Rapid tolerance to acute psychomotor impairment with carbamazepine in epileptic patients

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Thirteen patients with newly diagnosed epilepsy performed a battery of psychomotor function tests before and during the first 12 weeks of carbamazepine (CBZ) therapy. Movement time ($P < 0.025$), total choice reaction time ($P < 0.025$), finger tapping rate ($P < 0.005$) and number cancellation ($P < 0.05$) were all significantly impaired after 1 week's treatment, but had returned to baseline by 4 weeks. Mean ($\pm$ s.d.) serum CBZ concentrations and those of its active metabolite CBZ 10,11 epoxide (CBZ-E) were comparable at 1 (CBZ: 8.5 ± 2.1 mg l⁻¹, CBZ-E: 1.1 ± 0.68 mg l⁻¹) and 4 weeks (CBZ: 8.1 ± 4.4 mg l⁻¹, CBZ-E: 0.93 ± 0.27 mg l⁻¹). These results suggest the rapid development of tolerance to the acute deleterious psychomotor effects of CBZ.

Keywords carbamazepine psychomotor tests tolerance cognitive function epilepsy

Introduction

Impairment of cognitive function is a recognised side-effect of all first-line antiepileptic drugs. Newer drugs, however, such as carbamazepine (CBZ) and sodium valproate appear to be less sedative than phenytoin (Andrews *et al.*, 1986; Gallassi *et al.*, 1988; Gillham *et al.*, 1990), which is itself an improvement on the barbiturates (Meador *et al.*, 1990). Reports showing psychomotor impairment in patients taking CBZ when compared with healthy controls (Stores *et al.*, 1978; Tomson *et al.*, 1988) do not control for the deleterious effects of epilepsy itself, which can be shown in untreated patients (Brodie *et al.*, 1987). This problem can be partially overcome by demonstrating impairment with CBZ in healthy subjects (Macphee *et al.*, 1986a) and also in stabilised epileptic patients given an extra dose of CBZ and matched placebo (Macphee *et al.*, 1986b). However, these are acute observations and it is possible that tolerance develops. In the present study, a battery of psychomotor tests was performed before and for 12 weeks after commencing CBZ to assess the extent and time-scale of any psychomotor impairment in newly diagnosed epileptic patients naive to the drug.

Methods

Patients

Thirteen patients (six male, seven female, age range 18–60 years) took part in the study. All had epilepsy recently

diagnosed. Seven reported tonic-clonic seizures only, and six had partial seizures with or without secondary generalisation. None was taking medication likely to affect psychomotor function.

Protocol

Patients were seen at a preliminary visit for baseline psychomotor function testing. The entire battery was undertaken twice as a 'training' exercise before results from the third performance were recorded. Tests at this and all subsequent visits (0, 1, 2, 4 and 12 weeks) were performed in the same room, under the same lighting and at the same time of day (14.00–15.30 h). After the first visit, all patients were commenced on CBZ 200 mg twice daily. At subsequent visits, blood was drawn for assay of CBZ and CBZ 10,11 epoxide (CBZ-E), an active metabolite which contributes to CBZ neurotoxicity (Gillham *et al.*, 1988). Dosage was altered—as necessary—to maintain CBZ concentrations within the 'target range' of 4–10 mg l⁻¹ (Brodie & Feely, 1988).

Assays

CBZ was measured by enzyme immunoassay (Emit, Syva, Palo Alto). Inter-assay coefficients of variation at 1.5, 6 and 12 mg l⁻¹ were 3.1, 3.0 and 4.8% respectively. CBZ-E was measured by high performance liquid chromatography as previously described (Macphee *et al.*, 1984). Interassay coefficients of variation at 0.15, 0.6 and 1.2 mg l⁻¹ were 8.5, 6.6 and 7.7%.

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Psychomotor tests

A range of tests was used which assessed a variety of psychomotor and cognitive functions. This simple battery involved a minimum of gadgetry and took approximately 20 min to complete.

1. Critical flicker fusion threshold (CFFT) utilised the Leeds Psychomotor Tester and assessed patients' appraisal of the frequency above which flickering diodes appeared as constant light. Three tests were performed while increasing frequency and three while decreasing and the mean was calculated (CFFT_m). This test assesses 'integrative' function.
2. Choice reaction time (CRT), using the same equipment, measured the patient's reaction time in recognising a flash from one of six lights and touching one of six buttons equidistant from his or her index finger to extinguish it. A mean of thirty tests was recorded for recognition time (time to lift finger from starting point—CRT₁), movement time (time to extinguish the light—CRT₂) and total reaction time (CRT_{tot}). This test assesses sensorimotor performance.
3. Digit recall test was performed by asking the patient to repeat a number which was extended by one digit after each successful recall. Digits were phonated at 1 s intervals and the longest successful recall was recorded.
4. Finger tapping rate, using the index finger of the dominant hand, was determined over two periods of 30 sec on an electronic calculator keyboard in constant addition mode. This measures pure motor function of the simple 'ballistic' type.
5. Card sorting of a shuffled pack of conventional playing cards into aces, kings, etc. was employed as an overall assessment of cognitive function.
6. Number cancellation involved the detection of every '7' (a) or '2' (b) in a series of 'random' typed digits. Scoring was out of 40 in 45 s and assessed concentration with minimal motor activity.
7. Alertness score. Patients recorded their 'alertness' on a visual analogue scale of 100 mm marked from 'almost asleep' to 'wide awake'. A score from 1 to 100 was taken as a subjective measurement of alertness.

Statistics

Results at different time-points were compared using the Wilcoxon rank pairs test (non-parametric). Means and measures of dispersion are shown in Table 1 and Figure 1 for illustrative purposes.

Results

Compliance with drug therapy was good as assessed by tablet count. Six patients, however, failed to attend for the final visit at 12 weeks. Paired comparisons were still possible, but those for the last assessment were of low power. Four patients required an increase in CBZ dosage during the study. Three were increased to 600 mg daily and one patient who had inadvertently started with 200

Figure 1 Changes in a) total choice reaction time and b) finger tapping rate before and after the introduction of carbamazepine (CBZ). Values are mean $\pm$ s.e. mean. Performance of both tests (choice reaction time $P < 0.05$; finger tapping $P < 0.005$) deteriorated after 1 week but recovered thereafter to baseline levels.

mg once daily adopted the twice daily regimen after 2 weeks.

Mean (s.d.) psychomotor test results and serum CBZ and CBZ-E concentrations are shown in Table 1. Paired analysis showed impairment after 1 week in CRT₂, CRT_{tot}, finger tapping and number cancellation (b). Significant improvements compared with week 1 were shown at weeks 4 and 12 for all of the CRT measurements and finger tapping rate. The effect on CRT_{tot} and finger tapping is illustrated in Figure 1. At weeks 1 and 4 serum CBZ and CBZ-E concentrations were similar.

Correlations of all assay results with the psychomotor tests revealed significant associations (all $P < 0.005$) for both total and free CBZ concentrations with finger tapping ($r = -0.61, -0.57$) and CRT₂ ($r = 0.53, 0.60$). Total CRT correlated only with CBZ-E concentrations ($r = 0.41, p < 0.01$). CRT_{tot} results correlated with CRT₁ ($r = 0.93, P < 0.001$) but not CRT₂ ($r = 0.064$). Good performance at card sorting was associated with number cancellation (a) $r = 0.67, P < 0.01$; (b) $r = 0.60, P < 0.025$) but not finger tapping ($r = 0.06$) or any other test.

Discussion

These results show evidence of tolerance to the initial detrimental psychomotor effects of CBZ, best seen with finger tapping and CRT. Autoinduction of metabolism,

Table 1 Mean (s.d.) psychomotor test scores and carbamazepine (CBZ) and its epoxide (CBZ-E) concentrations in newly diagnosed epileptic patients before and during the first 12 weeks of therapy

	0	1	Week		
	(n = 13)	(n = 11)	2	4	12
			(n = 12)	(n = 11)	(n = 7)
CFFT mean	27.0	27.3	28.1	28.3	27.7
(Hz)	(2.8)	(2.9)	(3.1)	(3.1)	(3.4)
CRT ₁	0.49	0.53	0.45*	0.47*	0.48*
(s)	(0.16)	(0.24)	(0.12)	(0.18)	(0.15)
CRT ₂	0.27**	0.30	0.29	0.26**	0.25*
(s)	(0.06)	(0.07)	(0.07)	(0.06)	(0.09)
CRT _{tot}	0.76**	0.82	0.75**	0.73**	0.74*
(s)	(0.15)	(0.25)	(0.12)	(0.20)	(0.22)
Digit span	8.5	9.5	8.4	8.8	8.7
	(0.9)	(2.1)	(1.4)	(1.7)	(2.1)
Finger tapping	340***	315	323	339**	331
(taps min ⁻¹)	(26)	(35)	(23)	(31)	(51)
Card sorting	66.4	60.1	70.1	63.9	69.9
(s)	(37)	(14)	(29)	(20)	(30)
Number cancellation	36.3	37.0	36.1	36.1	35.5
(a)	(4.6)	(3.7)	(6.0)	(6.1)	(5.5)
Number cancellation	27.4*	25.7	27.4	27.3	29.6*
(b)	(6)	(5.9)	(6.3)	(6.8)	(7.5)
Alertness score	60.3	54.1	66.4	68.7	65.5
(VAS—mm)	(18)	(23)	(22)	(23)	(31)
CBZ concentration	0	8.5	7.3	8.1	7.1
(mg l ⁻¹)		(2.1)	(2.5)	(4.4)	(2.1)
CBZ-E concentration	0	1.1	1.0	0.93	0.82
(mg l ⁻¹)		(0.68)	(0.56)	(0.27)	(0.38)

Significantly better than at week 1, * $P < 0.05$, ** $P < 0.025$, *** $P < 0.005$.

with lowered concentrations of CBZ (Macphee & Brodie, 1985; Macphee *et al.*, 1987; Rapeport *et al.*, 1983), is obviously a complicating factor, as a relationship between CBZ concentrations and psychomotor impairment is possible (Gillham *et al.*, 1988), although not always demonstrable with these tests (Brodie *et al.*, 1987). The present results show some significant correlations but should be viewed with caution, since they involve a mixed population of 'longitudinal' and 'cross-sectional' data. Certainly decreasing drug concentrations are not the whole story, as mean serum concentrations of CBZ and its active metabolite were well maintained for the study's duration. As an example, all four patients who required an increase in drug dosage had increased CBZ concentrations at their next hospital visit, but some continued their improvement in CRT ($n = 2$), finger tapping ($n = 3$) and number cancellation ($n = 3$).

Correlations, interestingly, suggested that CRT_{tot} was almost entirely dependent on the recognition phase of the test, although patients showed significant changes in both movement phase and CRT_{tot}. The association of card sorting and number cancellation suggests that the former is more dependent on attention than on pure motor function.

This small study gives an indication of rapid tolerance to psychomotor impairment with CBZ, apparently not mediated by lowered drug concentrations. This raises doubts over the relevance of acute studies of cognitive function to the chronic use of anticonvulsant drugs in epileptic patients.

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