Comparison of two long-acting forms of quinidine

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1 The bioequivalence of two forms of long acting quinidine compounds was assessed (Kinidin durules[®] and Longacor[®]) using drug plasma level and QT ECG changes.

2 Six healthy volunteers received each preparation on two occasions in random order. The wash out period between successive experiments was at least 7 days.

3 There was no difference in $t_{\max}$, $C_{\max}$ and AUC for plasma level and adjusted QT. However, between patient variability was large.

4 A 20% difference in plasma levels could not be excluded but the difference in QT max and QT AUC between the two preparations did not exceed 20% ($P < 0.05$, Westlake's method).

5 This study illustrates the fact that pharmacodynamic equivalence, let alone therapeutic equivalence, does not necessarily imply plasma level equivalence, as assessed by the current method.

Keywords quinidine long acting preparations bioequivalence

Introduction

We have compared the bioavailability of two forms of quinidine compounds (Kinidin Durule[®] and Longacor[®]) aimed at providing prolonged plasma levels. The theoretical interest of such preparations would be to allow a lengthened interval between two intakes. Measurements of QT interval on the ECG were used as a mean to assess pharmacodynamic effects. Any difference in biochemical results which is not reflected in biological effects would be of no clinical importance.

Methods

Subjects

Six healthy volunteers participated to the trial. They were male (age ranged from 19 to 30 years) and weight ranged from 58 kg to 68.5 kg (mean: 61.6 kg). Before entry, the volunteers were given a full description of the nature and goals of the

study. Written informed consent was obtained. An independent physician visited them prior to the investigation. The following blood measurements were within normal ranges: calcium, urea, uric acid, cholesterol, proteins, creatinine, bilirubin, potassium, as well as white and red cell counts.

Study design

A cross-over randomized design was used (Table 1).

Procedure

For each volunteer two experiments were separated by at least 7 days. Blood samples (10 ml) were drawn immediately before and after intake of two tablets of either drugs (0, 15 min, 30 min, 1, 2, 3, 4, 6, 8, 12 and 24 h). Before blood drawing, an ECG was recorded (Siemens, 4 tracks, 100 min/s, 1 cm = 1 mV); for each subject one lead had been chosen previously which

Table 1 Experimental design

Patient	Treatment			
	1	2	3	4
1	B	A	A	B
2	A	B	A	B
3	B	B	A	A
4	A	A	B	B
5	A	B	B	A
6	B	A	B	A

A: Quinidine arabogalactane sulphate (Longacor)

B: Quinidine bisulphate (Kinidin durule)

provided the easiest measurement of QT duration. Blood pressure and heart rate were recorded each time. Experiments began at 08.30 h. Patients were fasting for 12 h and until 4 h after drug intake. Plasma levels of quinidine were determined with a high-performance liquid chromatography method according to the technique proposed by Guentert *et al.* (1979) and Bonora *et al.* (1979). The method is appropriate for the determination of quinidine and its main metabolites (dihydroquinidine and 3-hydroxy-quinidine). The minimum detectable concentration 0.1 µg/ml of plasma. The coefficients of variation were tested for a concentration of 0.5 µg/ml (20 samplings). It showed a within day coefficient less than 4.7% and day to day less than 6.5%.

Treatments

Kinidin Durules® is a sustained release tablet containing 250 mg quinidine bisulphate (QBS) equivalent to 200 mg of quinidine sulphate or 165 mg of quinidine. Sustained-release is due to a special tablet design. Therapeutic plasma levels are usually obtained 8 h after intake. Quinidine arabogalactane sulphate (QAGS) is a quinidine complex; the complexing agent is a polyosidic compound which is not absorbed. The tridimensional space complex configuration of arabogalactane sulphate explains the prolonged release of quinidine in aqueous milieu. Sustained plasma levels have been observed in previous experiments (Frigo *et al.*, 1977; Ochs *et al.*, 1980; Renais *et al.*, 1971). Tablets contain 165 mg of quinidine. The therapeutic efficacy of quinidine arabogalactane sulphate (0.275 mg two times daily) has been shown in the prevention of relapse of atrial fibrillation after cardioversion (Boissel *et al.*, 1981).

Pharmacokinetic parameters

For each experiment the following classical

parameters were determined: $C_{\max}$, $t_{\max}$ and area under the curve (AUC). Computation of area under the curve was performed using the trapezoidal method; for plasma concentrations below the threshold of sensitivity of the h.p.l.c. technique, values have been assigned to zero (Metzler, 1974). The last measures (24 h) were consistently below the detection threshold of the method.

Pharmacological effect

QT was measured by an independent technician on three consecutive beats. The average was used as observed QT (QT_o). A theoretical QT (QT_c) was computed for each heart rate from regression curve between QT and heart rate established for each subject from independent ECG recorded at different rates. The ratio R of observed and theoretical QT (QT_o/QT_c) was computed each time and used as input in statistical analysis. The total effect of each drug intake has been estimated by the integral of R along time. That quantity was approached by AUC of R which was computed according to the trapezoidal rule.

Statistical analysis

Statistical comparisons were made using classical ANOVA (two ways with repeated measures) and F-test, for $C_{\max}$, $t_{\max}$ and AUC calculated using the trapezoidal rule over a finite interval (Metzler, 1974). Non-significant results with classical statistical tests do not imply an equivalence of the compared measures. In the case of bioavailability studies, the question is more often whether two preparations could be considered equivalent rather than different. In order to deal with this problem methods have been developed such as the one proposed by Westlake. It is based on the construction of confidence intervals for the difference between treatments. With the Westlake method symmetrical confidence interval of the difference of the two means (reference drug and new drug) are constructed around zero. This yields for the mean of the new drug symmetrical limits around the mean of the reference drug. The investigator must decide beforehand, within which region equivalence can be accepted (Westlake, 1976; Spriet & Beiler, 1978). This region is called the bioequivalence interval. If the observed confidence limits are outside the settled values, one cannot conclude to equivalence. The usually recommended boundaries of the confidence interval for accepting bioequivalence lie between 15 and 35% (Westlake, 1976). Quinidine is known to have a rather narrow spectrum of effective plasma concentration. For accepting

bioequivalence the new formulation should be between 80 and 120% as available as the standard (with 95% confidence), the clinical implication being that variations over 20% in plasma levels could lead to unacceptable increase of the frequency of unwanted effects.

In addition, a linear regression model has been fitted to various sets of factors including patients, treatments, time since first experiment, residual effect of the previous experiment (Seal, 1964). This approach allows to take into account more confounding variables than ANOVA. It should be noted that the fitting of experimental data was rather good with the adjusted model since goodness of fit evaluated by r^2 coefficient was 48% for $C_{\max}$, 54% for $t_{\max}$ and 73% for AUC.

Results

Pharmacokinetics

Results of the pharmacokinetic study are given in Table 2 and Figure 1.

ANOVA No significant difference in $C_{\max}$ was observed between treatments. Although the difference was not statistically significant, the observed average of $t_{\max}$ with QBS was 5 h, and 3.7 h with QAGS ($P < 0.05$). The AUC did not differ significantly between the two treatments.

Linear model The linear model confirmed that the two preparations differed regarding $t_{\max}$ ($P < 0.05$). Furthermore, it showed that between patient variations of AUC were statistically significant ($P < 0.05$, means of AUC per patient varied from 7.98 to 15.74). There was no interaction effect between two consecutive experiments.

In order to evaluate the importance of intra subject variability, we computed the ratio of intra subject sum of squares upon total sum of squares. For AUC of plasma levels, QAGS gave

a higher ratio than QBS: 49% vs 16%. This would indicate that the plasma concentrations reached with a given dose of QAGS vary more in the same subject than with QBS.

Westlake The Westlake test failed to show an equivalence within an interval of 20% around the values of the reference drug (quinidine bisulphate) for each of the three parameters.

Pharmacodynamics

The results of ECG analysis are given in Table 3 and Figure 2.

ANOVA The delay up to $R_{\max}$ (referred as $t_{QT\max}$) was not statistically different between the two drugs. For $R_{\max}$ (referred as $QT_{\max}$) and QT AUC reflecting the overall effect, the mean values were not significantly different with the ANOVA.

Westlake Although $t_{QT\max}$ were not equivalent, for $QT_{\max}$ and QT AUC it is possible to accept equivalence within the 20% ranges.

Therefore as far as total effect on QT is concerned the two forms are bioequivalent although our data failed to show equivalence for plasma bioavailability.

Discussion

Bioavailability is a confusing term. It includes the amount of active drug which reaches the site of pharmacological action, as well as the speed at which it gets there. Comparative bioavailability and bioequivalence are not less confusing. The primary question is actually whether two formulations containing the same active substance are

Table 2 Plasma levels

	Quinidine arabogalactane sulphate (QAGS)		Quinidine bisulphate (QBS)		95% symmetrical limits for QAGS around the mean of QBS (Westlake test)
	Mean	(s.e. mean)*	Mean	(s.e. mean)*	
$C_{\max}$ ($\mu\text{g/ml}$)	1.056	(0.077)	1.002	(0.077)	$1.002 \pm 38.3\%$
$t_{\max}$ (h)	3.667	(0.322)	5.000	(0.322)	$5 \pm 49.6\%$
AUC ($\mu\text{g ml}^{-1} \text{ h}$)	12.555	(0.714)	12.683	(0.714)	$12.683 \pm 24.7\%$

*s.e. mean was computed using the residual variance obtained with the analysis of variance

Figure 1 Mean plasma level curves in six normal males after single doses of quinidine arabogalactate (●) and quinidine bisulphate (◆).

therapeutically equal. Metzler (1974) distinguished three levels: 1. chemical equivalence, the drugs containing equal amounts of the same active substance; 2. biological equivalence, when two chemically equivalent drugs deliver the same amount of active substance, to the circulating blood; 3. therapeutic equivalence, when the chemical equivalents produce the same therapeutic effect as measured by the control of symptoms or disease. A fourth level has been added (Alexandre & Devissaguet, 1980): pharmacological equivalence which is not different from biological equivalence when the time-courses of substances concentration at receptors are the same. In addition, due to differences in intestinal release, two drugs containing different amounts of active substance might lead to biological and/or pharmacological equivalence.

Often bioequivalence of two formulations is

assessed by comparing the time course of plasma levels. An important and overlooked basic assumption underlies this approach. One assumes that two formulations that do not differ very much in area under curve, peak level and time to peak of plasma concentrations are therapeutical equivalents. It is clear that such an assumption could be inappropriate. A better approach is to investigate pharmacological equivalence of the two formulations. However, due to the lack of sensibility of available tools, even two pharmacological equivalents might have different clinical efficacy. It is the case when the therapeutic effect of the active substance comes from a pharmacological action different from that investigated.

The use of the Westlake test in a bioequivalence study is of interest since the classical statistical tests like the ANOVA are only aimed at showing differences. However, this method has its own

Table 3 QTC effects

	Quinidine arabogalactane sulphate (QAGS)		Quinidine bisulphate (QBS)		95% symmetrical limits for QAGS around the mean of QBS (Westlake test)
	Mean	(s.e. mean)*	Mean	(s.e. mean)*	
QTC max (ratio observed/computed)	1.123	(0.009)	1.109	(0.009)	1.109 ± 4.21%
tQTC max (h)	2.79	(0.69)	4.50	(0.69)	4.50 ± 93.46%
AUC (Ratio x hours)	36.86	(0.22)	36.82	(0.22)	36.82 ± 2.61%

s.e. mean was computed using the residual variance obtained with the analysis of variance

Figure 2 Evolution of QT ratios (observed/theoretical) in six normal males after single dose of quinidine arabogalantane (●) and quinidine bisulphate (◆).

limits. It should be recognized that the bioequivalence interval set at 20% is somehow arbitrary and should probably be adapted to the type of drug and for expected effects. The power of the test (as with classical tests) is proportional with the number of subjects, in other words a lack of power leads also to situation of no possible conclusion.

In this study we investigated jointly time-course of plasma levels and one pharmacological effect of two quinidine formulations with a crossover designed trial. No statistical difference was detected either between the plasma levels parameters of the two compounds, or between the pharmacological effects.

However, the Westlake test could not allow to show an 'equivalence' for area under curve, peak level and time-to-peak of plasma levels. This was not surprising because of the lack of power of the test. The variability within and between subjects was higher than expected. A greater number of subjects would have probably been necessary.

Nevertheless with this same number of subjects the overall effects on the QT intervals were similar with both preparations. Since the overall effect could be viewed as the most important parameter, the two formulations could be said to be pharmacologically equivalent, despite the

non equivalence in time-to-peak. Since many metabolites of quinidine are pharmacologically active (Guentert *et al.*, 1979a) they may contribute to explain the present findings.

The correspondence between bioequivalence intervals of plasma levels and biological effects depends on the concentration effects, relationship and the portion of the curve investigated. Therefore, our results obtained with a low dose of quinidine are only valid for this dosage. One cannot extrapolate these results safely to other portions of the curve.

Conclusion

Despite the fact that it was not possible to conclude to pharmacokinetic bioequivalence of two compounds of long acting quinidine the overall pharmacodynamic effect on the ECG QT interval was found similar. This was an interesting finding since it demonstrated once again that the plasma concentration of a drug might not reflect the pharmacological effects.

It should be also kept in mind that an equivalence of the drugs on an ECG QT interval does not imply necessarily a therapeutical equivalence.

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