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The occurrence, management and outcome of antiepileptic drug side effects in 767 patients

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This study reports the nature of adverse drug reactions (ADR) occurring in 767 epilepsy clinic patients (adults and children), the drugs most commonly involved, how they were managed and the outcome of such management. One hundred and thirty four patients were found to have 155 separate ADRs. The majority appeared to be pharmacodynamic in nature, although 21 were clearly pharmacokinetic in origin and four due to drug interactions. The antiepileptic drugs (AED) perceived to be causative, in order of frequency were phenytoin, sodium valproate, carbamazepine, clonazepam, barbiturates, vigabatrin and clobazam. Management most often involved withdrawing the offending drug(s), usually replacing them with another AED. Of the 155 ADRs, 40.6% resolved totally, 27.7% showed a marked improvement, 16.1% improved, 14.8% did not change and one patient deteriorated.

This study emphasizes the need to be vigilant for ADRs and demonstrates that their management is essentially clinical with some 85% of patients experiencing benefit.

INTRODUCTION

As for all persons taking medication on a long term basis, people with epilepsy may be subject to adverse drug reactions (ADR). It is generally believed that antiepileptic drug ADRs are common[1]. The results of a questionnaire survey of people with epilepsy showed that 59% of the patients felt they were suffering some drug side effects, although this was likely to have been an overestimate. In this survey, the antiepileptic drugs (AEDs) most commonly incriminated were phenytoin (PHT, 34%), carbamazepine (CBZ, 30%), and sodium valproate (VPA, 23%)[2].

Since the study by the Mario Negri Institute Group[3], there has been little published data on antiepileptic drug ADRs. That study showed that 31% of the patients surveyed complained of ADRs with 30% of patients taking PHT reporting ADRs, 23% with phenobarbitone (PB), 15% with CBZ and 12% with VPA. Most studies have looked at ADRs from an epidemiological viewpoint[4], with a recent emphasis on cognitive side effects of AEDs[5–7].

The present study looks at the problem of antiepileptic drug ADRs from a different viewpoint without epidemiological significance. The study looks at ADRs in a clinical practice and asks the following pragmatic questions:

—What are they?
—What AEDs are most commonly involved?
—How were they managed?
—What was the outcome of such management?

The present study represents a clinical audit of the common problem[1] of drug side effects in 767 patients with epilepsy.

METHODS

All data were obtained from the author's adult and paediatric epilepsy practice over a period of 10 years. From the commencement of the practice, which deals mainly with people with 'difficult' epilepsy and has a referral base with a strong psychosocial emphasis, specific attention has been paid to the side effects of AEDs. At each consultation, patients or the parents of children were asked about drug side effects and if these were felt to be clinically valid, were

noted and coded. Using a coding system, it was possible to identify, from the clinical notes, which patients had drug side effects at the time of initial presentation and who developed them subsequently. Adverse drug reactions were defined as clinical symptoms or signs recognized from past experience and published reports as being related to the drug(s) in question. Since most patients were regular clinic attenders, it was almost always possible to follow them up and monitor progress over time, especially if a medication was withdrawn. Patients were generally seen every 1 to 3 months, at least initially. The majority of patients had been receiving treatment for some time and thus it was not anticipated that initial ADRs such as rashes would be observed. Information on previous ADRs was not recorded for study purposes since they could not be verified.

Information was obtained about age, sex, seizure type(s), the number of AEDs being taken at the time, which AEDs these were and which was likely to be causing the side effects. Additional information was obtained with respect to the side effects themselves, whether there was any specific pharmacological explanation for the side effects, the value of blood level assessments in the diagnosis of drug side effects, action taken to alleviate the problem and the result thereof.

Serum AED concentrations were only measured when it was felt to be clinically indicated.

The outcome was graded as: (i) complete recovery, when the symptoms/signs regressed totally; (ii) marked improvement, considerable, but not total, regression; (iii) Improvement, regression which was obviously incomplete, but which the patient found beneficial; (iv) no change and (v) deterioration, a deterioration in symptoms/signs as a result of altering therapy to try and modify the side effect(s). Outcome was assessed by discussion between the patient and the author.

The notes of 767 patients seen during the 10 year period were reviewed. Twelve patients, coded as having side effects, were excluded from the study because they had been seen only once or twice and thus follow up was inadequate to assess the effect of suggested therapeutic changes to modify the side effects. In the patients reported, follow up was from 6 months to 10 years. There were 77 patients who initially presented to the clinic with side effects, 40 other patients developed side effects whilst attending the clinic and finally 17 patients had side effects at the time of presentation and developed additional/different side effects whilst attending the clinic.

The present study was designed specifically as an audit of a clinical practice solely dealing with people with epilepsy. It is of no epidemiological value because of the nature of the clinical practice.

RESULTS

1. Patients with ADRs at initial presentation

Of the 77 patients with ADRs at initial presentation, 56 were adults (aged 14–59 years) and 21 children (1–13 years) with 35 being male. Twenty-four of the patients had primary generalized epilepsy, 19 had complex partial seizures (CPS), nine simple partial seizures (SPS), eight secondarily generalized seizures, five juvenile myoclonic epilepsy and the remainder had miscellaneous seizure types.

At the time of presentation, 28 of the 77 patients were receiving monotherapy, 27 were receiving two AEDs, 20 three AEDs and two were taking four anticonvulsants. Thirty eight of the patients were receiving CBZ, 34 PHT, 29 VPA, 19 barbiturates, 18 clonazepam (CZP), four diazepam (DZP), two sulthiame (SUL), one ethosuximide (ESM), one nitrazepam (NZ) and one clobazam (CLB).

Of the 28 patients on monotherapy, 10 were taking PHT, six VPA, five CBZ, four barbiturates, two CZP and one ESM. The most common combinations amongst the 27 patients taking two AEDs were PHT/CBZ (9), VPA/CBZ (4), CBZ/barbiturate (3) and PHT/VPA (3). Amongst the 20 patients on three AEDs the most common combinations were VPA/CBZ/CZP (4), VPA/PHT/CBZ (3), PHT/CZP/barbiturates (3) and PHT/VPA/benzodiazepine (3).

The AEDs presumed to be causative of the side effects at the time of presentation are shown in Table 1. The majority were related to PHT (23), CZP (10), CBZ (9), barbiturates (9) and VPA (9). In three patients who were receiving three AEDs each, it was not possible to ascertain which drug(s) were causative and it was simply felt that these patients were over-medicated.

Subsequent analysis will look in detail at those patients whose side effects were felt to be

Table 1: The AEDs presumed to be responsible for the side effects in 77 patients initially presenting with ADRs

Presumed causative AED(s)	Number of patients
PHT	23
CZP	10
CBZ	9
Barbiturates	8
VPA	8
Barbiturates/benzodiazepine	4
PHT/CZP	3
PHT/barbiturate	3
VPA/PHT	2
Two benzodiazepines	1
PHT/DZP	1
PHT/CLB	1
VPA/CBZ	1
PHT/CBZ/barbiturate*	1
VPA/CBZ	1
PB/VPA/acetazolmide*	1
VPA/SUL/barbiturate/CZP*	1

PB = Phenobarbitone.
* In these 3 patients, it was not possible to define which drug might be causative.

due to PHT, CZP, CBZ, barbiturates, VPA and the remaining miscellaneous combinations.

a. ADR with phenytoin (PHT) seen as the problem (n = 23)

Signs and symptoms included drowsiness and being 'slowed down' (19), cosmetic problems such as gum swelling, hirsutism and acne (10), slow, slurred speech (9), a deteriorating memory (8), acute intoxication (3), recurrent episodes of acute intoxication (2), weight increase (1) and break through bleeding with the oral contraceptive pill (1).

Serum phenytoin levels were only of value on six of the 23 occasions on which they were measured, with levels being above the recommended therapeutic range (40–80 μmol/l). In five of these six patients, the diagnosis of phenytoin intoxication was clinically evident and blood levels were solely confirmatory.

In 22 of 23 patients, PHT was withdrawn and was usually replaced with CBZ or VPA with no difficulties. In one patient, as the PHT was reduced there was an increase in seizure frequency and it was re-instated. With respect to the response to changing therapy, nine patients recovered completely from their ADR, nine showed a marked improvement, four some improvement and one patient, who had withdrawal fits, deteriorated. The smallest change was seen in those patients whose predominant complaint was of a deteriorating memory.

b. ADR with clonazepam (CZP) seen as the problem (n = 10)

Signs and symptoms included drowsiness (7), aggression (4), irritability (3), feeling 'doped up' (3), dribbling/drooling in two children and hyperactivity in one child. No serum clonazepam concentrations were measured.

Clonazepam was withdrawn in nine of the 10 patients, being replaced with VPA or CBZ in two patients each. Of these nine patients, one with profound drowsiness went into status epilepticus requiring ICU management, but came off CZP and is now well controlled with fewer side effects. A second patient was fine for 3 years after coming off CZP, but then had recurrent seizures and was represcribed CZP with a return of his side effects. One patient had a single seizure 3 months after beginning slowly to withdraw CZP and chose to go back onto the drug: her side effects returned. One patient recovered fully from CZP side effects, four showed a marked improvement, three improved and two showed no change.

c. ADR with carbamazepine (CBZ) seen as the problem (n = 9)

Signs and symptoms of carbamazepine included drowsiness (5), aggression (2), diplopia (2), nystagmus (2), irritability (1), personality change (1) and there were two acutely intoxicated patients (one therapeutically and the other, a suicidal gesture).

Serum CBZ concentrations, using a therapeutic range of 15–40μmol/l, were measured in seven of the nine patients receiving CBZ. They were useful on six of these occasions. In four of the nine patients, CBZ was withdrawn, in three the dose was reduced and in one patient no action was taken. In the intoxicated patients, CBZ was stopped for 48 h and then recommenced. In five patients there was complete recovery from their ADRs, a marked improvement was seen in three cases and in one person where no action was taken since they had complete seizure control, their side effects, which were quite mild, persisted.

d. ADR with barbiturates seen as the problem (n= 8)

Marked drowsiness was the predominant ADR seen in four patients. Hyperactivity/irritability

(2), tantrums (1), aggression (1) and feeling 'slowed down' (1) were also noted. Serum phenobarbitone concentrations were not measured in any of these patients since it was felt, clinically, that this would not assist in management.

The barbiturates were withdrawn in all patients and were replaced by CBZ or VPA in five cases. Three patients recovered fully from their ADR, four showed a marked improvement and the other patient improved a little.

e. ADR with sodium valproate (VPA) as the problem (n = 8)

The predominant problems were weight gain (3), tremor (3), hyperactivity (2), drowsiness (1) and hair loss (1). The magnitude of the weight gain was such that over 1 to 2 years these three patients reported gains from 60 to 74 kg, 51 to 63 kg and 58 to 67 kg, respectively. Serum valproate concentrations were not measured.

In two patients VPA was withdrawn, in three patients with juvenile myoclonic epilepsy and absolute seizure control no action was taken, in two VPA dosage was reduced and strict dietary advice was provided for the final patient.

In terms of response to these actions, a complete recovery was seen in one patient, a marked improvement in two, mild improvement in one and no change in four patients. The latter included the three people with weight gain. Tremor improved greatly with VPA dose reduction.

f. ADR in the remaining 19 patients

In this group of 19 patients, it was less easy to be certain of the drugs causing the ADRs. On clinical grounds, it was felt that the following combinations were responsible: barbiturate/benzodiazepine (4 patients), PHT/CZP (3), PHT/barbiturate (3), VPA/PHT (2), two benzodiazepines (1), PHT/DZP (1), PHT/CLB (1), VPA/CBZ (1) with three patients falling into the 'just too many drugs' category PHT/CZP/barbiturate, barbiturate/VPA/acetazolamide, VPA/SUL/CZP/barbiturate.

The predominant side effects were drowsiness (17 patients), slurred speech (6), falling asleep at work (6), feeling 'slowed down' (5), ataxia (4), deteriorating memory (4), nystagmus (2) and one patient each complained of diplopia, depression, learning problems, weight increase, cosmetic problems, drooling and aggression.

Serum AED concentrations were measured in 10 of 19 patients, but were only useful twice. On both occasions, the patients were felt to have an ADR owing to a VPA/PHT combination and in both cases the free PHT fraction was increased accounting for the symptomatology of PHT intoxication. One patient had a total PHT of 60 μmol/l and a free concentration of 16% and the other a total PHT of 80 μmol/l and a free concentration of 17%.

The drugs felt to be causing the ADR were withdrawn in all 19 patients and in six patients, CBZ or VPA were added. Two patients had withdrawal seizures, but were successfully withdrawn from the drugs in question. In addition, three patients had the doses of their other medications reduced. This led to be a complete recovery from ADR symptomatology in three patients, a marked improvement in 11, improvement in four and no change in one patient.

2. Patients developing ADRs whilst attending the clinic

Forty patients developed ADRs whilst attending the clinic, of whom 24 were adults (14–57 years old) and 16 children (2–13 years) with 23 being female. Twelve had primary generalized epilepsy, 11 CPS, six tonic seizures, three secondarily generalized seizures, three myoclonic seizures, two each had SPS, benign focal epilepsy (BFE) of childhood and juvenile myoclonic epilepsy and one patient had the Lennox-Gastaut syndrome.

At the time that the ADRs occurred, 13 patients were on monotherapy, 16 taking two AEDs, seven taking three AEDs and four patients were receiving four AEDs. Twenty-six of the patients were taking VPA, 21 CBZ, 14 PHT, seven vigabatrin (GVG), six CLB, three barbiturates, two ESM and one each CZP, DZP and NZ.

Of the 13 patients on monotherapy, six were taking VPA, five CBZ, one PHT and one was taking ESM. Amongst the 16 people taking two AEDs the combinations were—CBZ/VPA (5), PHT/VPA (4), VPA/CLB (2), VPA/GVG (1) and VPA/NZ (1). Among the seven patients taking three AEDs there were seven different combinations: PHT/VPA/CLB, PHT/VPA/CBZ, VPA/PHT/barbiturate, PHT/VPA/GVG, PHT/

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