

PHARMACOVIGILANCE IN EPILEPTIC PATIENTS USING ANTIEPILEPTIC DRUGS

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ABSTRACT - Objective: To investigate the occurrence of adverse effects of antiepileptic drugs (AED) in chronic epileptic patients in mono or polytherapy. **Method:** We evaluated consecutive patients that met the following inclusion criteria: age of 18 years or older, diagnosis of epilepsy for at least one year, stable dose of AED for at least three months. Patients were asked if they had any adverse event related to the AED. After that, they were interviewed according to a detailed semi-structure questionnaire. We also assessed specifically the adverse events in the last four weeks. The data were analyzed regarding the use of monotherapy x polytherapy, and the presence of probable depression (score >15) according to the Center for Epidemiologic Studies Depression Scale. **Results:** Sixty-five patients were evaluated, 35 women, mean age 38.3 years; 35 patients were in use of monotherapy and 35 in polytherapy. Only 45 (69.2%) patients spontaneously reported adverse effects. After the formal questionnaire, 63 (97%) patients referred experiencing an adverse event ($p < 0.001$). Seventeen men had adverse events, as opposed to 28 women ($p = 0.042$). When the last four weeks were evaluated, patients with probable depression presented adverse events more frequently ($p < 0.0001$). **Conclusion:** Our data suggest that adverse events are highly prevalent when a detailed questionnaire is applied and that depression may aggravate the number and intensity of side effects in patients using AEDs.

KEY WORDS: antiepileptic drugs, pharmacovigilance, epilepsy, depression, adverse events.

Farmacovigilância em pacientes com epilepsia em uso de drogas antiepilépticas

RESUMO - Objetivo: Investigar a ocorrência de efeitos adversos das drogas antiepilépticas (DAE) em pacientes com epilepsia crônica tanto em mono quanto em politerapia. **Método:** Avaliamos consecutivamente os pacientes que preencheram os seguintes critérios de inclusão: idade igual ou superior a 18 anos, diagnóstico de epilepsia por no mínimo um ano, doses estáveis de DAE por no mínimo três meses. Os pacientes foram instados a responder espontaneamente sobre a presença de efeitos colaterais das DAE. Após isto, um questionário formal sobre eventos adversos foi aplicado. Também avaliamos especificamente a presença de queixas nas últimas quatro semanas. Os dados foram analisados levando-se em conta o uso de mono ou politerapia e a presença ou não de provável depressão (índice >15) segundo o CES-D. **Resultados:** Sessenta e cinco pacientes foram avaliados, 35 mulheres, idade média 38,3 anos; 35 pacientes estavam em uso de monoterapia e 35 em politerapia. Somente 45 (69,2%) pacientes espontaneamente registraram a presença de efeitos adversos. Após o questionário formal, 63 (97%) pacientes tiveram queixas ($p < 0,001$). Dezesete homens e 28 mulheres reportaram eventos adversos ($p = 0,042$). Quando as últimas quatro semanas foram analisadas, os pacientes com provável depressão relataram mais freqüentemente a presença de efeitos adversos ($p < 0,0001$). **Conclusão:** Nossos dados sugerem que efeitos adversos são altamente prevalentes quando um questionário detalhado é aplicado e que depressão pode agravar o número e a intensidade de eventos adversos em pacientes com epilepsia utilizando DAE.

PALAVRAS-CHAVE: drogas antiepilépticas, farmacovigilância, epilepsia, depressão, eventos adversos.

Most patients with epilepsy depend on the medical treatment with antiepileptic drugs (AED) to achieve control of their seizures, which occurs in around 60-70% of the patients¹. A third of the epilep-

tic patients do not obtain seizure control with AED drugs. For them other treatment options are indicated, eventually surgery. Chronic use of AED may be associated with several systemic and central nervous

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system adverse events²⁻¹⁵. Polytherapy is sometimes used in refractory epilepsy despite significant increase in the number of the side effects^{16,17}. Moreover, there is a considerable incidence of co-morbidity among epileptic patients, such as depression, mainly in those with refractory epilepsy¹⁸⁻²¹. Quality of life is associated with seizure control, presence of depression and with adverse AED events as well²².

Adverse effects are highly prevalent in the medical treatment of epilepsy. For instance, carbamazepine (CBZ) is one of the main drugs used for focal and generalized seizures, and may cause sedation in 40% of the patients¹⁴.

The aim of this study was to investigate the occurrence of adverse events of AED in chronic epileptic patients in mono or polytherapy. We collected spontaneous complaints and compared with a detailed semi-structured questionnaire.

METHOD

This study was conducted at the epilepsy clinic of our university hospital from June 2003 to December 2004.

We evaluated consecutive patients that met the following inclusion criteria: aged 18 years or older, diagnosis of epilepsy for at least one year, stable dose of AED for at least three months, signature of informed consent. Exclusion criteria: uncertain diagnosis of epilepsy, patients with cognitive impairment, change in AED dose in the last three months, refuse to sign the informed consent.

Patients were asked if they had any adverse event related to the AED. After that, regardless of the answer, they were interviewed according to a detailed semi-structure questionnaire about the presence of adverse events associated with the AED, based on literature²² and adapted to Portuguese colloquial terms by the authors.

We also assessed specifically the adverse events in the last four weeks. They were rated as 1 to 4 points, according to the following scale: 1 - absent, 2 - rare, 3 - sometimes/mild, 4 - frequent/always²².

The data was analyzed regarding the use of monotherapy versus polytherapy, and the presence of probable depression (score >15) according to the Center for Epidemiologic Studies Depression Scale - CES-D²³. This scale allows to differentiate three groups of patients according to the score: if the score is 22 or higher, the patient may be suffering from a major depression; if the score is 15 to 21, the patient may be suffering from mild to moderate depression; if the score is below 15, this test does not indicate that the patient is depressed. The reason to choose this scale is that it has been used in the literature to evaluate epileptic patient during antiepileptic drug treatment²².

Statistical analysis was performed using the chi-square test, Fisher exact test and Student t-test.

RESULTS

Sixty-five patients were evaluated, 35 women, ages ranging from 20 to 70 years-old (mean=38.3 years). Thirty patients were in use of monotherapy and 35 in polytherapy.

Table 1. Frequency of adverse events in the last four weeks versus since the beginning of the treatment.

Adverse event	Patients in monotherapy		Patients in polytherapy	
	Beginning of treatment	Last four weeks	Beginning of treatment	Last four weeks
Emotional lability	–	14 (46.7 %)	–	17 (48.6 %)
Fatigue	14 (46.7 %)	15 (50 %)	15 (42.9 %)	18 (51.4 %)
Psychomotor agitation	–	16 (53.3 %)	–	19 (54.3 %)
Agressivity	4 (13.3 %)	11 (36.7 %)	4 (11.4 %)	10 (28.6 %)
Anxiety	–	15 (50 %)	–	15 (42,9 %)
Headache	3 (10 %)	8 (26.7 %)	2 (5.7 %)	17 (48.6 %)
Hair loss	4 (13.3 %)	5 (16.7 %)	11 (31.4 %)	9 (25.7 %)
Skin reactions	3	5 (16.7 %)	6 (17.1 %)	7 (20 %)
Diplopia or blurred vision	2 (6.7 %)	4 (13.3 %)	11 (31.4 %)	11 (31.4 %)
Dyspepsia	–	11 (36.7 %)	–	17 (48.6 %)
Gingival hypertrophy	6 (20%)	4 (13.3 %)	10 (28.6 %)	7 (20 %)
Tremor	–	12 (40 %)	–	11 (31.4 %)
Weight gain	–	5 (16.7 %)	–	3 (10 %)
Dizziness	5 (16.7 %)	6 (20 %)	9 (25.7 %)	11 (31.4 %)
Somnolence	14 (46.7 %)	16 (53.3 %)	11 (31.4 %)	11 (31.4 %)
Memory impairment	11 (36.7 %)	14 (46.7 %)	13 (37.1 %)	23 (65.7 %)
Sleep disturbance	–	10 (33.3 %)	–	13 (37.1 %)
Lack of concentration	–	10 (33.3 %)	–	15 (42.9 %)

Table 2. Adverse events in patients using one AED versus those on polytherapy. Data collected from a detailed semi-structured questionnaire.

Adverse event	Monotherapy		Polytherapy		p
	Yes	No	Yes	No	
Irritability	4	26	4	31	0.815
Dizziness	5	25	9	26	0.376
Memory impairment	11	19	13	22	0.968
Dispiritedness	14	16	15	20	0.758
Oversleeping	14	16	11	24	0.208
Unsteadiness	3	27	5	30	0.600
Headache	3	27	2	33	0.518
Diplopia	7	23	18	17	0.020
Change in appetite	8	22	10	25	0.864
Gingival bleeding or hypertrophy	6	24	10	25	0.423
Body hair growth	2	28	8	27	0.071
Alopecia	4	23	11	24	0.084
Unhappiness	12	18	11	24	0.471
Artralgia	1	29	3	32	0.380
Skin Rash/Allergy	3	27	6	29	0.405
Lack of libido	7	23	8	27	0.963
Difficulty of erection (men)	3	12	2	13	0.624

Table 3. Number of points attributed to adverse effects according to their intensity scored by each patient in the last four weeks [scoring scale and CES-D (Center for Epidemiologic Studies Depression Scale) detailed in Method].

CES-D <15	# of patients	CES-D > 15	# of patients
Scoring 1-20	03 (7.0%)	Scoring 1-20	0
Scoring 21-30	14 (32.5%)	Scoring 21-30	1 (4.5%)
Scoring 31-40	19 (44.2%)	Scoring 31-40	5 (22.7%)
Scoring greater than 40	07 (16.3%)	Scoring greater than 40	16 (72.8%)
Total	43 (100.0%)	Total	22 (100%)

When asked about the presence of adverse events, only 45 (69.2%) patients answered positively. However, after the formal questionnaire, 63 (97%) patients referred experiencing an adverse event related to AEDs ($p < 0.001$). Seventeen men had adverse events, as opposed to 28 women ($p = 0.042$).

Table 1 shows the data for each symptom in patients with monotherapy or polytherapy since the introduction of the AED and in the last four weeks. The Student t-test showed no difference between the presence of adverse events since the introduction of the AED either on monotherapy ($p = 0.309$) or polytherapy ($p = 0.143$).

We found that 19 patients in monotherapy had adverse events, as opposed to 26 in polytherapy ($p = 0.340$). Table 2 shows the individual analysis for

each symptom, and only diplopia was more frequent in patients with polytherapy.

Twenty-two patients had probable depression according to the Center for Epidemiologic Studies Depression Scale; and 18 of them presented adverse events. From the 45 patients without depression, 27 had adverse events ($p = 0.115$). However, when the last four weeks were evaluated separately, patients with probable depression presented adverse events more frequently ($p < 0.0001$, Table 3).

DISCUSSION

The recognition of the most frequent side-effects of AEDs helps clinical monitoring of medical treatment of epilepsy. AEDs more commonly used in our institution are carbamazepine, phenytoin, valproate

and clobazam. Our study revealed that hypersomnia, dizziness, gastrointestinal distress and loss of memory are among the most frequent adverse events in patients taking AED. Our result pointed out that proactive semi-structured query is important to detect adverse events, otherwise not mentioned spontaneously by patients. This finding is in keeping with other studies^{22,24}. The number of adverse effects was comparable between mono and polytherapy groups in our patients. However, when each side effect was individually analyzed, diplopia was found to occur more frequently in patients under polytherapy. Several studies have indicated that the incidence of adverse effects increase with the number of drug²⁵⁻²⁷. The small number of patients in this research probably explains because we found no difference between the two groups (monotherapy *versus* polytherapy).

We found that women reported side effects more frequently than men. Weight gain, cosmetic consequences of the treatment and teratogenic effects of AEDs - in those at childbearing age - usually bring greater concern for women^{12,28,29}. Therefore, they may be more aware of the possible side effects and prone to report them.

To the best of our knowledge, the Center for Epidemiologic Studies Depression Scale - CES-D²³ is not validated in our country; therefore, we cannot make definitive statements about its use and conclusion in this work. In our study, when the last four weeks were evaluated, patients with probable depression presented adverse events more frequently than patients without depression. Co-morbidity in epilepsy is a major issue nowadays and, for adults, depression is one of the main conditions associated with epilepsy³⁰⁻³². Adverse AED effects and depression may be the most important negative influences on a person's perception of their current health status²². The negative impact of depressive disorders in the quality of life of patients with epilepsy demands that their presence be investigated in every epileptic patient³³.

To conclude, our data suggest that adverse events must be proactively identified through a systematic questionnaire and that depression may aggravate the number and intensity of side effects in patients using AEDs.

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