Impairment of psychomotor function at modest plasma concentrations of carbamazepine after administration of the liquid suspension to naive subjects

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- 1 The influence of pharmaceutical formulation on the plasma drug concentration-time curve and the psychomotor responses to 400 mg carbamazepine has been assessed in 12 healthy male volunteers; three formulations and placebo were compared in a randomised, blind, crossover study.
- 2 The plasma concentration of carbamazepine rose to a maximum of 3–7 mg l⁻¹ by 2–3 h after administration of the liquid suspension. Conventional and controlled release tablet formulations gave lower peaks at about 8 and 32 h, respectively. From 32 h onwards the plasma concentrations from the three formulations were indistinguishable.
- 3 Significant impairment of psychomotor function was observed after the liquid suspension only; subjective sedation was significant at 1 and 2 h and the critical flicker fusion frequency threshold was lowered at 1–8 h. Digit-symbol substitution, choice reaction time and body sway gave less conclusive evidence of impairment.
- 4 The results do not support the hypothesis that a psychomotor effect from carbamazepine is a threshold phenomenon with a critical plasma drug concentration at about 8 mg l⁻¹.
- 5 A second hypothesis that rate of rise of plasma carbamazepine concentration has an important influence on psychomotor effect fits the observations. This interpretation is tentative since the use of a fixed dose of carbamazepine meant that differences due to rate of rise of drug concentration were confounded with differences due to peak height.

Keywords carbamazepine formulation psychomotor responses

Introduction

Adverse effects of carbamazepine on psychomotor function (sedation, dizziness, ataxia, double vision) have often been reported in patients receiving multiple dosage when the plasma concentration exceeds 8 mg l⁻¹; it has been suggested that there is a critical threshold at about this level (Hoppener *et al.*, 1980; Kutt & Penry, 1974; Meinardi, 1973; Riva *et al.*, 1984).

A single dose study in healthy volunteers also gave results compatible with this hypothesis; McPhee *et al.* (1986a) observed psychomotor impairment 10 to 18 h after carbamazepine (10 mg kg⁻¹ as conventional tablets) when mean concentrations were generally above 8 mg l⁻¹. At 34 h however, when concentrations were lower, no effects could be detected.

A second hypothesis suggests that the rate of rise of plasma carbamazepine concentration is an important

determinant of psychomotor effect (Lesser *et al.*, 1984; McPhee *et al.*, 1986b). Similar suggestions have been made in relation to other CNS active drugs; Mirsky *et al.* (1941) showed that subjects who were intoxicated within 2 h of starting to drink ethanol were sober several hours later when the blood concentration of ethanol was higher than at 2 h. During recovery from thiopentone anaesthesia, when the level was falling, consciousness was regained at a higher plasma concentration than that at which it was originally lost, when the level was rising (Dundee *et al.*, 1956). Garnham *et al.* (1975) observed CNS effects of indomethacin at relatively low plasma concentrations when conditions favoured rapid absorption.

The formulation most likely to give a rapid rise in plasma carbamazepine concentration is the liquid

suspension. The pharmacokinetics of carbamazepine administered in this form were studied by Wada *et al.* (1978); the plasma concentration rose steeply but psychomotor effects were not assessed. Several recent studies have compared the effects of different carbamazepine formulations (Canger *et al.*, 1990; Granata *et al.*, 1990; Patsalos *et al.*, 1990; Tedeschi *et al.*, 1989) but they have not included the liquid suspension.

Methods

Subjects

The 12 male volunteers were aged 20–55 years (mean 30.5), weighed 63–74 kg (mean 68.5) and did not smoke. Each gave written informed consent and received a physical examination with biochemical and haematological screen to exclude pathology. Females were not included because of the risk of decreased effectiveness of oral contraceptives. The protocol was approved by the Manchester Central District Health Authority, Clinical Research Ethics Committee.

Design of study

This was a double-blind, randomised, balanced, crossover study in which each volunteer received every treatment. Carbamazepine and matching placebos were provided by Ciba-Geigy Pharmaceuticals as three formulations of the proprietary product Tegretol®. Each active treatment (400 mg carbamazepine) was combined with placebos which matched the other two formulations. The treatments were: (a) liquid suspension (20 ml of 20 mg ml⁻¹) with placebos; (b) conventional tablets (2 × 200 mg) with placebos; (c) controlled release (Retard) tablets (2 × 200 mg) with placebos and (d) placebos alone. Consecutive treatments were separated by a washout period of at least 2 weeks.

The subjects practised each of the tests (detailed below) a few days before the start of the study. They agreed to abstain from drinks containing alcohol or caffeine from the night before to the end of each set of tests and to fast until 11.00 h on the morning of treatment. Pretreatment tests were made and a 5 ml venous blood sample taken; the treatment was then administered (at about 09.00 h) with 100 ml of orange juice. Tests and blood samples were repeated at 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 32 and 48 h after the treatment. Six subjects had blood samples taken at 54 and 72 h also. Between 0 and 8 h the samples were taken through a forearm venous cannula. Subjects did not drive on the treatment day.

Plasma concentration

Plasma concentrations of total carbamazepine and its 10–11 epoxide were determined by h.p.l.c. (Richardson, 1988). Authentic drug standards were obtained from Sigma. At ambient temperature with a flow rate of 1.7 ml min⁻¹ the retention times were 4 min for carbamazepine and 1.8 min for the epoxide. The limit of determination was 0.2 mg l⁻¹ and the interassay variation was 4.5% at a carbamazepine concentration of 5 mg l⁻¹.

Subjective condition

The subjects reported their condition on two different 100 mm visual analogue scales. Sedation was rated between 'wide awake' and 'nearly asleep'; incoordination was rated between 'well coordinated' and 'clumsy'. The distance from the poor performance end was measured in mm.

Digit symbol substitution

This test involved substituting digits for symbols according to the code given at the top of each test page. The number of symbols correctly substituted during a 90 s period was counted.

Psychomotor tests

The critical flicker fusion threshold (CFFT) test (Leeds Psychomotor Tester; Hindmarch, 1979) was used as an index of arousal. The subject was required to concentrate on a cluster of four light-emitting diodes at a distance of 1 m. Ambient light intensity was standardised. The frequency of flicker was increased and decreased slowly and smoothly; the subject indicated the points at which flicker a) became imperceptible and b) reappeared. The complete sequence was repeated three times and the means of the frequencies corresponding with a) and b) were recorded.

The choice reaction time (CRT) test (Hindmarch, 1975) was used as an index of vigilance and motor function. The subject was required to scan an array of small lights which were illuminated on a random basis. In response to this the subject lifted the finger off the base button and pressed the indicated button to extinguish the light. The total response time was recorded and the time before lift off (recognition time). On each occasion 30 observations were made and the mean calculated.

Ataxia

Subjects stood on an electronic sway meter 7.5 cm above the floor; this consisted of a circular wooden platform resting on a resilient rubber plate, into which had been embedded four pressure transducers spaced 90 degrees apart. The output from the transducers was amplified and passed to two potentiometers; one recorded the front-back component of sway and the other the left-right component. Recordings were made over 1 min with eyes open and 1 min with eyes closed. The mean amplitude of sway in each plane was obtained from the recorder trace using a graphics tablet in conjunction with an Apple IIe computer. The method has been described in more detail previously (Wildin *et al.*, 1990).

Analysis

All responses were expressed as the change from the baseline (pretreatment) value. The significance of differences due to treatments, subjects and times was assessed by analysis of variance. When differences due to treatments were significant ($P < 0.05$), the differences between an individual treatment and placebo was assessed by the studentised range test.

Results

Plasma concentration

The three formulations produced very different plasma concentration-time profiles (Figure 1). The liquid suspension gave a rapid rise to a maximum at 2–3 h post treatment. Conventional tablets gave a slow rise to a maximum at about 8 h and the controlled release tablets gave a very slow rise to a maximum at about 32 h.

Figure 1 Plasma concentrations ($\text{mg l}^{-1} \pm \text{s.e. mean}$) of carbamazepine after an oral dose of 400 mg as liquid suspension (■), conventional tablets (●) and controlled release tablets (▲) in 12 volunteers.

Beyond this point the plasma carbamazepine concentration decay curves for the three formulations were almost identical. Carbamazepine was still measurable at 72 h in the six subjects followed to that time. The comparative pharmacokinetic data are summarised in Table 1. In no subject did the total carbamazepine concentration attain 8 mg l^{-1} . The concentrations of the 10–11 epoxide were less than 10% of the total carbamazepine values and are not shown.

Subjective condition

Most subjects reported drowsiness during the first few hours after the liquid suspension. Sedation on the analogue scale was significant at 1 and 2 h after treatment (Table 2) but no significant effect was reported with the other formulations. A similar result was found with the subjective rating of incoordination, which showed a significant increase in clumsiness during the first few hours after the liquid suspension only (scores not shown).

Digit symbol substitution

Differences due to treatments were significant (analysis of variance). The lowest scores were recorded during the first 3 h after the liquid suspension (Table 3) but the differences from placebo at individual times were not significant. There was a marked improvement in scores during the second day on all treatments including placebo.

Table 2 Visual analogue sedation scores (change from pre-drug in mm) in volunteers given placebo or 400 mg carbamazepine in three formulations (mean $\pm$ s.e. mean, $n = 12$)

Time (h)	Placebo	Liquid suspension	Conventional tablet	Controlled release
1	0.7 ± 1.3	$-23.4 \pm 7.0^*$	-1.8 ± 3.1	-5.9 ± 2.9
2	-2.3 ± 2.2	$-15.6 \pm 6.2^*$	-1.3 ± 4.2	-5.3 ± 3.6
3	-3.7 ± 3.6	-9.7 ± 5.8	0.2 ± 4.7	-4.0 ± 3.0
4	-4.0 ± 3.5	-6.7 ± 5.9	1.8 ± 4.5	-1.8 ± 2.6
5	-2.6 ± 3.3	-2.7 ± 4.9	1.8 ± 4.2	-3.9 ± 3.6
6	-2.6 ± 3.2	2.5 ± 4.9	6.4 ± 4.6	-1.8 ± 2.2
8	-1.5 ± 2.4	4.1 ± 4.6	4.4 ± 4.7	-1.4 ± 2.5
12	-0.6 ± 2.8	2.1 ± 3.0	7.0 ± 4.4	0.7 ± 2.3
24	1.9 ± 1.7	3.2 ± 3.7	8.5 ± 3.6	0.1 ± 1.0
36	3.5 ± 1.6	7.3 ± 4.0	10.0 ± 3.7	1.0 ± 2.0
48	3.7 ± 1.2	7.6 ± 3.9	9.4 ± 3.1	0.2 ± 2.2

*significantly different from placebo ($P < 0.05$).

Table 1 Characteristics of plasma carbamazepine concentration-time curves after three different formulations. A – liquid suspension, B – Conventional tablets, C – controlled release tablets (mean and range; $n = 12$)

	C_{max} (mg l^{-1})	Time to peak (h)	$t_{1/2,z}$ (h)	$AUC(0,48)$ ($\text{mg l}^{-1} \text{ h}$)
A	5.5 (3.2–7.2)	3 (2–3)	42.6 (21–70)	159.8 (100.0–201.3)
B	3.7 (2.7–5.0)	8 (6–12)	50.5 (21–82)	140.6 (104.6–204.2)
C	2.6 (1.9–3.2)	32 (12–48)	37 (20–83)	110.0 (50.7–148.6)

Table 3 Digit symbol substitution scores (change from pre-drug) in volunteers given 400 mg carbamazepine in three formulations (mean $\pm$ s.e. mean, $n = 12$)

Time (h)	Placebo	Liquid suspension	Conventional tablet	Controlled release
1	-2.7 $\pm$ 1.9	-4.5 $\pm$ 2.7	-1.8 $\pm$ 2.1	-3.0 $\pm$ 2.1
2	-3.2 $\pm$ 2.2	-6.7 $\pm$ 2.4	-1.8 $\pm$ 1.3	-4.0 $\pm$ 1.5
3	-4.3 $\pm$ 1.5	-5.6 $\pm$ 2.3	-3.2 $\pm$ 2.1	-1.7 $\pm$ 2.2
4	-5.0 $\pm$ 1.7	-4.7 $\pm$ 2.2	-2.2 $\pm$ 2.1	-2.0 $\pm$ 2.3
5	-4.2 $\pm$ 1.4	-1.7 $\pm$ 2.3	-2.3 $\pm$ 1.8	-3.9 $\pm$ 1.8
6	-4.9 $\pm$ 2.3	-4.7 $\pm$ 1.5	-1.1 $\pm$ 2.0	-3.2 $\pm$ 1.9
8	-4.6 $\pm$ 1.8	-3.3 $\pm$ 2.6	-3.3 $\pm$ 1.8	-3.0 $\pm$ 1.6
12	-1.4 $\pm$ 2.2	-1.1 $\pm$ 2.5	0.0 $\pm$ 1.6	-1.6 $\pm$ 2.7
24	4.0 $\pm$ 1.6	3.4 $\pm$ 2.4	3.4 $\pm$ 1.9	3.8 $\pm$ 2.1
36	2.7 $\pm$ 2.2	4.0 $\pm$ 2.6	4.3 $\pm$ 2.6	4.4 $\pm$ 2.0
48	3.0 $\pm$ 2.1	1.2 $\pm$ 2.7	3.2 $\pm$ 1.8	2.1 $\pm$ 2.0

Table 4 Recognition time (change from pre-drug in s) in volunteers given placebo or 400 mg carbamazepine in three formulations (mean $\pm$ s.e. mean, $n = 12$)

Time (h)	Placebo	Liquid suspension	Conventional tablet	Controlled release
1	-0.001 $\pm$ 0.006	0.032 $\pm$ 0.013*	0.014 $\pm$ 0.007	0.011 $\pm$ 0.007
2	0.018 $\pm$ 0.009	0.037 $\pm$ 0.011	0.019 $\pm$ 0.008	0.010 $\pm$ 0.010
3	0.027 $\pm$ 0.012	0.029 $\pm$ 0.011	0.028 $\pm$ 0.012	0.009 $\pm$ 0.008
4	0.026 $\pm$ 0.007	0.040 $\pm$ 0.012	0.034 $\pm$ 0.011	0.016 $\pm$ 0.008
5	0.017 $\pm$ 0.010	0.040 $\pm$ 0.022	0.021 $\pm$ 0.013	0.021 $\pm$ 0.010
6	0.009 $\pm$ 0.009	0.031 $\pm$ 0.014	0.025 $\pm$ 0.013	0.021 $\pm$ 0.012
8	0.003 $\pm$ 0.010	0.012 $\pm$ 0.010	0.010 $\pm$ 0.011	0.001 $\pm$ 0.009
12	-0.001 $\pm$ 0.010	0.006 $\pm$ 0.009	0.013 $\pm$ 0.007	-0.007 $\pm$ 0.009
24	0.001 $\pm$ 0.011	-0.003 $\pm$ 0.007	0.004 $\pm$ 0.008	0.002 $\pm$ 0.009
32	-0.004 $\pm$ 0.010	-0.004 $\pm$ 0.008	0.000 $\pm$ 0.008	-0.004 $\pm$ 0.011
48	-0.003 $\pm$ 0.008	-0.006 $\pm$ 0.009	0.005 $\pm$ 0.007	-0.008 $\pm$ 0.010

*significantly different from placebo ($P < 0.05$).

Critical flicker fusion threshold

Significant depression of the CFFT (during both rising and falling phases) was seen throughout the whole of the first day after treatment with the liquid suspension (Figure 2). There was also a suggestion of the effect persisting into the second day. No effect was seen with either of the other two formulations.

Choice reaction time

Significant prolongation of recognition CRT was found with the liquid suspension 1 h after treatment (Table 4).

Ataxia

Differences due to treatment (analysis of variance) were significant in both planes and with eyes open and closed. After the liquid suspension sway was increased significantly at 1 h (front-back, eyes closed) and at 3 h (front-back, eyes open (Figure 3); left-right, eyes closed).

With the other two formulations the effects were not consistently in one direction; there was significant increase in sway with both at 1 h (front-back, eyes closed) and with the conventional formulation at 8 h (left-right, eyes closed). At 8 and 10 h however the controlled release produced an apparent reduction in sway (Figure 3).

Figure 2 Change in critical flicker fusion threshold (Hz $\pm$ s.e. mean) on the rising frequencies after placebo (Δ), carbamazepine 400 mg as suspension ($\blacksquare$), conventional tablet ($\bullet$) and controlled release tablet ($\blacktriangle$) in 12 volunteers. * indicates a significant ($P < 0.05$) difference from placebo.

Figure 3 Change in body sway in the front-back direction (eyes open) (sway units $\pm$ s.e. mean) after placebo (Δ) and carbamazepine 400 mg as the suspension ($\blacksquare$), conventional tablet ($\bullet$) and controlled release tablet ($\blacktriangle$) formulations in 12 volunteers. * indicates a significant ($P < 0.05$) difference from placebo.

Discussion

Plasma carbamazepine concentrations after treatment with the liquid suspension were consistent with the data of Wada *et al.* (1978) allowing for the difference in dosage. The maximum concentrations of 3–7 mg l⁻¹ (Table 1) were attained within 2–3 h and there was little decay before 8 h (Figure 1). Total area under curve (AUC) values were not determined but the lower AUC (0, 48 h) obtained after the controlled release formulation was consistent with the results of other investigators who have reported a small reduction in bioavailability with this formulation (Eeg-Olofsson *et al.*, 1990; Tomson *et al.*, 1989). During the first 2 h after the liquid suspension there was significant subjective sedation (Table 2) and throughout the first 8 h there was significant lowering of the CFFT (Figure 2). It is clear that carbamazepine can produce measurable impairment of psychomotor function in naive subjects at plasma concentrations well below the suggested threshold of 8 mg l⁻¹ in circumstances where the concentration has risen rapidly. The threshold hypothesis (Hoppener *et al.*, 1980; Kutt & Penry, 1974; Meinardi, 1973; Riva *et al.*, 1984) in its simplest form is therefore not tenable for naive subjects receiving a single dose.

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- In addition to the subjective and CFFT effects of the liquid suspension there was less conclusive evidence of slowing of cognitive function (digit symbol substitution), increased body sway and prolongation of recognition CRT. At the same dose the two other formulations produced no consistent psychomotor effects. With hindsight it would have been better to have used higher doses of these formulations; 600 mg as conventional tablets and 800 mg as controlled release would probably have given maximum concentrations comparable to those given by 400 mg as liquid suspension (Table 1). It would then have been possible to compare the psychomotor effects of similar plasma carbamazepine concentrations which had been attained at very different rates; differences due to concentration gradient would not have been confounded with differences due to peak height.
- McPhee *et al.* (1986a) also reported sedation, lowering of the CFFT and prolongation of the CRT but at plasma carbamazepine concentrations above 8 mg l⁻¹. In addition they observed impairment of card sorting. In discussion they refer to the probable importance of rate of rise of concentration but their use of an evening dose (23.00 h) prevented observation during the early part of the concentration/time curve. Had this rising phase been accessible to them, it is possible that they also would have detected psychomotor effects at carbamazepine concentrations below 8 mg l⁻¹.
- When comparing the two experiments it is interesting to note that the total plasma concentration of carbamazepine 34 h after conventional tablets (10 mg kg⁻¹; McPhee *et al.*, 1986a) was very similar to that 2–3 h after liquid suspension (400 mg; Table 1). In the first case, where the concentration was falling, there was no effect on CFFT but in the second, where the concentration had just risen rapidly, there was significant lowering of the CFFT (Figure 2). A similar observation was made by Lesser *et al.* (1984); lethargy was reported during the rising phase of concentration but absent later when the concentration had reached its peak. These observations give further support to the hypothesis that rate of change of plasma carbamazepine concentration is an important determinant of psychomotor effect. Differences in concentration gradient may partly explain the findings of McPhee *et al.* (1986b) that the same patients with the same high plasma concentrations of carbamazepine (well above 8 mg l⁻¹) will sometimes experience adverse effects and sometimes not.
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