Clinical and electrophysiological effects of intravenous quinidine in man¹

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Quinidine gluconate (total dose 4.4 to 9.1 mg/kg) was infused intravenously over 22 minutes in 20 patients with either frequent premature ventricular contractions or supraventricular arrhythmias, 16 of whom had bundle-branch block. Therapeutic plasma quinidine levels (3 to 7 mg/l) were achieved in 15. Heart rate, atrioventricular nodal, and infranodal conduction times did not change significantly. The QRS duration increased significantly from 128 ± 30 to 134 ± 29 ms at peak plasma quinidine levels ($P < 0.01$). Mild hypotension occurred during infusion in most patients. Two patients had a severe but transient toxic response characterised by hypotension, nausea, vomiting, and diaphoresis. Atrioventricular dissociation with escape His bundle or fascicular rhythm occurred in 1 patient with sinus bradycardia. Bundle-branch block does not contraindicate administration of quinidine. Quinidine gluconate administered intravenously (0.3 to 0.4 mg/kg per min) is frequently associated with hypotension and should be used only in an intensive care setting and with careful monitoring of blood pressure.

Oral administration of quinidine has proved to be effective and safe for the control of atrial and ventricular arrhythmias provided that plasma levels are kept within the therapeutic range (Sokolow and Ball, 1956), whereas the intravenous use of quinidine has been associated with serious untoward reactions (Armbrust and Levine, 1950; Chapman, 1945; Hepburn and Rykert, 1937; Riseman and Linenthal, 1941; Strong and Munroe, 1940) and is generally considered to be contraindicated (Selzer, 1972). Quinidine delays conduction and increases refractoriness of the His-Purkinje system and slows conduction in ventricular muscle. Because of these actions, quinidine is believed by some to be relatively contraindicated in patients with bundle-branch block (Sokolow and Perloff, 1961). In the study reported here, we attempted to correlate the electrophysiological effects of quinidine on atrioventricular and intraventricular conduction with plasma drug levels in patients with bundle-branch block in an effort to define a rate of intravenous administration of this drug in man which yields

therapeutic blood levels within a relatively short period of time but without undue toxic effects.

Subjects and methods

Twenty patients with either frequent premature ventricular contractions or supraventricular arrhythmias in whom prolonged therapy with oral quinidine was anticipated were studied. Informed consent was obtained and the study conducted in accordance with a protocol approved by the Committee on Human Experimentation of the University of California, San Francisco. No patient was receiving other antiarrhythmic agents at the time of the study. A hexapolar electrode catheter was introduced percutaneously via the right femoral vein, and His bundle recordings were obtained by previously described techniques (Damato *et al.*, 1969; Scheinman *et al.*, 1973). External scalar leads X, Y, and inverse Z of the Frank orthogonal system were recorded simultaneously with the His bundle electrogram at a paper speed of 100 mm/s. The atrioventricular nodal conduction time (AH interval) was measured from the earliest rapid deflection of the atrial electrogram to the initial deflection of the His bundle depolarisation. The conduction time from bundle to ventricle (HQ interval)

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was measured from the initial His deflection to the earliest onset of ventricular depolarisation recorded on the external leads; the onset of the V deflection in the His bundle recordings was not used.

Preliminary studies showed that infusion of less than 3 mg/kg body weight over 22 minutes failed to produce therapeutic blood levels of quinidine (3 to 7 mg/l). In the present study, quinidine gluconate was diluted in 50 ml 5 per cent dextrose in water and administered over 22 minutes by a Harvard constant infusion pump to provide a total dose of from 4.4 to 9.1 mg/kg quinidine gluconate (average 6.9) at infusion rates of 0.20 to 0.45 mg/kg per min (average 0.34). Blood specimens for quinidine assay were withdrawn every 5 minutes during infusion and for 20 minutes afterwards from a polyethylene catheter inserted into a vein in the opposite arm. Simultaneously with withdrawal of blood specimens, the systemic blood pressure was measured by the cuff method, the His bundle electrogram recorded, and 30 second electrocardiographic recordings were obtained in order to count premature beats. Patients were observed closely and asked to report any symptoms during the study.

Plasma quinidine levels were measured by two techniques: (1) a standard colorimetric method involving alkaline extraction into ethylene chloride (Brodie *et al.*, 1946), and (2) a more specific extraction procedure coupled to a thin layer chromatography separation (Ueda *et al.*, 1976). Plasma

quinidine levels are expressed as mg/l of quinidine base. Where applicable, the data were analysed using Student's paired *t* test.

Results

Pertinent clinical information, peak plasma quinidine levels, and electrophysiological data for each patient are summarised in Tables 1 and 2. Twelve patients manifested either left bundle-branch block, right bundle-branch block with left anterior fascicular block, or right bundle-branch block with left posterior fascicular block; of these, 8 had prolonged HQ intervals (>55 ms). Four patients had right bundle-branch block alone or isolated left anterior fascicular block; of these, one had a prolonged HQ interval. Four had no intraventricular conduction abnormality; of these, one had a slightly prolonged HQ interval (58 ms). Of the 20 patients, 13 had premature beats at the time of the study.

Plasma quinidine levels tended to increase progressively during infusion, and in all but one patient the peak quinidine level was achieved at the end of the infusion (Fig. 1). Therapeutic plasma quinidine levels were achieved (3 to 7 mg/ml) when the infusion was stopped in 15 patients. There was no significant difference in plasma quinidine levels determined by the colorimetric assay and the more specific chromatographic technique. Values referred

Table 1 Pertinent clinical and electrocardiographic data and amount of quinidine administered

Case No.	Cardiac disease	CHF	Conduction disturbance	Arrhythmia	Amount quinidine infused (mg/kg)	Peak quinidine plasma level (mg/l)
1	CAD	Yes	LAHB	PVC	7.5	3.1
2	CAD	Yes	LAHB, RBBB	PVC	7.1	4.9
3	CAD	Yes	LBBB	PAC	7.2	3.5
4	CAD	Yes	LAHB	PVC	9.1	4.3
5	CAD	Yes	RBBB	PVC	5.4	3.3
6	CAD	No	None	PVC	9.0	8.4
7	Cardiomyopathy	Yes	LPHB, RBBB	PVC	6.7	0.8
8	RHD	Yes	LBBB, SB	PAT*	7.3	5.8
9	Unknown	No	None	PVC	4.6	1.4
10	Unknown	No	LAHB, RBBB	PAC	5.8	4.6
11	Cardiomyopathy	Yes	LAHB, SB	PJC	6.6	4.1
12	Unknown	No	LBBB	PAC	7.4	3.0
13	CAD	No	None	PAT*	9.0	4.0
14	HHD	Yes	None	Atrial flutter	8.8	5.8
15	CAD	No	LPHB, RBBB	PVC	9.0	2.9
16	CAD	Yes	LBBB	PVC	5.4	5.3
17	HHD	Yes	LBBB	PVC	7.2	2.8
18	Unknown	Yes	LAHB, RBBB	PVC	5.2	3.7
19	Cardiomyopathy	No	LAHB, RBBB	PVC, PAC	6.0	1.6
20	Unknown	Yes	LBBB	PVC, PAC	4.4	3.2
Mean $\pm$ SD					6.9 $\pm$ 1.5	3.8 $\pm$ 1.7

CHF, congestive heart failure; CAD, coronary artery disease; RHD, rheumatic heart disease; HHD, hypertensive heart disease; LAHB, left anterior hemiblock; RBBB, right bundle-branch block; LBBB, left bundle-branch block; LPHB, left posterior hemiblock; SB, sinus bradycardia; PAC, premature atrial contractions; PVC, premature ventricular contractions; PAT, paroxysmal atrial tachycardia; PJC, premature junctional contractions.

*Not at time of study.

Table 2 Blood pressure and electrophysiological intervals before administration of quinidine and at peak plasma quinidine level

Case No.	Blood pressure (mmHg)		Intervals (ms)							
			RR		AH		HQ		QRS	
	Before	Peak	Before	Peak	Before	Peak	Before	Peak	Before	Peak
1	130/80	110/76	780	750	105	105	40	45	105	125
2	180/80	160/70	885	1000	105	105	45	50	135	145
3	170/70	160/60	730	750	100	90	65	65	140	140
4	120/80	90/55	810	700	120	115	45	45	100	100
5	135/90	115/70	580	600	90	85	95	100	110	110
6	110/70	90/60	600	640	90	85	58	65	105	135
7	120/70	80/50	820	870	75	80	80	70	170	180
8	110/60	105/60	1070	1120	75	80	80	60	155	170
9	120/85	80/60	880	720	80	50	45	50	80	80
10	170/105	110/60	850	780	80	80	60	60	125	135
11	110/70	80/50	1015	1100	190	180	50	50	100	120
12	114/72	102/64	720	670	80	75	55	65	145	160
13	110/85	90/70	740	650	60	60	45	50	70	80
14	200/90	165/90	380	460	—	—	55	50	80	80
15	140/85	130/80	750	600	90	85	50	50	130	140
16	125/60	125/60	610	650	110	115	70	70	140	150
17	130/80	105/70	760	665	125	115	70	70	170	170
18	130/70	140/80	665	600	110*	110*	—	—	130	130
19	140/90	120/80	600	640	95	100	85	85	150	160
20	100/70	58/0	835	835	90	100	85	80	140	140
Mean $\pm$ SD	132 $\pm$ 27/78 $\pm$ 11	113 $\pm$ 26/67 $\pm$ 11	754 $\pm$ 158	740 $\pm$ 171	99 $\pm$ 26	95 $\pm$ 27	66 $\pm$ 29	65 $\pm$ 27	128 $\pm$ 30	134 $\pm$ 29
	P < 0.01		NS		NS		NS		P < 0.01	

*A-to right bundle potential; His not obtained.

to henceforth are those determined by the chromatographic method.

EFFECTS ON SINUS RATE, ATRIOVENTRICULAR, AND INTRAVENTRICULAR CONDUCTION

There was no significant change in heart rate during or after quinidine infusion. Mean heart rate was 78 ± 16 beats/min before quinidine and 79 ± 18

beats/min at the time of peak plasma quinidine level. There was no significant difference between mean atrioventricular nodal conduction time before quinidine (99 ± 26 ms) and a peak plasma quinidine level (95 ± 27 ms). Two patients with prolonged control atrioventricular nodal conduction time (120 and 190 ms) showed slight decrease in AH time at peak plasma quinidine levels (to 115 and 180 ms, respectively).

The HQ interval was prolonged (>55 ms) in 10 of the 19 patients in whom it could be measured; the right bundle potential rather than the His potential was recorded in one patient. There was no significant difference between mean HQ before quinidine (66 ± 29 ms) and at peak plasma quinidine level (65 ± 27 ms). At peak plasma quinidine level, HQ was shorter in 4, longer in 7, and unchanged in 8 patients. In addition, there was no significant difference in absolute or per cent change in mean HQ before quinidine or at peak plasma quinidine level in the sub-group of 10 patients with prolonged control HQ compared with those with normal control HQ intervals. A His bundle electrocardiogram in a representative patient before quinidine infusion and at the time of peak plasma quinidine level is shown in Fig. 2. In one patient whose control tracing showed sinus bradycardia, left bundle-branch block, a split His potential, and a prolonged HQ interval, the sinus rate slowed even further and

Fig. 1 Mean ($\pm$ SD) plasma quinidine level during and after infusion of quinidine gluconate. $\uparrow$ indicates time of termination of the infusion.

Fig. 2 His bundle electrograms (HBE) of Case 17. (a) Before infusion of quinidine gluconate. A=atrial potential, H=His spike, V=ventricular potential. (b) HBE at peak plasma quinidine level. AH is 10 ms shorter than in (a) and HQ and QRS are unchanged.

atrioventricular dissociation developed (Fig. 3), with the block localised within the His bundle during drug infusion. Second degree or complete atrioventricular block did not develop in any other patient.

Mean QRS duration increased significantly from 128 ± 30 before quinidine to 134 ± 29 ms at peak plasma quinidine level ($P < 0.01$), but there was no significant difference in the absolute or per cent change in 7 patients with either normal or left anterior fascicular block compared with the 13 patients with bundle-branch block. In no patient

did the QRS duration increase by greater than 28 per cent.

EFFECTS OF CONGESTIVE HEART FAILURE

Of the 20 patients, 13 were in congestive heart failure with varying degrees of compensation at the time of the study. The group in heart failure showed no significant difference from those not in heart failure, in heart rate or atrioventricular or intra-ventricular conduction times either before or after quinidine infusion. Furthermore, there was no difference in the peak plasma level of quinidine

Fig. 3 His bundle electrograms of Case 18. (a) Control tracing showing two spikes (HH') falling between A and V representing split His potential with spontaneous atrial cycle length of 1100 ms. (b) 5 minutes after termination of infusion, atrioventricular dissociation is present. (The atrial cycle length is 1230; the ventricular cycle length is 1280 ms.) Because of proximity of the atrial and ventricular electrogram, His spikes are not seen in the first two complexes. (c) Atrioventricular dissociation within the His-Purkinje system. Note that HH' has lengthened. H' is missing in alternate beats, which is probably because of block within the His. The ventricular pacemaker is probably in the distal His bundle, but a focus in the right fascicle cannot be excluded.

achieved, when normalised for height and weight, in the patients in heart failure compared with the patients not in heart failure.

ARRHYTHMIA CONTROL

Five patients were having premature supraventricular beats and 8 were experiencing premature ventricular beats during the study. One of the subjects had both premature atrial contractions and premature ventricular contractions. Ectopic beats were decreased in frequency ($<75\%$ of control) at the time of peak plasma quinidine level in all 9 patients in whom therapeutic levels were achieved. The effect on frequency of premature ventricular contractions in a representative patient is shown in Fig. 4.

TOXIC SIDE-EFFECTS

The mean of the systemic blood pressures dropped significantly ($P < 0.01$) from control values ($132 \pm 27/78 \pm 11$ mmHg) by 5 minutes after starting infusion and was lowest ($113 \pm 26/67 \pm 11$ mmHg) at the end of infusion when plasma quinidine levels were highest. Five patients had a drop in systolic blood pressure to <100 mmHg but remained asymptomatic. In 2 other patients, diaphoresis and nausea occurred concomitantly with a distinct fall in blood pressure and small changes in heart rate; both responded favourably to raising the legs and stopping the infusion. Their plasma quinidine levels were not excessive (1.4 and 3.2 mg/l) at the time of hypotension and the rates of infusion (0.35 and 0.20 mg/kg per min) were no more rapid than in the remaining 18 patients (mean 0.34 mg/kg per min). No other toxic responses to quinidine infusion were observed, and no patients experienced tinnitus, vertigo, or diarrhoea.

Fig. 4 Frequency of premature ventricular contractions during quinidine infusion in Case 6 illustrating suppression of ectopic beats at termination of infusion and return of premature ventricular contractions afterwards.

Discussion

EFFECT OF QUINIDINE

Quinidine is considered by many to be the mainstay of chronic oral antiarrhythmic therapy. It is of obvious practical importance for the clinician to be aware of the relative risks of quinidine therapy for patients with atrioventricular or intraventricular conduction delay. Experimental studies in animals showed that administration of quinidine in amounts that produce blood levels considered to be within the therapeutic range in man result in little change in atrioventricular nodal conduction time (Wallace *et al.*, 1966) but definite increases in infranodal and intraventricular conduction times (Wallace *et al.*, 1966; Sokolow, 1951; Vaughan Williams, 1958; Swain and Weidner, 1957). For this reason, some believe that the presence of bundle-branch block constitutes a relative contraindication to the use of quinidine (Sokolow and Perloff, 1961). The electrocardiograms in 16 of our patients had either unifascicular or bifascicular block and 10 had prolonged infranodal conduction times. Therapeutic blood levels of quinidine resulted in no significant change in atrioventricular conduction times and in small increases in intraventricular conduction times. Though the QRS duration increased significantly ($P < 0.01$) after quinidine, the QRS axis did not change nor did a new bundle-branch block develop in any patient. In one patient with sinus bradycardia and a prolonged sinus node recovery time, sinus slowing, and atrioventricular dissociation associated with an escape His bundle or fascicular focus developed during quinidine infusion. The degree of atrioventricular block did not increase in any other patient.

The only other study in which His bundle recordings were used to assess the effects of quinidine gluconate in man is that of Josephson *et al.* (1974), in which the drug was administered intramuscularly. Their results are similar to ours with regard to the effect of quinidine on heart rate and atrioventricular nodal and intraventricular conduction times but differ in that a small but significant increase in infranodal conduction time (mean 6 ms) was observed in their study. The reason for the difference is uncertain, though in the study of Josephson *et al.* (1974), larger doses (600 to 800 mg quinidine gluconate) were administered and His bundle recordings were made at higher plasma quinidine levels (4.6 versus 3.8 mg/l). It is also possible that the hypotension caused by intravenous administration of the drug in our patients provoked catecholamine stimulation or increased sympathetic tone which tended to diminish the direct effect of quinidine on the infranodal conduction system.

Reports on the safety of intravenous administration of quinidine have yielded conflicting conclusions. Severe toxic reactions (Chapman, 1945; Hepburn and Rykert, 1937; Riseman and Linenthal, 1941; Strong and Munroe, 1940) and death (Armbrust and Levine, 1950; Acierno and Gubner, 1951) were attributed to the intravenous route and some clinicians have expressed the view that the intravenous route is never (Selzer, 1972) or almost never (Goldberg, 1974; Friedberg, 1966) acceptable medical practice. In these reports either large doses of quinidine were administered (intravenously) rapidly or the patients appeared to be moribund at the time of infusion. However, Clagett (1950) administered quinidine lactate intravenously in doses up to 3.25 g but at infusion rates comparable to ours, and the only side-effects observed were nausea and vomiting in 3 of the 13 patients studied. In his study, as in ours, quinidine administration was associated with a decrease or abolition of supra-ventricular or ventricular arrhythmias and did not produce bundle-branch or atrioventricular block or increased ventricular ectopia. Asymptomatic mild to moderate decreases in systemic blood pressure occurred in 17 of our patients, including reduction of systolic pressure to < 100 mmHg in 5, and a toxic reaction characterised by the abrupt onset of nausea, intense diaphoresis, and severe hypotension occurred in 2 patients during infusion. Both of these patients actually received smaller amounts of quinidine because infusion was terminated prematurely, and plasma quinidine levels were in the subtherapeutic or low therapeutic range (1.4 and 3.2 mg/l). In all patients who had a fall in blood pressure, the hypotension persisted for 5 to 10 minutes after termination of infusion. Our data suggest that careful monitoring of the systemic blood pressure is mandatory when quinidine is administered intravenously. Moreover, an alpha-sympathetic agonist should be readily available because the hypotensive effect of intravenous quinidine is most likely the result of reversible alpha-receptor blockade (Ferrer *et al.*, 1948; Luchi *et al.*, 1963) rather than of a direct myocardial action.

PLASMA QUINIDINE LEVELS

Although there was a progressive rise in plasma quinidine level in each patient during infusion of quinidine, the levels ranged widely even after correction for rates of infusion and body weight. This finding is probably related to the rate and extent of drug distribution because only trivial amounts of the drug would be expected to be metabolised or excreted over the relatively short period of the study. Regardless of differences in rate and extent of drug distribution, we found that doses of 7 to

9 mg/kg quinidine gluconate regularly resulted in peak plasma quinidine levels within the therapeutic range. Of further interest was the observation that mean peak plasma quinidine levels did not differ significantly between patients with (10) or without (10) heart failure. These findings are similar to those described by Bellet *et al.* (1971), who found no significant difference in mean plasma quinidine levels between normal subjects and patients with congestive heart failure 2 hours after an oral dose of 600 mg quinidine; however, the levels were significantly higher in patients with heart failure than in normal subjects 4, 6, and 24 hours after the oral dose. These findings are consistent with our own unpublished observations that the higher plasma quinidine levels found in patients with heart failure are related to decreased drug clearance rather than to diminished volume of distribution.

CLINICAL IMPLICATIONS

In this study, the haemodynamic and electrophysiological effects of intravenous administration of quinidine gluconate which resulted in a relatively rapid achievement of therapeutic plasma quinidine levels were assessed. All the patients but one who received 7 to 9 mg/kg achieved therapeutic plasma quinidine levels within 22 minutes. In a recent study by Wellens and Durrer (1974) 4 mg/kg of quinidine was infused intravenously at a rate of 0.8 mg/kg per min in patients with the Wolff-Parkinson-White syndrome and 5 of the 6 patients became hypotensive, with sweating, restlessness, and tachycardia. In our study, the average total dose was about twice as great, but the slower rates of infusion (mean rate of 0.34 mg/kg) probably accounted for the lower incidence of toxicity. Nevertheless, the slower rates of infusion used in the present study were still associated with an unacceptably high incidence of hypotensive reactions. This study has also shown that therapeutic levels of quinidine were effective in decreasing or abolishing cardiac arrhythmias and were safe for patients with atrioventricular or intraventricular conduction abnormalities in that no higher degrees of atrioventricular block or increased ventricular ectopic activity were encountered. One patient with sinus bradycardia, however, developed transient atrioventricular dissociation owing to further slowing of the sinus rate. For patients requiring parenteral quinidine therapy, intravenous administration appears to have several advantages over the intramuscular route: there is a more rapid and uniform achievement of therapeutic plasma levels; drug administration may be readily terminated should untoward effects occur; and the intravenous route is painless.

Nevertheless, the relatively high incidence of

hypotensive reactions encountered suggests that intravenous quinidine administration should be reserved for critical situations where first line drugs are ineffective and only used with ready availability of an alpha-sympathetic agonist. Though untoward effects disappeared shortly after termination of the infusion and no long-term sequelae were observed, this regimen should rarely, if ever, be used in critically ill patients with hypoxia and/or electrolyte abnormalities (Watanabe *et al.*, 1963; Watanabe and Dreifus, 1967; Holland, 1957), in patients with sinus bradycardia, or in patients receiving drugs that may potentiate quinidine effects.

Addendum

Since completion of this manuscript, 7 additional patients received 8 mg/kg of quinidine intravenously and no untoward effects were observed.

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