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Clinical Efficacy of the Therapeutic Changes in Patients in Anti-epileptic Polytherapy

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Abstract

Background: To analyze the results obtained with therapeutic changes in our series of patients treated with at least three antiepileptic drugs.

Methods: From 668 consecutive epilepsy patients treated in our real clinical practice were selected 42, treated with 3 or more antiepileptic drugs. After reviewing their medical histories we analyzed a total of 151 drug combinations

Results: Epidemiological data: women: 40.5 %, males: 59.5 %; mean age: 44.2 years (20-67); Mean time since epilepsy diagnosis,: 31.3 years (3-62); Mean seizure frequency: 11.8 /month (0-75); Focal Epilepsy: 73.8 %, Generalized Epilepsy: 21.4 %, Undetermined: 4.8 %. Mean number of combined antiepileptic drugs: 3,3 (2-6). In 35,8 % of the therapeutic changes there were a seizure frequency reduction (in more than 90 % the follow up overcame 6 months), in 19,2 % there were a worsening and in 30,5 % changes were not appreciated. In 14.6% treatment was modified due to adverse effects. In combinations which obtained good clinical response, the decrease in the percentage of seizures was 81.2% (Reduction >50% in 81,8 % of combinations).In 5,3 % of the combinations the patients achieved seizure freedom. The drugs more common used were: Carbamazepine (15 %), Valproate (12.8 %), Phenytoin (12.6 %), Phenobarbital and Levetirazetam (both 8.5 %), Lamotrigine and Topiramate (both 7.9 %).

Conclusion: Our data support the idea, less pessimistic than the traditionally accepted, that with the ac-tive therapeutic intervention in epileptic patients on polytherapy favorable results can be achieved.

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Introduction

It has been classically considered that two-thirds of epileptic patients will have an adequate response to medical treatment, but the rest will continue having seizures. The goal of treatment is to control the epi-lepsy with monotherapy, what is obtained in 47% of cases with the first antiepileptic drug (AED) used , and in additional 13% of cases replacing the first AED with other in monotherapy [1].Another 5 % will control the epilepsy with the third AED in monotherapy or in a polytherapy. The rest will require other drug combinations. Although some of these patients will benefit from surgical techniques, especially when the diagnosis is mesial temporal lobe epilepsy [2-3] , in many cases we have no indication for surgery, or the available techniques will not provide a complete control of the seizures (corpus callosotomy, multiple subpial transection, neurostimulation, etc.)[4] In addition, usually the reduction of drug therapy in patients who have undergone surgery and have achieved seizure control can be discrete and start up two years after the surgery [5].As we see, the percentage of epileptic patients who must rely on the polytherapy is high, and for them we do not have consolidated protocols that guide us in the AEDs combinations. Taking into account all the variables that must be considered when designing a study, the accurate times to obtain a reliable clinical response and the large number of pharmacological combinations available, it is very difficult to design studies to ensure minimal statistical power, this means that most of the papers published are observational, and generally include the double antiepileptic therapy [6,7].

In real clinical practice, because we don't have predictors of efficacy, obtaining seizures control is based on testing with each of the multiple FAE a priori indicated. This can take several months if we consider the times to obtain the optimal dose, the patterns of slow withdrawal, and a reasonable period of evalua-tion of efficacy.

In this work we analyze retrospectively the results obtained after pharmacological changes in our series of patients treated with at least three FAE.

Materials & Methods

Of a whole of 668 consecutive patients attended in our Epilepsy Outpatient Clinic, we select those that were taking three or more AEDs at the moment of being recruited: 48 patients. The review of the medical histories allows us to include in the study 42 of these patients (we have enough information).

We analyze the following epidemiological data: sex, age, duration of epilepsy, epilepsy type (focal, gene-ralized and indeterminate), seizures frequency/month (at the time of be included in the study and before and after each therapy change).

The primary objective of this study is to evaluate the treatment response in each drug combination (changes in seizures frequency); in the cases in which the response to the treatment is good we consider the follow up time after the therapeutic changes. As secondary objectives are evaluated the percentage of therapeutic changes that resulted in adverse events andthe percentage of therapeutic changes that resulted in increase of seizure frequency. The statistical Chi square (software SPSS 15.0) was used for the analysis of significance.

Results

Patients

The epidemiological data from the sample are shown in table 1.

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Of the 42 patients, 36 (85.7%) showed improvement in at least one of the therapeutic combinations tested, 19 (45.2%) worsening and 12 (28.6%) adverse events.

Gender	Females (%)	17 (40,5)
	Males (%)	25 (59,5)
Age (years)	Mean	44,2
	Minimun-Maximun	20-67
Time since onset of epilepsy (years)	Mean	31,3
	Minimun-Maximun	3-62
Seizure frequency/ month*	Mean	11,8
	Mínimun-Maximun	0-75
Epilepsy type	Focal (%)	31 (73,8 %)
	Generalized (%)	9 (21,4 %)
	Indeterminated (%)	2 (4,8%)

Table 1: Epidemiological data.
* At the time patients are included in the study.

Therapeutic combinations

On having performed the retrospective study of the different therapeutic patterns in these patients, we could analyze a whole of 151 combinations. In them, the mean number of AEDs that were taken on polytherapy was 3,3 (minimum 2, maximum 6).

The most frequent result of therapeutic change was the reduction in the seizure fre-quency (54 combinations -35,8 % -), followed by the absence of changes (46 combina-tions -30,5 % -), an increase in the seizure frequency (29 combinations -19.2 % -), and the presence of adverse events (22 combinations -14.6 % -).

Considering the combinations that led to clinical improvement, the follow-up was two months in one patient (1.9 %), four months in two patients (3.7 %), five months in one patient (1.9 %) and more than 6 months in 50 patients (92.6 %).

Analyzing the overall change in the seizure frequency before-and-after of all the com-binations (excluding those in which there were adverse events, since the follow-up times were short) the mean seizure frequency/month changed from 24.7 (min-max: 0-300), to 18.9 (0-300), which represents a global improvement of 24%.

In the combinations associated with improvement, the mean number of monthly sei-zures changed from 24.5 (0.2 -300) to 4.6 (0-45): improvement of 81.2 %; in those combinations which seizure frequency was increased the change was from 4.3 (0-45) to 16.1 (0.2 -200): 73.3% increase.

The reduction in the seizure frequency was more than 50 % in 81,8 % of the combina-tions in which improvement was achieved (45 of 55 combinations). In 5,3 % (8 combi-nations) the patients remained seizure free.

Therapeutic combinations were many and none prevailed; the following were used most frequently:

Carbamazepine + Phenobarbital+ Phenytoin (3.3%)
Carbamazepine + Clonazepam + Topiramate +Valproate (2%)
Carbamazepine + Lamotrigine + Valproate (2%)
Clonazepam + Levetiracetam + Valproate (2%)
Clonazepam + Lamotrigine + Valproate (2%)
Phenobarbital + Phenytoin+ Lamotrigine (2%)
Phenytoin + Lamotrigine + Topiramate (2%)

The percentage of use of each AED is shown in Figure 1.

The percentage of presence of each AED in combinations which led to improvement and clinical worsening is shown in table II. We found no significant differences in the distribution of drugs in the two groups (p = 0, 269).

Analyzing each drug, the most marked difference corresponds to lamotrigine, present in 10.29% of the combinations that resulted in improvement and 5.56% of those asso-ciated with worsening; it suggests a trend but without statistical significance (p = 0, 195).

The combination of lamotrigine and valproate, whose synergy is known, was present in a similar manner in both groups (33% of the combinations with improvement and 40% of the worsening)[8].

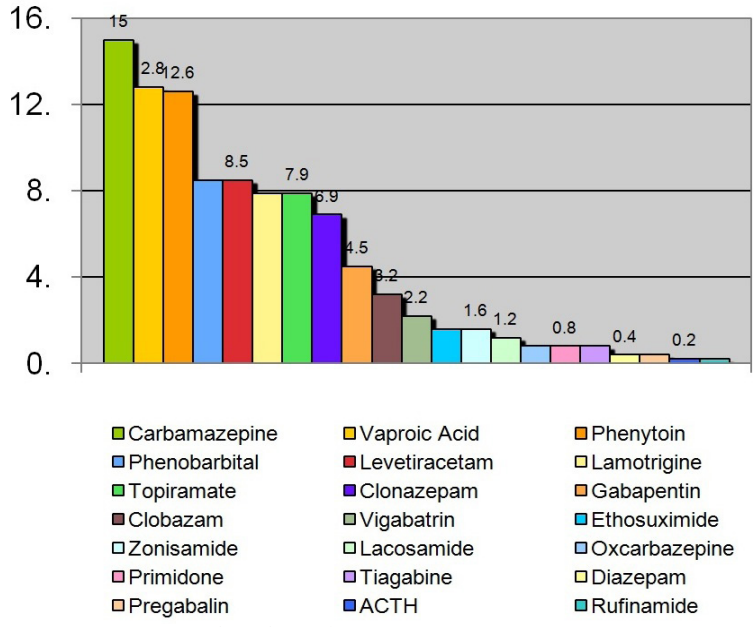

Figure 1: Percentage of use for each AED.

AED	Improvement (%)	Worsering (%)
ACTH	0.57	0
Carbamazepine	14.28	12.22
Clobazam	3.43	2.22
Clonazepam	7.43	5.56
Diazepam	1.14	0
Ethosuximide	2.86	1.11
Phenobarbital	7.43	10
Phenytoin	12	12.22
Gabapentine	4.57	2.22
Lacosamide	1.14	2.22
Lamotrigine	10.29	5.56
Levetiracetam	10.29	11.11
Oxcarbazepine	0.57	1.11
Primidone	0.57	0
Rufinamide	0.57	0
Tiagabine	1.14	2.22
Topiramate	6.86	8.89
Vigabatrin	1.14	3.33
Valproic Acid	13.14	17.78
Zonisamide	0.57	2.22

Table 2: percentage of presence of each AED in the drug combination groups that showed improvement or clinical worsening.

Discussion

In the decade of seventies recommendations aimed to initiate the antiepileptic treat-ment in combination; in fact, pharmaceutical preparations combined drugs. The change to monotherapy was reported in the 80 as a consequence of new scientific evidence[9, 10]. From the generalization of the monotherapy as initial treatment, only 11-13% of patients resistant to treatment that changed to combination therapy improved substantially, but in most cases at the expense of more undesirable events, which opened the alternative to sequential monotherapy [11]; currently the debate continues on whether or not to use the combination or the sequential monotherapy [12]. In the 90s the polytherapy were more easily provided by joining the market several drugs with new mechanisms of action and less interactions. These new molecules have a pharmacological profile most suitable for combination therapy, although time has not allowed them to demonstrate that they are associated with best results [13].

The combination of drugs may enhance the undesirable events if these are common in the antiepileptic drugs used. However, adverse events are dose-dependent, and it has been proposed that the “drug load" is more critical than the number of drugs: twice the standard dose of an antiepileptic will predictably cause the same adverse effects as two drugs in a standard dose [14,15].In addition, combined AEDs also can obtain a supra-additive benefit, like the observed with lamotrigine plus valproate [8].

Most of the studies analyzing clinical efficacy of polytherapy in epilepsy in the past few years come from published articles from new drugs that have been launched to the market [16].These, in a certain way, are in contradiction with the classical concept of lack of response from the third AED tested, and draw a more optimistic scenario.

For Luciano et al. [13] the typically low percentages of success with polytherapy are not right.They find in their patients, when adding a drug to the treatment, a significant improvement in 37% of cases, with a 16% of seizure freedom; the minimum follow-up was 12 months. Of their patients, 58 % remain with seizures after 5 years of treatment, but after 10 years decrease to 35 % and at age 15 to 24 %. They report that 23% of the patients who did not respond to at least at one AED can do if up to six therapeutic trials are performed.

Our data also suggest better results in changes in polytherapy than the classically ad-mitted. Referring to 151 analyzed combinations in polytherapy, we have found good response in 35.8% of them, with mean reduction in seizure percentages of the 81.2%, and reduction over 50% in the 81.8% of these combinations.These data are similar to those presented by Luciano et al. [13], while we have obtained less patients a complete control of seizures (5.3%). Most of our 42 patients (86%)improved in at least one of the therapeutic changes.

Our results may, in part, be "hypertrophied" by the well-known effect of “honeymoon" [17]; but, since in more than 90% of the combinations in which clinical benefit was registered the follow up was for more than 6 months, and in more than 95% was of four months or more, we believe that the influence of this effect is small.

In our study, adverse events led to change treatment in 14.6% of the combinations (and in at least one combination in 28.6% of the patients); it is not very high percen-tage given the characteristics of our patients, and they are in line with data already published in where don't seems to appear more side effects in patients on polytherapy than on monotherapy [18].

The most commonly drugs in our series (carbamazepine, valproate, phenytoin, pheno-barbital, levetiracetam, lamotrigine) are comparable to those referred to in the study from Rufo-Campos et al. [7], an exhaustive analysis of polytherapy and most commonly used AEDs in refractory epilepsy in Spain;this study is carried out in 2005 and, in their patients, the time passed from the first seizure was 24,3 years; in our review this interval is 31,3 years, so we can consider that the date of debut is similar in the pa-tients of both studies (beginning of the decade of eighties);this could justify the pre-ponderance of the classic antiepileptic drugs. The two studies distance 7 years, which may explain the higher of levetiracetam and topiramate in our work.

Comparing drug combinations that resulted in clinical improvement with those which triggered the seizures increase, we have not found significant differences in the percentages of the different drugs; only a tendency to be more present lamotrigine in the clinical group with improvement that in the worsening ($p = 0, 195$).Our data do not allow us to draw conclusions in this regard, while other authors have presented favor-able results in terms of the efficacy of lamotrigine in the treatment of refractory epi-lepsy [19].

Conclusion

Our data suggest that changes in antiepileptic polytherapy can lead to better outcomes than classically admitted, with a low rate of adverse events.

Lamotrigine tends to be more present in the group with clinical improvement, but its presence in association with valproate was similar manner in both groups (improve-ment and worsening).

In conclusion, our data support the idea, less pessimistic than the traditionally ac-cepted, that with the active therapeutic intervention in epileptic patients receiving polytherapy, favorable results can be achieved.

Competing Interests

The authors have declared that no competing interests exist.

Author Contributions

Both the author substantially contributed to the study conception and design as well as the acquisition and interpretation of the data and drafting the manuscript.

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