Serum Quinidine Levels after Administration of Three Different Quinidine Preparations

R. Henning and G. Nyberg
Department of Medicine I, Sahlgrenska Hospital, Göteborg, Sweden
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Summary. In a single-blind cross-over study, 6 healthy volunteers took three different formulations, each containing 0.33 g of quinidine base, every 12 h for 96 h. A mean steady state serum level of 1.8 mg/l of quinidine base was produced by bisulphate tablets that dissolved rapidly. Long-acting Quinidine Durules® (sustained-release quinidine bisulphate) produced a mean steady state serum level that was 23% lower (NS) and Longacor® (quinidine arabogalactone sulphate) led to one that was 46% lower (p < 0.05). The time taken to reach a steady state was longer after Longacor® than Quinidine Durules®. The results are discussed in relation to the conventional clinical use of quinidine, methods of estimating its concentration in serum, and the relative value of different formulations of quinidine salts.

Key words: Quinidine bisulphate, quinidine arabogalactone sulphate, sustained-release quinidine bisulphate, serum levels.

Introduction

Quinidine has played an important role in the prophylaxis and treatment of cardiac arrhythmias since the 1920s. Before the introduction of DC-shock [17] quinidine was used for conversion of atrial fibrillation but it is much more important today as a prophylactic against the recurrence of fibrillation after successful conversion. Its efficacy has been demonstrated in recent studies [3, 4, 12, 29]. The ability of quinidine to depress ventricular ectopic beats is more controversial [1, 13, 19].

The first salt to be employed, quinidine monosulphate, is probably still the most widely used compound for oral treatment, in spite of its rapid absorption and excretion which necessitate frequent administration to maintain a sufficiently steady blood level.

In the past 20 years, many attempts have been made to improve oral treatment with quinidine by employing other salts or pharmaceutical formulations in attempts to obtain smoother blood levels with longer intervals between doses. The aim of the present study was to compare the sustained-release formulation of quinidine bisulphate, Quinidine Durules® [8], used in Scandinavia for about 15 years, with a recently developed salt, quinidine arabogalactone sulphate, Longacor® [20], with respect to absorption, serum levels and bio-availability. Since quinidine bisulphate in a rapidly absorbed tablet form had not been studied in this way previously, it, too, was included for comparison purposes.

Material and Methods

Seven healthy men of ages ranging from 22—62 years, volunteered to take part in a clinical comparison of three formulations of quinidine:

1. Quinidine bisulphate 0.25 g in a rapidly dissolving tablet that contained 0.165 g of quinidine base.
2. Quinidine Durules® (AB Hässle, subsidiary of AB Astra, Sweden), containing 0.25 g of quinidine bisulphate.
3. Longacor® (Nativelle, France) that contained quinidine arabogalactone sulphate 0.275 g in capsules, which is equivalent to 0.164 g of quinidine base.

The dose was two tablets or capsules every 12 h. Before the trial, the subjects underwent conventional physical examination and their medical histories were taken. One of the older subjects was known to have hypertension but was not being treated with antihypertensive drugs.

The following laboratory tests were done beforehand: hemoglobin, hematocrit, white blood cell and thrombocyte counts, erythrocyte sedimentation rate, serum creatinine, liver function tests — bilirubin, thymol turbidity, alkaline phosphatase, SGOT and SGPT. The ECG was recorded at rest and during isometric work that consisted of a sustained hand-grip for 1 min at 50% of maximal attainable value.

All laboratory tests were normal, except for elevated bilirubin and transaminase levels in one subject, a 37 year old man who was excluded from the trial.
Before the study, every subject was given a test dose of quinidine monosulphate 0.5 g (2 tablets) and the ECG was checked 2 h afterwards. None of the volunteers reported subjective side effects after the test dose and no ECG changes were seen.

Each drug was taken during a five day period and the serum level of quinidine was measured on the first day at 0 and two hours after the first dose, on the third day, at 48 and 50 h after the first dose, and, on the fifth day, at 96, 98, 101 and 104 h after the first dose. On each occasion urine pH was also measured.

The subjects were instructed to take the tablets twice daily at 8 am and 8 pm. Each subject was given a diary card to record the time of taking each dose. According to the cards the time of dosing rarely differed by more than 20 min from the prescribed time. In one subject, there was a delay of 2 h in taking the evening dose on one occasion, but this probably had no effect on the measured serum levels, as they were not estimated on the day after this delay.

The trial was single-blind and the order of treatment was allocated randomly according to a latin square design. Two-tailed Student's t-test for paired differences was used to evaluate the results unless otherwise stated. The parametric F-test was employed to test the variances and a few parametric correlation coefficients were also calculated.

The plasma concentrations of quinidine were determined by Cramér-Isacsson's method [6]. Blood for quinidine analysis was collected in heparinized tubes and the plasma was centrifuged within 3 h and stored in a deep freeze for subsequent analysis. Quinidine levels are given as mg base per litre plasma.

**Results**

The serum levels found on all test occasions are given in Table 1, both for the individual subjects and as averages.

The mean serum level for each formulation during the 12 h between the 96th and 108th h of treatment are shown in Table 2. The mean serum level over the dosage interval (12 h) has been calculated according to the formula

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\text{mean serum level} = \frac{1}{(\text{dosage interval})} \times (\text{area under serum level curve})
\]

As previous studies [5, 14, 15, 20, 24], as well as the present results, have confirmed that a steady...