

Carbamazepine substitution in severe partial epilepsy: implication of autoinduction of metabolism

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Summary: Established partial seizures are often refractory to treatment and many patients receive polypharmacy. An attempt was made to improve seizure control with the substitution of carbamazepine (CBZ) for existing treatment in 7 consecutive unremitting cases of partial epilepsy referred by their physicians as 'intractable'. This produced a significant improvement in control of partial ($P < 0.02$) and secondary generalized ($P < 0.01$) seizures, with 5 patients experiencing a 50% or greater reduction in seizure frequency. A single patient suffered a generalized seizure during the period of changeover. In 3 cases auto-induction of CBZ metabolism resulted in temporary loss of seizure control which was restored by an increase in dose. A policy of planned substitution of CBZ in partial epilepsy previously regarded as intractable may be successful in selected patients. The possible deleterious effect of CBZ auto-induction should be anticipated.

Introduction

Partial seizures are more difficult to control than other types of epilepsy in the adult (Reynolds *et al.*, 1983). Many such patients receive two or more drugs (Guelen *et al.*, 1975) without evidence of improved response (Shorvon *et al.*, 1978) but increased potential for toxicity (Reynolds, 1975). They represent a major source of morbidity in the community, and often require multiple resources of medical, psychiatric and social care.

Carbamazepine (CBZ) has been shown to be of value in the reduction of polypharmacy (Maheshwari & Padmini, 1981) but scrutiny of recent studies suggests this drug may have been overlooked in the approach to poorly controlled epilepsy (Goodridge & Shorvon, 1983). CBZ and phenytoin (DPH) are considered the first line agents in partial epilepsy (Davidson, 1983) and double-blind clinical trials have not demonstrated important differences in efficacy between them (Simonsen *et al.*, 1976; Troupin *et al.*, 1977; Kosteljanetz *et al.*, 1979; Ramsay *et al.*, 1983). Notably, however, equal numbers of patients have improved control on either agent and therefore therapeutic equivalence between CBZ and DPH cannot be assumed for the individual patient. Accordingly we have introduced the policy of substitution with CBZ for older agents with reduction of polypharmacy in patients who have poorly controlled partial seizures regarded by the referring physician as intractable. Our

initial experience with the first 7 consecutive cases is outlined below.

Patients and methods

Seven patients with severe complex partial epilepsy referred consecutively from clinicians within the Western Infirmary/Gartnavel General Hospital complex were studied. Five patients received DPH alone, one a combination of phenytoin, primidone and sodium valproate and the last phenobarbitone, sodium valproate and low dose CBZ, having previously received DPH. Clinical details and inter-ictal electroencephalogram (EEG) findings are shown in Table I.

Frequency of seizures was assessed in a baseline period (range 4–36 months) when the patient was under regular medical review and following modification of therapy (range 5–18 months), using a monthly seizure frequency chart completed by the patient or his family. Prior to conversion, patients were required to have plasma concentrations of at least one major anticonvulsant in the 'therapeutic' range (Reynolds, 1980). If concentrations of established medication were higher than this, dosage was first reduced to exclude paradoxical seizures prior to introduction of CBZ (Troupin & Ojemann, 1975).

CBZ was introduced in an initial dosage of 200 mg b.d. and increased as necessary to produce target plasma trough and peak concentrations of 6–10 mg/l while maintaining existing therapy. Subsequent withdrawal of previous anticonvulsants was

Table I Clinical details and inter-ictal EEG of 7 patients with partial epilepsy

Case no.	Sex	Age (y)	Seizure type	Duration (y)	Aetiology	Inter-ictal EEG abnormality
1.	F	34	Complex partial Secondary generalized	12	Perinatal injury	Right temporal theta
2.	M	56	Secondary generalized	7	Sub-arachnoid haemorrhage Cerebral infarct	Right frontal delta
3.	M	31	Complex partial Secondary generalized	3	Cerebral haemorrhage	Right temporal delta
4.	F	30	Complex partial Secondary generalized	26	Perinatal injury Cerebral palsy	Right fronto-temporal theta
5.	F	54	Complex partial Secondary generalized	41	Cerebral infection	Left fronto-temporal theta
6.	M	29	Complex partial Secondary generalized	8	? Perinatal injury	Right temporal delta
7.	M	19	Complex partial Secondary generalized	11	? Perinatal injury	Left fronto-temporal theta and delta

undertaken in hospital over a period of 7–21 d. If seizures continued, CBZ dosage was increased as necessary to the limit of subjective tolerance, as evidenced by the development of unacceptable sedation, diplopia, nausea or ataxia. Plasma CBZ concentration was monitored but CBZ dosage only altered if seizure frequency increased or toxicity became apparent. Comparison of pre- and post-conversion monthly seizure frequencies was made using Student's *t* test for paired values.

Results

Pre- and post-conversion drugs with doses, steady-state concentrations and observation periods are given in Table II. All patients benefited from the introduc-

tion or optimization of CBZ in improved seizure control. Five patients had a 50% or greater reduction in seizure frequency. Reduction in both secondary generalized seizures ($P < 0.01$) and complex partial episodes ($P < 0.02$) occurred (Figure 1). Temporary loss of seizure control developed in patients 5, 6 and 7. This was accompanied by a fall in circulating steady state CBZ concentration of 25%, 23% and 30%, respectively, on unaltered dosage. In each case an increment in CBZ dose restored the previous levels and all 3 patients once again became seizure free. The problem is illustrated by clinical details from Case 5.

Case 5

This 54 year old unmarried woman was referred in January 1983. She had suffered from meningitis at age

Table II Pre- and post-conversion drugs, doses, steady state concentrations, and observation periods in 7 patients with severe partial epilepsy

Case no.	Pre-conversion				Post-conversion			
	Drug	Dose (mg/d)	Steady state concentrations (mg/l)	Observation period (months)	Drug	Dose (mg/d)	Steady state concentrations (mg/l)	Observation period (months)
1	DPH	300	14.9–16.9	12	CBZ	1200	3.4–7.7	5
2	DPH	400	16–21	4	CBZ	800	8.5–9.8	8
3	DPH	600	48	36	CBZ	1200	10.7–14.5	6
4	DPH	350	14	5	CBZ	1200	6.2–11.5	9
5	DPH	350	14.2–22	6	CBZ	1800	9.4–10.3	8
6	PB	60	4.6	6	CBZ	1800	9.4–16.3	6
	VALP	2000	64					
	CBZ	400	6.7					
7	DPH	400	11.6	6	CBZ	1800	11.3–16.5	18
	PRIM	750	10.3 (PRIM) 26.1 (PB)		VALP	2000	37–52	
	VALP	1800	47					

CBZ = carbamazepine; PB = phenobarbitone; VALP = sodium valproate; DPH = phenytoin; PRIM = primidone.

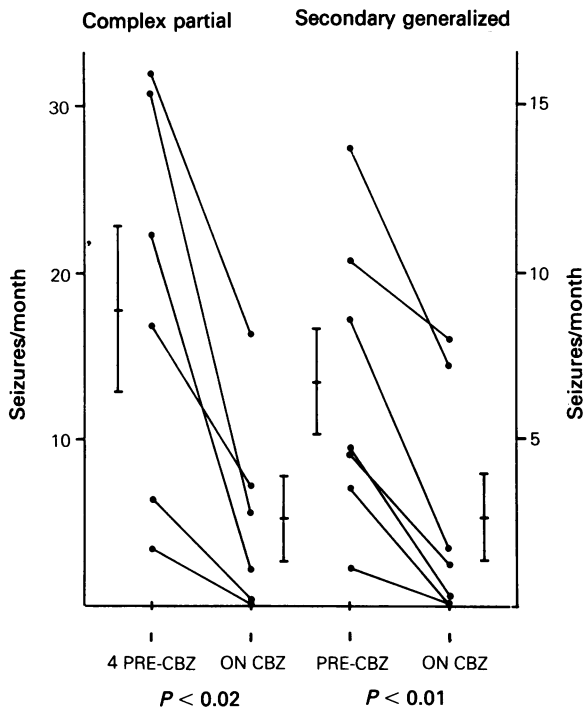


Figure 1 Frequency of partial and secondary generalized seizures per month before and after CBZ therapy in 7 patients with severe partial epilepsy. Statistics were obtained using Student's *t* test for paired values.

3, complicated by mild mental retardation and had developed epilepsy 10 y later. In 1981, she became confused and incontinent with frequent falls. Long-standing drug therapy consisted of phenytoin 100 mg/d, primidone 250 q.i.d. and phenobarbitone 90 mg t.i.d. An elevated serum phenobarbitone concentration of 90 mg/l ('therapeutic' range 10–40 mg/l) with low DPH levels encouraged the patient's physician to convert her to DPH monotherapy. Throughout the remainder of 1981 and during the whole of 1982, however, the patient continued to have frequent partial seizures and several generalized tonic-clonic fits each month despite steady-state DPH concentrations of around 20 mg/l.

On referral to the Clinical Pharmacology Unit in January 1983, CBZ was substituted for DPH over a 21 day period without deterioration in seizure control. Seizure frequency markedly declined thereafter and the patient became seizure free on CBZ 400 mg b.d. In April, partial seizures recurred and the circulating CBZ level was noted to have fallen over the previous 2 months from 10.4 mg/l to 7.8 mg/l (Figure 2). The CBZ dosage was increased to 400 mg t.i.d. with restoration of circulating CBZ concentrations to around

10 mg/l. The patient remains well and is currently seizure free. As compliance with drug therapy was consistently supervised by her sister, the deterioration in this patient's epilepsy was thought to be a consequence of auto-induction of CBZ metabolism.

Discussion

CBZ is an effective anticonvulsant for partial and secondary generalized epilepsy given singly (Cereghino *et al.*, 1974) or in combination (Cereghino *et al.*, 1975). Our preliminary results, using CBZ as an alternative monotherapy or in replacing polypharmacy, are in general agreement with those of Callaghan and his colleagues (1978) who reported a 50% or greater reduction in seizure frequency in 9 patients of a group of 19 on previous monotherapy or combination therapy. A more recent study evaluated CBZ or DPH substitution in 18 patients treated with 2 or more anticonvulsants (Lesser *et al.*, 1984). Treatment with a single drug was equal or better than polypharmacy but only a few patients became seizure-free. While appreciating that our study group was small, all were 'intractable' cases and 4 had associated neuro-psychiatric handicap in which a poorer prognosis is recognized (Reynolds *et al.*, 1983).

In any policy of substitution and reduction of anticonvulsant polypharmacy there is a risk of exacerbating seizures (Shorvon & Reynolds, 1979), particularly if barbiturates are to be withdrawn (Fischbacher, 1982). The best approach to transition is poorly defined and in this preliminary study we did not find deterioration of control even over a 1 week period of

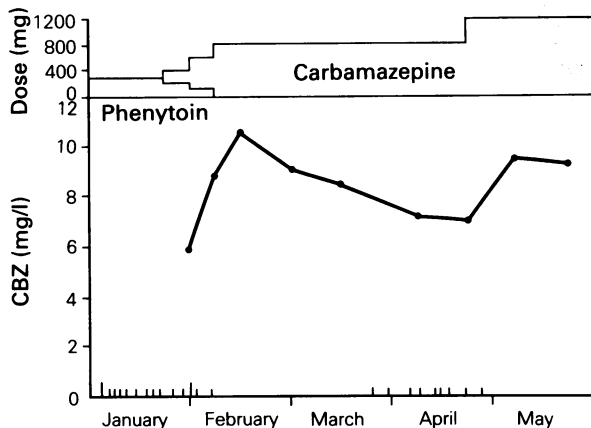


Figure 2 Deteriorating seizure control on fixed dose of carbamazepine (CBZ) with falling plasma concentrations attributable to auto-induction in Case 5. Generalized (longer lines) and partial (shorter lines) seizures are illustrated at the foot.

withdrawal (Cases 1 and 2). This may reflect a policy of ensuring a 'target' CBZ concentration of between 6–10 mg/l before reduction of existing therapy. One patient (Case 3) did, however, suffer a generalized convulsion following reduction of DPH concentration from above to within the 'therapeutic' range, a problem previously highlighted (Reynolds *et al.*, 1981).

CBZ characteristically stimulates its own metabolism by auto-induction of hepatic mono-oxygenase enzymes (Eichelbaum *et al.*, 1975) in a dose-dependent manner (Rapeport *et al.*, 1983). This may occur over a period of several weeks following each increment of increased dosage. Cases 5, 6 and 7 illustrated the clinical relevance of this, where falling plasma CBZ concentrations were associated with an increase in seizure frequency. All 3 patients insisted that compliance with drug therapy was perfect and indeed it was supervised throughout by relatives in Case 5 and 6. Minor fluctuations in plasma levels may cause loss of control (Rodin *et al.*, 1974) and if auto-induction is overlooked, a patient may be deemed non-compliant or CBZ may be discontinued or another anticonvulsant added. If reduced plasma concentrations of CBZ are apparent then adjustment of CBZ dosage should be made before breakthrough seizures develop. Poor compliance may present a similar picture but a brief period of hospital admission for supervision of therapy and plasma concentration monitoring will differentiate these problems.

CBZ therapy may be associated with apparent improvement in mental function and this was reported in Cases 4 and 5. This is consistent with positive psychotropic properties postulated for the drug

(Dalby, 1975). These beneficial effects are difficult to distinguish from those resulting from withdrawal of other anticonvulsants. A combination effect of CBZ usage and reduction in polypharmacy may be operative (Thompson & Trimble, 1982). In 2 patients (Cases 6 and 7) high plasma CBZ concentrations of 16 mg/l were necessary to obtain maximal benefit from the drug. Intermittent diplopia was the only adverse effect reported in this study.

Management of established partial seizures is difficult, with approximately 30% of patients considered to be intractable (Reynolds *et al.*, 1983). Surgery will only benefit a select population and although recently developed agents e.g. γ -vinyl GABA hold some hope for the future (Rimmer & Richens, 1984), a new strategy is required within the present anticonvulsant armamentarium. We feel that this report provides some limited evidence of benefit from an adequate trial of CBZ following failure with DPH or older agents. Although it would be desirable to identify CBZ responsive patients before withdrawal of other drugs, this has proved elusive (Rodin *et al.*, 1974). Accordingly, until large scale clinical trials validate this approach, selection of patients must remain empirical. Clearly problem cases, as reported here, may be most appropriate. CBZ therapy should not remain a neglected alternative in patients with epilepsy poorly controlled with polypharmacy or older agents.

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