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Adverse Reactions to Antiepileptic Drugs: A Follow-Up Study of 355 Patients with Chronic Antiepileptic Drug Treatment

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Summary: Three hundred fifty-five patients receiving chronic antiepileptic drug (AED) treatment were followed in 15 university and hospital centers for an average of 11 months to assess the effects of intensive monitoring of adverse drug reactions (ADRs) on the frequency of reports and on the overall management of epilepsy. One hundred forty-eight patients (41.6%) had one or more ADRs during the entire follow-up period. ADRs were reported by 31% of patients at admission and by 20% at last visit, with a downward trend in the number of reports. Concurrently, the number of patients who were seizure-free rose from 24.5 to 42.8%. During the observation period, the number of prescriptions fell from 640 to 568, mostly for phenobarbital (PB), phenytoin (PHT), and valproate (VPA). The outcome of the most common ADR was only partially related to drug changes. Even with the limitations of the unstandardized criteria used for ADR reporting, the present study shows that intensive monitoring of drug-related clinical events is not only a valuable tool to provide a comprehensive survey of drug toxicity in clinical practice, but is also an educational effort to improve the quality of care for patients with epilepsy. **Key Words:** Anticonvulsants—Epidemiology—Epilepsy—Drug-induced abnormalities—Italy.

The problem of drug toxicity in patients receiving chronic antiepileptic drug treatment has been repeatedly emphasized (for reviews see: Reynolds, 1975; Schmidt, 1982; Beghi et al., 1986*b*). However, the commonest sources of information on drug toxicity are case reports and clinical trials (Beghi et al., 1986*a*). In both, the reported events do not represent the ideal situation for a meaningful assessment of the prevalence and characteristics of adverse drug reactions (ADRs) seen in daily practice. Case reports are drawn from populations at unknown risk, and patients recruited in clinical trials are not entirely representative of the epilepsy population at large. The frequency and types of ADRs recorded in studies dealing with intensive monitoring of clinical practice are a better reflection of the prevalence and clinical implications of drug toxicity as they are perceived in routine health care delivery frameworks. In a multicenter survey of clinical practice conducted in our country with 509 patients receiving chronic antiepileptic drug (AED) treatment (Collaborative Group for Epidemiology of Epilepsy, 1986), 31% had one or more ADRs, with a wide range of occurrence between centers. Of the 232 recorded events, 109 were definite, 84 were possible, and 26 were doubtful. Symptoms and/or signs of drug toxicity were reported by the patient in 54.5% of the cases, were clinically important in 52.5%, permanent in 49.5%, and intolerable in 13.5%. ADRs were present in 22% of monotherapy patients, in 34.2% of patients treated with two drugs, and in 44.4% of patients receiving three or more drugs. Occurrence of ADRs varied by drug: phenytoin (PHT) (33%), phenobarbital (PB) (23%), carbamazepine (CBZ) (15%), and valproate (VPA) (12%). Somnolence was the most common com-

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plaint, followed by gingival hyperplasia, nystagmus, and ataxia.

A random sample of 355 cohort cases was followed to assess the effects of prolonged monitoring of drug toxicity on frequency of ADRs and on overall management of the disease. We report the results of that follow-up study.

MATERIAL AND METHODS

A cohort of 509 patients receiving AED treatment for >3 months was recruited in the outpatient services of 15 Italian university and hospital departments, including six epilepsy centers. Patient data, general characteristics of the epilepsy, drug treatment, and ADRs have been previously reported (Collaborative Group for Epidemiology of Epilepsy, 1986). Three hundred fifty-five unselected patients were then followed for an average period of 11 months (range 1–36 months). The number of follow-up visits varied between patients depending on the number and types of requests and on the length of the observation period. During each follow-up visit, seizure frequency and types, data relevant to the diagnosis or drug, and ADRs (including new occurrences) were recorded. Seizure frequency at admission was calculated based on the previous 6 months. All data collected during the follow-up were processed using a Statistical Package for the Special Sciences (SPSS) and, where indicated, statistical analysis was done using the chi-square test for independent variables.

RESULTS

The characteristics of the 355 follow-up patients generally overlapped those of the original cohort (Table 1). Only a significant change in seizure distribution was found, with a relative decrease of mixed and unclassified seizures and an increase of complex partial, tonic/clonic, and absence seizures.

One or more ADRs were reported in 148 patients (41.6%) during the observation period. Adverse reactions are reported in Table 2. ADRs were 284, with 207 cases reporting none; 67 cases, one; 49 cases, two; 17 cases, three; and 15 cases, four or more. The average number of ADRs per subject was 1.7 among monotherapy patients, 2 among patients treated with two drugs, and 2.5 among patients taking three or more drugs. At admission, 110 (31%) of patients reported ADRs. The number fell to 71 (20%) at the last follow-up visit. When the percentage of patients with ADRs was plotted against time (Fig. 1), there was a downward trend in the

TABLE 1. *Characteristics of the 355 follow-up patients with comparison to the original cohort of 509 cases*

Variable	No. of cases	Follow-up	Original
A. Age distribution (yr) mean (±SE)		24.8 (±0.9)	23.7 (±0.7)
B. Percent with disease duration of			
<1 yr	21	6.0	7.0
1–3 yr	66	18.5	21.5
4–10 yr	97	27.0	26.5
>10 yr	165	46.5	43.5
Not specified	6	2.0	1.5
C. Percent with seizures in the previous 6 months			
None	87	24.5	29.5
1–3	74	21.0	20.0
4–10	54	15.0	14.0
>10	106	30.0	28.0
Not specified	34	9.5	8.5
D. Percent with associated disorder[a]			
None	186	52.3	50.5
Anoxia/birth trauma	66	18.5	20.5
Head trauma	35	9.8	11.0
Infection	21	5.9	6.0
Hereditary disease	14	3.9	3.5
Metabolic/toxic	9	2.5	2.7
Malformations	8	2.2	2.7
Others[b]	40	11.2	12.0
E. Percent with seizure pattern (in %)			
Partial	172	48.0	49.0
Generalized	131	37.0	24.0
Mixed and unspecified	50	14.0	26.0
Unilateral	1	0.5	1.0
Unclassified	1	0.5	—

[a] Percentages do not equal 100% because two or more associated disorders were concurrently present in some patients.
[b] Including vascular, neoplastic, and degenerative disorders.

TABLE 2. *Adverse drug reactions*

Reaction		Total
Central nervous system		181
Somnolence	62	
Nystagmus	23	
Ataxia	21	
Vertigo, unsteadiness	18	
Diplopia and other ocular disorders	12	
Tremor and other extrapyramidal signs	9	
Slowness of mentation	7	
Headache	5	
Irritability, belligerence	5	
Mental function impairment	4	
Other[a]	15	
Skin and connective tissue		50
Gingival hyperplasia	28	
Rash	6	
Acne	6	
Hirsutism	5	
Alopecia	2	
Enamel decalcification	2	
Other	1	
Gastrointestinal and liver		26
Nausea, vomiting, abdominal pain	24	
Liver disorders	2	
Other		27
Weight gain	8	
Hypotonia	6	
Blood cell changes	6	
Asthenia	3	
Early sexual development	1	
Hypotension	1	
Flushing	1	
Dyspnea	1	
Total		284[b]

[a] Stupor (2); dysmetria (2); depression, anxiety (2); enuresis (2); hypertonicity (1); dysarthria (1); coma (1); hiccup (1); psychosis (1); status epilepticus (1); insomnia (1).

[b] The sum of the adverse reactions is more than the number of patients with ADRs because in 81 cases two or more ADRs were concurrently present.

number of reports (27% at 6 months, 20% at 12 months, and 11.5% at 16 months).

Seizure frequency and treatment regimens at admission and at last visit are illustrated in Table 3. The proportion of seizure-free patients rose from 24.5% at admission to 42.8% at last visit. The number of patients with >20 seizures decreased from 20 to 8.7%. Among the 87 seizure-free patients at admission, 26% had ADRs, as compared to 32% of cases with uncontrolled seizures (chi-square: 1.11; p = NS). Conversely, at the last visit, the percentages of patients with ADRs in the two groups were 15 and 24%, respectively (chi-square: 3.93; $p < 0.05$). Overall, previously recorded ADRs had disappeared at last visit in 62.2% of seizure-free patients and in 22.2% of cases with relapses.

During the follow-up, there was a slight increase of the number of monotherapy cases (40.5–50%) and a concurrent decrease of patients taking three or more drugs (18–10%). The number of prescriptions fell from 640 to 568, mostly for PB, PHT, and VPA. The drug most frequently prescribed at the last visit was CBZ. Drugs containing fixed combinations of PHT and PB were withdrawn in 25 of 38 patients (66%).

The percentage of adverse reactions varied according to the number of drugs concurrently taken, although a lower percentage of patients had ADRs at the last visit than at admission (Table 4). There were also fewer ADRs for the individual drugs, except for barbiturates and benzodiazepines.

At last visit, drug plasms levels were assayed in 23% of patients with ADRs (37 of 161) and in 18% of patients without ADRs (34 of 194) (chi-square: 1.31; p = NS). Overall, plasma levels values were within

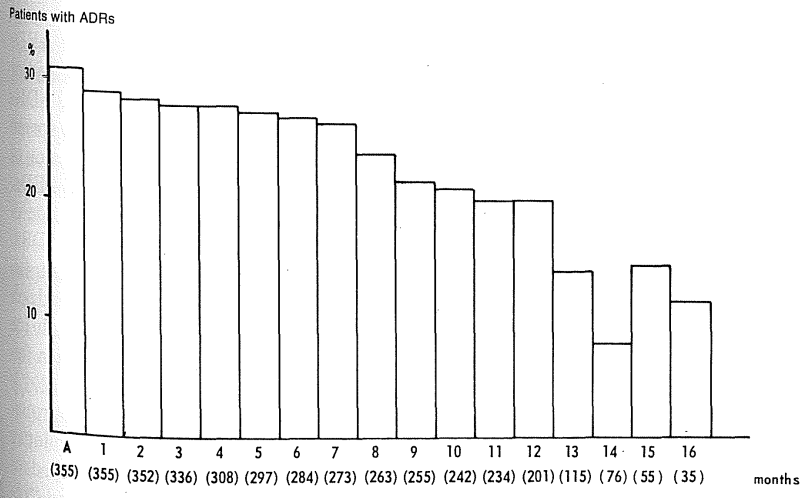

FIG. 1. Percentage of adverse drug reactions (ADRs) during follow-up. Numbers in parentheses refer to patients in each interval. Patients seen for >16 months were not considered because they were few. A: first study visit.

TABLE 3. *Seizure frequency and treatment at first study visit and at last study visit in 355 patients with chronic AED treatment*

Variable	First visit		Last visit	
	No. of cases	%	No. of cases	%
Seizure frequency[a]				
None	87	(24.5)	152	(42.8)
1–3	74	(20.8)	39	(11)
4–10	54	(15.2)	76	(21.7)
11–20	35	(9.9)	45	(12.7)
>20	71	(20)	31	(8.7)
Not specified	34	(9.6)	12	(3.4)
Antiepileptic treatment				
No. of drugs				
None	—	(—)	3	(1)
1	144	(40.5)	177	(50)
2	147	(41.5)	137	(50)
3+	64	(18)	38	(10)
Drug				
Phenobarbital and other barbiturates	219	(34)	176	(31)
Carbamazepine	124	(19.5)	140	(25)
Phenytoin	102	(16)	88	(15.5)
Valproate	99	(15.5)	77	(13.5)
Primidone	38	(6)	40	(7)
Benzodiazepines	33	(5)	29	(5)
Ethosuximide	18	(3)	12	(2)
Other	7	(1)	6	(1)
Total no. of prescriptions	640	(100)	568	(100)

AED, antiepileptic drug.
[a] See text for explanation.

normal limits in 78% of cases with and in 81% of cases without ADRs (chi-square: 0.04; p = NS). Of 31 patients with abnormal plasma level values, only one had a toxic plasma drug concentration.

The most common ADRs (i.e., those with 10+ reports) are shown in Fig. 2 along with the clinical decision on whether treatment was altered. Somnolence disappeared during follow-up in two-thirds of cases, 47% of which had changes in treatment. Gingival hyperplasia improved in one-third of cases, 56% without change in treatment. Ataxia evolved favorably in 86% of cases, mostly after changes in treatment. Drug changes were made in the majority of patients with diplopia, all of whom had complete recovery. Both vertigo and nystagmus disappeared in 61% of cases, mostly without changes in treatment. Treatment modifications were recorded in 50% of cases with gastrointestinal (GI) disturbances, and symptoms did not recur in the majority of patients.

TABLE 4. *Percentage of patients with ADRs by number of drugs and drug at first and last study visit*

Variable	First visit (% ADRs)	Last visit (% ADRs)
No. of drugs		
1	20.0	15.0
2	37.5	22.0
3+	40.5	34.0
Drug[a]		
ESM	50.0	—
PHT	36.0	29.0
VPA	31.5	7.0
BZD	20.0	33.0
PB and other barbiturates	17.0	19.0
CBZ	15.5	7.0
PRM	—	—

ESM, ethosuximide; PHT, phenytoin; VPA, valproate; BZD, benzodiazepines; PB, phenobarbital; CBZ, carbamazepine; PRM, primidone.
[a] Only monotherapy patients were considered.

DISCUSSION

Patients receiving chronic treatment with AEDs are at high risk of developing symptoms and/or signs of drug toxicity. In the present survey, ADRs were present in 41.6% of patients surveyed for an average period of 11 months. The high frequency of reports can be due in part to incorrect use of AEDs. Our findings indicate that intensive surveillance of ADRs can lead to a progressive decrease in ADRs, resulting in a better diagnostic assessment (as shown by the decreasing number of unclassified seizures) and an improved therapeutic approach (as shown by the smaller percentage of cases with uncontrolled seizures).

There are a number of reports on the improvement of the quality of care to patients with epilepsy after intensive surveillance, with concurrent reduction in the number of seizures in the so-called "re-

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