The effects of age on carbamazepine pharmacokinetics and adverse effects

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The pharmacokinetics and effect of single oral doses of carbamazepine (400 mg) were compared in a group of six young volunteers aged between 20 and 25 years, and a second group of five elderly volunteers aged between 66 and 84 years. No age related changes in salivary or plasma pharmacokinetics or in psychomotor function were detected.

Keywords carbamazepine pharmacokinetics age

Introduction

Carbamazepine is a major anticonvulsant for the treatment of tonic-clonic and partial seizures and also for pain syndromes, especially trigeminal neuralgia, which occur most frequently in the elderly. Some patients are intolerant of carbamazepine, usually because of the central side effects of drowsiness, blurred vision, dizziness, or ataxia. Although there is a clinical impression that these side effects occur at lower doses in the elderly, there have been no studies of carbamazepine kinetics or central effects in the elderly comparable to studies of centrally acting drugs, for example benzodiazepines, which have been shown to have different kinetics in the elderly compared to the young (Stevenson, 1984; Schmucker, 1984).

Altered tissue responsiveness and/or altered pharmacokinetics may underlie any such increase in sensitivity to carbamazepine in the elderly. This study attempted to examine some of these possible causes with psychomotor function tests and pharmacokinetic parameters in groups of healthy young and healthy elderly volunteers given single oral doses.

Methods

Six healthy young volunteers, two female, aged between 20 and 25 years, weighing between 50.8 and 76.2 kg, and five elderly subjects, two female,

aged between 66 and 74 years, weighing between 52.0 and 86.0 kg participated in the study. All subjects were free of medication and had normal heart, liver and kidney function from an ECG and a routine blood chemistry analysis. The study was approved by the local ethical committee and all subjects gave their informed consent.

The subjects were studied double-blind with randomly allocated placebo controls. One hour after a light breakfast (tea and toast) each subject took 400 mg carbamazepine (Tegretol) or an identical placebo. Tests for psychomotor function were carried out 2 and 5 h after dosing. These were choice reaction time and critical flicker fusion threshold using the Leeds psychomotor tests (Hindmarch, 1980) and body sway using the Wright's ataxiometer (Wright, 1971). Saliva samples were collected following oral stimulation with a citric acid crystal 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144 and 168 h after dosing and 10 ml venous blood specimens were also obtained after 5, 24 and 48 h. Serum was separated and both saliva and serum was stored at -20°C pending analysis. One week later the study was repeated with the active drug in place of placebo or *vice versa*.

Specimens were assayed for carbamazepine and carbamazepine 10, 11 epoxide by high performance liquid chromatography (Mihaly *et al.*, 1977).

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Recoveries of spiked serum samples averaged 99% for carbamazepine and 102% for the epoxide with a between batch coefficient of variation of 8.8% and 9.1% respectively at a concentration of 1 mg l^{-1} . The minimum detectable concentration was 0.2 mg l^{-1} .

The area under the saliva drug concentration-time curves (AUC) was calculated by the trapezoidal method with extrapolation to infinity using the elimination rate constant (k_{el}), obtained by fitting the elimination phase of the curve to a single compartmental model by a nonlinear least squares method. Differences between group and changes within groups after drug administration were compared using the *t*-test for unpaired and paired data.

Results

Serum and salivary pharmacokinetics for the two groups are summarised in Table 1. There were no statistically significant differences in mean pharmacokinetic parameters between a group of elderly subjects and a group of young adults. Neither were there any significant differences in the average saliva to plasma ratios. Carbamazepine 10, 11 epoxide could not be detected in the serum of three out of five elderly subjects and the average concentrations appear to be lower than in young adults but owing to large inter-subject variations these differences do not reach statistical significance.

Table 2 shows the means for each group for the tests of psychomotor function. Critical flicker fusion threshold and choice reaction time are not measurably influenced by the drug but body sway increased in both groups at both 2 and 4 h after dosing. The increase in body sway tends to be greater in the elderly than the young but because of the small numbers in each group this difference was not statistically significant.

Discussion

The aim of this study was to compare salivary pharmacokinetics and psychomotor performance in groups of young and elderly volunteers given single oral doses of carbamazepine. Age-related changes in receptor sensitivity could be inferred if differences in psychomotor performance was demonstrable in the absence of altered pharmacokinetics or if the two changes were demonstrably inconsistent.

This study has failed to detect significant differences between elderly and young volunteers in their salivary pharmacokinetics or in psycho-

Table 1 Effect of age on carbamazepine (CBZ) pharmacokinetics

		Age (years)	M/F	Dose (mg kg ⁻¹)	k_{el} (h ⁻¹)	AUC (mg l ⁻¹ h)	Sa/Se	Se CBZ (mg l ⁻¹)		Se Epoxide (mg l ⁻¹)	
								5 h	24 h	5 h	24 h
Young (6)	Mean	23	4/2	6.05	0.018	68.7	0.24	4.75	4.02	0.2	0.41
	s.d.	2		1.08	0.006	9.8	0.03	0.83	0.63	—	0.19
Elderly (5)	Mean	70	3/2	5.98	0.019	73.5	0.23	4.84	4.04	0.2	0.23
	s.d.	4		1.27	0.003	12.0	0.03	0.84	0.40	—	0.32

AUC = area under concentration-time curve in saliva

Sa = saliva; Se = serum

Epoxide CBZ 10,11 epoxide

Table 2 Results of psychomotor function tests 2 and 4 h after dosing

	CFFT (Hz)		CRT (ms)		Body sway (units min ⁻¹)	
	Placebo	Active	Placebo	Active	Placebo	Active
<i>2 h post dose</i>						
Young mean	26.0	27.1	240.0	246.9	19.4	21.9
s.d.	3.6	1.9	54.4	45.3	11.0	8.4
Elderly mean	27.8	26.4	277.8	273.2	19.1	27.2
s.d.	3.3	2.8	58.1	86.1	4.1	19.7
<i>4 h post dose</i>						
Young mean	26.7	27.4	218.8	231.1	18.8	20.7
s.d.	3.0	2.0	28.4	54.9	6.4	7.5
Elderly mean	28.2	26.7	284.6	290.4	15.9	22.3
s.d.	2.8	2.8	67.9	107.8	5.6	5.1

CFFT—critical flicker fusion threshold

CRT—choice reaction time

motor performance. The tests used, though established for examining psychomotor function, may not be appropriate for the measurement of dizziness and drowsiness produced by carbamazepine.

The use of saliva as a non-invasive technique for drug monitoring and pharmacokinetic studies with carbamazepine has been recommended by several authors (MacKichan *et al.*, 1981; Kristensen & Larsen, 1980; Paxton & Donald, 1980) and our own use of it in this study has demonstrated its practicality. Our elimination constants and average saliva to serum ratios were similar to those obtained by previous workers (Paxton & Donald, 1980; Eadie & Tyrer 1980). The absence of data on absorption and

bioavailability is regrettable and reduces the range of pharmacokinetics parameters available for comparison. Salivary sampling following oral administration of a drug always suffers from the risk of contamination with the ingested drug which precludes the determination of absorption rates (Moreland *et al.*, 1982). In this study we think this problem was minimised. Age-related differences in bioavailability and volume of distribution are possible but in view of the known propensity of carbamazepine to induce its own metabolism it would seem likely that any age-related changes in these parameters would be minor in comparison with the known inter-subject variances in clearance (Rawlins *et al.*, 1975).

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