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# Salivary kinetics of prednisolone in man

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Salivary concentrations of several drugs have been shown to be proportional to the total (free + bound) concentration in plasma, e.g. salicylate (Graham & Rowland 1972) and digoxin (Huffman 1975), or the free (unbound) concentration in plasma, e.g. diphenylhydantoin (Bochner et al 1974). Plasma protein binding and the degree of ionization at salivary pH can both affect the salivary drug concentration, and it is often necessary to correct for these factors before a correlation between plasma and salivary concentrations can be established. Nevertheless measurement of salivary drug values may yet prove to be a useful non-invasive technique for the monitoring of at least some drugs (Danhof & Breimer 1978).

We have investigated prednisolone as an example of a non-ionizable compound which may be expected to exhibit a direct correlation between plasma and saliva concentration. The clinical pharmacokinetics of this drug have been reviewed by Pickup (1979).

*Method*

Five normal healthy male volunteers age 21–40 years took part. At the time one subject (No. 2) was a regular cigarette smoker and 4 subjects were non-smokers. None of the subjects was taking any other drugs. Mixed salivary and plasma concentrations of prednisolone were measured following slow intravenous administration of two different doses of prednisolone-21-phosphate. A tracer dose of tritiated prednisolone (specific activity 45 Ci mmol$^{-1}$, Radiochemical Centre, Amersham, Bucks.) was given 10 min after the phosphate as an intravenous bolus injection in isotonic saline 0.9% NaCl (5 ml). The solution was passed through a millipore filter immediately before injection and flushed in with an additional 5 ml of saline to help reduce retention of the radioactive compound in the injection system. Subjects were initially given a dose of tracer (i.e. 10 μCi of 6·7 (N)[$^3$H]prednisolone) + 0·15 mg kg$^{-1}$ and then one week later they received tracer + 0·3 mg kg$^{-1}$. On both occasions ethanol, cigarettes and coffee were not allowed for the 12 h preceding the dose.

Saliva was collected without artificial stimulation at 0·5, 1·0, 1·5, 2·0, 2·5, 3·0, 4·0 and 5·0 h after drug administration. Simultaneous venous blood samples were also taken into lithium heparin tubes by means of an indwelling cannula in the arm not used for injection purposes. The plasma was separated by centrifugation and both plasma and saliva were stored at −20 °C to await analysis. Saliva and plasma samples were then analysed for prednisolone by an established method (Pickup et al 1977).

* Correspondence.

Table 1. Ratio of saliva to plasma concentrations for subject 1 after 2 different doses of prednisolone.

| | Cs/Cp | |
|---|---|---|
| Time (h) | 0·15 mg kg$^{-1}$ | 0·30 mg kg$^{-1}$ |
| 0·5 | 0·081 | 0·185 |
| 1·0 | 0·076 | 0·159 |
| 1·5 | 0·065 | 0·098 |
| 2·0 | 0·052 | 0·122 |
| 2·5 | 0·048 | 0·139 |
| 3·0 | 0·059 | 0·152 |
| 4·0 | 0·036 | 0·106 |
| 5·0 | 0·044 | 0·119 |
| Mean | 0·058 | 0.135 |

*Results*

For each subject the ratio of salivary (Cs) to plasma concentration (Cp) (as dmin$^{-1}$) was calculated for each

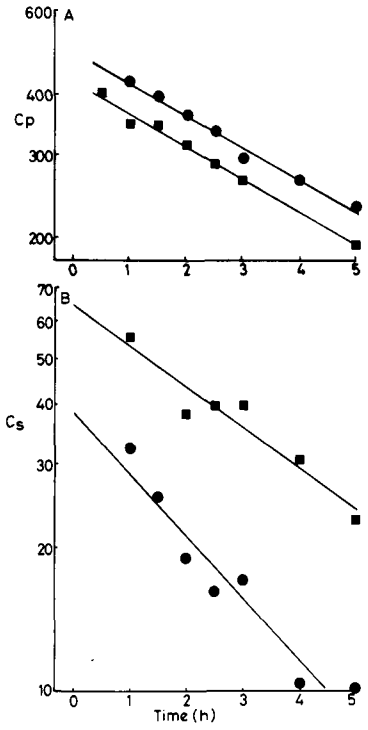


FIG. 1. Plasma (A) and salivary (B) concentrations of prednisolone in subject 1. ●, Tracer 0·15 mg kg$^{-1}$. ■, Tracer 0·30 mg kg$^{-1}$.

Table 2. The ratio of saliva to plasma concentration (Cs/Cp) (Mean values (± s.e.m.) for each subject over 5 h.

| Subject | Tracer + 0·15 mg kg$^{-1}$ | Tracer+ 0·3 mg kg$^{-1}$ |
|---|---|---|
| 1 | 0·058 ± 0·0055 | 0·135 ± 0·0104 |
| 2 | 0·093 ± 0.0044 | ND |
| 3 | 0·060 ± 0·0059 | 0·109 ± 0·0069 |
| 4 | 0·133 ± 0·0168 | ND |
| 5 | 0·175 ± 0·0290 | ND |

ND—Insufficient or no data obtained.

Table 3. The half life (t½ (h)) of prednisolone in plasma and saliva for subjects 1 and 3.

| | Tracer + 0·15 mg kg$^{-1}$ | | Tracer + 0·3 mg kg$^{-1}$ | |
|---|---|---|---|---|
| Subject | Plasma | Saliva | Plasma | Saliva |
| 1 | 4·42 | 2·30 | 4·30 | 3·49 |
| 3 | 2·66 | 1·93 | 2·49 | 2·52 |

sample time. The ratio (Cs/Cp) was variable even for a given individual and dose up to 5 h (Table 1). However, the mean ratios over 5 h are shown in Table 2, and are seen to be subject-and dose-dependent.

The plasma and salivary half lives (t½) were calculated by regression analyses and are shown in Table 3. The t½ in plasma did not increase when the dose rose from tracer + 0·15 mg kg$^{-1}$ to tracer + 0·3 mg kg$^{-1}$. However, the higher dose of prednisolone resulted in lower plasma concentrations than the lower dose (Fig. 1). With saliva, the t½ increased with increasing dose. These data for subject 1 are plotted in Fig. 1A, B.

*Discussion*

The results indicate that there is no direct relationship betweeen total plasma prednisolone and salivary concentrations except possibly for a given individual at a given dose.

It is likely that the non-linear plasma protein binding of prednisolone results in a dose-dependent concentration of free drug in plasma, and that this diffusible component determines the salivary concentration. Indeed, Pickup et al (1977) demonstrated an increase in apparent volume of distribution ($V_D$) and plasma clearance (Cl) with increasing dose of prednisolone. This may also explain the lower plasma concentrations of prednisolone arising from the higher dose. The proportion of drug in saliva is greater at the larger dose (Table 2), possibly reflecting the increased proportion of unbound drug in plasma after the larger dose. It is therefore possible that the salivary value may provide an indication of the unbound (free) plasma prednisolone concentration which may be more relevant in relation to its pharmacological activity.

Unfortunately, this explanation does not account for the observed variation in t½ for saliva. The t½ calculations for saliva were based on widely scattered data and only two subjects, but nevertheless the calculated increase in salivary t½ with inceasing dose was quite marked in both cases. Although the reason for this is unknown, it may be due to saturation of an active transport mechanism between the salivary glands and the local blood supply.

In conclusion, our results indicate that the relation between plasma and salivary concentrations of prednisolone is dependent on dose and the individual. The t½ data suggest that it is unlikely that salivary prednisolone concentrations even reflect the unbound plasma concentrations.

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