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BLOOD QUINIDINE LEVELS AND CARDIAC EFFECTS IN WHITE BRITISH AND NIGERIAN SUBJECTS

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1 Differences between whites and blacks have been described in the incidence and patterns of cardiac disease and in electrocardiographic features.

2 The objective of the present study was to see if the ECG response to the same plasma and red blood cell quinidine concentration differed between whites and blacks.

3 It was found that following a standard single oral dose of quinidine both plasma and red blood cell quinidine concentrations tended to be lower in seven healthy white British subjects than in seven healthy Nigerians.

4 The change in QTc interval (ΔQTc) after quinidine, however, tended to be greater in the white British subjects than in the Nigerians.

5 At a single plasma quinidine concentration the ΔQTc tended to be higher in white British subjects than in Nigerians.

6 At a single red blood cell quinidine concentration, ΔQTc was significantly higher in British white subjects than in Nigerians.

7 The inter-ethnic differences found could be due to both environmental and genetic factors. Further work will be required to decide the relative importance of both these factors on plasma quinidine levels and QTc responses.

Introduction

The incidence and type of cardiac diseases vary from one ethnic group to the other (Epstein *et al.*, 1975; Tunstall Pedoe *et al.*, 1975; Abu-Zeid *et al.*, 1978), for example ischaemic heart disease which is common in Europeans is uncommon in Africans, heart muscle disease frequently seen in Africans is hardly encountered in Europeans (Abrahams *et al.*, 1960; Parry & Ikeme, 1966; Akinkugbe, 1972), and the incidence of the cardiac complications of hypertension appears to be common in Africans (Akinkugbe, 1972). Dietary and other environmental factors as well as genetic susceptibility had been postulated to explain the differences observed, but no completely satisfactory explanation has been put forward.

Inter-ethnic differences in the electrocardiograms of healthy people have been described (Pyke, 1963; Clarke, 1964; Goldman, 1979).

Subjects with cardiac disease exhibit a slower decline of quinidine plasma level than others (Swisher *et al.*, 1954). Good correlations were found between plasma quinidine levels and cardiac effect and it was suggested that a subject with marked effect without correspondingly high plasma quinidine might be showing increased sensitivity to the drug (Edwards *et al.*, 1974).

Q–T interval in the electrocardiogram is measured from the onset of Q wave to the end of the T wave. The Q–T interval varies with the heart rate and must be corrected (Q–Tc). This is easily done by use of the nomogram (Kissin *et al.*, 1948; Goldman, 1970) which gives the Q–Tc for a heart rate of 60 beats/min. QTc measures as described by Taran & Szilangyi (1953), are reasonably accurate, reproducible and reliable and are a quantitative index of the cardiac effects of quinidine.

It seemed possible that there might be a difference in the ECG responses to Africans and Europeans to similar quinidine levels and this investigation was designed to look into this possibility.

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Methods

The subjects investigated were white British (Europeans) or Nigerians (Africans) aged between 19 and 32 years, who gave informed consent. The investigation protocol was approved by the appropriate Ethical Committees in Liverpool and Ibadan; both investigators in addition did preliminary studies on themselves. The same investigator did the observations both in Liverpool and Ibadan. A test dose of an oral quinidine durule 200 mg was given to each subject and if no untoward effects occurred the actual investigation was commenced not earlier than 72 h later. The subject reported without breakfast on the morning of the investigation. A control electrocardiogram (ECG) was recorded using standard methods and precautions (Goldman, 1970) paper speed of 5 cm/s and amplitude of deflection was 2 cm; 10 ml of venous blood were withdrawn from the antecubital vein into an heparinized bottle. Then 400 mg of quinidine durules (all obtained from the Royal Liverpool Hospital, Pharmacy Department) were given orally with 200 ml water on an empty stomach, subsequently both ECG recordings and 10 ml blood samples were taken at 0.5, 1, 1.5, 2, 3, 4 and 6 h after quinidine administration.

Fluorometric estimation of quinidine in blood

The same observer did the quinidine assay both in Liverpool and Ibadan. Each blood sample was centrifuged within 15 min of collection and the plasma was aspirated into a clean bottle while the red blood cells (RBC) were left in the original bottle. Both samples were kept in a deep freeze (−120°C) until assayed. Plasma quinidine was estimated as described by Edwards *et al.* (1974) except that either a Perkin Elmer model 204 or an M.P.F. fluorometer was used. Each assay was related to standard quinidine obtained from the same source (British Drug Houses). RBC quinidine was similarly estimated on the thawed samples.

Rate-corrected QT (QTc) estimations from ECG recordings

All the QT measurements and QTc calculations from the ECG recordings were done by the same observer in Liverpool and Ibadan. Six QT intervals were measured from each of 6 leads (male subjects) or 3 leads (female subjects). The mean of the 36 (for males) or 18 (for females) QT intervals was found. The apparent difference—the number of QT measurement for males (36 from 6 leads) and females (18 from 3 leads) does not result in any significant difference in QTc calculations. Any such minor differences are also nullified by the fact that there were approximately equal numbers of females in the two groups. The corresponding mean heart rate was similarly calculated and the rate-corrected QT (QTc) was read off from the nomogram of Kissin *et al.* (1948).

Calculations

The following values were calculated for each time interval in each subject: control QTc, change in QTc (ΔQTc), plasma quinidine concentrations, red blood cell (RBC) quinidine concentrations; the mean values for these parameters were also found for each ethnic group.

Results

The seven white British subjects consisted of four males and three females aged 20 to 32 years with a mean of 24.9 years ± 1.8 (s.e. mean), while the Nigerians were five males and two females aged 19 to 30 years with a mean of 25.6 ± 1.3 (s.e. mean). The body weight and height range of subjects in both ethnic groups were similar.

Table 1 shows the time course of plasma quinidine concentrations and the level tends to be higher in

Table 1 Plasma quinidine concentrations in 7 Nigerian and 7 British subjects following a single oral dose of quinidine 400 mg

Time (h)	Nigerians Mean plasma quinidine (μg/ml)	s.d.	s.e. mean	British Mean plasma quinidine (μg/ml)	s.d.	s.e. mean
Control	0	0	0	0	0	0
0.5	0.39	0.22	0.08	0.37	0.12	0.05
1	0.82	0.38	0.14	0.74	0.24	0.09
1.5	1.13	0.45	0.17	0.90	0.21	0.08
2	1.37	0.50	0.19	1.02	0.23	0.09
2.5	1.56	0.49	0.19	1.14	0.36	0.14
3	1.70	0.57	0.22	1.25	0.51	0.19
4	1.68	0.49	0.19	1.22	0.45	0.17
6	1.60	0.57	0.22	1.21	0.38	0.14

Nigerians than in white British especially 2 to 6 h following drug ingestion.

Table 2 shows the time course of erythrocyte quinidine concentrations and the level tends to be higher in Nigerians than in white British especially 2 to 6 h following drug ingestion.

Table 3 shows the time course of QTc in the two ethnic groups and there is no significant inter-ethnic difference.

Table 4 shows the time course of ΔQTc (i.e. change in QTc from control) and the values tend to be higher in white British than in Nigerians.

Figure 1 shows that relationship between ΔQTc and plasma quinidine concentrations for each person

Table 2. Red blood cells quinidine concentrations in 7 Nigerian and 7 British subjects following a single oral dose of quinidine 400 mg

Time (h)	*Nigerians Mean RBC quinidine (μg/ml)*	*s.d.*	*s.e. mean*	*British Mean RBC quinidine (μg/ml)*	*s.d.*	*s.e. mean*
Control	0	0	0	0	0	0
0.5	0.18	0.14	0.08	0.16	0.05	0.02
1	0.37	0.20	0.08	0.31	0.10	0.04
1.5	0.55	0.22	0.08	0.42	0.13	0.05
2	0.69	0.19	0.07	0.53	0.17	0.06
2.5	0.88	0.20	0.08	0.59	0.19	0.07
3	0.98	0.27	0.10	0.64	0.22	0.08
4	1.03	0.33	0.13	0.72	0.28	0.11
6	1.12	0.40	0.15	0.69	0.27	0.10

Table 3 Corrected QT interval (QTc) in 7 Nigerians and 7 British subjects following oral quinidine 400 mg

Time (h)	*Nigerians Mean QTc (ms)*	*s.d.*	*s.e. mean*	*British Mean QTc (ms)*	*s.d.*	*s.e. mean*
Control	0.414	0.033	0.012	0.401	0.021	0.008
0.5	0.421	0.035	0.013	0.415	0.019	0.007
1	0.427	0.036	0.014	0.429	0.021	0.008
1.5	0.433	0.038	0.014	0.433	0.023	0.009
2	0.441	0.040	0.015	0.435	0.025	0.009
2.5	0.443	0.036	0.014	0.439	0.023	0.009
3	0.438	0.031	0.012	0.444	0.021	0.008
4	0.431	0.29	0.011	0.444	0.027	0.010
6	0.427	0.035	0.013	0.440	0.018	0.007

Table 4 Change in QTc (ΔQTc) in 7 Nigerians and 7 British subjects following oral quinidine 400 mg

Time (h)	*Nigerians Mean (ms)*	*s.d.*	*s.e. mean*	*British Mean (ms)*	*s.d.*	*s.e. mean*
Control	0.414	0.033	0.012	0.401	0.021	0.008
	Mean ΔQTc	s.d.	*s.e. mean*	Mean ΔQTc	*s.d.*	*s.e. mean*
0.5	0.008	0.0078	0.003	0.014	0.0073	0.0028
1	0.014	0.0095	0.0036	0.028	0.014	0.0054
1.5	0.019	0.013	0.0048	0.032	0.015	0.0056
2	0.027	0.017	0.0065	0.034	0.016	0.006
2.5	0.030	0.014	0.0053	0.038	0.016	0.0062
3	0.025	0.011	0.0042	0.042	0.017	0.0066
4	0.017	0.012	0.0046	0.043	0.021	0.0079
6	0.014	0.037	0.014	0.039	0.015	0.0055

studied. The white British tend to have lower plasma concentrations and higher ΔQTc values than the Nigerians. By using interpolated values the ΔQTc values for the two ethnic groups can be compared at an arbitrarily chosen plasma quinidine concentration. For example, at 0.7 μg/ml for seven white British the mean ± s.d. ΔQTc = 0.027 ± 0.015, and for six Nigerians the mean ΔQTc = 0.016 ± 0.007: $t = 1.23$ d.f. 11, $P > 0.10$.

Figure 2 shows the relationship between QTc and

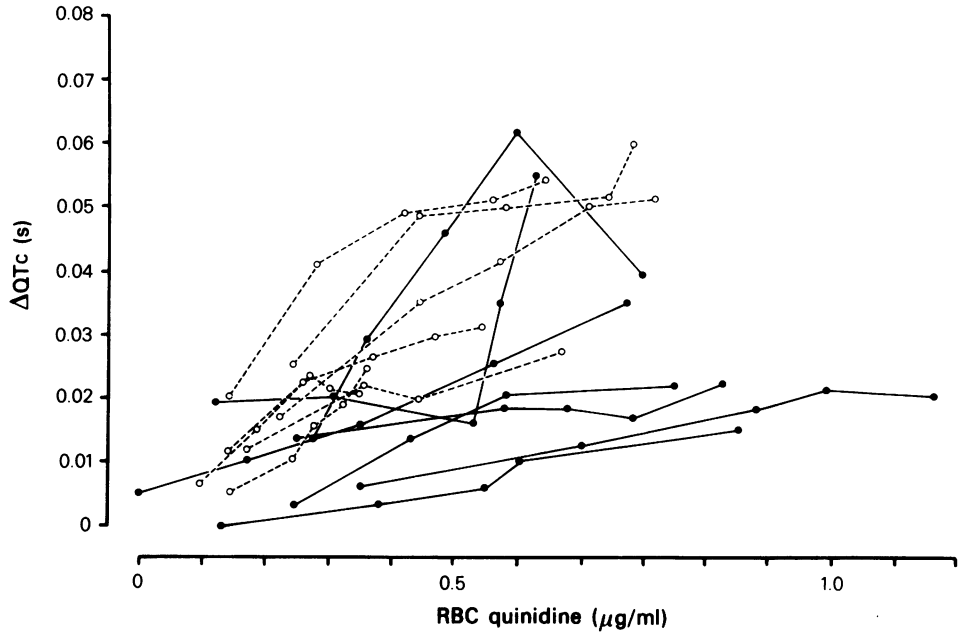

Figure 1 ΔQTc related to plasma quinidine concentration for each of the 14 persons studied. One line joins the results for one person. ● Nigerian, ○ White British.

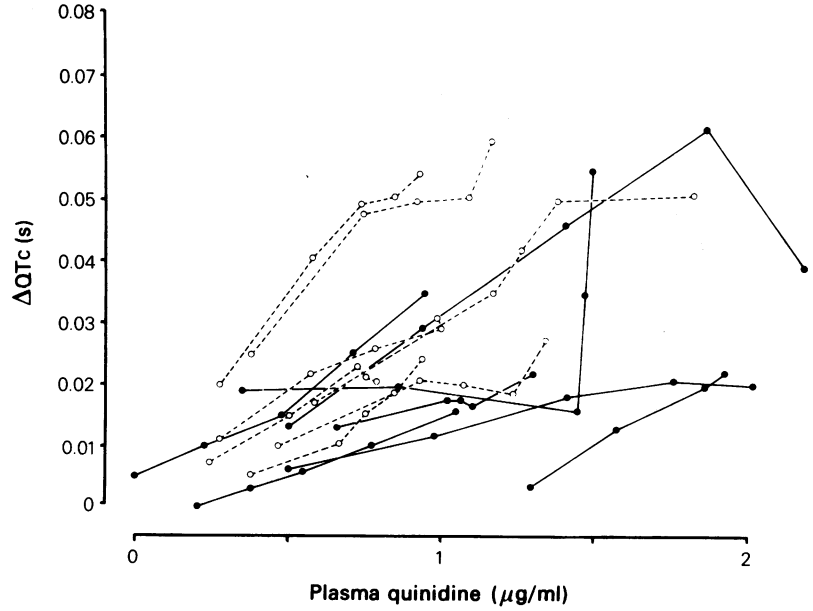

Figure 2 ΔQTc related to red blood cell quinidine concentration for each of the 14 persons studied. One line joins the results for one person. ● Nigerian, ○ White British.

erythrocyte quinidine concentrations. White British subjects although having lower drug concentrations have higher ΔQTc values. By using interpolated values the ΔQT values for the two ethnic groups can be compared at an arbitrarily chosen erythrocyte quinidine concentration. For example at 0.35 μg/ml for seven white British subjects the mean ± s.d. ΔQTc = 0.029 ± 0.009 and for seven Nigerian subjects the mean ΔQTc = 0.013 ± 0.008; $t = 3.29$ d.f. 12, $P < 0.01$.

(The values used in Figures 1 and 2 are those obtained up to and including 2.5 h after drug ingestion. The 3, 4 and 6 h values are more scattered, but confirm a similar trend (as shown by the mean values in Tables 1, 2, 3 and 4).

Discussion

It has recently been pointed out by de Vries *et al.* (1980) that fluorimetric determination of quinidine concentration in plasma is not specific. The apparent values obtained are higher than those found by an h.p.l.c. method. However, at the times and places the present work was carried out the fluorimetric method was the best available. The number of subjects observed in each ethnic group appears small and cannot yet be projected to the whole population; but the carefully executed investigations produced interesting results from which further work can take off.

The results of this study show how an inter-ethnic variability in drug response (ΔQTc on quinidine) is due to two components. First, there is an inter-ethnic difference in the pharmacokinetics and secondly, there is an inter-ethnic difference in the pharmacodynamic response to the same drug concentration.

Plasma and intra-erythrocyte quinidine concentrations tend to be higher in Nigerians than in white British subjects. A somewhat similar finding in the case of antipyrine was described by Branch *et al.* (1978). It is possible that the white British subjects have their drug metabolism induced to a greater degree than the Nigerian subjects. However, other environmental and also genetic influences may account for the inter-ethnic difference in pharmacokinetics.

The ratio of the concentrations of quinidine inside the red cells as compared with that in the plasma is not significantly different between the two ethnic groups. It was thought that intra-erythrocyte quinidine concentration might given an indication of the concentration inside the myocardial cell. There is a wide range of ΔQTc at a single drug concentration in both ethnic groups, but white British hearts are more susceptible to the action of the drug than are Nigerian hearts.

The relative lack of responsiveness of Nigerian hearts ΔQTc to the same quinidine concentration may be due to genetic or environmental factors, and there is at present no evidence to indicate their relative importance.

If white and black subjects sharing a common environment (diet, accommodation, activities etc.) were studied along similar lines to those described above, further light might be shed on the relative importance of genetic and environmental influences on both the pharmacokinetic and pharmacodynamic aspects.

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