Preliminary Study on the Efficacy and Tolerability of Newer Anticonvulsants in a Population of Epileptic Patients

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Key Words

Adverse effects of antiepileptic drugs · Efficacy · Epilepsy

Abstract

Objective: To study the efficacy and safety of newer antiepileptic drugs. **Subjects and Methods:** Clinical records of 461 epileptic patients attending the Consorcio General Hospital, Valencia, Spain, were reviewed. Demographic data, adverse reactions and clinical outcome were recorded. **Results:** One hundred and five patients experienced a total of 151 adverse drug reactions to antiepileptic medications. Adverse drug reactions occurred in the central nervous system (54.9%), skin (17.0%), gastrointestinal tract (13.2%), liver (4.9%), mouth (4.4%) and others (5.6%). The newer anticonvulsants were withdrawn in 19.1% of patients because of side effects, while older drugs were withdrawn in 9.3% of patients. Of the 461 patients, 78 (17.4%) experienced a $\geq 50\%$ reduction in seizure frequency when one of the newer anticonvulsants was added to their therapy. Older anticonvulsants were better tolerated than newer drugs. Tiagabine was the worst tolerated of all the drugs. **Conclusion:** Our findings show that patients with simple par-

tial secondary generalized epilepsy had a greater benefit when a newer anticonvulsant was added to the treatment regimen.

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Introduction and Objective

Antiepileptic drug therapy is the mainstay of treatment for most patients with epilepsy. The overall goal is to completely prevent seizures without causing side effects, preferably with a single medication and a dosing schedule that is easy for the patient to follow. For over 60 years, pharmacologic management of epilepsy had been restricted to very few drugs, but the number of available drugs for epilepsy has increased dramatically in recent years.

It is assumed that the main benefit of the new antiepileptic drugs may be in reducing the incidence and severity of adverse reactions and in doing so, they may prove to be more effective [1–3] than the older drugs. Hence, we decided to perform a comparative study between the new and older antiepileptic drugs for their efficacy, tolerability and overall effectiveness [4, 5].

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Table 1. Adverse drug reactions to antiepileptic drugs

Drug	Patients who used that drug	Adverse drug reactions	Patients who stopped the drug because of side effects
<i>Newer drugs</i>			
Gabapentin	47	11 (23.4)	11 (23.4)
Lamotrigine	38	7 (18.4)	6 (15.8)
Vigabatrin	32	4 (12.5)	3 (9.4)
Topiramate	32	8 (25.0)	6 (18.8)
Tiagabine	18	6 (33.3)	6 (33.3)
Oxcarbazepine	5	1 (20.0)	1 (20.0)
Levetiracetam	1	0	0
<i>Older drugs</i>			
Valproic acid	316	35 (11.1)	23 (7.3)
Carbamazepine	201	26 (12.9)	17 (8.5)
Phenytoin	162	32 (19.8)	27 (16.7)
Phenobarbital	146	12 (8.2)	10 (6.9)
Clonazepam	30	3 (10)	3 (10)
Primidone	16	1 (6.3)	1 (6.3)
Clobazam	14	5 (35.7)	3 (21.4)
Ethosuximide	2	0	0

Figures in parentheses indicate percentages.

Subjects and Methods

Clinical records of 461 (210 female and 251 male) epileptic outpatients attending the Consorcio General Hospital, Valencia, Spain, were reviewed. Age, sex, diagnosis, drugs used, adverse reactions and outcome were recorded. Patients' age was between 3 months and 84 years (median, 29 years). The tolerability and efficacy of 7 newer antiepileptic drugs, i.e. gabapentin, topiramate, vigabatrin, oxcarbazepine, levetiracetam, tiagabine and lamotrigine, were also studied.

All adverse drug reactions to antiepileptic therapy were recorded. An adverse drug reaction was assigned to a drug when it was developed after the drug had been started or the drug dose increased, and it disappeared or highly decreased again after the drug had been withdrawn or the drug dose reduced. If a reaction, such as hair loss due to valproic acid, was known and described in the literature as temporary, it was related to the new drug, even though it was not withdrawn or dose reduced. When a patient experienced several different adverse effects to a drug, for example, ataxia, vomiting and dizziness, only one adverse drug reaction was tabulated, but if this same patient later experienced an adverse effect to a different drug, for example phenytoin-induced gingivitis, this adverse drug reaction was added for the same patient. Sometimes, adverse effects did not figure explicitly in the clinical history, but a sentence like this could be found: 'the drug was not tolerated by patient'.

Efficacy of newer anticonvulsants was measured as follows: when a new antiepileptic drug was started, the number and intensity of crises 1 year after and 1 year before were registered. When a 1-year period was not available, it was shortened to 6 months. If the new

drug was stopped earlier than 6 months because of side effects, efficacy was not evaluated. If the reason for stopping the drug before 6 months was lack of efficacy, a period shorter than 6 months was used for efficacy measurement. In the absence of a previous treatment to the newer anticonvulsant, comparison was made with a later one not containing the newer drug, if available. When the newer anticonvulsant was present from the beginning of treatment and had never been withdrawn, or when less than 6 months had passed since the newer anticonvulsant was prescribed at full doses, efficacy was not evaluated.

Three levels of efficacy were considered: (a) there was a fall of 25–50% in the number of crises or, at least, a notorious decrease in the intensity of crisis; (b) the fall in the number of crises was greater than 50%, and (c) an absence of crisis took place. Worsening of crisis was considered when the number of crises increased by more than 25%. Values are cited in the text as means $\pm$ SD. For statistics, Jandel Scientific SigmaStat program was used.

Results

Adverse Drug Reactions to Antiepileptic Drugs

Of the 461 patients, 105 (57 females and 48 males) had ever experienced adverse drug effects to antiepileptic drugs, amounting to a total of 151 adverse drug reactions, 81 in females and 70 in males. Female patients were more likely to develop adverse effects to antiepileptic drugs than males, but the difference was not statistically significant ($\chi^2 = 2.74$, $p = 0.053$).

The adverse reactions are summarized in table 1 and were located in the central nervous system (54.9%), skin (17.0%), gastrointestinal tract (13.2%), liver (4.9%), mouth (4.4%), appetite (2.8%) and others (2.8%). The adverse effects observed for different drugs and the number of patients who experienced them were as follows.

Valproic Acid. Gastrointestinal effects (nausea, vomiting, abdominal pain): 11; elevated liver enzymes: 4; hair loss: 5; tremor: 4; skin rash: 1; drowsiness: 2; mental confusion: 1; weight gain: 2; neutropenia: 1; leukopenia: 1; 'not tolerated': 8.

Carbamazepine. Gastrointestinal effects (nausea, vomiting, abdominal cramps): 4; drowsiness: 6; toxic erythema: 2; elevated liver enzymes: 3; dizziness: 4; diplopia: 1; asthenia: 1; urticaria: 2; rash: 1; allergic periorbital reaction: 1; confusion: 1; leukopenia: 1; torpidity: 1; ataxia: 1; 'not tolerated': 7.

Phenytoin. Gingivitis or gingival hyperplasia: 8; mental confusion: 9; memory impairment: 6; tremor: 7; rash: 4; erythema: 2; dizziness: 1; gastritis: 1; hypertrichosis: 1; ataxia: 3; elevated liver enzymes: 1; swelling sensation in the face: 1; urticaria: 4; behavioral changes: 1; 'not tolerated': 1.

Table 2. Efficacy results for newer anticonvulsants

Drug	Patients	Removed because of side effects	Worsening	No effect	25–50% decrease in number or intensity of crises	>50% decrease in number of crises	Absence of crisis	Insufficient data
Gabapentin	47	11	6	17	6	2	4	1
Lamotrigine	38	6	3	13	3	2	5	6
Topiramate	32	6	2	10	6	3	2	3
Vigabatrin	32	3	5	15	3	2	3	1
Tiagabine	18	6	2	4	2	2	2	0
Oxcarbazepine	5	1		2			1	1
Levetiracetam	1			1				

Table 3. Efficacy of newer anticonvulsants related to type of epilepsy

Type of epilepsy	Gabapentin	Lamotrigine	Vigabatrin	Topiramate	Tiagabine	Oxcarbazepine	Levetiracetam
SP	5 (0)	4 (0)	5 (2)	6 (3)	1 (0)		
PSG	14 (5)	13 (5)	9 (2)	12 (5)	11 (4)	1 (0)	
CP	9 (4)	5 (1)	5 (1)	3 (0)	3 (1)	3 (1)	
CPSG	3 (0)	3 (1)	3 (0)	4 (1)	1 (1)		1 (0)
Generalized	8 (1)	9 (3)	5 (2)	6 (2)			
Lennox-Gastaut	1 (0)	1 (0)	1 (0)				
Not defined	7 (2)	3 (0)	4 (1)	1 (0)	2 (0)	1 (0)	
Total	47 (12)	38 (10)	32 (8)	32 (11)	18 (6)	5 (1)	1 (0)

Figures in parentheses indicate number of patients who experienced improvement of seizure.

SP = Simple partial; PSG = partial secondary generalized; CP = complex partial; CPSG = complex partial secondary generalized.

Phenobarbital. Ataxia: 1; fatigue: 4; dizziness: 3; extreme muscular relaxation: 1; drowsiness: 4; impaired learning: 1; behavioral changes: 1; 'not tolerated': 2.

Primidone. Gastric disturbances: 1.

Benzodiazepines (Clobazam and Clonazepam). Drowsiness: 2; memory and learning impairment: 3; fatigue: 2; asthenia: 1; 'not tolerated': 3.

Tiagabine. Confusion: 3; ataxia: 3; difficulty with concentration: 2; drowsiness: 1; fatigue: 1; memory impairment: 1; weight loss: 1.

Topiramate. Agitation: 1; hyperkinesias: 1; paresthesias: 1; polyuria: 1; anorexia: 3; dizziness: 1; gastric disturbances: 1; 'not tolerated': 1.

Gabapentin. Drowsiness: 3; facial edema: 1; ankle edema: 1; impaired memory: 1; rash: 1; increased appetite: 1; ataxia: 2; elevated liver enzymes: 1; 'not tolerated': 4.

Lamotrigine. Rash: 3; tremor: 2; gastric disturbances (nausea, vomiting or abdominal pain): 2; drowsiness: 1; insomnia: 1; hair loss: 1.

Vigabatrin. Insomnia, drowsiness, dizziness, confusion and agitation: 1; weight gain: 1; drowsiness: 1; ataxia: 1; fatigue: 1; asthenia: 1; dysphagia: 1; gastroesophageal reflux: 1; hypertrichosis: 1.

Oxcarbazepine. 'Not tolerated': 1.

In our population, anticonvulsants induced adverse drug reactions in a proportion of 14.3% of patients and the drugs were withdrawn in 11.0% of patients due to the side effects. The adverse effects were significantly greater in the newer than older drugs: 21.4% in newer drugs versus 12.9% in older drugs ($\chi^2 = 7.95$, $p = 0.0048$). Consequently, more newer than older drugs were withdrawn:

9.1% newer drugs versus 9.5% older drugs ($\chi^2 = 12.6$, $p = 0.0004$).

Efficacy of Newer Anticonvulsants

Of the 461 patients, 103 (50 females and 53 males) had ever used at least 1 of the following 7 anticonvulsants: gabapentin, topiramate, vigabatrin, oxcarbazepine, levetiracetam, tiagabine and lamotrigine. Of these, only 1 patient used the same newer antiepileptic (lamotrigine) at two different times, getting the same result (absence of crisis) on both occasions. This case was tabulated only once.

Efficacy results are summarized in tables 2 and 3. Efficacy could not be evaluated in 12 patients; benefit was obtained in 48 of the 161 times (29.8%) a newer antiepileptic was used. The percentage of patients who showed an improvement in seizures for each drug was as follows: oxcarbazepine 25.0%; vigabatrin 25.8%; gabapentin 26.1%; lamotrigine 31.3%; tiagabine 33.3%, and topiramate 37.9%. The percentage of patients who experienced a 50% or greater reduction in seizure frequency was: global 17.4%; gabapentin 13.0%; vigabatrin 16.1%; topiramate 17.1%; lamotrigine 21.9%; tiagabine 22.2%, and oxcarbazepine 25%. Response by type of epilepsy was 20% for complex partial secondary generalized, 24% for simple partial, 29% for complex partial, 29% for generalized and 35% for simple partial secondary generalized epilepsy.

Discussion

In this study, women were more likely to develop adverse drug reactions to anticonvulsants than men, but it was not statistically significant. Although newer anticonvulsants are thought to be better tolerated than older drugs [6–8], in this preliminary study with 461 epileptic patients, the newer anticonvulsants were more poorly tolerated (19.1% of withdrawals due to side effects) than older drugs (9.5% of withdrawals due to side effects). Vigabatrin was the best tolerated of the newer drugs, while tiagabine was the worst tolerated of all drugs (33.3% of drug intolerance).

With regard to efficacy, our findings are similar to previous studies [8, 9], which failed to establish that any of the newer anticonvulsants is better than any other, warranting further study involving a larger sample size. The newer drugs have shown some efficacy in all types of epilepsy, although in our group of patients, they were more efficacious in simple partial secondary generalized epilepsy (35% of patients with this type of epilepsy experienced an improvement of their seizures).

Conclusion

Our findings show that patients with simple partial secondary generalized epilepsy had a greater benefit when a newer anticonvulsant was added to the treatment regimen.

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