Pharmacokinetics of Diethylcarbamazine: Prediction by Concentration in Saliva

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The concentration of diethylcarbamazine in saliva was used to determine pharmacokinetic parameters, in comparison to plasma and urine concentrations. Six healthy adult male volunteers were administered 150 mg diethylcarbamazine with 400 ml of water. At seven different time intervals, blood, urine and saliva samples were taken, and different pharmacokinetic parameters measured.

The plasma-saliva concentration ratio was calculated as 1.53 whereas the observed ratio was 3.82. The half lives, times to reach peak plasma concentration, and elimination rate constants did not show any significant difference in the different samples. The plasma peak concentration and areas under the curve were significantly (p<0.05) increased from those of the saliva. At 24 h, when diethylcarbamazine was absent in urine, the plasma and saliva concentrations were almost zero. Diethylcarbamazine is secreted in saliva, and its concentration in saliva can be used to monitor drug therapy.

Key words diethylcarbamazine; saliva concentration; pharmacokinetic parameter; urinary excretion

Drugs can enter the gastrointestinal tract by salivary excretion. The transport mechanism is primarily passive diffusion of the non-ionised moiety. However, active secretion also appears to exist, since it has been found that probenecid reduces penicillin excretion into saliva. Several drugs have been found to be excreted into the saliva. Transfer from plasma to saliva seems to follow passive diffusion and convective transport.

Diethylcarbamazine (DEC) has been found to be beneficial in respiratory and pulmonary filariasis. Coma and unconsciousness are the two main features in the fatalities accompanying DEC administration. Since the use of saliva concentration is an ideal method for drug therapy monitoring because it is non-invasive and a large number of samples can be obtained, and is thus particularly useful in ambulatory paediatric and geriatric patients.

The aims of this study were a) to find out if DEC is excreted in saliva, b) to quantify the extent of excretion, and c) to calculate the plasma/saliva ratio. Since DEC has been shown to be beneficial in respiratory and pulmonary filariasis, it is desirable to investigate its salivary secretion.

MATERIALS AND METHODS

Six healthy adult male volunteers aged 20—27 years (undergraduate and post graduate students of College of Health Sciences, Nnamdi Azikiwe University, Nnewi campus, Anambra State, Nigeria), who were normal according to medical history and physical examination, participated in this study after giving informed consent. Subject were not on any form of medication. After an overnight fast, they were given 150 mg DEC with 400 ml of water. Food was withheld for 4 h post drug. Blood, urine, and saliva samples were taken at 0, 1, 2, 4, 8, 12 and 24 h after DEC administration. The saliva samples were collected over 5 min intervals after volunteers had gaggled their mouth with water. Saliva flow was stimulated by having each volunteer masticate bubble gum. In vitro studies indicated that there was no adsorption of drugs to the bubble gum. Blood and saliva samples were immediately frozen and stored for subsequent analyses.

Assay Method The saliva samples were diluted with 2 ml of water and stored frozen at −20 °C until analysis. DEC concentrations were determined by the colorimetric method. Saliva samples (0.5 ml) were added to test tubes and shaken vigorously with 2 ml of 30% NaOH and 5 ml of ethane-1,2-dichloride. The samples were then analysed at 432 nm using a Ciba Corning colorimeter model. The plasma and urine samples were treated similarly.

The calibration curves were prepared using DEC concentrations of 1000, 500, 250, 125, 62.5, 31.25, 15.625, 7.813, 3.906 and 1.952 μg/ml.

Pharmacokinetic Analysis To analyse the saliva DEC concentration—time data, we assumed that DEC kinetic after oral administration could be described by a one-compartment open model with linear kinetics. The concentration—time data for each study period from 1—24 h after completion of DEC administration were fitted by non-linear least square regression to the following equation:

\[ C = C_0 e^{-\frac{0.693}{K} t} \]

Where C is the concentration at time t and C₀ is concentration when t=0.

The elimination half life was calculated from the elimination rate constant by the formula

\[ T_{1/2} = \frac{0.693}{K} \]  \hspace{1cm} (1)

The area under the saliva concentration—time curve \( AUC \) was calculated from 0—24 h by the trapezoidal rule and was extrapolated to infinity by adding the DEC concentration at 24 h divided by K.

\[ AUC_{0-\infty} = AUC_{0-24} + \frac{C_{24}}{K} \]  \hspace{1cm} (2)

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The volume of distribution ($V_d$) in saliva or plasma was calculated for each treatment by dividing the DEC dose by the initial saliva/plasma concentrations when $t$ is equal to zero respectively.

The total body clearance was obtained by the product of $K$ and $V_d$. 6,7 Renal clearance of DEC was calculated by dividing the amount of DEC recovered in urine by the area under the curve for saliva concentration versus time from 12 to 24 h. The percentage of non-rerenal clearance for each treatment was obtained by subtracting the renal clearance from the total body clearance and multiplying the quantity by 100 divided by the total body clearance. The method of residuals was used to determine the absorption rate constant ($K_a$) while the concentration maximum ($C_{max}$) and corresponding time ($T_{max}$) were read off from the saliva concentration versus time curve.

**Statistical Analysis** The difference between two related samples was analysed with a paired t-test. 8 Differences were considered statistically significant at $p<0.05$ (two tailed). The data are expressed as mean±S.E.M. The saliva–plasma concentration ratio ($R_{ps}$) was calculated using the equation proposed by Matin and colleagues for the prediction of plasma–saliva concentration ($R$) for bases given by

$$R_{ps} = \frac{1}{1-10}\left(pK_a - pHs\right)\times F_p\times F_s$$

where $pHs$=saliva pH, $pHp$=plasma pH, $F_p$=fraction of unbound drug in plasma and $F_s$=fraction of unbound drug in saliva.

**RESULTS AND DISCUSSION**

Effective chemotherapy of microbial infections requires that sufficient concentration of drug(s) be present at the site of infection. In this regard, it has been suggested that saliva reflects drug levels in the liquid coating of the nasopharynx. 10,11 In view of the aforementioned studies, investigation of the concentration of DEC in saliva was examined.

The mean pharmacokinetic parameters, viz., total body clearance, renal clearance, percentage non-renal clearance, concentration maximum, area under the curve at infinity, volume of distribution, elimination rate constant, absorption rate constant, elimination half life, absorption half life, mean absorption time, are shown in Table 1. Figure 1 shows the concentration of DEC in saliva compared to the concentration in serum plotted against the length of time after the administration of DEC. The shapes of the mean plasma and saliva concentration–time profiles were identical and resembles those obtained in the individual subjects.

DEC concentrations were detected in all plasma and saliva samples. The elimination half lives, times to reach peak concentration, and elimination rate constants did not show significant differences between the two samples.

The plasma value for peak concentration and area under the curve from zero to 24 h and zero to infinity were significantly ($p<0.05$) higher than those of saliva. The mean plasma level at 24 h of maximum concentration of the drug was $49.0±8.17\mu g/ml$ compared to $16.23±1.74\mu g/ml$ for the saliva. Bioavailability analysis of the plasma and saliva concentration–time data indicated that the DEC was appreciably absorbed into the plasma ($AUC_{0-24h}$ 428.64±9.17) and saliva ($AUC_{0-24h}$ 112.26±6.52 $\mu g \cdot h^{-1}\cdot ml^{-1}$) though not to the same extent.

DEC has a $pK_a$ of 6.0. The plasma–saliva DEC concentration ratio was calculated as 1.53 based on a $pK_a$ of 6.0. $F_p$ and $F_s$ in Eq. 3 were 0.002857 and 0.000748 respectively, and the $pH$ was equal to 7.4. The value of $pH$s taken to be 6.5, the mean $pH$ of saliva samples reported by Matin et al.12 This calculated value differs from the value of 3.82 obtained from the experiment. The Matin equation presumed no partitioning of the drug, whereas Eatman et al.12 maintained that discrepancies between the experimental and calculated values of the plasma–saliva concentration ratios of sulphanethoxazole and Trimetoprim may have resulted from partitioning of the drugs in the buccal cavity. This was also stated in a recent study.13

The relationship between the cumulative amount of DEC excreted in the urine and the plasma–saliva level time curve is shown in Fig. 2. It is evident from this figure that at 24 h when DEC is completely absent in the urine, the saliva and plasma concentrations also are almost zero. The use of saliva and plasma concentrations is an ideal method for drug ther-
apy monitoring because it is non invasive, a large number of samples can be obtained and is particularly useful in ambulatory, paediatric and geriatric patients. From this study, saliva concentration of DEC can be used to predict the elimination half-life ($t_{1/2}$), elimination rate constant ($K$) and time to attain maximum concentration ($T_{max}$).

REFERENCES