Withdrawal symptoms from phenytoin, carbamazepine and sodium valproate

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SUMMARY A prospective, double-blind, placebo-controlled investigation of possible withdrawal symptoms from phenytoin, carbamazepine and sodium valproate is reported in patients with active epilepsy, on combination therapy. There was an increase in seizures on reduction and withdrawal of carbamazepine, but there was no convincing evidence of withdrawal symptoms from any of these drugs.

There are well described constellations of symptoms following the withdrawal of ethanol,¹⁻⁷ barbiturates⁸⁻¹³ and benzodiazepines,¹⁴⁻²⁶ summarised in table 1.

There have been few investigations of possible withdrawal syndromes after cessation of non-barbiturate antiepileptic drugs (AEDs). Thirty eight patients took 200 to 400 mg phenytoin daily for 1 to 8 months, stopped the drug abruptly and no withdrawal symptoms were noted.²⁷⁻²⁸ Demers-Desrosiers *et al*²⁹ reported two epileptic patients, with no previous history of psychosis, who became psychotic a day after withdrawal of AEDs. Both patients were taking barbiturates as well as phenytoin, and carbamazepine in one, so it is not possible to ascribe the symptoms to withdrawal of either phenytoin or carbamazepine.²⁹ Carbamazepine is structurally similar to the tricyclic antidepressants and there are reports of symptoms following withdrawal of these agents (table 1).³⁰⁻³⁹

We report a prospective, placebo-controlled, double-blind study to determine the occurrence of withdrawal symptoms following the reduction and discontinuation of carbamazepine, phenytoin and sodium valproate, in patients with active epilepsy, with each drug being reduced at one of two rates. The effect of these drug changes on seizures is considered in a separate paper (Duncan *et al*, in preparation).

Methods

Patients

Ninety five patients were studied, including a control group of 25 patients who remained on stable therapy. All had active epilepsy, were taking two or more AEDs, and were

Table 1 Clinical features of drug withdrawal

Alcohol	Barbiturates	Benzodiazepines	Tricyclics
Anxiety	Anxiety	Anxiety	Anxiety
Agitation	Agitation	Agitation	Agitation
Restlessness	Restlessness	Restlessness	Restlessness
Depression	Weakness	Depression	Irritability
Weakness	Disorientation	Weakness	Weakness
Pruritus	Delirium	Impaired memory	Mania
Delirium	Inc. reflexes	Depersonalisation	Confusion
Inc. reflexes	Insomnia	Derealisation	Insomnia
Insomnia	Anorexia	Insomnia	Anorexia
Anorexia	Nausea	Anorexia	Nausea
Nausea	Vomiting	Nausea	Vomiting
Vomiting	Sweating	Vomiting	Sweating
Sweating	Tremor	Sweating	Abdominal
Tremor	Dizziness	Tremor	cramp
Dizziness	Headache	Dizziness	Diarrhoea
Headache	Twitching	Headache	Headache
Twitching	Weight loss	Twitching	Muscle pain
Muscle pain	Fever	Muscle pain	Chills
Fever	Impaired perception:	Numbness	Coryza
Impaired perception:	Visual	Paraesthesiae	Vivid dreaming
Visual	Hyperacusis	Photophobia	
Auditory	Olfactory	Impaired perception:	
Tactile	Gustatory	Hyperacusis	
Hallucinations:	Hallucinations:	Tactile	
Visual	Visual	Gustatory	
Auditory	Auditory	Hallucinations:	
Tachycardia	Seizures	Visual	
Palpitations		Auditory	
Nystagmus		Paranoia	
Seizures		Incoordination	
		Flu-like symptoms	
		Seizures	

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Table 2 Characteristics of the four AED groups

Variable	AED removed			
	Phenytoin	Carbamazepine	Sodium valproate	Control
Sex				
Male	16	17	13	19
Female	7	7	12	6
Reduction rate				
Fast	10	13	14	13
Slow	13	11	11	12
Psychiatric deficit				
Absent	18	21	21	23
Present	5	3	4	2
(Number of patients)				
Age (yr)				
Median	35*	31	25	42†
Range	19-65	19-59	17-48	25-65
IQ (Full scale)				
Mean, SD	78, 10.9	82, 13.9	81, 14.9	76, 13.0
Seizure nos. in prior 6 months				
Median	82	72	102	58
Range	5-598	1-2210	12-910	3-404
Dose of removed AED at baseline (mg)				
Median	300	1100	2000	
Range	200-450	600-2000	600-2400	
Baseline serum level of AED removed (μmol/l)				
Mean, SD	37.8, 16.7	26.4, 7.6	340, 96	

*Phenytoin vs sodium valproate ($p = 0.01$).

†Control vs sodium valproate ($p < 0.0001$), carbamazepine ($p = 0.006$).

inpatients at the Chalfont Centre for Epilepsy for the duration of the study. The clinical characteristics of the patients are summarised in table 2. The drug changes made were part of a programmed rationalisation of therapy for each patient, and were not subject to randomisation. Each patient, however, was randomised to fast or slow reduction of each AED (table 3). Patients in the control group remained on stable therapy for 8 or 10 weeks. The entire study was double-blind, with matching placebos replacing active drug in a step-wise fashion. Informed consent was obtained from all patients and the study was approved by the National Hospitals ethical committee.

Assessments

Patients were assessed weekly, for the 2 weeks before, during and the 4 weeks after AED reduction and withdrawal. All assessments were made by the same investigator and each patient's assessments were carried out at the same time of day throughout the study. Assessments consisted of:

(1) A 28 item symptom checklist,^{4 16 18 22-24 40-42} each item being scored as present or absent in the preceding week. A symptom was considered as possibly related to AED reduction if it occurred anew in the reduction period or the first week after the completion of drug withdrawal. If a symptom was noted in the 2 weeks before reduction it was discounted as a possible withdrawal symptom.

(2) Self Rating scales^{2 7 18 24} consisting of five point scales of severity of symptoms of anxiety, tension, depression, tremor, nausea, palpitations and faintness, over the preceding 7 days.

(3) Examination for tremor, limb and gait ataxia, reflex hyperactivity, nystagmus and postural hypotension. Signs developing in the reduction period or the first week after withdrawal were considered as possibly related to AED reduction.

Statistical analysis

The development of new symptoms and signs on AED reduction in the four drug reduction groups and in the groups having fast and slow rates of reduction were compared with cross-tabulation, χ^2 test with Yates' correction and odds ratios.⁴³

The symptom rating scales were assessed in two ways:

(1) To identify patients with a significant increase in a rating scale on AED reduction. A significant increase was defined as a score, during reduction or the first week after withdrawal, that was both two or more points higher than the mean of the two baseline scores and higher than each of the two baseline scores. The numbers of patients with significant increases, in the AED groups, were compared with cross-tabulation, χ^2 test with Yates' correction and odds ratios.

(2) To identify more subtle changes in symptom rating scales. The means of the scores in the baseline period, the reduction period and the 4 individual weeks after reduction, were analysed non-parametrically. Changes in individual drug groups were examined by Friedman's two way analysis of variance and Wilcoxon's signed rank test. Differences between groups were analysed by the Kruskal-Wallis and Mann-Whitney U tests.⁴⁴

Results

Overall, there were no significant differences in the numbers of patients developing symptoms and signs in the fast and slow streams of AED reduction (table 4). In the four separate AED groups, the slow control group had a greater incidence of new tremor, on examination, than did the fast controls ($\chi^2 = 4.42$, 1 DF, $p = 0.03$, OR = 19.8, 1-409). No symptoms or signs developed in the three drug reduction groups with an incidence that was significantly different from the control group.

There was no significant difference between the numbers of patients with an increase in rating scale scores in the fast and slow streams, or when the three active reduction groups were compared with the controls (table 4). Friedman's test for each symptom rating scale, on the fast and slow streams of each AED group, was non-significant with the exception of shak- ing in the carbamazepine slow group ($\chi^2 = 10.9$, 5

Table 3 Reduction rates of AEDs

AED	Decrement	Interval between decrements (days)	
		Fast	Slow
Phenytoin	50 mg	2	5
Carbamazepine	200 mg	2	5
Sodium valproate	200 mg	2	4

Table 4 Numbers of patients developing new symptoms and signs on AED reduction

Symptom	AED reduced							
	Phenytoin		Carbamazepine		Sodium valproate		Control	
	Fast	Slow	Fast	Slow	Fast	Slow	Fast	Slow
Anxiety	1	2	1	2	1	1	3	0
Agitation	3	4	0	2	1	2	1	2
Irritability	2	3	3	2	1	1	0	1
Lack of energy	1	2	1	3	2	3	3	5
Imp. memory/concentration	1	1	2	0	1	4	1	0
Depression	3	3	3	2	0	1	3	2
Depersonalisation	0	1	2	0	1	0	0	0
Derealisation	0	1	0	0	0	0	0	0
Insomnia	1	3	4	0	2	1	1	4
Anorexia	0	2	1	2	2	2	0	2
Headache	0	2	2	2	1	1	3	3
Muscle ache	1	2	3	2	2	2	2	3
Twitching	3	0	3	1	3	2	0	2
Nausea/vomit	1	4	0	0	2	0	1	2
Tremor	1	3	2	0	1	1	1	1
Sweating	1	3	0	0	3	3	0	1
Dizziness	1	4	1	0	2	2	1	2
Distorted smell/taste	0	0	0	0	0	0	0	0
Paraesthesiae	0	0	0	0	0	0	0	0
Photophobia/sore eyes	0	0	0	0	1	0	0	1
Incoordination	2	0	1	1	1	2	0	1
Hyperacusis	0	0	0	0	0	0	0	0
Flu-like illness	0	0	0	0	0	0	0	1
Hypo/paraesthesiae	0	0	0	0	0	0	0	0
Paranoia	0	1	1	0	0	0	0	0
Hallucinations								
auditory	0	0	0	0	0	0	0	0
visual	0	0	0	0	0	0	0	0
Disorientation	0	0	0	0	0	0	0	0
<i>Sign</i>								
Post hypotension	1	0	0	2	0	0	0	1
Tremor	0	1	2	0	0	2	0	5
Limb ataxia	0	0	0	0	0	0	0	0
Hyper-reflexia	0	0	2	1	0	1	1	1
Inc. blink reflex	0	0	0	0	0	0	0	0
Nystagmus	1	0	0	0	0	0	0	1
Gait ataxia	1	1	1	0	0	0	0	1
<i>Numbers of patients with increased symptom rating scale scores</i>								
Anxiety	3	3	0	3	2	4	2	1
Tension	2	3	0	2	3	2	2	1
Depression	0	3	2	3	4	5	2	1
Shaking	2	3	3	1	4	3	1	1
Nausea	0	2	0	0	3	4	0	1
Palpitations	2	1	1	0	1	2	0	0
Faintness	0	0	2	0	3	2	0	0
Total patient numbers	10	12	13	10	14	11	13	12

DF, $p = 0.05$). This was the result of a higher level of shaking in the baseline than reduction ($Z = -2.4$, $p = 0.02$) periods, in this group. This reduction of shaking was not a consistent effect of carbamazepine reduction as, if the fast and slow streams were analysed together there were no longer any significant changes with time. Nonparametric tests did not reveal any other significant changes. Two patients became very withdrawn, and one of these also became suspicious, paranoid and uncooperative, after the withdrawal of carbamazepine. In both cases, however, the changes in affect followed a marked increase in seizures and the restoration of carbamazepine, in these two patients, was followed by an immediate reduction in seizure frequency, and return of affect to normal.

Discussion

There have not been any previous systematic investigations of symptoms following withdrawal of phenytoin, carbamazepine or sodium valproate. The present study was prospective, placebo-controlled and double-blind. Withdrawal symptoms cannot be clearly identified without a blind, controlled study and these aspects have been neglected in some previous investigations.

In this study, there was no convincing evidence for the development of a withdrawal syndrome, following the reduction and cessation of treatment with these drugs. There was no significant change in seizure numbers in the phenytoin, sodium valproate or control

groups. Seizures increased on carbamazepine reduction and this increase was maintained through the 4 weeks after withdrawal (Duncan *et al*, in preparation). The two patients who were noted to have a change in affect after withdrawal of carbamazepine both had a marked increase in seizures at this time, so it is not possible to ascribe these changes directly to the withdrawal of the drug, rather than to a post-ictal effect.

Several possible reasons for the absence of an identifiable withdrawal syndrome in this study need consideration. The size of the patient groups was relatively small. The patient groups were well matched for important variables, the minor differences in age are not likely to have influenced the results. AED reduction was gradual, over 1 to 7 weeks, baseline drug levels were not high, and all patients were also taking at least one other AED. Further, there was a low prevalence of psychiatric disturbance (13/95) in the subjects of this investigation, compared with most studies of the withdrawal of sedative drugs, and patients with such problems may be more likely to note symptoms. The assessment of possible withdrawal symptoms was made weekly; it is possible that minor, transient symptoms were not noted by the patients, but it is not likely that any significant reactions were overlooked. The assessment schedule was deliberately simple; it is conceivable that a more sophisticated enquiry may have yielded positive results. The statistical analysis, however, was sensitive and was designed to identify both numbers of patients who had new symptoms and a significant increase in rating scales, and also to detect more subtle underlying changes in scores.

Phenytoin, carbamazepine and sodium valproate are relatively non-sedating and do not have the acute, intense, habit-forming psychotropic effects that are associated with barbiturates, benzodiazepines and alcohol, and this may explain why there were no rebound effects following withdrawal of these AEDs. However, carbamazepine and sodium valproate have been noted to ameliorate the symptoms of the alcohol withdrawal syndrome^{4 45 46} and carbamazepine has been claimed to minimise the effects of alprazolam withdrawal.⁴⁷ If verified, these findings would indicate that there may be some cross-tolerance between sedative drugs and carbamazepine and sodium valproate.

Carbamazepine has a similar structure to tricyclic antidepressants, and there is a well defined tricyclic withdrawal syndrome. Most features of this syndrome, however, respond to atropine, suggesting that they are the result of cholinergic supersensitivity, and carbamazepine has some anticholinergic activity.⁴⁸ In the current investigation, there was no convincing evidence of a "tricyclic withdrawal syndrome"

following removal of carbamazepine.

In conclusion, it does not seem likely that a significant withdrawal syndrome could have developed in these patients and not been noted. A likely explanation of the negative result is that withdrawal of phenytoin, carbamazepine and sodium valproate at these rates, in patients who are remaining on one or more other AEDs, is not associated with any significant withdrawal symptoms, other than seizures. It appears improbable that withdrawal symptoms are likely to be a clinical problem, when these AEDs are discontinued in clinical practice.

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