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Relationship between Quinidine Plasma and Saliva Levels in Humans

Keyphrases □ Quinidine—plasma and saliva concentrations compared, humans □ Saliva—determination of quinidine levels, correlated with plasma levels

To the Editor:

Increasing applications of the principles of pharmacokinetics to clinical situations (1) have emphasized the need for rapid, noninvasive techniques for monitoring drug concentrations in biological fluids, especially with pediatric patients or whenever a large number of serial samples is indicated. Since several drugs such as salicylate (2), sulfonamides (3), barbiturates (4), tetracyclines (5), phenytoin (6), theophylline (7), and digoxin (8) are secreted in saliva, this measurement appears to have potential use, especially when these levels can be correlated with plasma levels in patients.

There are no previous reports concerning salivary concentrations of quinidine. However, blood level monitoring of quinidine is occasionally useful clinically, since the drug exhibits an extremely narrow range between a usually effective serum level (2 μg/ml) and a usually toxic serum level (8 μg/ml) (9).

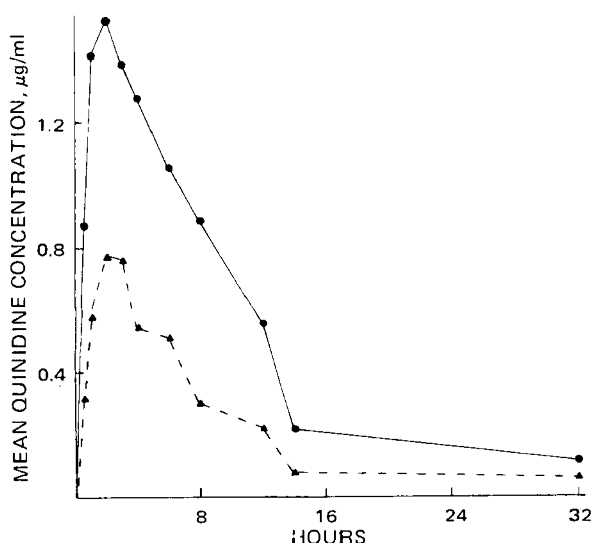

Figure 1—*Mean plasma and saliva concentrations as a function of time for Subject 1. Each concentration is the mean of two determinations. Key:* ●, *plasma concentrations; and* ▲, *saliva concentrations.*

Table I—Relationship between Plasma and Saliva Concentrations of Quinidine in Three Subjects

Subject	Mean Plasma–Saliva Ratio ($\pm SD$)	Correlation Coefficient	Statistical Significance
1	2.29 (±0.89)[a]	0.885	$p < 0.001$
2	1.55 (±0.70)[a]	0.681	$p < 0.01$
3	2.35 (±0.70)[b]	0.825	$p < 0.001$

[a] Eighteen determinations. [b] Nineteen determinations.

Thus, a technique that would obviate the need for collecting serial blood samples would be of value.

The data reported here on saliva levels of quinidine were obtained in conjunction with a larger study on the bioequivalency of various commercially available quinidine sulfate tablets in humans. The specific value of this study relates best to the possible use of saliva in bioavailability studies rather than for clinical monitoring.

Three adult, normal, male subjects involved in the bioequivalence study were selected randomly and, in addition to providing blood samples (by venipuncture), were requested to expectorate into 10-ml test tubes from approximately 5 min before until 5 min after each blood collection or until 3–5 ml of mixed saliva had been obtained. Blood and saliva quinidine levels were determined at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 32 hr after administration of two 200-mg tablets of any one of four brands of quinidine sulfate. These same subjects repeated this procedure a second time with at least a 1-week interval between administrations. The values reported in Table I for each subject were pooled from the two different runs and involve 18 or 19 determinations/subject since saliva levels were not always sufficiently high to be determined at the 24- and 32-hr time periods.

Aliquots (0.5 ml) of plasma or saliva (centrifuged to remove sputum) at each time period were assayed by the fluorometric method of Cramer and Isaksson (10) with only slight modifications. Blank specimens of serum and saliva were assayed in the same manner as the samples, and the appropriate blank corrections were applied. Figure 1 shows a plot of plasma and saliva quinidine concentrations as a function of time for one of the three subjects (Subject 1 of Table I).

Although a significant correlation exists between plasma and saliva levels of quinidine, differences in the extent of correlation are evident among the three subjects (Table I). While a number of studies (2, 6) showed an even better correlation between plasma and saliva levels of other drugs, the present study nonetheless suggests that quinidine can be detected in human saliva in measurable concentrations and that these concentrations are related to their corresponding plasma levels. The pH of the saliva samples was not measured, although fluctuations in saliva pH could possibly account for the observed intrasubject variability in plasma saliva ratios for the weak base quinidine (11).

Plasma samples in this study consisted of both bound and unbound drug, and better correlations might have resulted if unbound quinidine in plasma

had been determined since often only the free and nonionized drug establishes an equilibrium between blood and saliva concentrations (3, 4). For example, Killman and Thaysen (3) found that unbound sulfonamides in human saliva were proportional to the concentration of unbound drug in the plasma. Similar findings were reported for phenytoin (6). Thus, we are presently developing methods to study unbound quinidine in plasma so that these values can then be compared to saliva levels to determine if even better plasma–saliva level correlation exists for this drug.

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Dissolution of Model Gallstones in Bile Acid Solutions I: Implications for T-Tube Infusion Treatment of Retained Common Duct Stones with the Cholate System

Keyphrases □ Dissolution—gallstones, *in vitro*, T-tube infusion treatment with sodium cholate □ Gallstones—*in vitro* dissolution, T-tube infusion treatment with sodium cholate □ Sodium cholate—infusate for *in vitro* dissolution of gallstones by T-tube infusion

To the Editor:

The problem of retained common bile duct stones affects about 5% of the patients undergoing cholecystectomies (1–3). Considerable effort has been directed by clinicians[1] (2–6) to find a nonsurgical solution to the problem which will save the patient a high risk operation.

One study (2) showed that retained common bile duct stones can be dissolved using a T-tube infusion; sodium cholate solution was used as the infusate. The investigators were able to dissolve retained stones in 12 of 22 patients within 14 days of continuous infusion at a rate of 30 ml/hr. With the same technique and a similar formula, retained stones were dissolved in five of six patients within 5 days (3).

However, recent controlled T-tube infusion studies were less successful[1]. Only two of six patients showed dissolution of the retained stones. This difference in results between the studies was not expected since there was only a 25% difference in the cholate concentration levels between the formulations tested.

This communication presents a probable physical–chemical explanation for the differences observed. This explanation is based upon the surface resistance to the cholesterol dissolution in bile acid media and the influence of electrolytes upon it.

Compressed cholesterol monohydrate pellets were used as model cholesterol stones. Infusion media were prepared according to Way *et al.* (2) and La-Russo *et al.*[1], using a purified grade of cholic acid[2]. The pH of the media was adjusted to pH 7.5 with sodium hydroxide.

Dissolution experiments were conducted using the apparatus and procedures reported previously (7). Equilibrium solubilities were measured after allowing excess amounts of ^{14}C-cholesterol monohydrate to equilibrate with the infusion media with continuous shaking at 37°.

Dissolution rates and solubility values are shown in Table I. The resistance to dissolution, R, was calculated from the equation:

$$\frac{J}{A} = \frac{C_s}{R} \qquad \text{(Eq. 1)}$$

where J/A is the dissolution rate per unit surface area, and C_s is the solubility.

The data show that the rate of cholesterol dissolution in the Way *et al.* (2) and Lansford *et al.* (3) infusion medium is about nine times faster than that in the La Russo *et al.*[1] medium. This large difference in the rate of dissolution cannot be explained on the basis of a diffusion-controlled mass transport mechanism, because the solubility increases by only about a factor of two (Table I) and the diffusivities are not expected to vary significantly.

These results, therefore, point to the likely importance of surface kinetic factors in the dissolution process. A significant interfacial resistance has been shown (7–11) to govern the rate of cholesterol monohydrate and cholesterol gallstone dissolution in bile media generally, and it is proposed that interfacial resistance is the primary factor responsible for the difference in cholesterol dissolution and, hence, the

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