Br. J. clin. Pharmac. (1985), **20**, 619–629

Lamotrigine (BW430C), a potential anticonvulsant. Effects on the central nervous system in comparison with phenytoin and diazepam

A. F. COHEN, L. ASHBY, D. CROWLEY, G. LAND, A. W. PECK & A. A. MILLER
The Wellcome Research Laboratories, Beckenham, Kent

1 Twelve healthy male volunteers received phenytoin 0.5 and 1 g, lamotrigine (a new anticonvulsant) 120 and 240 mg, diazepam 10 mg and placebo orally in a double-blind, cross-over, randomized trial.

2 Maximum drug concentrations at 4 h, measured in plasma were 11.5 ± 2.2 μg ml^{-1} for phenytoin and 2.7 ± 0.4 μg ml^{-1} for lamotrigine. These levels were in the therapeutic range for phenytoin and the putative therapeutic range for lamotrigine.

3 Side effects after diazepam (mainly sedation) and phenytoin (mainly unsteadiness) differed markedly from lamotrigine which produced no important side effects. Subjective effects as measured by visual analogue scales were caused by phenytoin and diazepam but not by lamotrigine.

4 Diazepam impaired eye movements, adaptive tracking and body sway. Phenytoin impaired adaptive tracking, increased body sway and impaired smooth pursuit eye movement. Lamotrigine produced only a possible slight increase in body sway.

5 There were significant correlations between performance and saliva levels of phenytoin and diazepam.

6 It was concluded that the tests used were suitable for monitoring CNS effects of anticonvulsants and that lamotrigine possibly could have a more favourable CNS side effect profile than phenytoin.

Keywords anticonvulsants phenytoin diazepam lamotrigine normal volunteers plasma concentrations eye movements tracking body sway

Introduction

Lamotrigine (Figure 1) has an anticonvulsant profile in animals that is similar to phenytoin but it also has activity in some of the tests where ethosuximide and diazepam are active and phenytoin is inactive (Miller *et al.*, 1984). It is a potent agent with a long duration of action in animals, and in man has been shown to have pharmacokinetic advantages over phenytoin (Cohen *et al.*, 1984a). Therapeutic plasma levels of lamotrigine are not known but by comparison with phenytoin in animal models it can be predicted that the compound should have clinical effects in man at plasma concentrations from 1.5–3 μg ml^{-1}. Initial evidence for this has been obtained from single dose studies in epileptic

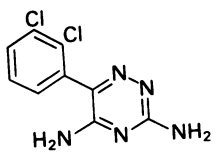

Figure 1 Structural formula of lamotrigine.

patients. Interictal spikes (Jawad *et al.*, 1985) and photosensitivity (Binnie *et al.*, 1985) were reduced by lamotrigine at plasma concentrations in this range.

In mice the compound is superior to phenytoin since it causes ataxia only at 47 times the anticonvulsant ED_{50}, while for phenytoin this ratio was 24. Lamotrigine causes ataxia in marmosets at least five times the expected anticonvulsant dose (50 mg kg^{-1}). In man phenytoin causes ataxia and nystagmus at plasma concentrations over 20 $\mu g\ ml^{-1}$, which can be easily demonstrated clinically (Jones *et al.*, 1983). However not much is known about the effects of phenytoin on coordination and eye movements at therapeutic levels. Smooth pursuit eye movements were impaired in a group of epileptic patients (Bittencourt *et al.*, 1983) but many of them were receiving an additional anticonvulsant. In human volunteers phenytoin alone did not affect eye movements (Bittencourt & Richens, 1981a) but it has been suggested that plasma concentrations in these volunteers were too low.

The absorption of phenytoin is dose related (Jones *et al.*, 1983) and this makes it difficult to attain therapeutic plasma levels in normal volunteers after single dose administration which for practical reasons is desirable. Several studies have been published in which effects of phenytoin in normal volunteers were measured using different dosage schedules and test methods (Haward, 1983; Houghton *et al.*, 1973; Idestrom *et al.*, 1973; Booker *et al.*, 1967; Stephens *et al.*, 1967). However no clear effects were seen in any of these studies, possibly because plasma concentrations were inadequate. In several studies (Haward, 1973; Booker *et al.*, 1967; Stephens *et al.*, 1967) they were not acutally measured. It is also possible that the tests used were inappropriate for the detection of the effects of the drug since its toxic effects suggest that coordination is more likely to be impaired than cognitive function.

Adaptive tracking (Nicholson, 1979), saccadic and smooth pursuit eye movements (Tedeschi *et al.*, 1983; Norris, 1971; Bittencourt *et al.*, 1981b), and body sway (Scott *et al.*, 1982) have all been shown to be affected by sedative drugs. It is not known however if these tests are sensitive to drug induced ataxia. However discrete movement of the limbs and the control of posture are both under cerebellar control and the tests should theoretically be appropriate for the detection of effects caused by phenytoin.

In this study we attempted to achieve therapeutic plasma concentrations of phenytoin in normal volunteers and see if central nervous system effects could be detected. We also compared lamotrigine and phenytoin in their ability to affect the tests. Diazepam was used as a positive control known to produce sedation.

Methods

Twelve male volunteers were recruited for this study. Their average age was 28.9 years (range 20–37). Their average height (± s.d.) was 178.6 ± 10.3 cm and their weight 76.3 kg (range 58–103 kg). They all gave written consent after a full explanation about the study and the drugs involved. The study was approved by the Protocol Review Committee of the Wellcome Research Laboratories. The subjects underwent a full medical and neurological examination as well as an ECG and haematological and biochemical screening. They had no abnormalities in any of these measures. The subjects were not on any regular drug treatment. They were not allowed caffeine containing drinks or smoking during the study day. They abstained from alcohol from 24 h before the beginning until the end of the study day.

Design

The study was designed as a double-blind cross-over randomised trial. Treatments were administered at intervals of at least 7 days. The order of treatment administration was determined by two 6 × 6 counter balanced Latin squares. Subjects were studied in groups of four on 3 week days. When a subject occasionally missed an occasion, treatment order was maintained and the subject finished the trial 1 week later.

Treatments

In order to achieve therapeutic plasma concentrations of phenytoin without having to administer very large single doses, the 1 g dose of phenytoin was administered in two 500 mg doses. One dose was given 12 h before the dose on the morning of the trial day. A placebo capsule was given in the evening for treatments other than phenytoin 1 g. Therefore all subjects received a capsule 12 h before the study day containing either placebo or on one occasion phenytoin. The treatments on the trial day were lactose (L), lamotrigine 120 mg (B120) and 240 mg (B240), phenytoin sodium 500 mg (P500) and 500 + 500 mg (P1000), and diazepam 10 mg (D10).

All treatments were supplied in identical gelatine capsules and administered with 100 ml water. The formulation of the capsules containing phenytoin sodium complied with the require-

ments of the British Pharmacopoeia 1980 for disintegration times. The amount of phenytoin dissolved from the capsules after 45 min amounted to 91.4 ± 5.6% (USP basket 100 rev min^{-1} in 900 ml deionised water as the dissolution medium). This indicates that the capsules should have good bioavailability (Shah *et al.*, 1983).

Performance tests

Adaptive tracking An adaptive tracking test (Nicholson, 1979) was used to assess eye hand coordination and effects on attention as described earlier (Cohen *et al.*, 1984b). The test lasted for 10 min and was performed in an air conditioned laboratory with standardised lighting. The test yielded two scores. One, the overall performance score, is expressed as a percentage of the maximum possible performance on the instrument, the other score is the standard deviation of the performance levels that were continually monitored during the test. This is used as a measure of variability in performance. Subjects were trained to a constant level of performance with at least 10 pre-study sessions.

Body sway Body sway was measured using a Wright Codoc ataxiameter (Scott *et al.*, 1982). This instrument measures the anterio-posterior body sway cumulatively over a 1 min epoch. The subjects were standing with their feet slightly apart and their eyes closed. Three 1 min epochs were recorded. The average was used for statistical analysis.

Eye movement tests Eye movements were binocularly recorded by electro-occulography (EOG). Electrodes used were of the Ag/Ag Cl syntered disc type (Beckman) and were applied 1 cm laterally to the outer canthus of each eye with a reference electrode in the middle of the forehead. Amplification was by an EOG amplifier (Nihon-Kohden) with a band width from DC to 100 Hz. Electrode resistance was kept under 5 k ohm. Signals were recorded via a chart recorder as well as sampled at 250 Hz, analogue to digital converted, and stored by a microcomputer for off-line analysis.

The subject was seated with the head fixed at a distance of 50 cm from a large oscilloscope screen. Accommodation to the light conditions in the room occurred during the tracking test which always preceded the eye movement test. The target was a spot subtending approximately 0.1° of visual field. Smooth pursuit was tested by moving the spot horizontally in a sinusoidal manner at 30° eye rotation. Frequency increased from 0.2 to 1.3 Hz over a period of approximately 70 s. The subject was instructed to follow the spot visually without moving his head. Analysis of the signals was performed according to a variation of the method described by Bittencourt *et al.* (1981). For different target velocities, the percentage of time was measured in which the subject's eye movement matches the target velocity. An overall percentage of the time the subject's eye movement is in smooth pursuit throghout the session was also measured.

The saccadic eye movement system was tested with the same equipment. During this part of the test the target changes position instantaneously and the subjects were instructed to follow the spot visually. Twelve saccades of 25°, 30° and 35° eye rotation were produced. The peak velocity of the saccade, the duration of the saccade and the latency (reaction time) were measured by off line computer analysis (Smith *et al.*, 1981). The average peak saccadic velocity, duration and reaction time were used for statistical analysis.

Subjective effects These were measured using visual analogue scales. Several of the scores obtained were grouped into categories indicating mental sedation, physical sedation and tranquilisation (Norris, 1971). Side effects were recorded after each test session. The subjects were also asked if they thought they had received an active drug.

Drug concentrations

At 4 h after treatment a blood sample was obtained by venepuncture. After each test session a saliva sample was obtained by expectoration. Salivary flow was stimulated by chewing a piece of paraffin wax (Parafilm). It has been shown for phenytoin (Forney *et al.*, 1983) and for lamotrigine (Cohen *et al.*, 1984a) that salivary concentrations correlate well with unbound plasma concentrations of these drugs.

A better relation between saliva concentrations and the unbound concentration of phenytoin in plasma is obtained by measuring the concentration in a protein free ultrafiltrate of saliva (Forney *et al.*, 1983). Phenytoin saliva samples were therefore filtered through an Amicon YMT ultra filter at 25° C. Approximately 250 μl of filtrate was obtained from 1 ml saliva. Concentrations of lamotrigine and diazepam were measured directly in saliva. Lamotrigine concentrations were measured with a selective and sensitive (lower limit of sensitivity 10 ng ml^{-1}) h.p.l.c. method. Phenytoin concentrations were measured using polarization fluoroimmunoassay (McGregor *et al.*, 1978). A specific chromatographic assay for diazepam could not be used

because of the very low concentrations of diazepam in saliva (1–2 ng ml^{-1}) which are below the limit of sensitivity of these assays. Diazepam-like activity was therefore measured in serum and saliva samples using a radioreceptor assay which employed sheep-brain homogenate and [^{3}H]-diazepam (Hunt *et al.*, 1979). Concentrations for lamotrigine and phenytoin are given as $\mu g\ ml^{-1}$. For conversion to $\mu mol\ l^{-1}$ the lamotrigine concentrations are to be multiplied by 3.90 and the phenytoin concentrations by 3.96. Diazepam concentrations can be converted to $nmol\ l^{-1}$ by multiplying by 3.51.

Statistical analysis

All results were analysed by multiway analysis of variance (ANOVA), with $P < 0.05$ taken as significant. Pairwise differences between the treatments were assessed using Newman-Keuls multiple range test.

The relationship between saliva concentrations and performance could not be assessed reliably in individual subjects because there were only five data points available per subject.

The baseline responses obtained by the different performance tests varied considerably between the subjects. To enable to study this relationship in the group of subjects a correction for this was applied in the following manner. The responses for each subject were plotted against the logarithm of the drug concentration after correction for the subject differences. This entailed subtracting the subject mean from the observed data for each subject. A line that corresponded best to the data (excluding the responses at zero concentration) was then calculated using the method of least squares.

Test schedule

The test battery could only be administered to one subject at a time and treatments were staggered at 30 min intervals. The schedule shown is for the first subject on the study day. The tests were always administered in the following order.

1. Adaptive tracking
2. Eye movement test
3. Body sway test
4. Visual analogue scales
5. Salivary sampling

Preceding day

20.00 h administration of treatment.

Study day

07.30 h Arrival at laboratory, application of EOG electrodes
08.00 h Test battery 1
08.30 h Administration of treatment
10.30 h Test battery 2
12.30 h Test battery 3, collection of blood sample by venepuncture
14.30 h Test battery 4
16.30 h Test battery 5, transport home

Subjects were served a light sandwich lunch between 12.00 h and 13.30 h and a snack after 15.30 h. They were allowed fruit drinks *ad libitum* from 2 h after treatment administration onwards.

Results

Adaptive tracking

No treatment × session interactions were seen in the ANOVA and therefore statistical analysis of the average of the post-treatment sessions is shown in Table 1. Diazepam reduced tracking performance compared with placebo as expected from other studies. This impairment lasted until 8 h after drug administration demonstrating the long duration of action of this benzodiazepine (Figure 2).

Overall post-treatment tracking performance was also reduced by P1000. This effect was smaller than that caused by diazepam and reached significance only in the single session 6 h after administration of the second 500 mg dose. There was a dose related trend towards impairment on the lower dose of phenytoin but this did not reach significance. No impairment was seen after lamotrigine. The time course of these effects is shown in Figure 2.

The variability in the performance of the subjects during the test, which has been shown to be increased by sedative drugs, was only increased by diazepam. Phenytoin did not increase variability (Table 1).

Body sway

There was a significant treatment × session interaction ($P = 0.007$) for body sway and results are therefore analysed for each time point. Antero-posterior body sway was increased by D10 at 2 h and 8 h after drug administration but body sway was also increased significantly predrug. P1000 also increased body sway compared with placebo at 2 h after administration of the second dose as well as 12 h after the administration of the first 500 mg. There was again a dose related trend towards increased sway after P500. B240 increased body sway at 2 h. However the sway on this treatment was also significantly increased before treatment administration (Figure 3).

Table 1 Tracking and saccadic eye movements. Multi-way ANOVA showed no treatment × session interaction for any of these measures and therefore the mean of all the post-treatment sessions was analysed

	Placebo	*Lamotrigine 120 mg*	*Lamotrigine 240 mg*	*Phenytoin 500 mg*	*Phenytoin 1000 mg*	*Diazepam 10 mg*	*Overall s.e. mean*
Tracking performance (%)	78.61	79.05	78.29	76.34	75.75*	73.08*†	0.712
Variability in tracking performance (%)	5.65	5.38	5.64	6.27	6.11	7.60**††	0.300
Mean peak saccadic velocity (° s^{-1})	386.9	386.2	396.3	385.3	384.7	343.5**††	8.16
Mean duration of saccade (ms)	145	147	146	145	153	163*	5.0
Precision of saccade (RMS of difference between stimulus and response)	1.64	1.79	1.78	1.84	1.73	1.97	0.089
Reaction time to ln saccade (ms)	218	219	216	221	227	223	3.0

*different from placebo ($P < 0.05$)
**different from placebo ($P < 0.01$)
†different from all other treatments ($P < 0.05$)
††different from all other treatments ($P < 0.01$)

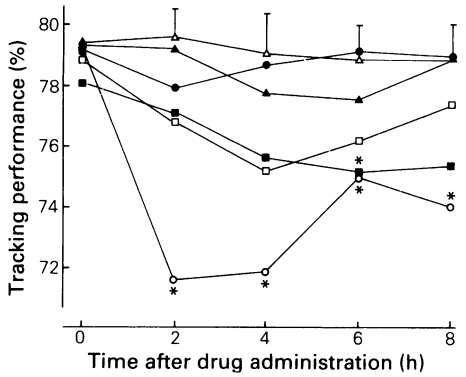

Figure 2 Adaptive tracking performance after phenytoin multidose (■), phenytoin single dose (□), diazepam 10 mg (○), lamotrigine 240 mg (▲), lamotrigine 120 mg (△) and lactose (●). Treatment means are shown. Bars indicate overall s.e. mean. * = different from placebo ($P < 0.05$).

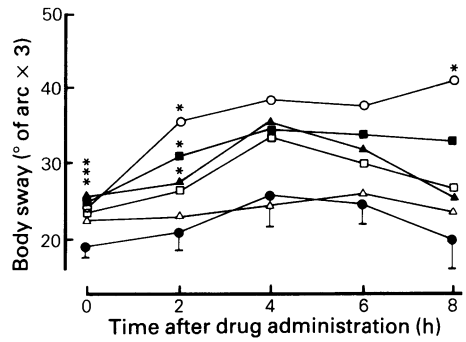

Figure 3 Body sway after phenytoin multidose (■), phenytoin single dose (□), diazepam 10 mg (○), lamotrigine 240 mg (▲), lamotrigine 120 mg (△) and lactose (●). Treatment means are shown at different times after drug administration. Bars indicate overall s.e. mean. * = different from placebo ($P < 0.05$).

Eye movement tests (Tables 1 and 2)

As expected diazepam reduced the mean peak velocity of the saccades compared with all the other treatments up to 8 h after drug administration (Figure 4). It also increased the duration of the saccades. Interestingly the saccadic latency (reaction time) was not affected by diazepam nor was the precision of the saccadic response compared with the stimulus which has been described before (Rothenberg & Selkoe, 1981). None of the other treatments affected saccadic eye movements.

No nystagmus, either on far lateral gaze or spontaneous was seen after any of the treatments.

Table 2 Smooth pursuit eye movements. The percentage smooth pursuit in the different velocity bands of the stimulus are shown. There was no treatment × session interactions and the mean of the post-dose session is therefore analysed

Stimulus velocity (° s^{-1})	*Smooth pursuit (%)*						
	Placebo	*Lamotrigine 120 mg*	*Lamotrigine 240 mg*	*Phenytoin 500 mg*	*Phenytoin 1000 mg*	*Diazepam 10 mg*	*s.e. mean*
0–10	96.3	95.8	95.9	94.8	94.3†	94.7*	0.39
10–20	92.8	92.3	92.1	91.1	90.4**	90.1**	0.47
20–30	86.1	85.2	84.8	83.7	82.0**	80.3**	0.82
30–40	78.1	77.5	77.1	75.7	73.0	70.5**	1.32
40–50	63.6	63.7	63.1	61.3	59.3	54.3*	1.89
60–70	54.3	55.1	54.7	52.4	51.6	46.0*	1.17
70–80	50.7	51.6	50.2	48.9	47.2	42.5	2.08
80–90	44.7	44.8	42.8	41.4	42.2	37.1	1.93

**significantly different from placebo ($P < 0.01$)
*significantly different from placebo ($P < 0.05$)
†significantly different from all other treatments ($P < 0.05$)

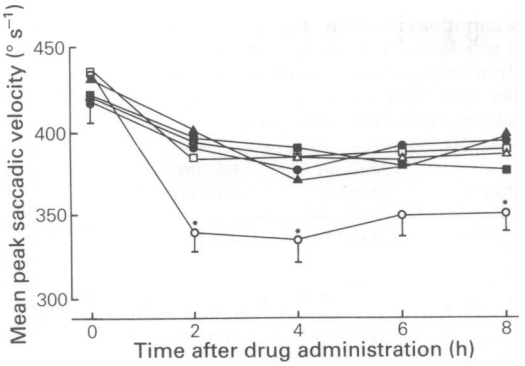

Figure 4 Mean peak saccadic velocity at different times after phenytoin multidose (■), phenytoin single dose (□), diazepam 10 mg (○), lamotrigine 240 mg (▲), lamotrigine 120 mg (△) and lactose (●). * = different from placebo ($P < 0.05$). Bars indicate s.e. mean.

The analysis of the smooth pursuit eye movements is shown in Table 2. The two doses of phenytoin and diazepam reduced smooth pursuit especially in the low velocity bands. This trend continued at higher velocities but the standard error increased and only diazepam reduced smooth pursuit significantly up to the 60–70° s^{-1} velocity band. An example of the smooth pursuit performance before and after a dose of 10 mg diazepam of one subject is shown in Figure 5.

Plasma salivary concentrations

There was a good correlation between saliva and plasma concentrations of both lamotrigine and phenytoin. The correlation between diazepam plasma and saliva concentrations was not significant. The average plasma concentrations 4 h after drug administration and for P1000 at 4 h after administration of the second dose are shown in Table 3. The average saliva/plasma ratio was 0.12 for phenytoin, 0.50 for lamotrigine and 0.03 for diazepam.

Table 3 Plasma concentrations (mean ± s.d.) at 4 h after treatments

	Drug plasma concentration at 4 h
P500	6.2 ± 2.0 μg ml^{-1}
P1000	11.5 ± 2.2 μg ml^{-1}
B120	1.3 ± 0.2 μg ml^{-1}
B240	2.7 ± 0.4 μg ml^{-1}
D10	67.5 ± 36.3 ng ml^{-1}

P, phenytoin; B, lamotrigine; D, diazepam

Relation between saliva concentrations and effects

The correlations between the logarithm of the saliva concentrations of the active treatments and the results are shown in Table 4. All active treatments other than lamotrigine showed significant correlations between the test results and the logarithm of the saliva concentrations when the response of the subjects as a group was significantly impaired. The correlation between test results and diazepam-like activity in saliva is shown in Figure 6.

Subjective effects

For brevity only the grouped scales are shown in Table 5. Since no treatment × session interactions were shown the average score over the four post-treatment sessions was analysed. Diazepam and the high dose of phenytoin made the subjects more mentally and physically sedated. No effects were seen after any dose of lamotrigine. There were no effects on tranquilisation. The effects on the lines that are not included in the grouped scores generally showed similar effects.

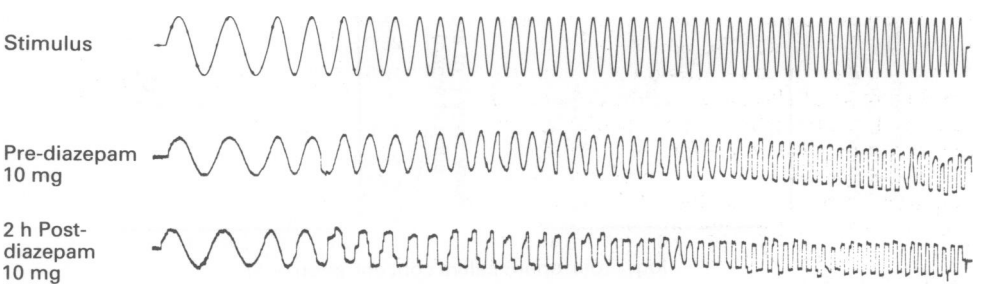

Figure 5 Smooth pursuit of subject 8 before and after administration of 10 mg of diazepam. Note the marked increase in saccadic movement.

Table 4 Correlation between saliva concentrations and tests. When a specific treatment had an overall significant effect responses for the group were plotted against the logarithm of the saliva concentrations and a line of best fit calculated after correction for subject differences. The coefficient of correlation is shown. When two doses of a drug were employed data from these were pooled

	Body sway	*PSV*	*Smooth pursuit*	*Adaptive tracking*
Diazepam	0.62***	-0.70***	-0.65***	-0.61***
Lamotrigine (both doses)	NS	—	—	—
Phenytoin (both doses)	0.32***	—	-0.27***	-0.21*

* = $P < 0.05$, *** = $P < 0.001$, NS = $P < 0.05$
— = No overall significant effect detected.

The subjects rated themselves more clumsy ($P < 0.05$) in the session 12 h after the first treatment of the P1000 dose. No effects on any of the scales were seen after lamotrigine.

Analysis of side effects shown in Table 6 showed that many subjects on phenytoin complained about feelings of unsteadiness and sedation. On no occasion however was ataxia or nystagmus clinically demonstrable. The subjects were also very sleepy after diazepam and this was reflected in the high incidence of reports of sedative side effects.

Discussion

This study demonstrated that the effects of phenytoin on coordination and balance can be detected at therapeutic plasma levels using appropriate tests in normal subjects. They were also able to identify the side effects subjectively, sometimes even 12 h after administration of 500 mg of phenytoin. However on no occasion could ataxia or nystagmus be demonstrated clinically. It was noteworthy that phenytoin did not affect saccadic eye movements but significantly reduced

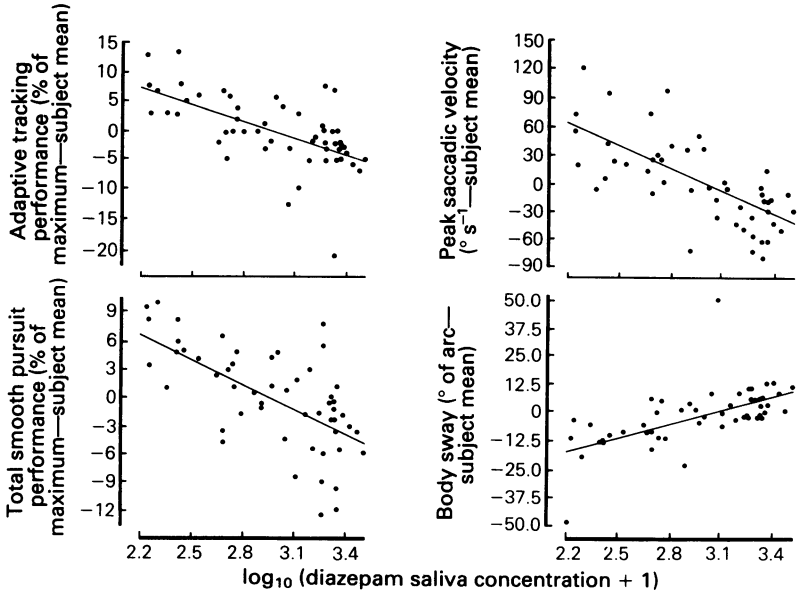

Figure 6 Relation between the logarithm of salivary concentrations of diazepam and CNS tests where it caused overall significant impairment. The line of best fit is shown. Statistical analysis in Table 4.

Table 5 Visual analogue scales. Mean scores in mm are shown. Only the grouped visual analogue lines are shown. Grouping in categories (Norris, 1971). ANOVA did not demonstrate a treatment × session interaction, therefore the mean of all post-dose sessions are analysed

	PL	*B120*	*B240*	*P500*	*P1000*	*D10*	*s.e. mean*
Mental sedation	46.2	45.5	48.2	49.3	54.7*	55.6*	2.12
Physical sedation	42.3	41.3	43.4	44.5	49.4*	50.6*	1.77
Tranquilisation	37.0	35.6	36.9	38.8	38.3	37.5	1.07

*different from placebo ($P < 0.05$)
PL, placebo; B, lamotrigine; P, phenytoin; D, diazepam

Table 6 Side effects. Number of subjects out of twelve that had a side effect which could be classified under the following four categories at any time after administration of the treatment

	Lactose	*Lamotrigine 120 mg*	*Lamotrigine 240 mg*	*Phenytoin 500 mg*	*Phenytoin 1000 mg*	*Diazepam 10 mg*
Sedation	4	3	5	5	7	10
Disturbance of hearing and balance	—	—	2	3	7	—
Disturbance of vision	—	—	1	7	2	3
Headache	1	—	—	3	3	1

smooth pursuit. Benzodiazepines and other sedatives have been shown to reduce saccadic eye velocities in several studies (Tedeschi *et al.*, 1983; Norris, 1971; Bittencourt *et al.*, 1981b). The only study known to us where phenytoin influenced smooth pursuit was in patients also receiving additional anticonvulsants (Bittencourt *et al.*, 1983).

It is possible that the separate control mechanisms for the two types of movement are affected differently by the two drug types. Saccadic velocity is thought to be regulated by the so called 'burst' neurones in the parapontine reticular formation (Fuchs & Kaneko, 1981) while retinal, cortical and cerebellar pathways are more important in the control of the smooth pursuit eye movements (Robinson, 1968). Sedative drugs [benzodiazepines (Bittencourt *et al.*, 1982b), phenobarbitone (Norris, 1971) and amylobarbitone (Tedeschi *et al.*, 1982)] influence both saccadic and smooth pursuit and this probably indicates a general depressant effect. In our study, however, phenytoin impaired smooth pursuit but did not affect saccadic eye movements, possibly suggesting effects more localised to the cerebellum. Muscle relaxant effects of diazepam might contribute to its effects on eye movements but this is unlikely because of the similar actions of barbiturates, which are not muscle relaxants.

A similar difference between phenytoin and diazepam was seen in the adaptive tracking test. It is often stated that this test only measures eye-hand coordination. We have recently shown however that sedation causes a reduction in performance on this test as well, mainly by increasing the within test variability (Cohen *et al.*, 1984b). Phenytoin decreased tracking performance without increasing the within-test variability, possibly more a measure for concentration during the test. Diazepam by contrast increased this variability showing again the differences in central sedative action between these two drugs.

Despite these differences in CNS profile subjective effects as measured by visual analogue scales of the compounds were similar. The increased scores indicating sedation could be caused by the fact that the words on the VAS do not adequately describe the subjects feelings after phenytoin. These feelings might then be reflected in higher sedation scores because of lack of alternatives. This impression is supported by the marked differences in side effects between the two compounds, being mainly sedation after diazepam and effects on balance and coordination after phenytoin.

Lamotrigine differed from the other drugs by failing to affect adaptive tracking or eye movements. It did not cause subjective effects and the subjects were unable to detect it as an active

treatment. It did however increase body sway but this effect could be spurious, the pre-treatment baseline reading also differing from placebo. Additionally there was no relation between saliva concentrations and effect. It therefore appears that lamotrigine at putative therapeutic doses caused less CNS effects than phenytoin. Confirmation of our postulated therapeutic range is now required to establish the clinical relevance of these findings.

The ratio of saliva and plasma concentrations of the active treatments corresponded well to their published free (e.g. non-protein bound) concentrations in plasma. The plasma and saliva concentrations of phenytoin and lamotrigine were also significantly related. This was not true for diazepam but this was possibly caused by the fact that a non specific assay was used which measured active metabolites as well.

Significant correlations were found between saliva concentrations of the drugs and CNS effects. There was however also a large variability in the data and it is therefore not possible to draw conclusions about quantitative aspects of these concentration-response relations. However the tests used in this study appeared to be sufficiently sensitive to be of value in the study of these relationships. The saliva concentrations of phenytoin have been shown to correlate well with CSF concentrations (Schmidt & Kupferberg, 1975) and it might be that saliva concentrations when they reflect the free fraction of drug in plasma, are more suitable for the study of concentration-effect relationships than total plasma concentrations.

In conclusion this study has shown that side effects of anticonvulsants can be measured in healthy volunteers at concentrations in the low therapeutic range. The test battery used seems to be of value for detection of drug induced ataxia as well as sedative effects. The new potential anticonvulsant lamotrigine is likely to have a more favourable CNS side effect profile than phenytoin and diazepam.

The authors gratefully acknowledge the statistical assistance and advice provided by Mrs C. Burke and Mr D. A. Jones.

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(Received 20 May 1985, accepted 20 August 1985)