Investigation and management of loss of efficacy of an antiepileptic medication using carbamazepine as an example

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Summary

Cases reported as loss of efficacy (secondary failure) of carbamazepine (CBZ) for epilepsy were analysed to determine the cause. In these cases, seizures previously controlled with CBZ, recurred or increased in frequency. The following causes were identified in 131 cases where adequate information was available: use for types of epilepsy where this drug is not recommended, lowering of the blood levels of the drug on switching over from branded to a generic CBZ, change in the galenic form, drug interactions, progression of the underlying brain pathology such as a brain tumor, and unexplained increase in the blood levels of the drug. In cases where the increase in seizures was transient no special measures or changes in therapy were required. Unexplained failure occurred only in seven cases (5.3%). Based on this information, a flow chart was designed to evaluate such a problem step by step and to take appropriate measures. Only when true therapeutic failure is identified, should another antiepileptic drug be substituted for CBZ. Similar approach can be used for other antiepileptic drugs.

Introduction

Since its introduction in 1963, carbamazepine (CBZ) has become the most widely used first line antiepileptic medication. A review of the clinical trials[1] indicated that this medication was successful in controlling seizures (at least 50% reduction) in three-quarters of the treated patients. CBZ is effective for the prophylaxis of generalized tonic-clonic and partial seizures but not for absence epilepsy or myoclonic seizures.

The great majority of CBZ failures are primary and represent the approximately 25% of patients who are non-responsive. Secondary failure is the term used in cases where seizures, previously controlled with CBZ, recur or increase in frequency. Sometimes this is reported as an adverse drug reaction and CBZ is usually discontinued in these cases. there is no description in literature of the steps of decision making in such cases. The object of this study was to identify the causes of lack of efficacy of CBZ and formulate a plan of action for such cases.

Material and methods

All the cases reported as loss of efficacy of CBZ or deterioration of seizures and entered in the single case files of Ciba-Geigy Headquarters, Basel from 1976 to 1990 were reviewed. There were 299 such reports but only 131 cases contained adequate information for analysis, ie the diagnosis and follow-up with measures taken for management of the case.

Results

The most common cause of deterioration of seizures was the use of CBZ for certain forms of epilepsy where it is suspected to aggravate seizures and is not recommended. There were 59 cases in this group (45%). These patients had absence seizures and mixed forms of epilepsy. Twenty-seven cases (20.6%) occurred when brand CBZ (Tegretol) was switched to generic CBZ and seizure control was obtained on resuming original brand. Unexplained failure occurred only in seven cases (5.3%). An equal number of failures occurred due to drug interaction, ie introduction of another drug which lowered CBZ level. Inadequate

Table 1. Drugs which alter serum carbamazepine levels (based on reports filed at Central Drug Monitoring, Ciba-Geigy, Basel and literature on drug interactions)

Drugs which increase serum carbamazepine levels
Allopurinol
Cimetidine
Propoxyphene
Diltiazem
Isoniazid
Nicotinamide
Danazol
Disulfiram
Verapramil
Viloxazine
Acetazolamide
Desipramine
Erythromycin
Josamycin
Troleandromycin
Fluoxetine
Phenelzine
Drugs which decrease serum carbamazepine levels
Other anticonvulsant drugs
—phenytoin*
—phenobarbital
—primidone*
—valproic acid
—progabide
Theophylline
Isoretinoin
Chloramphenicol
Cytostatic drugs

*Has also been reported to increase CBZ levels

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blood levels of CBZ occurred in nine cases (6.9%) during switchover from one galenic from of CBZ to another. Progression of organic brain disease could explain this event in six cases (4.6%). In four cases (3.1%), seizures were attributed to increased levels of CBZ; the cause of this was not identified but improvement occurred after reduction of dosage. In 12 cases (9.2%), increase in seizures was transient and no special measures were applied/required.

Discussion

The reports analysed by no means represent all the failures of CBZ therapy because many such cases go unreported. However, this study reveals several causes of deterioration of seizures (secondary failure) in epileptic patients on CBZ therapy. Several of these causes are already known. The most frequent cause of aggravation of seizures was the use of CBZ in types of epilepsies where the use is not recommended by the manufacturer. Bird *et al.*[2] made the incidental observation that absence seizures are aggravated by CBZ. Several other authors have reported exacerbation of seizures in children or carbamazepine-induced seizures[3-7]. The types of epilepsy reported to be aggravated by Tegretol are: (1) myoclonic epilepsy; (2) Lennox-Gastaut syndrome; (3) absence epilepsy,

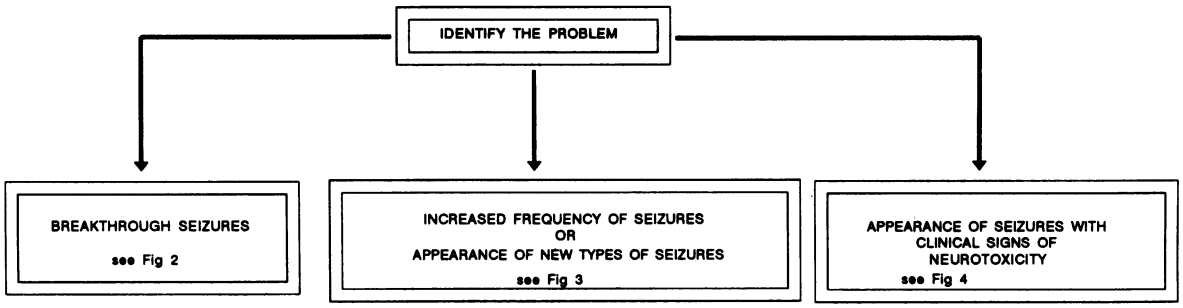

Figure 1. A guide to the management of an epileptic patient where carbamazepine loses efficacy (secondary therapeutic failure)

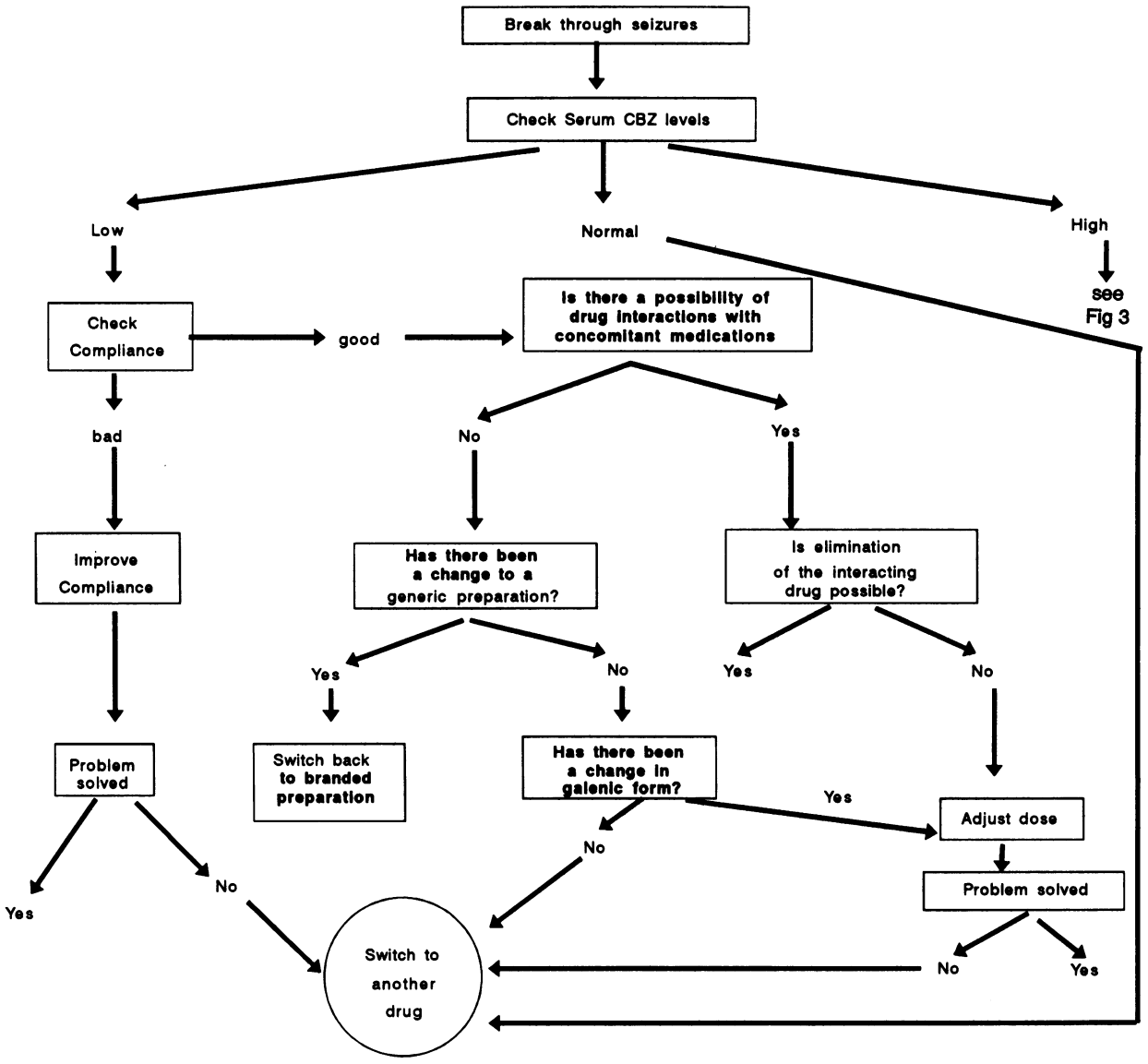

Figure 2. Breakthrough seizures

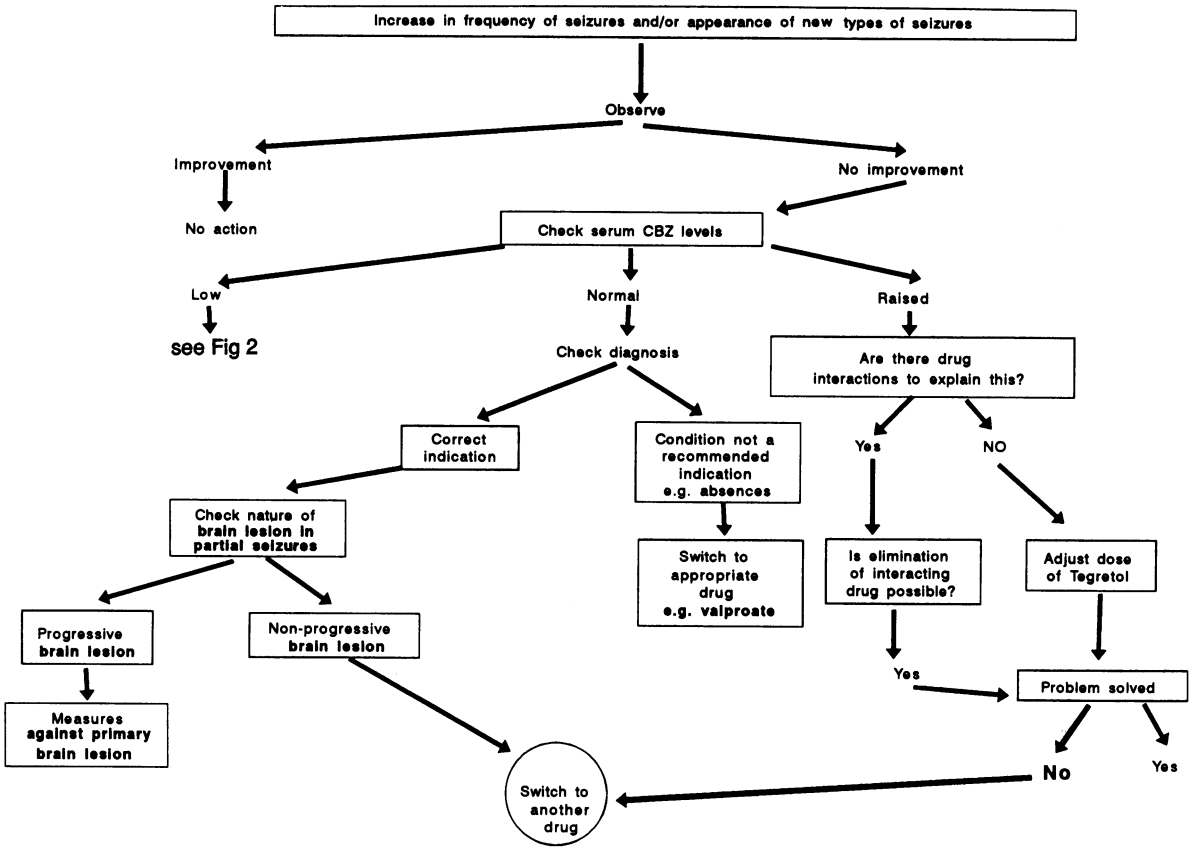

Figure 3. Increased frequency of seizures or appearance of new types of seizures

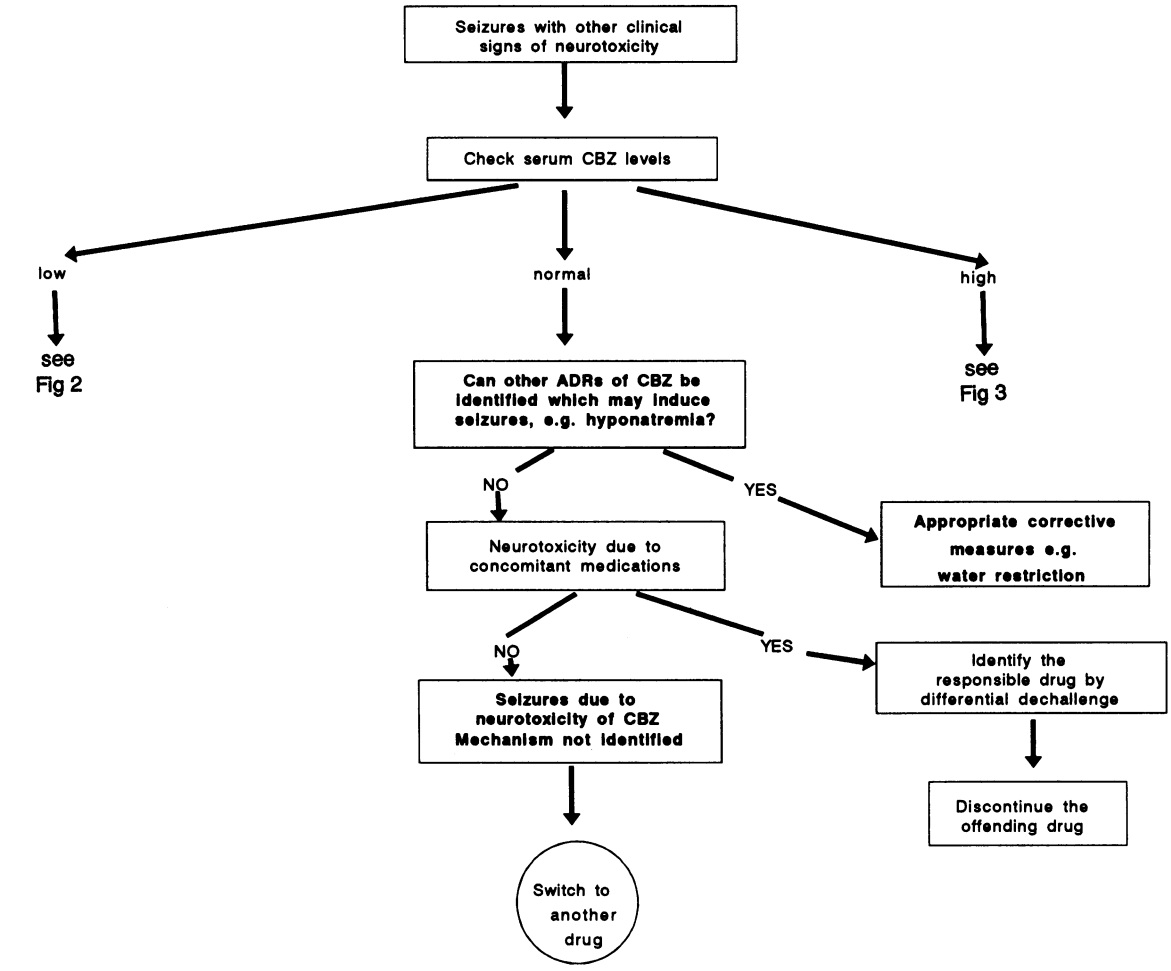

Figure 4. Appearance of seizures with clinical signs of neurotoxicity

both typical and atypical forms; and (4) mixed seizure disorders including typical and atypical absence seizures.

Several of the reported cases, even though they were treated by CBZ therapy for complex partial epilepsy, had a history of absence seizures and many had spike and wave patterns in the EEG. Such exacerbation of seizures usually subsided on discontinuation of CBZ.

Unexplained failure occurred only in a small number of cases. Various drugs are known to interact with and change blood levels of CBZ (see Table 1). Paradoxical intoxication with CBZ has been described by Troupin and Ojemann[8]. This is characterized by increasing seizure rate and high blood levels of carbamazepine (over 20 μg/ml) but no other adverse reactions are usually seen at these blood levels. Seizure rate diminished in these cases after reduction of dosage and subsequent decrease in blood concentrations of CBZ. Based on this information, a flow chart has been constructed as a guide to the investigation of a patient in this situation (Figures 1-4). Suggestions have been made for appropriate measures including switchover to other medications where indicated. Switchover to generic preparation has been known as a possible cause of breakthrough seizures which disappear on restitution of brand CBZ[9]. The observed drop in blood CBZ levels was only slight in these cases. Although serum CBZ levels are generally used as a guide to dosage, high CBZ epoxide levels may occur with normal CBZ levels. This has been implied as a cause of exacerbation of partial seizures and onset of non-epileptic myoclonus in one case[10]. Tolerance to CBZ has been postulated as a cause of secondary failure based on animal experimental studies[11] but this has not been documented clinically. If there is an unexplainable therapeutic failure with CBZ it may be substituted by another suitable first line antiepileptic drug (monotherapy). Polytherapy treatment should only be considered in patients refractory to monotherapy trials with several first line antiepileptic drugs using adequate dosages.

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