Carbamazepine dose-frequency requirement in children

G. W. RYLANCE, T. A. MORELAND, AND G. M. BUTCHER

Departments of Child Health, Pharmacology and Therapeutics, Ninewells Hospital and Medical School, and of Pharmacology and Therapeutics, University of Dundee

SUMMARY The dose-frequency requirement for carbamazepine (CBZ) in children was investigated using serial saliva samples to determine the daily fluctuation in drug levels. Mixed saliva was collected from 6 children (aged between 6 and 13 years) in a steady state, on each of two different dose-frequency regimens of once to 3 times daily, with a constant total daily dose. Increasing the dose-frequency resulted in smaller fluctuations in saliva concentration and a shorter time with levels outside the therapeutic range. Toxic features and convulsions appeared to be related to peak and trough concentrations. There was no apparent relationship between the total dose and the mean saliva concentration. The saliva CBZ half-lives in 2 children were 7.3 and 12.7 hours, and the apparent volumes of distribution (saliva) were 1.6 and 1.5 l/kg respectively. Saliva CBZ concentrations are an efficient and convenient means of tailoring individual dosage, and can be used to provide the pharmacokinetic data that rational prescribing demands.

Plasma level monitoring of anticonvulsant drugs in the management of convulsive disorders is being used increasingly (Kutt and McDowell, 1968; Kutt and Penry, 1974). The practice is now routine in most centres for phenobarbitone and phenytoin, for which established therapeutic ranges exist. For carbamazepine (CBZ), a therapeutic plasma concentration range in adults has been suggested from studies relating plasma levels with clinical effects (Morselli and Frigerio, 1975; Troupin *et al.*, 1975).

Saliva drug levels as a substitute for plasma levels have been shown to be useful for some anticonvulsant drugs in adults (Schmidt and Kupferberg, 1975; Troupin and Friel, 1975; Reynolds *et al.*, 1976), and for CBZ in children (Bartels *et al.*, 1977; Rylance *et al.*, 1977). The saliva levels of phenytoin, phenobarbitone (after correcting for saliva pH), and CBZ are similar to the concentrations of the free or unbound drug in plasma water (Schmidt and Kupferberg, 1975; Troupin and Friel, 1975; McAuliffe *et al.*, 1977), and may therefore be of greater therapeutic significance than the plasma concentration.

Some drugs are eliminated more rapidly by

children than by adults (Svensmark and Buchthal, 1964; Borofsky *et al.*, 1972; Chang *et al.*, 1972), and the half-life of CBZ in 3 children receiving long-term treatment was reportedly shorter, 7.3-18.9 hours (Rane *et al.*, 1976; Rylance *et al.*, 1977), than in adults, 16.4-36.5 hours (Eichelbaum *et al.*, 1975; Faigle *et al.*, 1976). One consequence of this is that similar dosage produces lower steady-state drug levels in children than in adults (Morselli *et al.*, 1975; Monaco *et al.*, 1976). In addition, faster drug elimination would be expected to produce greater fluctuations in drug levels in children on a similar dose-frequency regimen as adults. Because of this and other pharmacokinetic factors, the dose-frequency regimens recommended for use in adults may be inappropriate for use in children.

In this study, the influence of dose-frequency on saliva CBZ levels was determined in a group of children.

Methods

Six children aged between 6 and 13 years attending the outpatient clinic of Ninewells Hospital, Dundee, were studied; approval was granted by the local hospital ethical committee. All children had received treatment with CBZ for at least 12 weeks before the study began, 3 receiving CBZ alone, and 3 receiving either phenytoin or ethosuximide in addition to CBZ.

Department of Child Health, University of Dundee, Dundee

G. W. RYLANCE, lecturer

T. A. MORELAND, Wellcome research fellow in paediatric pharmacology

University of Sheffield

G. M. BUTCHER, medical student

Mixed saliva was collected after stimulation with citric acid and flavouring (Bacon *et al.*, 1978) at approximately hourly intervals from 0900 to 2300 hours and from 0600 to 0900 hours the next day, the children spending the night in hospital. This procedure was carried out twice for each child. The total daily dose remained constant each time, but the dose-frequency was changed so that 2 children received CBZ once daily on the first occasion and twice daily on the second, and the other 4 received the drug two- and three-times daily (Table 1). The approximate times of CBZ administration were: once daily 0900 hours; twice daily 0900 and 2100 hours; thrice daily 0900, 1600, and 2300 hours. The children were maintained on each dose regimen for at least 6 days before saliva sampling, to enable a steady state to be reached.

Proprietary CBZ tablets were used except in Cases 4, 5, and 6 on thrice-daily regimens, when part of each dose was given as powdered proprietary tablet. To avoid contamination of the initial samples by CBZ retained in the mouth, the children swallowed water to rinse their mouths and brushed their teeth.

Saliva samples were stored at -20°C until assayed for CBZ by a modification of the method for serum described by Least *et al.* (1975). 2 ml saliva were added to a 10 ml glass-stoppered tube containing 5 ml chloroform, 1 ml 0.5 M sodium hydroxide, and 0.1 ml codeine in chloroform, 268 $\mu\text{mol/l}$ (internal standard). The mixture was shaken vigorously for 10 min and the aqueous layer was removed and discarded. The organic layer was transferred to a tapered glass-stoppered tube and evaporated to dryness under nitrogen at 45°C . The sides of the tube were washed with 0.5 ml chloroform and evaporated as before. The residue was dissolved in 10 μl dry pyridine and 20 μl N,O-bis-(trimethylsilyl)-acetamide, incubated for 30 min at room temperature, and 1 μl aliquots injected into the GLC column. A Pye 104 gas chromatograph with dual flame ionisation detectors was used. The glass columns were 2 m $\times$ 4 mm in diameter, packed with

3% OV17 on Gas Chrom Q 100/120. Operating conditions were: injection port 300°C , oven 240°C , detector 300°C , nitrogen 50 ml/min, hydrogen 50 ml/min, air 250 ml/min. The sensitivity of the assay enabled the determination of CBZ down to 2 $\mu\text{mol/l}$. The mean coefficient of variation of the method over the concentration range 2–70 $\mu\text{mol/l}$ was 3.5%.

The area under the CBZ concentration-time curve (AUC) was calculated for one dose interval (τ) for each child on each regimen using the trapezoidal rule. The mean steady-state saliva CBZ concentration ($\bar{C}_{ss}S$) was then calculated from the relationship, $\bar{C}_{ss}S = \text{AUC}/\tau$.

The daily fluctuation in saliva drug levels was expressed as a percentage thus:

$$\text{Fluctuation} = \frac{(\text{Highest} - \text{lowest concentration})}{\bar{C}_{ss}S} \times 100\%$$

The first-order elimination rate constant (k) in Cases 1 and 2 receiving the drug once daily was obtained from the regression line fitted to the logarithm of the saliva concentration versus time curve by the method of least squares.

Clearance (C), the apparent volume of distribution (V_{dss}), and the saliva half-life ($t_{1/2}$) were calculated from the saliva data using the equation:

$$\bar{C}_{ss}S = \frac{F \cdot D}{k \cdot V_{dss} \cdot \tau}$$

where D is the dose given at each time interval (τ), $C = k \cdot V_{dss}$, $t_{1/2} = 0.693/k$, and F = fraction of dose absorbed, assumed to be unity.

Results

The 24-hour saliva CBZ concentration profiles of the 6 children on each regimen are shown in the Figure. The therapeutic range in saliva (5.5–15 $\mu\text{mol/l}$) was derived from the reported saliva/plasma

Table 1 Mean steady-state saliva carbamazepine concentrations and the daily fluctuation in concentration in children on different dose-frequency regimens

Case	Sex	Age (years)	Dosage (mg/kg)	Other drugs	Once daily		Twice daily		Thrice daily	
					Concentration* ($\mu\text{mol/l}$)	Fluctuation (%)	Concentration* ($\mu\text{mol/l}$)	Fluctuation (%)	Concentration* ($\mu\text{mol/l}$)	Fluctuation (%)
1	M	6	27	—	8.7	160	8.0	74		
2	M	13	17	Phenytoin	8.9	186	8.8	74		
3	F	13	11	—			13.1	60	13.6	38
4	F	10	37	Phenytoin			12.4	92	10.6	74
5	M	10	21	—			12.6	113	16.3	66
6	M	8	15	Ethosuximide			5.6	212	5.8	60

*Steady-state saliva carbamazepine concentration.

Conversion: SI to traditional units—carbamazepine: 1 $\mu\text{mol/l} \approx 23.6 \mu\text{g}/100 \text{ ml}$.

Figure Saliva carbamazepine (CBZ) concentrations in Cases 1 and 2 on once- (***) and twice- (●—●) daily dosage, and in Cases 3–6 on twice- (●—●) and thrice (▲—▲) daily dosage. Arrows indicate dose administration times for CBZ given once (***), twice (↑) and thrice (↑↑) daily. Horizontal broken lines indicate upper and lower limits of the therapeutic saliva CBZ concentration range. Conversion: SI to traditional units—carbamazepine: 1 $\mu\text{mol/l} \approx 23.6 \mu\text{g/100 ml}$.

concentration ratio in children (Rylance *et al.*, 1977), and the recommended plasma concentration range in adults (Morselli and Frigerio, 1975; Troupin *et al.*, 1975).

The saliva levels peaked at between 1 and 6 hours, and in Cases 1, 2, 4, and 5, two peaks were observed. There was no contamination except in Case 3 on a twice-daily dosage regimen (Figure). The greatest fluctuation was found in Case 2 receiving CBZ once daily, and the smallest fluctuation in Case 3 on three doses a day (Figure). In all children, increasing the frequency of drug administration resulted in smaller fluctuations in saliva concentration. Frequent drug administration also resulted in a shorter time being spent with saliva levels outside the therapeutic range.

Both children on a once-daily regimen had saliva concentration fluctuations $>160\%$ of the mean steady state (Table 1). Increasing the frequency of drug administration to twice daily reduced the fluctuation to $<75\%$. In the 4 other children, the

fluctuation fell from 60–213% on twice-daily dosage to 38–75% on thrice-daily dosage.

The mean steady-state saliva concentrations resulting from the two dose regimens in each child, were similar in 4 children and in only 2 (Cases 4 and 5), was the difference $>1 \mu\text{mol/l}$ (Table 1). There was no apparent correlation between the mean steady-state concentration and the total daily dose in any child.

Assuming complete bioavailability, the mean ($\pm\text{SD}$) saliva clearance of CBZ in the children on twice-daily dosage was $0.398 \pm 0.167 \text{ l/kg per hour}$. The saliva CBZ half-lives in Cases 1 and 2 receiving the drug once daily were 7.3 and 12.7 hours, and the apparent volumes of distribution (saliva) for CBZ in these children were 5.78 and 6.12 l/kg respectively.

Toxic features were observed in 2 of the 6 children. Case 1 was ataxic about midday and was often sleepy by midafternoon when receiving CBZ once daily, and Case 3 became dizzy in the early afternoon on twice-daily doses.

None of the children had convulsions during the study period and 3 children had been convulsion-free for the previous 9 months. Two patients had each had one convulsion during the preceding month on their usual dose-frequency regimen, Case 5 at 0800 hours on twice-daily CBZ, and Case 6 at 2300 hours also on two doses a day. Case 4 had had convulsions at approximately monthly intervals during the previous 9 months at varying times of the day, on twice-daily administration.

Discussion

Minimum plasma concentrations and therapeutic ranges for CBZ have been suggested for adults, and the therapeutic concentration range in saliva adopted in this study was derived from these (Morselli and Frigerio, 1975; Troupin *et al.*, 1975), and from the saliva/plasma CBZ ratio in children (Rylance *et al.*, 1977). The mean steady-state saliva concentrations were within this range for all but one child (Case 5), and as expected, the frequency of drug administration did not influence concentration. The higher concentration in Case 5 receiving CBZ three-times daily was possibly a result of the greater bio-availability of the powdered drug used for him, although this was not observed in Cases 4 and 6 who also had part of their thrice-daily doses given in the powdered form.

Although the mean saliva CBZ concentrations indicated that the children were well controlled, there was considerable fluctuation about the mean. The concentrations rose steadily after drug administration reaching peak levels within 1–6 hours in all children, except for Case 3 on twice-daily dosage, in whom the concentration rose immediately after drug administration due to contamination by unabsorbed drug. Contamination was not observed at other times, nor was it observed in the other children. In 4 children the initial peak was followed by a short decline in concentration before peaking again.

The saliva clearance of CBZ was greater than that reported in adults (Westenberg *et al.*, 1978), and together with the two saliva CBZ half-lives which were similar to the plasma half-lives reported for children by Rane *et al.* (1976), indicate that children metabolise CBZ more rapidly than adults do.

A shorter CBZ half-life in children would be expected to produce a greater fluctuation in drug level than in adults, and indeed large variations in saliva concentration were observed in the children receiving the drug once or twice daily. Administration of CBZ thrice daily reduced the fluctuation in saliva drug levels, but large differences between peak and trough levels were still seen in 2 children (Cases

4 and 5). Although the CBZ concentration at the site of action will probably vary to a lesser extent than in plasma or saliva, large fluctuations in saliva will obviously reflect an increased risk of toxicity and/or convulsions. Two of the children in this study (Cases 1 and 3) showed toxic effects when saliva drug levels were at their peak and above the therapeutic range, and convulsions had occurred in two children (Cases 5 and 6) in the preceding month when receiving CBZ twice daily. The seizures occurred just before drug administration when the levels were presumed to be at their lowest.

Johannessen *et al.* (1976) found no direct relationship in adults between the frequency of drug administration and the daily fluctuation in serum levels. However, sampling was probably not frequent enough to detect change in fluctuations arising from the different dose-frequency regimens.

The data from our study suggest that children require more frequent doses of CBZ than do adults. Certainly, once-daily administration results in too great a fluctuation in concentration. Frequent administration may lead to reduced patient compliance, and can prove difficult if the child needs to take the drug during school hours. As many convulsions occur at night (Gibberd and Bateson, 1974), and this is the longest dose interval, it may be possible to improve control by giving a larger dose in the evening.

Single saliva CBZ determinations in children give a poor estimate of the mean steady-state concentration. This is demonstrated when the mean steady-state concentrations obtained for 5 of the children in this study are compared with single outpatient determinations carried out in the same children at random times while on the same dose-frequency regimens (Table 2). The outpatient values differ markedly from the mean steady-state levels.

Serial saliva samples are easily obtained from children of at least 4 years of age, and also from younger children if saliva flow is stimulated and a mucus extractor used (Bacon *et al.*, 1978), but because of possible contamination, care must be

Table 2 Mean steady-state saliva carbamazepine concentrations and single outpatient levels on the same regimen

Case	Dose-frequency each day	Concentration* ($\mu\text{mol/l}$)	Outpatient level ($\mu\text{mol/l}$)
1	Twice	8.0	5.9, 15.7†
2	Twice	8.8	6.2
3	Thrice	13.6	12.3
4	Twice	12.4	7.6
5	Twice	12.6	8.4

*Steady-state saliva carbamazepine concentrations.

†Two levels determined one month apart.

Conversion given in footnote to Table 1.

taken in obtaining samples and interpreting their values in the period shortly after drug administration. Saliva concentration profiles are a convenient and effective means of assessing CBZ dose regimens in individuals, and it may be possible to use a similar approach for other anticonvulsant drugs.

T.A.M. gratefully acknowledges the Wellcome Trust for financial support. We thank Professor R. G. Mitchell, Dr C. C. Forsyth, and Dr S. G. F. Wilson for permission to study their patients, and Professor R. G. Mitchell and Dr I. H. Stevenson for their advice in the preparation of the manuscript.

References

- Bacon, C. G., Mucklow, J. C., Saunders, A., Rawlins, M. D., and Webb, J. K. G. (1978). A method for obtaining saliva samples from infants and children. *British Journal of Clinical Pharmacology*, **5**, 89–90.
- Bartels, H., Oldigs, H.-D., and Gunther, E. (1977). Use of saliva in monitoring carbamazepine medication in epileptic children. *European Journal of Pediatrics*, **126**, 37–44.
- Borofsky, L. G., Louis, S., Kutt, H., and Roginsky, M. (1972). Diphenylhydantoin: efficacy, toxicity, and dose-serum level relationship in children. *Journal of Pediatrics*, **81**, 995–1002.
- Chang, T., Dill, W. A., and Glazko, A. J. (1972). Ethosuximide. Absorption, distribution, and excretion. In *Anti-epileptic Drugs*, pp. 417–423. Edited by D. M. Woodbury, J. K. Penry, and R. P. Schmidt. Raven Press: New York.
- Eichelbaum, M., Ekbom, K., Bertilsson, L., Ringberger, V. A., and Rane, A. (1975). Plasma kinetics of carbamazepine and its epoxide metabolite in man after single and multiple doses. *European Journal of Clinical Pharmacology*, **8**, 337–341.
- Faigle, J. W., Brechbuhler, S., Feldmann, K. F., and Richter, W. J. (1976). The biotransformation of carbamazepine (Tegretol). In *Epileptic Seizures—Behaviour—Pain*, pp. 127–140. Edited by W. Birkmayer. Hans Huber: Berne.
- Gibberd, F. B., and Bateson, M. C. (1974). Sleep epilepsy: its pattern and progress. *British Medical Journal*, **2**, 403–405.
- Johannessen, S. I., Gerna, M., Bakke, J., Strandjord, R. E., and Morselli, P. L. (1976). CSF concentrations and serum protein binding of carbamazepine and carbamazepine 10, 11-epoxide in epileptic patients. *British Journal of Clinical Pharmacology*, **3**, 575–582.
- Kutt, H., and McDowell, F. (1968). Management of epilepsy with diphenylhydantoin sodium. *Journal of the American Medical Association*, **203**, 969–972.
- Kutt, H., and Penry, J. K. (1974). Usefulness of blood levels of antiepileptic drugs. *Archives of Neurology*, **31**, 283–288.
- Least, C. J., Jr, Johnson, G. F., and Solomon, H. M. (1975). Therapeutic monitoring of anticonvulsant drugs: gas chromatographic simultaneous determination of primidone phenylethylmalonamide, carbamazepine, and diphenylhydantoin. *Clinical Chemistry*, **21**, 1658–1662.
- McAuliffe, J. J., Sherwin, A. L., Leppik, I. E., Fayle, S. A., and Pippenger, C. E. (1977). Salivary levels of anticonvulsants: a practical approach to drug monitoring. *Neurology*, **27**, 409–413.
- Monaco, F., Riccio, A., Benna, P., Covacich, A., Durelli, L., Fantini, M., Furlan, P. M., Gilli, M., Mutani, R., Troni, W., Gerna, M., and Morselli, P. L. (1976). Further observations on carbamazepine plasma levels in epileptic patients. *Neurology*, **26**, 936–943.
- Morselli, P. L., and Frigerio, A. (1975). Metabolism and pharmacokinetics of carbamazepine. *Drug Metabolism Reviews*, **4**, 97–113.
- Morselli, P. L., Monaco, F., Gerna, M., Ricchia, M., and Rutio, A. (1975). Bioavailability of two carbamazepine preparations during chronic administration to epileptic patients. *Epilepsia*, **16**, 759–764.
- Rane, A., Höjer, B., and Wilson, J. T. (1976). Kinetics of carbamazepine and its 10, 11-epoxide metabolite in children. *Clinical Pharmacology and Therapeutics*, **19**, 276–283.
- Reynolds, F., Ziroyanis, P. N., Jones, N. F., and Smith, S. E. (1976). Salivary phenytoin concentrations in epilepsy and in chronic renal failure. *Lancet*, **2**, 384–386.
- Rylance, G. W., Butcher, G. M., and Moreland, T. A. (1977). Letter: Saliva carbamazepine levels in children. *British Medical Journal*, **2**, 1481.
- Schmidt, D., and Kupferberg, H. J. (1975). Diphenylhydantoin, phenobarbital, and primidone in saliva, plasma, and cerebrospinal fluid. *Epilepsia*, **16**, 735–741.
- Svensmark, O., and Buchthal, F. (1964). Diphenylhydantoin and phenobarbital serum levels in children. *American Journal of Diseases of Children*, **108**, 82–87.
- Troupin, A. S., and Friel, P. (1975). Anticonvulsant level in saliva, serum, and cerebrospinal fluid. *Epilepsia*, **16**, 223–227.
- Troupin, A. S., Green, J. R., and Halpern, L. M. (1975). Carbamazepine (Tegretol) as an anticonvulsant. A controlled double-blind comparison with diphenylhydantoin (Dilantin). *Acta neurologica Scandinavica*, **60**, Supplement, 13–26.
- Westenberg, H. G. M., van der Kleijn, E., Oei, T. T., and de Zeeuw, R. A. (1978). Kinetics of carbamazepine and carbamazepine-epoxide, determined by use of plasma and saliva. *Clinical Pharmacology and Therapeutics*, **23**, 320–328.

Correspondence to Dr G. W. Rylance, Department of Child Health, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, Angus.

Received 24 October 1978