QUINIDINE DOSAGE, WITH SPECIAL REFERENCE TO AN ORAL LOADING DOSE SCHEDULE

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- 1 Plasma concentrations of quinidine were analyzed in 52 cardiac patients after different oral loading doses and during different maintenance dosage intervals using both conventional and sustained release preparations of quinidine.
- 2 The majority of patients reached therapeutic plasma concentrations in the order of 2–4 µg/ml within 3 h after a loading dose of 600–800 mg of rapidly absorbed ordinary quinidine sulphate tablets and institution of maintenance therapy with sustained release tablets 1 h after the loading dose.
- 3 The dosage interval of 12 h during maintenance therapy with sustained release tablets gave as acceptable plasma drug fluctuations as an 8 h interval.
- 4 A large individual variation in plasma concentrations was noticed. Thus monitoring of therapy by plasma concentration analyses is desirable.

Introduction

A large interindividual variation in quinidine plasma concentration after fixed oral dose has been described (Sokolow & Ball, 1956; Cramér & Isaksson, 1963; Conn & Luchi, 1964; Kessler, Lowenthal, Warner, Gibson, Briggs & Reidenberg, 1974). Recent studies have accordingly reported considerable individual variation in mean plasma clearance of quinidine (Mahon, Mayersohn & Inaba, 1976; Ueda, Hirschfeld, Scheinman, Rowland, Williamson & Dzindzio, 1976a; Ueda, Williamson & Dzindzio, 1976b; Conrad, Molk & Chidsez, 1977). As only 15–20% of a quinidine dose is excreted unchanged in the urine, major sources of variation should be degree of absorption, distribution volume and particularly the rate of metabolism. Accordingly plasma concentrations of quinidine are reduced by treatment with phenobarbitone and phenytoin probably due to an increased rate of quinidine metabolism (Data, Wilkinson & Nies, 1976). Equivocal data have been reported regarding the effects of disease states particularly congestive heart failure and renal insufficiency, on quinidine kinetics (Brown, Holzman & Creelman, 1953; Ditlefsen & Bjerkelund, 1966; Bellet,

Roman & Boza, 1971; Kessler *et al.*, 1974; Crouthamel, 1975; Conrad *et al.*, 1977).

The slow release preparation of quinidine bisulphate (Kinidin Durules) has a rate of absorption that is about half that of an ordinary tablet (quinidine sulphate) resulting in lower absorption peaks (Mahon *et al.*, 1976). In some acute clinical situations it may be necessary to achieve therapeutic plasma concentrations rapidly and thus a slow rate of absorption is disadvantageous while during chronic treatment the slow absorption rate may allow conveniently longer dosage intervals compared to ordinary tablets (Cramér, Varnauskas & Werkö, 1963; Goldberg & Chakrabarti, 1964; Henning & Nyberg, 1973). A comparison of quinidine plasma concentrations following single oral doses of some short- and long-acting formulations of quinidine given to healthy young volunteers has recently been reported (Frigo, Perucca, Teggia-Drogki, Gatti, Mussini & Salerno, 1977). The present study was designed to evaluate an oral loading dose schedule for the acute clinical situation and to compare different dosage intervals during chronic treatment with quinidine.

Methods

Fifty-two patients with clinical indications for quinidine treatment were studied. Twenty-one patients received quinidine prophylactically after DC-conversion and thirty-one patients received it because of ventricular arrhythmias after acute myocardial infarction. Most patients received other cardiovascular drugs like digoxin and diuretics. One patient was regularly treated with vinbarbital and another with phenytoin. Patients with quinidine intolerance, second degree and complete AV-block, first degree AV-block in combination with left anterior hemi-block and right

bundle branch block, systolic blood pressure less than 90 mmHg, severe left heart failure (more than basal pulmonary crepitations and/or congestion on chest X-ray) or marked renal insufficiency (serum creatinine more than 2 mg%) were not included in the study. The serum creatinine in this group varied between 0.5 and 2.0 mg% (mean 1.0 mg%). Twenty-one patients had pathologic liver tests (i.e. alanine aminotransferase activity exceeding aspartate aminotransferase activity) and fifteen patients had congestive heart failure with basal crepitations and enlarged heart volume on chest X-ray.

Plasma quinidine was analysed by a spectrophotofluorometric, double extraction method (Cramér & Isaksson, 1963). While the specificity of various methods for quinidine has been questioned (Kessler *et al.*, 1974) the specificity of this method has been confirmed by both gas liquid chromatography (Huffman & Hignite, 1976; Midha & Charette, 1974) and liquid chromatography (Conrad *et al.*, 1977). The therapeutic plasma concentration range with this method is said to be 2–4 µg/ml of quinidine base (Byrne-Quinn & Wing, 1970).

The three different loading doses used in this study are shown in Table 1. Clinical data concerning the 49 patients in the different groups are presented in Table 2. As can be seen from the table the groups appear comparable in terms of sex, age, body weight, renal-, hepatic- and cardiac function, treatment with other cardiovascular drugs and indications for quinidine therapy.

Venous blood samples for determination of quinidine plasma concentration were withdrawn in heparinized vacuum tubes (Vacutainer, Becton, Dickinson & Co) before and at regular time intervals after the loading dose. The Vacutainer system has subsequently been shown to affect the protein binding of quinidine (Fremstad & Bergerud, 1976) reducing the measured total plasma concentration by 4–8% (Shand, 1976). This has not been corrected for in this study.

Table 1 Initial doses in the oral loading dose patient groups.

Group (number of patients)	Dose (g)	Preparation	Time (h)
I (10)	0.4/0.8	SRT	0
	0.4	SRT	4
	0.4	SRT	12
II (9)	0.8/1.0	SRT	0
	0.4	SRT	4
	0.4	SRT	12
III (19)	0.6/0.8	OT	0
	0.4	SRT	1
	0.4	SRT	9
IV (11)	0.6/0.8	OT	0
	0.6	SRT	1
	0.6	SRT	13

SRT=sustained release tablets (Kinidin Durules, Hässle, Sweden).

OT=ordinary tablets (Kinidin, ACO, Sweden). Initial doses were differentiated according to body weight above or below 75 kg.

Table 2 Clinical details (mean $\pm$ s.d.) about the patients in the different groups.

	<i>Male/ female</i>		<i>Age</i>	<i>Body weight</i>	<i>Serum creatinine</i>	<i>ALAT > ASAT¹</i>	<i>Heart failure</i>	<i>Other² CV-drugs</i>	<i>DC/AMP³</i>
	<i>n</i>	<i>(numbers)</i>	<i>(years)</i>	<i>(kg)</i>	<i>(mg%)</i>	<i>(number)</i>	<i>(number)</i>	<i>(number)</i>	<i>(number)</i>
Group I	10	6/4	61 ± 15	68 ± 10	0.9 ± 0.3	4	3	7	4/6
Group II	9	7/2	62 ± 10	75 ± 10	1.0 ± 0.4	3	2	5	4/5
Group III	19	12/7	66 ± 9	67 ± 11	1.0 ± 0.4	7	5	10	8/11
Group IV	11	9/2	66 ± 12	72 ± 16	1.0 ± 0.3	4	2	5	4/7

¹ Patients with pathologic liver tests, i.e. alanine aminotransferase activity exceeding the aspartate aminotransferase activity.

² CV=cardiovascular.

³ Indication for quinidine therapy. DC=prophylactically after DC-conversion. AMI=ventricular arrhythmias after acute myocardial infarction.

In thirteen patients the quinidine plasma concentrations were studied during two different dosage intervals with Kinidin Durules. At first 0.4 g was given three times daily and, after 5 days, 0.6 g twice daily. The plasma concentrations were determined at regular intervals during one dosage interval after 5 days treatment with each dose regimen.

Results

Figure 1 shows the mean plasma concentration values of the loading dose groups. In groups I and II in which only Kinidin Durules were used the mean values at 6 h were 1.6 and 1.7 $\mu\text{g/ml}$ respectively and at that time only four out of nineteen patients were within the accepted therapeutic range. In group III where quinidine in ordinary tablets was used as loading drug the mean concentration after 3 h was 2.6 ± 1.6 ($\pm$ s.d.) $\mu\text{g/ml}$. Thirteen patients out of nineteen were within the therapeutic range at that time, three were above and three were below.

The three patients in group III with plasma levels above the therapeutic range at 12 h, are shown in Figure 2. Patient EB had congestive heart failure with rapid atrial fibrillation and a serum creatinine of 1.5 mg%, patient SB had a serum creatinine value of 1.7 mg%. In these two patients quinidine treatment was stopped although no side effects were noted. The third patient MZ had no signs of heart failure or renal insufficiency and at a later occasion his plasma levels were within the therapeutic range.

In group IV (Figure 1) the mean plasma concentration after 3 h was 2.1 ± 0.9 $\mu\text{g/ml}$ and five patients out of eleven were within the therapeutic range. However, after 12 h the mean plasma concentration had

Figure 1 Mean plasma concentration of quinidine ($\pm$ s.d.) in the four different groups. Bar indicates $\pm$ s.d. and the shaded area the therapeutic range. $\blacktriangle$ group I, $\blacksquare$ group II, $\bullet$ group III and $\circ$ group IV.

Figure 2 The three patients with the highest plasma concentration of quinidine at 12 h in group III. For further explanation see Results. The shaded area indicates the therapeutic range.

declined to 1.8 ± 0.5 $\mu\text{g/ml}$ and only two patients were within the therapeutic range.

In Figure 3 the results of the dose interval study during maintenance therapy are summarized. With an 8 h dosage interval the maximum concentration was 3.5 ± 1.3 ($\pm$ s.d.) $\mu\text{g/ml}$ at 2 h after dose and minimum concentration 3.0 ± 1.4 $\mu\text{g/ml}$ at 8 h. With a 12 h interval the maximum concentration was 3.9 ± 2.1 $\mu\text{g/ml}$ at 6 h and minimum concentration 2.7 ± 1.1 $\mu\text{g/ml}$ at 12 h. In both groups three patients achieved concentrations above 4 $\mu\text{g/ml}$, 5.1, 5.2, 5.2 $\mu\text{g/ml}$ in the 8 h group and 6.3, 6.4, 4.4 in the 12 h group. The mean difference between maximum and minimum concentrations was 0.9 ± 0.4 $\mu\text{g/ml}$ in the 8 h group and 1.0 ± 0.6 in the 12 h group.

Figure 3 Mean plasma concentrations of quinidine with dosage intervals of A ($\bullet$ — $\bullet$) 8 h and B ($\blacksquare$ — $\blacksquare$) 12 h. Bar indicates $\pm$ s.d. and the shaded area the therapeutic range.

Discussion

This study shows that the combination of rapidly absorbed quinidine sulphate and sustained release quinidine results in the achievement of accepted therapeutic plasma concentrations in a majority of patients within 2–3 h. If only a slow release preparation is used this time will extend to several hours after commencing treatment. A maintenance dosage with slow-release-preparation should be started 1 h after the loading dose with a dosage interval not longer than 8 h at least for the first two doses. A more rapid loading dose procedure by oral medication is limited by occurrence of too high plasma levels during the first hours after the loading dose. In particular patients in congestive heart failure and renal insufficiency can achieve high plasma concentrations as is evident from the two patients in this study. It was of interest that the two patients in group III treated with phenytoin and vinbarbital both had very low plasma concentrations which is in agreement with the reported interaction between these drugs and quinidine (Data *et al.*, 1976).

During maintenance treatment a dosage interval of 12 h seems to be possible with regards to fluctuation in plasma levels. Our results are in agreement with those

of Mahon *et al.* (1976) who predicted fluctuations between 3.9 and 2.1 $\mu\text{g/ml}$ during treatment with slow release tablets with 12 h dosage intervals.

Large individual differences in plasma concentration are evident in this study. In group III plasma concentrations at 12 h raised from 0.9 to 6.8 $\mu\text{g/ml}$ and in the 8 h interval maintenance group the range at 8 h was 0.7–5.4 $\mu\text{g/ml}$. Both results indicate a 7.7-fold difference. In recent pharmacokinetic studies total plasma clearance values for quinidine were found to differ in normal subjects after single oral doses between 0.18–0.61 $\text{l kg}^{-1} \text{h}^{-1}$, and after i.v. quinidine between 0.09–0.50 $\text{l kg}^{-1} \text{h}^{-1}$ in patients (Mahon *et al.*, 1976; Ueda *et al.*, 1976a; Ueda *et al.*, 1976b; Conrad *et al.*, 1977). The calculated corresponding difference in eight hourly dose required for a mean therapeutic concentration of 3 $\mu\text{g/ml}$ in a 70 kg individual would range from 151 to 1192 mg. The need for individualized dosing of quinidine is evident and in many cases therapy has to be monitored by plasma concentration analyses.

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