Failure of a first regimen of monotherapy to control the newly diagnosed epilepsies. What to do next?

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SUMMARY

Background. Monotherapy is the choice regimen to treat newly diagnosed epilepsies. However, if it fails, several strategies may be followed.

Aim. To discuss the treatment options when an initial monotherapy regimen fails.

Methods. We reviewed the relevant literature on the topic by using PubMed.

Review and Discussion. Approximately 64% of people with epilepsy (PWE) de novo are free of seizures with the first appropriate antiepileptic drug (AED) in monotherapy. The type (first versus second generation) of the first AED to use depends on the physician's personal choice provided that it is a first-line AED. There is a tendency to prefer a substitution rather than a combination of a failed first AED when it was produced associated with an idiosyncratic reaction, was poorly tolerated at a moderate dose, or produced no improvement in seizure control. In contrast, there is some evidence to prefer secondary polytherapy whenever the PWE tolerate its first AED but with a suboptimal response. In this case, and particularly mainly if a first generation AED was used as a first-line treatment, I prefer to choose a new generation AED given their more favourable pharmacokinetic and pharmacodynamic profiles. A very often used strategy is transitional polytherapy between two regimens of monotherapy.

Conclusion. Any therapeutic decision should take into account factors such as seizure type or syndrome, possibility of drug side effects, comorbidities, comedications, age, teratogenic potential, and compliance. Whatever the option to be taken, the PWE, his family or the caregivers should take part in the decision making.

Key words: antiepileptic drugs • drug therapy combination • epilepsy

BACKGROUD

During the last three decades, monotherapy has been the regimen of choice to initiate pharmacological treatment of people with newly diagnosed epilepsy. Indeed, studies in the seventies and eighties during the last century have shown that the majority of people with epilepsy (PWE) were free of seizures with only one antiepileptic drug (AED), that the introduction of a second one was of benefit in a limited number of cases, and that change from polytherapy to a monotherapy regimen significantly decreased AEDs side effects (SE) and drug interactions (DI) but kept clinical efficacy (CE) the same (Shorvon et al., 1978; Schmidt, 1983; Matson et al., 1985). Furthermore, a classic study (Kwan and Brodie, 2000a) showed that approximately 64% of PWE de novo

were free of seizures for at least one year with the first appropriate AED in monotherapy. An additional regimen of duotherapy resulted in clinical efficacy in only 3% more cases and the remaining 35 to 40% were difficult to treat. The majority of these persons will constitute the refractory epilepsies. A similar study designed to determine the probability of seizure freedom with successive AED regimens in newly diagnosed epilepsies showed that the chance declines with the number of AED regimens used (Brodie et al., 2012).

With regards to CE, there is no evidence of any significant difference between the first versus the second generation of AEDs when used as monotherpy for newly diagnosed epilepsies.

However, this cannot be said with regards to SE and DI for which the second generation of AEDs are better (Kwan and Brodie, 2006). Hence, the type of the first AED to use entirely depends on the physician's personal choice provided it is a first-line AED for that particular seizure type or epileptic syndrome, and also taking into account some particular aspects of the PWE, like their gender, age and comorbidities.

AIM

In this manuscript we aim to address the different pharmacological treatment options when a first regimen of monotherapy fails to control newly diagnosed epilepsies in adults.

METHODS

Literature search for publications written in English, French or Spanish, mainly within the last twenty years, using PubMed data base and with the following key words: monotherapy, polytherapy, antiepileptic drugs, clinical efficacy, side effects, drug interactions

REVIEW AND DISCUSSION

Introduction

Which strategies can one use when a first regimen of monotherapy fails to control newly diagnosed epilepsy? Trying another regimen of monotherapy with a second-line AED? In this regard, with first or second generation AEDs? Starting secondary polytherapy? Thinking about transitional polytherapy? A study addressing this subject showed that those PWE who received substituted monotherapy and those receiving add-on treatment had similar seizure-free rates and incidence of intolerable SE (Kwan and Brodie, 2000a). A review of the literature on the topic carried out in 2002 (Deckers, 2002) also failed to show evidence of benefit of one strategy over the other. In this manuscript we will review this subject trying to reach a best clinical practice consensus.

Another regimen of monotherapy

At first glance, this is the most rationale decision provided another first-line AED may be used. Indeed, if a second AED is added, more than 13% of CE is considered to be achieved (Kwan and Brodie, 2006). However, it may depend on other considerations (e.g., age, associated comorbidities or comedication) of the specific PWE with whom we are dealing with.

There seems to be a tendency to prefer a substitution rather than a combination of a failed first AED when it produced an idiosyncratic reaction, was poorly tolerated at a moderate dose, or produced no improvement in seizure control (Stephen and Brodie, 2012). However, if this decision is the one to be taken, should we choose first or second generation ADEs? This is a matter without consensus and that should be considered individually. From just a personnel point of view, we tend to start monotherapy for newly diagnosed epilepsies with a first generation AED, valproate (VPA), for both generalized and focal seizures, and this AED or carbamazepine (CBZ)/oxcarbazepine for focal seizures. Besides the well established CE of these two AEDs, and having in mind some reviews (Perucca and Tomson, 2011) and relevant guidelines available (NICE, 2012; Glauser et al., 2013), we take in consideration personnel (long experience with these drugs, including knowledge of their pharmacokinetic and pharmacodynamic profiles and the most frequent SE) and economic factors. However, we concede that there should be several exceptions to this practice, for example women of childbearing age, the elderly, and the comedicated persons. The SANAD study is also worth to be mentioned although it is not already a recent one, and, for instance, levetiracetam and zonisamide were not included on it. In this unblinded randomised trial in hospital-based outpatient clinics, VPA was found to better tolerated than topiramate and more efficacious than lamotrigine (LTG) for generalised and unclassifiable epilepsies, and considered to remain the AED of first choice for this type of epilepsies (Marson et al., 2007a), but with the need of keeping in mind women of childbearing age. Regarding partial epilepsies, the some study provided evidence of LTG being more efficacious than CBZ for time to treatment failure outcomes (Marson et al., 2007b).

Hence, and based in the initial designed strategy, if we decide for another regimen of monotherapy there is not much room left to apply for another first generation AED, given the fact that we no longer use phenytoin and phenobarbital, and a second generation AED should be started. For those cases in which second generation AEDs were chosen for the first attempt of monotherapy, the decision concerning the type of drug to be used as second-line AED should be, once more, individualized. Yet, we recommend that another second generation AED will be the one to be chosen given their more favourable pharmacokinetic and pharmacodynamic profiles compared to the first generation AEDs.

A successful conversation from one AED to another requires effective communication between the clinician and the PWE, including concerns and issues, like medication SE, medication cost or medication dependence (Smith et al., 2009).

Another regimen which may be used, mainly when starting treatment with first generation AEDs, is secondary monotherapy and which implies transitional polytherapy.

Polytherapy

In general, three regimens of polytherapy may be considered. Secondary polytherapy is the most frequent one, and means the use of more than one AED following a failed first regimen of monotherapy. Initial polytherapy means that such a regimen is chosen since the very beginning to treat newly diagnosed epilepsies. Finally, transitional polytherapy concerns the use of such a regimen for a limited length of time, between two regimens of monotherapy.

Initial polytherapy is beyond the scope of this review. Sufficient to say that for those cases in which epilepsy, at the time of the first treatment, is clinically suspected to be refractory (Kwan and Brodie, 2000a), and whenever there is a need to "burn stages" for an early epilepsy surgery, this strategy, namely rationale polytherapy, should be considered.

Regarding secondary polytherapy, a study already highlighted (Kwan and Brodie, 2000a) showed that a regimen of duotherapy given to those approximately 35% of PWE that continued to experience seizures after a first AED, resulted in seizure control in only a further 3% of persons. A recent study showed no significant superiority between strategies of a second monotherapy versus a polytherapy regimen with regards to CE or SE when a first regimen of monotherapy fails (Millul et al., 2013). In contrast, it is acceptable to prefer combination therapy whenever the PWE tolerates his/her first AED but with a suboptimal response (Stephen and Brodie, 2012). Another study (Kwan and Brodie, 2000b) showed a non-significant trend to favour a duotherapy regimen over a second monotherapy regimen in PWE in whom the first AED failed due to clinical inefficacy. Hence, this is an ongoing topic which must and should be addressed case by case.

Concerning the possibility of increasing SE due to polytherapy, a multicenter double-blind randomized study which included only first generation AEDs showed no differences between mono and polytherapy (Deckers et al., 2001). Furthermore, a study undertaken in tertiary centers showed that the number of SE did not differ between PWE taking monotherapy as opposed to polytherapy (Canevini et al., 2010). In contrast, self-reported SE of people on mono and polytherapy revealed significantly higher SE for those on polytherapy. However, even without reaching statistical significance, drug dosages were higher in the polytherapy group (Andrew et al., 2012). Hence, because this an important issue to keep in mind when deciding the next step after a failed initial regimen of monotherapy, it is also not definitely settled and should be individually evaluated.

Those PWE who, for whatever reason, failed to respond to the initial AED but to whom we want to keep a monotherapy regimen will need another AED (Garnett et al., 2009), and the respective switch may be rapid or slow. A rapid switch means abruptly stopping the initial AED and starting the newly chosen AED and is performed when the PWE suffers an idiosyncratic, life-threatening reaction. The slow switch involves a transitional period of polytherapy. One method for a slow switch is to begin a slow dose reduction of the initial AED and, at the some time, start the titration of the second AED. Another approach, the one we prefer, is to maintain the dose of the baseline AED while the dose of the planned second AED is titrated to the required dose. Subsequently, the first AED is tapered off.

CONCLUSIONS

This is an issue for which guidelines can not be easily adopted given the disparity of situations that can occur in clinical practice. If, given its well known advantages, the decision is to choose always an initial monotherapy regimen, different PWE features may account for individualized decisions. If secondary monotherapy is appropriate, slow transitional polytherapy is a wise

strategy. If secondary polytherapy is requested after a first monotherapy regimen, it seems reasonable to add a second generation AED to the first AED, particularly if the latter is a first generation AED. However, any therapeutic decision-making should take into account factors such as seizure type or syndrome, possibility of drug SE, comorbidities, comedication, age, teratogenic potential, and the ability of the PWE to adhere with the prescribed AED regimen. Different strategies are required for different scenarios, but whatever they will be, the PWE, his family or the caregivers should take part in the decision making.

CONFLICT OF INTERESTS DISCLOSURE

The author has no conflict of interests to declare.

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