

Short reports

Saliva carbamazepine and phenytoin level monitoring

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SUMMARY Saliva carbamazepine and phenytoin samples were used to monitor treatment in 35 children aged between 2 and 14 years during a 2-year period. All phenytoin levels and over half the carbamazepine levels that were above the therapeutic range were associated with adverse effects. Dose and carbamazepine saliva levels were significantly related but no such relationship was found for phenytoin. There was no apparent relationship between the saliva level of either drug and convulsion control.

A knowledge of the concentration of a drug is now considered an important and sometimes an essential part of the management of a number of conditions. The need for regular monitoring of phenytoin (DPH) levels in epilepsy is accepted, and a good case can be made for the routine monitoring of carbamazepine (CBZ) levels.¹

Saliva CBZ and DPH levels in mixed saliva show a good correlation with plasma levels^{2,3} and may provide a convenient and non-invasive means of drug level monitoring in children. An optimal therapeutic response with minimal risk of adverse effects is likely to be achieved in a majority of children if saliva CBZ concentrations are maintained within 5-15 $\mu\text{mol/l}$ (1.2-3.5 $\mu\text{g/ml}$) and if saliva DPH concentrations are within 2-10 $\mu\text{mol/l}$ (5-25 $\mu\text{g/ml}$).¹

We report our experience of measuring saliva levels of CBZ and DPH in epileptic children during a 2-year period.

Methods

Mixed saliva samples were collected from 35 children, aged between 2 and 14 years, after stimulation of saliva flow with strawberry-flavoured citric acid crystals. Twenty of the children were receiving CBZ, of whom 16 were using tablets and 4 syrup formulations. Fifteen children were receiving DPH,

and of these, 9 used chewable tablets, 3 used capsules, and 3 used the suspension form. Older children provided samples by spitting the saliva directly into a specimen container, but in young children (<5 years), saliva was aspirated from beneath the tongue and behind the lower lip by means of a disposable mucus extractor. Altogether 473 samples were collected at various times of day, at home and in school, and in hospital inpatient and outpatient departments from September 1977 to August 1979. Of the CBZ samples, 221 (88%) were collected between 0800 and 2000 hours and 160 (62%) between 0800 and 1600 hours. DPH samples collected between 0800 and 2000 hours numbered 174 (81%), and between 0800 and 1600 hours, 115 (54%) samples were collected.

Saliva was assayed for CBZ by a modification⁴ of the gas-liquid chromatography method for serum described by Least *et al.*⁵ and for DPH by radioimmunoassay⁶ using antisera supplied by Dr G W Aherne, University of Surrey.

The number of samples taken from each child varied. In those children who gave at least 5 samples, intra-individual variation on different dose frequency regimens was compared using Wilcoxon's rank sum test for unpaired samples.

CBZ and DPH level-dose relationships were determined using all samples and also using those samples collected at 3 and 5 hours after dose administration.

Results

Details of the number of children, amount of each drug, and number of children taking other drugs are shown in the Table.

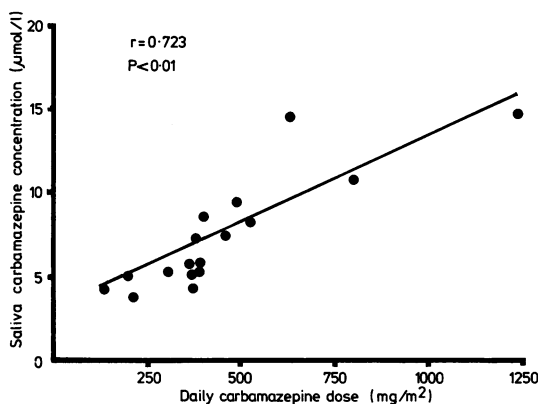
Carbamazepine. The mean saliva CBZ concentration in the 258 samples collected from 20 children receiving a mean daily dose of 535 mg/m² was 8.52 $\mu\text{mol/l}$ (2.01 $\mu\text{g/ml}$).

In 77.5% of the samples, the concentration was

Table Number of samples, size of dose, and number of children taking other drugs

Drug	No of children	Age at midpoint of study (years)		Dose (mg/m ²)		No of samples	No of children on other drugs		
		Mean	Range	Mean	Range				
Carbamazepine	20	7.9	(2.1-14.3)	412	(135-1240)	258	1*	1†	1†‡
Phenytoin	15	9.3	(2.5-14.1)	175	(111-244)	215	1*	1§	3§§ 1**

*Ethosuximide, †phenytoin, ‡sodium valproate, §primidone, §§phenobarbitone, **nitrazepam



Conversion: SI to traditional units—1 µmol/l ≈ 0.236 µg/ml

Figure Relationship between carbamazepine dose and the level 5 hours after dose in 17 children.

within the suggested therapeutic range, below the range in 13.9% (n = 36), and above it in 8.5% (n = 22). Over half (54%) of the levels above the therapeutic range were associated with adverse effects (ataxia, dizziness, or drowsiness) in the children during the previous 5 days.

There was no apparent relationship between drug level and the degree of convulsion control.

In the 13 children in whom more than 5 CBZ levels had been determined, the mean coefficient of variation in concentration on twice-daily dosage, 22.6% (n = 11), was not significantly different from that on thrice-daily dosage, 23.4% (n = 6).

There was a weak, but significant correlation between the saliva CBZ concentration and the daily CBZ dose per unit surface area (r = 0.30; P < 0.001). There were better correlations between the CBZ concentrations in 23 samples collected from 16 children 3 hours after dose administration (r = 0.61; P < 0.01) and the 5-hour post-dose level in 17 samples from 17 children (r = 0.72; P < 0.01), and the daily dose per unit surface area.

Phenytoin. The mean saliva DPH concentration in 215 samples from 15 children was 4.34 µmol/l (10.1 µg/ml) on a mean daily dose of 181 mg/m².

The concentration was within the suggested therapeutic range in 77.5% of the samples, below the range in 13.9% (n = 36), and above it in 8.6% (n = 22). All the levels above the therapeutic range were associated with toxic effects (ataxia, extreme drowsiness, or speech disturbance) in the children during the previous 5 days.

There was no apparent relationship between the DPH level and the degree of convulsion control.

In the 11 children in whom more than 5 samples had been collected, the mean coefficient of variation in concentration on once-daily dosage, 42.2% (n = 5), was not significantly different from that on twice-daily, 24.1% (n = 5), or thrice-daily dosage, 43.6% (n = 6).

There was no significant correlation between the saliva DPH concentration, the 3-hour post-dose level (n = 9), the 5-hour post-dose level (n = 11), and the DPH dose per unit surface area.

Of the 23 children who had received CBZ or DPH for more than one year before the study and whose treatment had been monitored using blood samples, 90.9% attended all appointments during the study period compared with 56.6% during the year before the introduction of saliva sampling (P < 0.01).

Discussion

In monitoring CBZ and DPH levels, saliva has two main advantages over plasma. Firstly, saliva levels reflect the free, and therefore the pharmacologically active fraction of each drug. This offers a particular advantage in children with renal and hepatic disease, in whom changes in protein binding may be expected, although such conditions are rare in children. Competitive displacement from plasma protein binding sites may occur, but drugs producing such interactions are infrequently used in paediatric practice; of 7 children receiving multiple drugs in this study, only one was receiving a drug (sodium valproate) which might influence protein binding.

A second advantage of saliva is that it can be collected conveniently and non-invasively. Out-patient clinic attendance improved greatly after the

introduction of saliva drug level monitoring and no child refused to have a saliva sample collected. Clinicians sometimes do not attempt plasma drug level monitoring because of a child's or parents' unfavourable reaction, and others refrain from blood sampling in certain circumstances because the child-parent-doctor relationship may suffer, and the success of treatment be compromised.

Saliva samples may be contaminated by unabsorbed drug, particularly if liquid or chewable formulations are used.⁷ This can be virtually excluded by careful cleansing and washing of the mouth and teeth both after dosing and before sampling, although it may be difficult to collect uncontaminated samples in the first 2½ hours after drug administration if DPH chewable tablets are used. In normal circumstances, and regardless of whether such precautions are taken, the level 5 hours after the dose will not be contaminated.

Wide fluctuations in the free concentrations of CBZ and DPH occur between doses even when administered at accepted dose intervals.^{4,8} A direct relationship between drug level and effect is therefore not always apparent, and in this study there was no obvious relationship between the concentration of CBZ or DPH and the degree of control of convulsions. The fact that CBZ has an active metabolite, the 10, 11-epoxide, may further explain the lack of relationship for this.

Most studies so far reported on drug level monitoring have been unable to show a good relationship between the dose of CBZ and the concentration of the drug in blood or other tissue fluid. This may be due to inter-individual variability, or to dose-dependent autoinduction of CBZ metabolism. The elimination of DPH by both first and zero order kinetics may partly explain why there is a poor relationship between its dose and saliva level. Another reason may be that fluctuation between doses for both drugs is such that random levels do not reflect the mean steady-state concentration. In this study a significant correlation between CBZ dose and drug level was evident, particularly between dose and the 3- and 5-hour post-dose levels. The good relationship between dose and the 3- and 5-hour post-dose levels may reflect diminishing saliva contamination with time from dosing, or it may suggest that levels in the elimination phase are better related to the dose than those at the time of absorption. The good correlation between the dose and the 5-hour sample suggests that this may be an appropriate time for routine monitoring of treatment. No significant dose-level relationship was found for DPH.

This study has failed to show any significant difference between the intra-individual fluctuations in concentration (as reflected by the coefficients of

variation) of CBZ on twice- and thrice-daily dose regimens, and of DPH on once-, twice-, and thrice-daily regimens. In contrast previous studies have shown that the fluctuation in saliva CBZ concentration between doses is considerably greater when the drug is administered in 2 rather than 3 daily doses,⁴ and that fluctuation in saliva DPH concentration in children on once-daily dosage is large and may be clinically unacceptable.⁸ However, the coefficients of variation in this study may not be representative of the actual daily fluctuation in concentration on any regimen since over four-fifths of the CBZ and DPH samples were collected within the 24-hour period (0800 to 2000 hours) when drugs are normally given to children, and considerably greater fluctuation would be expected during the other 12-hour period of the day.

Saliva sampling is a convenient and non-traumatic method of monitoring CBZ and DPH treatment in children, both for child and clinician. For most children, the convenient and non-invasive nature of the method is likely to be of greater importance than the other advantage of the use of saliva, that of reflecting the free and active drug fraction. However, it should be stressed that some saliva drug levels (for example phenytoin) may be much lower than the equivalent plasma level and may approach the lower limit of sensitivity of the assay method used in some laboratories.

References

- 1 Rylance G W, Moreland T A. Drug level monitoring in paediatric practice. *Arch Dis Child* 1980; **55**: 89-98.
- 2 Bartels H, Oldigs H-D, Gunther E. Use of saliva in monitoring carbamazepine medication in epileptic children. *Eur J Pediatr* 1977; **126**: 37-44.
- 3 Cook C E, Amerson E, Poole W K, Lesser P, O'Tuama L. Phenytoin and phenobarbital concentrations in saliva and plasma measured by radioimmunoassay. *Clin Pharmacol Ther* 1975; **18**: 742-7.
- 4 Rylance G W, Moreland T A, Butcher G M. Carbamazepine dose frequency requirement in children. *Arch Dis Child* 1979; **54**: 454-8.
- 5 Least C J, Jr, Johnson G F, Solomon H M. Therapeutic monitoring of anticonvulsant drugs: gas chromatographic simultaneous determination of primidone, phenylethylmalonamide, carbamazepine, and diphenylhydantoin. *Clin Chem* 1975; **21**: 1658-62.
- 6 Robinson J D, Morris B A, Aherne G W, Marks V. Pharmacokinetics of a single dose of phenytoin in man measured by radioimmunoassay. *Br J Clin Pharmacol* 1975; **2**: 345-9.
- 7 Ayers G J, Burnett D. Letter: Drug formulation and salivary phenytoin measurements. *Lancet* 1977; **i**: 656.
- 8 Rylance G W, Fowles R G, Moreland T A. Phenytoin in children; kinetics and adequacy of regimen using saliva. In: Canger R, Angeleri F, Penry J K, eds. *Advances in epileptology*. New York: Raven Press, 1980: 457-61.

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