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Salivary excretion of mexiletine after bolus intravenous administration in rats

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Abstract—Salivary excretion of mexiletine was investigated following bolus intravenous administration (10 mg kg^{-1}) in rats. Parotid and mandibular saliva was collected separately by stimulating salivation with constant rate infusion of pilocarpine (3 mg kg^{-1} h^{-1}). The mexiletine levels in blood plasma and parotid and mandibular saliva declined biexponentially with time in almost parallel fashion. Although the mexiletine levels in both types of saliva were lower than that in plasma, the drug level in parotid saliva was always higher than that in mandibular saliva. Significant correlations were observed when all data relating mexiletine concentration in plasma and saliva were included ($P < 0.001$). The saliva/plasma drug concentration ratios (S/P ratios) did not vary to a large extent (0.56 ± 0.10 for parotid saliva, 0.21 ± 0.06 for mandibular saliva), but there was a consistent tendency for the higher plasma drug levels in the distribution phase to produce relatively high S/P ratios for both parotid and mandibular saliva. Moreover, the plasma mexiletine levels calculated by the equation of Matin et al (1974) employing the observed values for the saliva drug level, saliva pH and free fraction of mexiletine in plasma were significantly higher than the observed drug levels. Therefore, it is suggested that the salivary excretion of mexiletine could not be explained quantitatively by simple, passive secretion based on pH-partition theory.

The salivary excretion of drugs has been studied essentially from a clinical point of view, namely to find a reliable method to utilize the saliva drug level for therapeutic drug monitoring. It has been suggested that saliva samples might be substituted for plasma (or serum) in therapeutic drug monitoring or in clinical pharmacokinetic studies if there is a constant correlation of saliva and plasma drug levels over a wide range of concentration (Dvorchik & Vesell 1976; Horning et al 1977). However, relatively large variations in the saliva to plasma concentration (S/P) ratio for several drugs have limited the clinical use of saliva in monitoring drug levels (Danhof & Breimer 1978).

Mexiletine, which is one of the class Ib antiarrhythmic drugs, has been widely used in arrhythmic patients. Since the therapeutic range is relatively narrow (0·5–2·0 μg mL^{-1} (Talbot et al 1973)), its therapeutic monitoring by using blood samples from the patients is desirable. It has been reported that mexiletine was excreted into the saliva with higher levels than those in plasma or serum of man (Beckett & Chidomere 1977; Katagiri et al 1989, 1991), so that a possible utilization of the saliva sample in place of blood plasma (or serum) may provide a non-invasive, sensitive method to monitor this drug. However, pharmacokinetic studies on the salivary excretion mechanism of mexiletine have only been carried out on whole saliva samples (Katagiri et al 1989, 1991).

In the present study, salivary excretion kinetics of mexiletine was investigated following bolus intravenous administration in rats using parotid and mandibular saliva.

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Materials and methods

Materials. Mexiletine hydrochloride was kindly supplied by Boehringer Ingelheim Japan Co. Ltd (Kawanishi, Japan). Fluorescamine used for fluorometric derivatization was purchased from F. Hoffman-La Roche Co. Ltd (Basle, Switzerland). 1-Pentane sulphonic acid (Pic B-5) used as an ion-pairing reagent was purchased from Waters (Milford, USA). All other reagents and solvents were commercial products of analytical grade.

Animals. Male Wistar rats (360–380 g, 12 weeks old) were anaesthetized with pentobarbitone (50 mg kg^{-1}, i.p.) after overnight fasting for 12 h. Body temperature was kept at 37·5°C by using a heated pad placed under the supine rat.

Drug administration and collection of blood and saliva samples. After tracheotomy and catheterization, cannulae were made according to the method described by Watanabe et al (1987).

The femoral vein was cannulated with a polyethylene tubing (PE-50) for infusion of pilocarpine hydrochloride at a constant rate of 3·0 mg (free base) kg^{-1} h^{-1} to stimulate salivation. The jugular vein was also cannulated with silicone polymer tubing (i.d. 1·0 mm, o.d. 1·5 mm; Dow Corning, Tokyo, Japan) for administration of mexiletine and for collection of blood samples. Bevelled polyethylene tubing (PE-10) was inserted into the mandibular and parotid duct orifices in the buccal cavity to collect saliva samples separately. Following constant rate infusion of pilocarpine for 2–3 h (Watanabe et al 1987), mexiletine was administered intravenously as a bolus dose of 10 mg kg^{-1} to rats. Saliva samples were collected periodically for 20 min. Blood samples (0·13 mL) were withdrawn at the midpoint of the periodical saliva collection intervals and were centrifuged to obtain plasma after heparinization.

Analytical procedures. Concentrations of mexiletine in plasma and saliva were determined by the HPLC method of Grech-Bélanger et al (1984) with modifications in the extraction method. A sample (50 μL) of plasma or saliva was rendered alkaline with 100 μL of 4 M NaOH and was made up to 500 μL with distilled water. This mixture was extracted with 3 mL of diethylether and the organic extract (2 mL) was evaporated to dryness after addition of 50 μL of 0·1 M hydrochloric acid in acetone. Finally after fluorescent derivatization of mexiletine in the extracted residue with fluorescamine in acetone, 10 μL was injected into the HPLC.

Data analysis. The plasma and saliva mexiletine concentration-time data were analysed according to the two-compartment model with rapid intravenous administration using a non-linear least squares microcomputer program MULTI (Yamaoka et al 1981). The statistical evaluation of the data was performed using Student's *t*-test.

Results

Plasma and saliva mexiletine concentrations after bolus intravenous administration. Fig. 1 shows the mexiletine concentration time profiles for plasma, and parotid and mandibular saliva after bolus i.v. administration of mexiletine. The drug concentration in the three biological fluids decreased biexponentially with time in almost parallel fashion. The mexiletine levels in both types of saliva were always lower than those in plasma. Parotid saliva showed higher mexiletine levels than did mandibular saliva. The pharmacokinetic parameters are summarized in Table 1. The values for α, β and $t_{\frac{1}{2}\beta}$ were almost the same among the three biological samples.

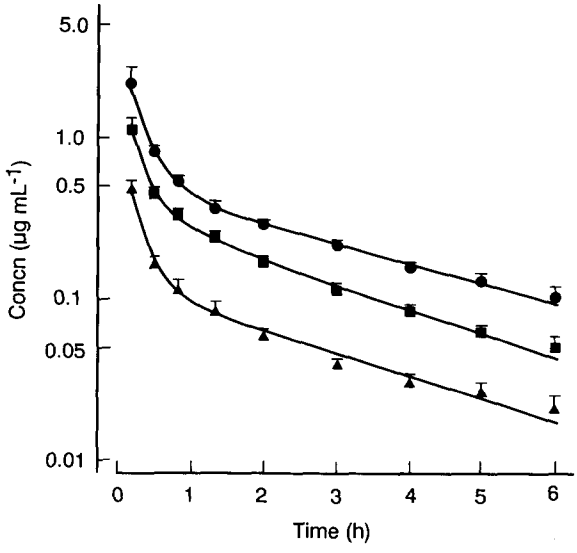

FIG. 1. Plasma and saliva levels of mexiletine after bolus intravenous administration of 10 mg kg^{-1} of the drug in rats. Each point and vertical bar represent the mean and s.d. of 4 or 5 rats. Key: ●, plasma; ■, parotid saliva; ▲, mandibular saliva.

Correlation between plasma and saliva drug concentrations. The regression equations for both parotid and mandibular saliva against plasma mexiletine concentrations are shown in Table 2. There were significant correlations for all data (n = 38) between plasma (x) and saliva (y) concentrations (parotid: r = 0·970, $P < 0.001$; mandibular: r = 0·865, $P < 0.001$).

S/P ratio and saliva pH. The mean S/P ratio of mexiletine and saliva pH are also shown in Table 2. The S/P ratio of parotid saliva (0·56 ± 0·10) was significantly higher than that of mandibular saliva (0·21 ± 0·06). In contrast, the pH of parotid saliva was significantly lower than that of mandibular saliva ($P < 0.05$).

Estimation of plasma mexiletine level from the saliva level. Matin et al (1974) have proposed that, for a weak base, the S/P ratio can be calculated from the following equation based on pH-partition theory,

$$\frac{C_s}{C_p} = \frac{1 + 10^{(pK_a - pH_s)}}{1 + 10^{(pK_a - pH_p)}} \cdot \frac{f_p}{f_s}$$

where pH_s = pH of saliva, pH_p = pH of plasma, pK_a = pK_a value of the drug, f_p = free fraction of drug in plasma, and f_s = free fraction of drug in saliva. The saliva free fraction was assumed to be approximately unity. The plasma free fraction for mexiletine was determined by ultrafiltration at two different concentrations

Table 1. Pharmacokinetic parameters for plasma and saliva mexiletine after bolus intravenous administration in rats.

		Saliva	
Parameter[a]	Plasma	Parotid	Mandibular
A (μg mL^{-1})	1·42 ± 0·33	—	—
B (μg mL^{-1})	0·279 ± 0·051	—	—
α (10^{-2} min^{-1})	6·60 ± 2·63	7·28 ± 1·29	9·04 ± 3·67
β (10^{-3} min^{-1})	4·80 ± 1·04	5·76 ± 1·29	5·27 ± 1·35
$t_{\frac{1}{2}\beta}$ (min)	150·2 ± 34·0	125·9 ± 31·8	138·2 ± 33·2

Each value represents the mean ± s.d. of 5 rats. [a] Estimated by program MULTI [Weight(i) = 1/Ci].

Table 2. Regression equation for saliva against plasma mexiletine levels and comparison of the S/P ratio and saliva pH in parotid and mandibular saliva after bolus intravenous administration in rats.

Saliva	Regression equation[a]	S/P ratio (mean ± s.d.)	Saliva pH (mean ± s.d.)
Parotid	y = 0·566x + 0·004 (r = 0·970)[b] (n = 38)	0·56 ± 0·10 (n = 38)	8·17 ± 0·15 (n = 10)
Mandibular	y = 0·182x + 0·008 (r = 0·865)[b] (n = 38)	0·21 ± 0·06[c] (n = 38)	8·32 ± 0·17[d] (n = 13)

Number of data points is shown in parentheses. [a] Saliva and plasma mexiletine levels are represented as y and x, respectively. [b] $P < 0.001$. [c] Significantly different from the value of parotid saliva ($P < 0.01$). [d] Significantly different from the value of parotid saliva ($P < 0.05$).

around 2·0 and 0·14 $\mu g\ mL^{-1}$ in total plasma. At all time points, the plasma mexiletine level calculated from the corresponding saliva level (both parotid and mandibular) was significantly higher (approx. 2·7–7·7 times) than the observed levels ($P < 0.05$, data not shown).

Discussion

There are few reports on the salivary excretion mechanism of weak basic drugs, including studies on procainamide in rats (Watanabe et al 1987; Iwamoto et al 1988). In the present study, both parotid and mandibular saliva levels of mexiletine were lower than the plasma levels in rats. However, it has been reported that the levels of mexiletine in whole (mixed) saliva are higher than the plasma or serum drug levels in man (Beckett & Chidomere 1977; Katagiri et al 1989, 1991). A similar difference was reported for procainamide between man (Galeazzi et al 1976) and rats (Watanabe et al 1987). This apparent species-difference in the excretion of mexiletine into saliva may be due to the different experimental conditions, including anaesthesia and stimulation of salivation.

The mexiletine level in each type of saliva declined in parallel with plasma drug level (Fig. 1, Table 1). These results suggest that the saliva level might be substituted for the plasma level or could be used to predict the plasma pharmacokinetics of the drug. The observed S/P ratio for parotid saliva was larger than that for mandibular saliva ($P < 0.01$) and the pH value in parotid saliva was significantly lower than that in mandibular saliva ($P < 0.05$). According to the equation of Matin et al (1974), a decrease of saliva pH results in a higher S/P ratio for a weak base. Thus, it was considered that a glandular difference in the observed S/P ratio of mexiletine could be qualitatively explained by this difference in saliva pH. This glandular difference was the same as that reported for another basic drug, procainamide, in rats (Watanabe et al 1987). Similar explanations for the gland-type differences in salivary excretion have been suggested for other drugs in experimental animals (Watanabe et al 1981a, b, 1985a, b; Hayashi et al 1988).

The calculated mexiletine levels in plasma from saliva data were always significantly higher than the observed levels. These results suggested that the equation based on the pH-partition theory proposed by Matin et al (1974) would be only qualitatively applicable to the salivary excretion of mexiletine in rats suggesting some specific mechanism for the salivary secretion of mexiletine.

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