurgitation, could have affected our results, especially since increases in heart rate and blood pressure may have opposing effects on the beat-to-beat magnitude of regurgitation. Nevertheless, the statistical method we employed, that is, using each patient as his or her own control during the repetition of an identical procedure, should exclude any bias in the results due solely to changes in haemodynamics.

Echocardiograms were recorded with a Picker ultrasonoscope using a 2.5 MHz transducer focused at 7.5 cm. Recordings were made on a Honeywell Visicorder, model 1856, at a paper speed of 100 mm/s. An electrocardiogram and an indirect carotid arterial pulse tracing were recorded simultaneously with the echocardiogram. The patients were studied in the partial left lateral decubitus position. The 'standard intercostal space' technique was employed to obtain reproducible echocardiograms of the endocardial surface of the left ventricle at the level of the chordae tendineae (Popp *et al.*, 1975). Left ventricular dimensions were measured between the endocardial surfaces of the posterior wall and the left side of the septum (Fig. A). The end-diastolic dimension (EDD) was measured at the peak of the R wave of the electrocardiogram. The end-systolic dimension (ESD) was measured before the dicrotic notch on the carotid arterial pulse tracing at the point on the echocardiogram where

Fig. Echocardiographic recordings during tocainide therapy. (A) Basal state echocardiogram. For the beat illustrated values were: mean VCF, 1.20 diam/s; mean VPW, 0.75 s⁻¹; left ventricular ejection time 321 ms. The heart rate was 65 beats/min. EDD, end-diastolic dimension; ESD, end-systolic dimension; CH, chordae tendineae; CPT, carotid arterial pulse tracing; ECG, electrocardiogram. (B) After administration of atropine the heart rate increased to 95 beats/min, mean VCF increased to 1.31 diam/s, and mean VPW increased to 0.88 s⁻¹. Left ventricular ejection time (LVET) decreased to 261 ms. (C) During phenylephrine administration the systolic arterial pressure increased by 60 mmHg, and the heart rate fell to 85 beats/min. Mean VCF decreased to 0.95 diam/s, mean VPW decreased to 0.49 s⁻¹, and LVET increased to 340 ms. PWE, posterior wall excursion during systole.

the perpendicular distance between the endocardial surfaces was smallest. The left ventricular ejection time (LVET) was measured from the indirect carotid arterial pulse tracing (Fig. B).

The mean normalised velocity of circumferential fibre shortening (mean VCF [diam/s]) was calculated as:

$$\frac{EDD - ESD}{EDD \times LVET} \quad [1]$$

The mean normalised posterior wall velocity (mean VPW [s⁻¹]) was calculated as:

$$\frac{PWE}{EDD \times LVET} \quad [2]$$

where PWE = total excursion of the posterior wall endocardium during systole (Fig. C). All calculations were made using the average of at least 3 cardiac cycles. For data reduction a repeated measures analysis of variance was used (Winer, 1971).

Results

Individual patient data are detailed in Tables 2-4. During tocainide the mean heart rate in the basal state was 61 ± 2 (SE) beats/min. This increased to 87 ± 6 beats/min after atropine (P < 0.01). During phenylephrine infusion the mean heart rate fell slightly to 81 ± 5 beats/min (NS vs atropine). Mean heart rates during placebo administration were not significantly different from these values.

The mean systolic arterial pressure in the basal state was 123 ± 6 mmHg during placebo and 131 ± 5 mmHg during tocainide (P < 0.01). After atropine these values were 124 ± 6 mmHg (placebo) and 131 ± 5 mmHg (tocainide) (P < 0.02). These values were not significantly different from the respective values in the basal state. During infusion of phenylephrine the mean systolic blood pressures for the placebo and tocainide groups were 175 ± 6 mmHg and 176 ± 6 mmHg, respectively (NS). The phenylephrine-induced increases in systolic

blood pressure, which averaged 51 mmHg (range 28 to 88 mmHg) during placebo and 45 mmHg (range 32 to 79 mmHg) during tocinide, differed significantly from values after atropine ($P < 0.01$).

The average mean VCF in the basal state after tocinide was 1.29 ± 0.06 diam/s. Though this

increased to 1.39 ± 0.08 diam/s after atropine, the results did not reach statistical significance. During the phenylephrine infusion the average mean VCF decreased to 1.17 diam/s ($P < 0.01$ vs atropine, NS vs basal state). Placebo values were not significantly different from these.

Table 2 *Effects of oral tocinide on blood pressure and heart rate in basal state and after atropine and phenylephrine*

Case no.	State	Systemic systolic blood pressure (mmHg)		Heart rate (beats/min)	
		Placebo	Tocainide	Placebo	Tocainide
1	Basal	158	156	58	62
	At	160	158	78	78
	Ph	194	195	79	68
2	Basal	106	110	55	60
	At	114	112	95	90
	Ph	142	144	94	90
3	Basal	112	128	62	63
	At	125	125	99	95
	Ph	165	165	95	82
4	Basal	150	150	71	70
	At	145	150	87	84
	Ph	194	194	83	82
5	Basal	108	134	59	61
	At	98	133	66	69
	Ph	186	182	63	63
6	Basal	119	122	49	47
	At	110	122	102	102
	Ph	160	161	128	112
7	Basal	118	127	67	61
	At	118	122	71	71
	Ph	166	166	75	75
8	Basal	118	128	53	50
	At	123	127	77	68
	Ph	198	206	60	57
9	Basal	119	116	51	65
	At	119	118	82	85
	Ph	161	161	81	82
10	Basal	120	138	65	67
	At	124	142	98	125
	Ph	184	185	79	99
Mean basal		123	131	59	61
SEM		6	5	2	2
P		< 0.01		NS	
Mean At		124*	131*	86†	87‡
SEM		6	5	4	6
P		< 0.02		NS	
Mean Ph		175†§	176†§	83†‡	81†‡
SEM		6	6	6	5
P		NS		NS	

Basal, basal state; At, after atropine; Ph, during pressure loading with phenylephrine; SEM, standard error of the mean; P, significance level; vs, versus; NS, not significant; * not significant vs basal state; † not significant vs atropine; ‡ P < 0.01 vs basal state; § P < 0.01 vs atropine.

Table 3 *Effects of oral tocinide on left ventricular dimensions and ejection time during acute alterations in heart rate and blood pressure*

Case no.	State	EDD (cm)		ESD (cm)		LVET (ms)	
		Placebo	Tocainide	Placebo	Tocainide	Placebo	Tocainide
1	Basal	6.55	6.23	3.75	3.55	281	277
	At	6.39	6.21	3.70	3.44	249	259
	Ph	6.24	6.25	3.86	3.83	256	269
2	Basal	4.87	4.96	3.06	3.18	334	320
	At	4.94	5.05	3.47	3.49	261	267
	Ph	5.24	5.18	3.70	3.70	299	286
3	Basal	4.13	4.07	2.11	2.28	330	293
	At	3.92	3.76	2.01	2.13	247	242
	Ph	4.04	4.10	2.33	2.47	285	270
4	Basal	7.33	7.30	4.49	4.67	319	307
	At	7.15	7.27	4.37	4.80	297	288
	Ph	7.31	7.26	4.85	4.92	334	323
5	Basal	4.85	5.02	3.16	3.37	293	315
	At	4.65	4.88	2.97	3.21	276	294
	Ph	5.03	5.16	3.69	3.62	325	330
6	Basal	5.79	5.59	3.16	3.23	373	380
	At	4.88	4.70	2.81	2.85	267	273
	Ph	4.59	4.89	2.75	3.03	265	285
7	Basal	6.14	6.24	3.19	3.20	316	312
	At	6.10	5.97	3.37	3.48	308	308
	Ph	6.18	6.20	3.19	3.28	305	297
8	Basal	5.48	5.70	2.87	3.28	342	351
	At	4.63	4.89	2.82	2.99	273	305
	Ph	5.55	5.47	3.58	3.67	345	368
9	Basal	5.57	5.70	3.53	3.51	315	302
	At	5.11	5.66	3.33	3.58	281	278
	Ph	5.56	5.79	3.92	4.08	303	301
10	Basal	5.69	5.67	3.52	3.45	323	310
	At	4.70	4.71	3.05	2.99	264	219
	Ph	6.00	5.95	4.07	3.93	341	293
Mean basal		5.64	5.65	3.28	3.37	323	317
SEM		0.29	0.27	0.20	0.18	8	9
P		NS		NS		NS	
Mean At		5.24**	5.31**	3.19*	3.32*	272‡	273‡
SEM		0.31	0.31	0.20	0.21	6	9
P		NS		NS		NS	
Mean Ph		5.57*¶	5.63*¶	3.59**§	3.65**§	306*¶	302*¶
SEM		0.29	0.28	0.22	0.21	10	10
P		NS		NS		NS	

Basal, basal state; At, after atropine; Ph, during pressure loading with phenylephrine; SEM, standard error of the mean; P, significance level; vs, versus; NS, not significant; * not significant vs basal state; ** P < 0.05 vs basal state; ‡ P < 0.01 vs basal state; § P < 0.01 vs atropine; ¶ P < 0.05 vs atropine; EDD, end-diastolic dimension; ESD, end-systolic dimension; LVET, left ventricular ejection time.

Effects of tocainide on left ventricular performance

Table 4 Effects of oral tocainide on ultrasound measures of left ventricular performance in basal state and during acute alterations in heart rate and blood pressure

Case no.	State	Mean VCF (diam/s)		Mean VPW (s ⁻¹)	
		Placebo	Tocainide	Placebo	Tocainide
1	Basal	1.52	1.56	1.01	0.94
	At	1.69	1.72	1.11	1.12
	Ph	1.49	1.44	0.96	0.97
2	Basal	1.11	1.12	0.60	0.64
	At	1.14	1.16	0.66	0.59
	Ph	0.99	1.00	0.52	0.62
3	Basal	1.48	1.40	1.05	1.04
	At	1.97	1.79	1.37	1.22
	Ph	1.49	1.47	1.11	1.04
4	Basal	1.22	1.17	0.71	0.68
	At	1.31	1.18	0.76	0.71
	Ph	1.01	1.00	0.58	0.56
5	Basal	1.19	1.16	0.94	0.91
	At	1.31	1.16	0.99	0.96
	Ph	0.82	0.90	0.58	0.66
6	Basal	1.22	1.11	0.67	0.60
	At	1.59	1.44	0.78	0.62
	Ph	1.51	1.33	0.88	0.71
7	Basal	1.52	1.56	0.81	0.64
	At	1.45	1.35	0.77	0.88
	Ph	1.59	1.59	0.76	0.78
8	Basal	1.39	1.21	0.72	0.65
	At	1.43	1.27	0.88	0.88
	Ph	1.03	0.89	0.57	0.58
9	Basal	1.16	1.27	0.75	0.68
	At	1.24	1.32	0.88	0.76
	Ph	0.97	0.98	0.59	0.56
10	Basal	1.18	1.26	0.74	0.74
	At	1.33	1.67	0.91	1.10
	Ph	0.94	1.16	0.49	0.63
Mean basal		1.30	1.29	0.80	0.75
SEM		0.05	0.06	0.05	0.05
P			NS		NS
Mean At		1.44*	1.39*	0.91**	0.87**
SEM		0.08	0.08	0.07	0.07
P			NS		NS
Mean Ph		1.17*§	1.17*§	0.70*§	0.71*§
SEM		0.10	0.09	0.07	0.05
P			NS		NS

Basal, basal state; At, after atropine; Ph, during pressure loading with phenylephrine; SEM, standard error of the mean; P, significance level; vs, versus; NS, not significant; * not significant vs basal state; ** P < 0.05 vs basal state; § P < 0.01 vs atropine. Mean VCF, mean velocity of circumferential fibre shortening; mean VPW, mean normalised posterior wall velocity.

The average mean VPW during tocainide administration was $0.75 \pm 0.05 \text{ s}^{-1}$. This increased to $0.87 \pm 0.07 \text{ s}^{-1}$ after atropine ($P < 0.05$), and then decreased to $0.71 \pm 0.05 \text{ s}^{-1}$ ($P < 0.01$ vs atropine, NS vs basal state) during phenylephrine infusion. Placebo values did not differ significantly from these values.

During the increase in heart rate after atropine, the mean left ventricular end-diastolic dimension in the placebo and tocainide groups decreased (both $P < 0.05$ vs basal state), and returned to basal state levels during phenylephrine infusion. The mean left ventricular end-systolic dimension did not change significantly in either group after atropine, but increased in both groups during phenylephrine infusion ($P < 0.01$ vs atropine, $P < 0.05$ vs basal state). In both the placebo and tocainide groups the mean left ventricular ejection times shortened after atropine ($P < 0.01$ vs basal state), and then returned towards basal state values during phenylephrine infusion ($P < 0.05$ vs atropine, NS vs basal state). Thus, for the placebo and tocainide groups alike, the increases in mean VCF values after atropine were largely the result of reductions in the left ventricular ejection time, and the decreases in mean VCF values during phenylephrine infusion were largely the result of increases in end-systolic dimensions and a return towards basal levels of left ventricular ejection times.

A typical response to an acute increase in heart rate and systemic arterial pressure is shown in the echocardiograms in the Fig. Though these recordings were made during tocainide therapy the response was the same whether the patient was taking tocainide or placebo.

Discussion

Little information is available concerning the effects of tocainide on left ventricular function. Duce *et al.* (1973), in a study of 6 conscious dogs, reported that oral tocainide in a dose of 25–200 mg/kg every 1 to 4 hours produced no alterations in systemic arterial or central venous pressure. However, Coltart *et al.* (1974) found moderate depression of cardiac function in 4 anaesthetised dogs given single oral tocainide doses of 120 mg/kg. Significant increases in left ventricular end-diastolic pressure and significant decreases in heart rate and left ventricular dP/dt were observed; plasma tocainide concentrations in both studies ranged from 15 to 30 µg/ml.

There are 5 previous reports of preliminary data concerning the use of tocainide as an antiarrhythmic agent in humans and in no study was cardiac depression observed (McDevitt *et al.*, 1976; Winkle *et al.*, 1976; Woosley *et al.*, 1977; Ryan *et al.*, 1978; Winkle *et al.*, 1978). However, the doses of tocainide employed were, per kg body weight, less than one-tenth the dose used by Coltart *et al.* (1974) in their animal study. Further, in none of these studies was the response to any controlled stress, such as acute increases in systemic arterial pressure, evaluated. In the present study the mean plasma drug concentration in the tocainide group at the time of the echo-

cardiographic studies was 5.3 $\mu\text{g/ml}$, the range being from 2.0 to 7.3 $\mu\text{g/ml}$.

Nine of 10 patients had levels within the lower limits of the usual therapeutic range ($> 4 \mu\text{g/ml}$). These therapeutic levels were the result of choosing a dose of 400 mg of tocainide every 8 hours. This dose level was selected as a safety precaution because at the outset of the study the potential for myocardial depression of tocainide was unknown.

When mean VCF and mean VPW values are used to compare the inotropic status of the myocardium in an individual on different occasions as was done in this study it is important that heart rates and blood pressures are matched (Hirshleifer *et al.*, 1975). In the basal state the mean heart rates were similar in the tocainide and placebo groups but the mean systemic systolic blood pressures were slightly higher in the tocainide group. Experimental studies (Ross *et al.*, 1966; Mahler *et al.*, 1975) and studies in humans (Hirshleifer *et al.*, 1975; Quinones *et al.*, 1975) have documented a reduction in the extent and velocity of myocardial shortening as resistance to ejection is increased. However, despite the increase in mean basal state systolic blood pressure during tocainide, no significant reduction in mean VCF or mean VPW occurred. After atropine the mean heart rates for the placebo and tocainide groups did not differ significantly from each other. However, just as in the basal state, the mean systolic arterial pressure was higher in the tocainide group than in the placebo group. Again no significant differences were found between the mean VCF and mean VPW values in both groups.

The effects of acute alterations in systemic arterial pressure on isovolumic and ejection phase indices of left ventricular performance have previously been studied in our laboratory (Mahler *et al.*, 1975). This same technique has also been used to study the effects of drugs on left ventricular function (Mahler *et al.*, 1974; Crawford *et al.*, 1975; Gorwit *et al.*, 1975; Crawford *et al.*, 1976). In both normal conscious dogs (Mahler *et al.*, 1974) and normal human subjects (Crawford *et al.*, 1976) oral digoxin had a protective effect on left ventricular performance during acute pressure loading. In these studies the positive inotropic effect of digoxin was more apparent during than before acute pressure loading. By contrast, using similar techniques, we have been able to show that beta-adrenergic blockade exerts a modest but definite depressant effect on left ventricular function (LeWinter *et al.*, 1978). Further, another antiarrhythmic agent, quinidine gluconate, can be shown to be a myocardial depressant during acute afterloading when sympathetic tone is suppressed by beta-adrenergic blockade (Engler *et al.*, 1978). Therefore, we reasoned that if

tocainide is a myocardial depressant, a further reduction in left ventricular performance compared with placebo values should be demonstrable during acute pressure loading. However, no latent alteration in left ventricular performance due to tocainide was 'unmasked'—the average mean VCF and mean VPW values during phenylephrine infusion were similar whether the patients were receiving tocainide or placebo.

Thus, under the conditions of our study tocainide in a typical therapeutic dose of 400 mg each 8 hours had no myocardial depressant action. However, no patient had severely depressed left ventricular function in the basal state (partly because patients with coronary artery disease and congestive cardiomyopathy were specifically excluded). The effect of tocainide on ventricular function when severely depressed function is present at rest or when higher drug doses are used is, therefore, still unknown. Thus the effects of tocainide on cardiac performance resemble those of lignocaine, which in large doses in experimental animals produces myocardial depression (Austen and Moran, 1965; Nayler *et al.*, 1969; Asokan *et al.*, 1968) but in conventional doses in man is devoid of significant cardiovascular effects (Harrison *et al.*, 1963; Grossman *et al.*, 1969; Rahimtoola *et al.*, 1971). Tocainide, however, has a major advantage that lignocaine does not have: it can be administered orally.

In summary, tocainide is an oral antiarrhythmic agent with no evident myocardial depressant effect when typical therapeutic drug doses are used in patients without severe left ventricular dysfunction. If the reported efficacy of tocainide is further confirmed, and if no severe toxic problems result from chronic administration of the drug, then it ought to be a useful antiarrhythmic agent. In this short-term study no laboratory abnormalities occurred during tocainide administration, but further long-term testing is required to demonstrate that the drug has no adverse systemic effects.

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