COMPARISON OF QUINIDINE PLASMA CONCENTRATION CURVES FOLLOWING ORAL ADMINISTRATION OF SOME SHORT- AND LONG-ACTING FORMULATIONS

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- 1 The time-course of quinidine plasma concentrations and selected kinetic parameters were studied in healthy male volunteers given single oral doses of four different quinidine formulations. Comparison was made with quinidine sulphate in a rapidly dissolving form.
- 2 Plasma half-lives did not significantly differ among treatments.
- 3 Quinidine polygalacturonate appears to be equivalent to quinidine sulphate in respect to both the absorption and elimination kinetics. When both quinidine bisulphate (Kinidin Durules) and quinidine arabogalactansulphate (Longacor) were administered plasma levels peaked significantly later than after quinidine sulphate. However, while the former seems to be absorbed to the same extent as quinidine sulphate, the latter exhibits lower bioavailability in respect to all other preparations.
- 4 Therapeutic relevance of such observations is discussed.

Introduction

Quinidine is still extensively used in antiarrhythmic therapy. However the disposition kinetics of various available formulations are still uncompletely known. Most information concerns quinidine sulphate, which at present is rarely used in maintenance therapy, where it has been widely replaced by long-acting preparations. Among these, quinidine bisulphate (QBS) as a slow releasing form has been extensively studied in respect both to its kinetics (Cramer, Warnauskas & Werkö, 1963; Cullhed, Hamfelt & Malers, 1966) and clinical effectiveness (Byrne-Quinn & Wing, 1970; Härtel, Louhija, Kontinen & Halonen, 1970; Resnekov, Gibson, Waich, Muir & McDonald, 1971; Török, Bajkay, Gulyás & Makláry, 1970). Quinidine polygalacturonate (QPG) and the more recently developed arabogalactansulphate (QAGS) have been little investigated (Gerstenblith, Katabi, Stein & Tirsch, 1966; Maurice, Scebat & Uzan, 1974; Renais, Scebat & Lenègre, 1971). Moreover comparative studies on absorption kinetics and bioavailability after single oral doses are lacking. Recently Henning & Nyberg (1973) have compared plasma levels following multiple dosing of two kinds of sustained release

formulations. In the present paper plasma levels, bioavailability and some other kinetic parameters have been compared after single oral doses of the above-mentioned long-acting preparations. Quinidine sulphate (QS) in a rapidly dissolving form was included as reference preparation.

Methods

Eight healthy male volunteers, aged between 23–37 years gave their written informed consent to take part to the trial. The group was homogeneous in respect to sex, age and body weight (Table 1). All were either medical students or medical graduates. Before the trial each subject underwent physical examination. Conventional laboratory tests were all within normal limits. ECG was recorded at rest and after exercise. Before the trial each volunteer received a test dose of quinidine sulphate (200 mg, one tablet) and the ECG was checked 2 h later. No subjective side effects or ECG changes were noted. The trial was performed using a latin square design. The volunteers were divided in four groups of two subjects each in order of increasing body weight. The sequence of treatments for each group is shown in Table 1. Each volunteer

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received single oral doses at 2 week intervals of the following preparations:

1. quinidine sulphate tablets 200 mg (Chinidina solfato Erba, Carlo Erba, Italy) in a rapidly dissolving form containing the equivalent to 166 mg of quinidine base;
2. quinidine polygalacturonate tablets (Ritmocor, Malesci, Italy) containing the equivalent to 120 mg of quinidine base;
3. quinidine bisulphate tablets 250 mg (Kinidin Durules, AB, Hässle, Sweden) equivalent to 164 mg of quinidine base;
4. quinidine arabogalactansulphate capsules 275 mg (Longacor, Nativelle, France) equivalent to 164 mg of quinidine base.

Doses were three tablets for the sulphate preparation and four tablets or capsules for the others, i.e. 480 mg of quinidine base for QS and QPG and 660 mg of quinidine base for QAGS and QBS. Preliminary studies prompted us to administer lower doses of QS and QPG in order to obtain similar peak plasma levels for all preparations. In our opinion this was justified: (i) to operate in comparable absorption kinetics for all preparations in order to minimize differences due to factors such as first pass effect or saturation phenomena, which could lead to wrong estimations of bioavailability; (ii) to keep the magnitude of single oral doses for the various treatments within the same ratio used during chronic therapeutic administration; (iii) for ethical reasons not to expose the volunteers to the risk of sudden high plasma levels.

Each drug was given with 30 ml of fresh water at 08.00 h after an overnight fast. Continental breakfast was permitted only 2.5 h after administration. Blood samples (7 ml each) were collected in heparinized tubes at 0, 0.5, 1, 2, 3, 4, 6, 9, 12 and 24 h. All subjects complained of vertigo and postural tachycardia during the 4–8 h following administration. Therefore they were kept in supine position during the first 6 h. No other side effect was observed. Quinidine plasma levels were determined

fluorimetrically in triplicate within 24 h of sampling by the double extraction method of Cramer & Isaksson (1963) as modified by Kessler, Lowenthal, Warner, Gibson, Briggs & Reidenberg (1974). This method is specific in that it determines mainly unchanged quinidine and dihydroquinidine (Härtel & Korhonen, 1968; Härtel & Harjanne, 1969; Reidenberg, 1974; Kessler *et al.*, 1974).

Statistical analysis was performed by analysis of variance for cross-over design. The absorption rate constant (K_{abs}), the time and height of peak plasma levels, time during which therapeutic levels were maintained, area from 0–24 h, area from 0 to ∞ and plasma half-lives were calculated.

The selected therapeutic range was 1–4 $\mu\text{g/ml}$ as suggested by Byrne-Quinn & Wing (1970) and by Resnekov *et al.* (1971). Areas were calculated according to the trapezoidal rule. In a semilogarithmic plot plasma levels showed a linear decline with time 6–9 h post administration. Half-lives were estimated by least squares regression from the linear part of the curve. The absorption rate constants were calculated by linear regression from the graphical estimates of the residuals (Wagner & Metzler, 1967). Areas from 0 to ∞ were estimated by means of the following formula (Wagner, 1967):

$$\text{area}_{0-\infty} = \text{area}_{0-24} + \frac{T_{1/2} C_t}{0.693}$$

where C_t is the concentration at the last sampling time and $T_{1/2}$ the biological half life of the drug.

Results

1. Comparison of the time-course of plasma levels for different treatments

The time-course of plasma levels after administration of QS, QAGS, QBS and QPG is shown in Figure 1. The mean values at different times are summarized in Table 2, while corresponding analysis of variance is reported in Table 3.

Table 1 Experimental design showing details of subjects and sequence of quinidine treatments in eight healthy volunteers

Groups	Subjects	Weight (kg)	Height (m)	Age (years)	Sequence of treatments			
I	MF	60	1.60	25	QS	QPG	QAGS	GBS
	PE	62	1.66	26				
II	GMF	63	1.74	37	QPG	QBS	QS	QAGS
	PS	66	1.73	23				
III	AE	68	1.78	23	QBS	QAGS	QPG	QS
	GR	70	1.75	25				
IV	MTD	72	1.81	27	QAGS	QS	QBS	QPG
	BA	76	1.83	25

Figure 1 Mean quinidine plasma levels for eight subjects after oral administration of quinidine sulphate (○), quinidine polygalacturonate (■), quinidine bisulphate (●) and quinidine arabogalactansulphate (Δ).

No significant differences among treatments were observed in plasma levels at 3 h and 4 h. Moreover plasma levels following QS and QPG do not significantly differ at any time except for the first 30 min. After 6 h long-acting preparations QBS and QAGS gave significantly higher plasma levels than QS and QPG. Over the same period QBS produced more sustained plasma concentrations than QAGS except

at 24 h. In respect to the first samplings, the rise of plasma levels was slower after treatment with QAGS as compared to other treatments.

2. Comparison of selected kinetic parameters

Treatments with QS and QPG appeared to be equivalent in respect to all the kinetic parameters studied (Tables 4 and 5). Time of peak was significantly delayed in the QBS and QAGS time-concentration curves when compared with QS. QBS peaked significantly later also when compared with QPG. Absorption rate constants were significantly higher for short-acting (QS and QPG) as compared to long-acting preparations (QBS and QAGS). Peak plasma levels were not significantly different among all preparations except than between QBS and QAGS where borderline significance was found. As regards the duration of therapeutic levels and areas under the time-concentration curves only treatment with QBS gave significantly higher values than other treatments, while analysis of variance failed to show any statistical difference among QS, QPG and QAGS. However when areas were corrected to account for different dose schedules, by assuming a linear relationship between area and dose, no significant difference was found among QS, QPG and QBS while area following QAGS was lower. Treatments did not significantly differ in respect to half-lives.

Table 2 Mean ($n=8$) quinidine plasma levels ($\mu\text{g/ml}$) and corresponding coefficients of variation following the administration of a single dose of quinidine in four different formulations

Time (h)	Plasma quinidine ($\mu\text{g/ml}$)			
	QS	QPG	QBS	QAGS
0.5	0.45 (82.22)*	1.04 (60.58)	0.43 (65.12)	0.14 (107.14)
1	1.55 (43.23)	1.65 (36.97)	1.11 (26.13)	0.62 (30.64)
2	2.19 (12.78)	2.14 (28.97)	1.93 (18.65)	1.34 (36.57)
3	2.21 (17.65)	2.39 (24.27)	2.27 (20.26)	1.81 (28.18)
4	2.14 (19.63)	2.22 (20.27)	2.46 (19.51)	2.10 (23.33)
6	1.85 (23.78)	1.88 (21.81)	2.47 (13.76)	2.02 (25.25)
9	1.34 (23.88)	1.39 (29.50)	2.02 (11.39)	1.69 (30.77)
12	0.99 (27.27)	1.01 (36.63)	1.52 (11.84)	1.33 (25.56)
24	0.34 (29.41)	0.30 (66.67)	0.56 (23.21)	0.48 (27.08)

* Bracketed values are coefficients of variation of the means, as percentage, i.e. $\text{s.d./mean} \times 100$.

Table 3 Analysis of variance for comparison of mean plasma quinidine levels at different times after single dose administration of four different formulations

Time (h)	Among QS/QPG/QBS/QAGS	Between QS/QPG	Between QS/QBS	Between QS/QAGS	Between QPG/QBS	Between QPG/QAGS	Between QBS/QAGS
0.5	$P < 0.01$	$P < 0.01$	NS	NS	$P < 0.01$	$P < 0.001$	NS
1	$P < 0.01$	NS	NS	$P < 0.001$	$P < 0.05$	$P < 0.001$	NS
2	$P < 0.01$	NS	NS	$P < 0.01$	NS	$P < 0.01$	$P < 0.05$
3	NS	NS	NS	NS	NS	NS	NS
4	NS	NS	NS	NS	NS	NS	NS
6	$P < 0.001$	NS	$P < 0.001$	NS	$P < 0.001$	NS	$P < 0.01$
9	$P < 0.001$	NS	$P < 0.001$	$P < 0.01$	$P < 0.001$	$P < 0.05$	$P < 0.01$
12	$P < 0.001$	NS	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.01$
24	$P < 0.001$	NS	$P < 0.001$	$P < 0.05$	$P < 0.001$	$P < 0.01$	NS

Table 4 Mean values for kinetic parameters derived from quinidine plasma concentration v. time data, and corresponding coefficients of variation in parentheses

	QS	QPG	QBS	QAGS
Time of peak (h)	2.25 (45.78)	2.75 (57.45)	5.12 (35.35)	4.25 (27.29)
Peak concentration ($\mu\text{g/ml}$)	2.42 (13.64)	2.49 (6.02)	2.55 (13.33)	2.18 (21.56)
Duration of therapeutic levels (h)	11.70 (24.70)	12.24 (32.03)	17.56 (9.63)	13.94 (30.49)
Area 0–24 ($\mu\text{g ml}^{-1}\text{ h}$)	27.19 (19.42)	27.91 (23.57)	36.01 (11.75)	29.46 (21.35)
Area 0– ∞ ($\mu\text{g ml}^{-1}\text{ h}$)	31.02 (20.50)	31.29 (30.56)	42.75 (12.70)	35.06 (20.71)
$T_{1/2}$ (h)	7.87 (18.17)	6.60 (31.21)	8.16 (14.34)	8.16 (19.97)
K_{abs} (h^{-1})	1.37 (37.34)	1.27 (78.17)	0.49 (15.55)	0.50 (39.04)

Table 5 Analysis of variance for comparison of selected kinetic parameters

	Among QS/QPG/QBS/QAGS	Between QS/QPG	Between QS/QBS	Between QS/QAGS	Between QPG/QBS	Between QPG/QAGS	Between QBS/QAGS
Time of peak	$P < 0.01$	NS	$P < 0.05$	$P < 0.01$	NS	NS	NS
Height of peak	$P < 0.05$	NS	NS	NS	NS	NS	$P < 0.05$
Duration of therapeutic levels	$P < 0.001$	NS	$P < 0.001$	NS	$P < 0.001$	NS	$P < 0.01$
Area 0–24	$P < 0.001$	NS	$P < 0.001$	NS	$P < 0.001$	NS	$P < 0.001$
Area 0– ∞	$P < 0.001$	NS	$P < 0.001$	NS	$P < 0.001$	NS	$P < 0.01$
$T_{1/2}$	NS	NS	NS	NS	NS	NS	NS
K_{abs}	$P < 0.001$	NS	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	NS

Discussion

Quinidine is considered an effective as well as a potentially dangerous drug. However its clinical safety and effectiveness in long-term antiarrhythmic therapy can be improved, provided a proper dosage schedule is instituted in order to maintain adequate steady plasma levels (Byrne-Quinn & Wing, 1970; Härtel *et al.*, 1970; Hillestad, Bjerkelund, Dale, Maltau & Stortein, 1971; Sokolow & Ball, 1956). Although the extent of therapeutic range is still controversial, many investigators consider the range 1 to 4 $\mu\text{g/ml}$, as determined by the method of Cramer & Isaksson (1963), to be optimal for a satisfactory therapeutic response and safe enough to avoid the risks of overdosage (Byrne-Quinn & Wing, 1970; Resnekov *et al.*, 1971). Such a range is now widely accepted in clinical practice for chronic administration. However, the attainment of therapeutic plasma levels during chronic treatment is made difficult by large inter-individual variations in the rate of absorption and elimination which make the effect of fixed dosage poorly predictable (Sokolow & Ball, 1956; Sokolow & Perloff, 1961). Therefore, in order to limit the risks of serious toxic reactions when the therapeutic range is overcome, individualization of quinidine therapy by means of plasma levels monitoring is often recommended (Kessler, 1974).

Due to the short half life of the drug (Kessler *et al.*, 1974; Ueda, Hirschfeld, Scheinman, Rowland, Williamson & Dzindzio, 1976) rapidly absorbed formulations such as quinidine sulphate must be administered every 4–6 h. In our experiments, following single oral doses of quinidine sulphate plasma levels rose rapidly, peaked after 2.25 h and then fell off with an exponential decline. These findings are in agreement with previous results (Cramer *et al.*, 1963; Goldberg & Chakrabarti, 1964; Kalmansohn & Sampson, 1950).

Long-acting preparations are now available, which were developed to avoid frequent administration, to improve compliance and to avoid exposing the patient to high plasma levels at the time of maximal absorption. Among these QPG, QBS and QAGS are widely used in clinical practice. QPG has been introduced as a moderately long-acting preparation which could be administered three times daily (Cullhed *et al.*, 1966; Gerstenblith *et al.*, 1966; Goldberg & Chakrabarti, 1964). However, from our experiments, QPG does not significantly differ from the rapidly absorbed QS in respect to both the absorption and elimination kinetics. Our findings are at variance with those obtained by Goldberg & Chakrabarti (1964), who reported QPG to give smoother plasma levels and a delayed time of peak as compared to QS. However, a plasma concentration curve similar to that found in our study has been described by Cullhed *et al.* (1966).

QBS is a long-acting preparation in that quinidine bisulphate, embedded in a porous insoluble plastic tablet, is slowly released into the gut (Cramer *et al.*, 1963). In our experiments single oral doses of QBS, able to produce the same maximal concentration as QS and QPG, produce a delayed time of peak and significantly more prolonged therapeutic levels when compared to QS and QPG. Our data are in close agreement with those reported by Cramer *et al.* (1963). QAGS has been claimed to produce long lasting therapeutic plasma levels when given twice daily (Maurice *et al.*, 1974; Renais *et al.*, 1971). Henning & Nyberg (1973) in a comparative study where QABS and QBS were administered in the same dosage schedule found that QAGS produce significantly lower plasma levels. In the present study QAGS is able to delay slightly but significantly the time of peak in respect to QS but does not produce more sustained levels than QS and QPG, possibly because of the lower bioavailability. In fact, when areas under the time-concentration curve are corrected in order to minimize differences in dosage schedules for all preparations by assuming linear relationship between area and dose, there is striking similarity between QS (37.38 $\text{mg kg}^{-1} \text{ h}$), QPG (38.38 $\text{mg kg}^{-1} \text{ h}$) and QBS (36.01 $\text{mg kg}^{-1} \text{ h}$) while area for QAGS is significantly lower (29.46 $\text{mg kg}^{-1} \text{ h}$). It is remarkable that QBS appears to be absorbed to the same extent though at a lower rate as compared to QS and QPG but shows higher bioavailability than QAGS. In fact, since the absorption and elimination rates are similar for QBS and QAGS, the lower bioavailability of the latter may account for its significantly lower peak height and less sustained therapeutic levels. The main differences in bioavailability of long-acting preparations between our study and that of Henning & Nyberg (1973), namely 71% vs 53% for QAGS and 96% vs 77% for QBS, could be accounted for by different experimental design, i.e. single oral dose vs chronic treatment, and by the influence of some uncontrolled factors affecting prolonged administration, as suggested by Henning & Nyberg (1973) themselves. The kinetic parameters in this study have been calculated from single-dose experiments. Therefore our conclusions are based on the assumption that the volume of distribution did not differ in each subject after administration of different preparations. The volume of distribution may change in some physiopathological situations (Klotz, 1976) but in our experimental conditions we can reasonably assume that it remained constant. In conclusion, since QPG does not produce sustained therapeutic plasma levels it should be employed in the same dosage schedule as QS. On the contrary both QBS and QAGS are able to produce smoother and more prolonged plasma levels, even though QAGS appears to be less completely absorbed. The lower bioavailability is the main drawback of QAGS and it

could be responsible for greater variability in the steady state plasma levels.

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