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Original articles

Therapeutic strategies in the choice of antiepileptic drugs

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Abstract

The choice of treatment of newly diagnosed epilepsy involves many factors such as age, sex, life style, general health and concomitant medication. The seizure type, syndrome, and the pharmacology, efficacy and safety of the antiepileptic drugs (AEDs) should also be considered. Some of the new AEDs appear to provide at least equivalent efficacy with better tolerability. Some of these drugs have the potential to become drugs of first choice in newly diagnosed epilepsy. At the present time, we also must consider the criteria of reimbursement of these drugs. In this paper, we try to describe common and practical strategies to start a treatment of newly diagnosed epilepsy.

Key words : Idiopathic generalised epilepsies ; partial epilepsy ; new antiepileptic drugs.

Introduction

The natural history of newly diagnosed epilepsy and the response to the treatment are not well known at the present time. Some long-term studies (Schmidt and Gram, 1995 ; Brodie,1999) suggested that about 50% of patients will be seizure free with the first tried antiepileptic drug (AED).

Treatment failure is often related to several independent factors. The most frequent cause of treatment failure is poor compliance (Leppik and Schmidt, 1988), but not respecting the dose schedule or incompatible life style are also frequent causes that are often underestimated by practitioners.

The second most important factor in treatment failure is misdiagnosis of seizure type or epileptic syndrome. Some AEDs can worsen certain seizures or syndromes. Some patients may suffer from a combination of epileptic and/or non epileptic seizures, etc.

A progressive lesion or cause may be responsible for refractory seizures and should be reassessed after failure of AED treatment.

Finally, tolerance, tolerability and the presence of specific adverse events can explain some cases of treatment failure and must be carefully investigated.

According to a recent study including 470 newly diagnosed patients (Kwan and Brodie, 2001), only 47% of patients will be seizure free after a first monotherapy. If the first monotherapy is substituted with a second AED, 13% more patients will become seizure free. However, after trying a third AED, only 1% of patients will be seizure free. A bitherapy will add 3% more seizure free patients. The authors conclude that 36% of patients will continue to experience seizures.

The strategy before a first failure remains open. Some suggest increasing the dose to the maximum tolerated dose before changing. Monotherapy is considered to be better than polytherapy, while some papers speak about "rational polytherapy". However, according to Kwan and Brodie (2001), the benefit of increasing the dose after a failure at moderate doses is minimal, at least for those AEDs that were studied : valproate (VPA), carbamazepine (CBZ) and lamotrigine (LTG).

The aim of this discussion is to find common and easy strategies for the management of AEDs based on the clinical practice of each Center and the international guidelines (ILAE 2001, Buenos Aires ; Karceski, Morrell and Carpenter 2001).

Because poor compliance is the first cause of treatment failure, the practitioner should carefully and clearly inform the patient, and, if possible, use a drug given maximally twice a day (Cramer *et al*., 1995). Plasma levels, when available, may help in checking patient compliance. However, with newer AEDs, this possibility disappears in most cases.

First, idiopathic generalized epilepsies (generalized seizures) will be discussed and then partial seizures with/without secondary generalization. Neonatal seizures and some specific pediatric syndromes will be discussed separately. Status epilepticus will not be discussed and will be the object of another consensus.

Treatment of generalized seizures (Fig. 1)

For idiopathic generalized epilepsies, VPA remains the first choice, whatever the syndrome. If the patient becomes seizure free, the treatment has

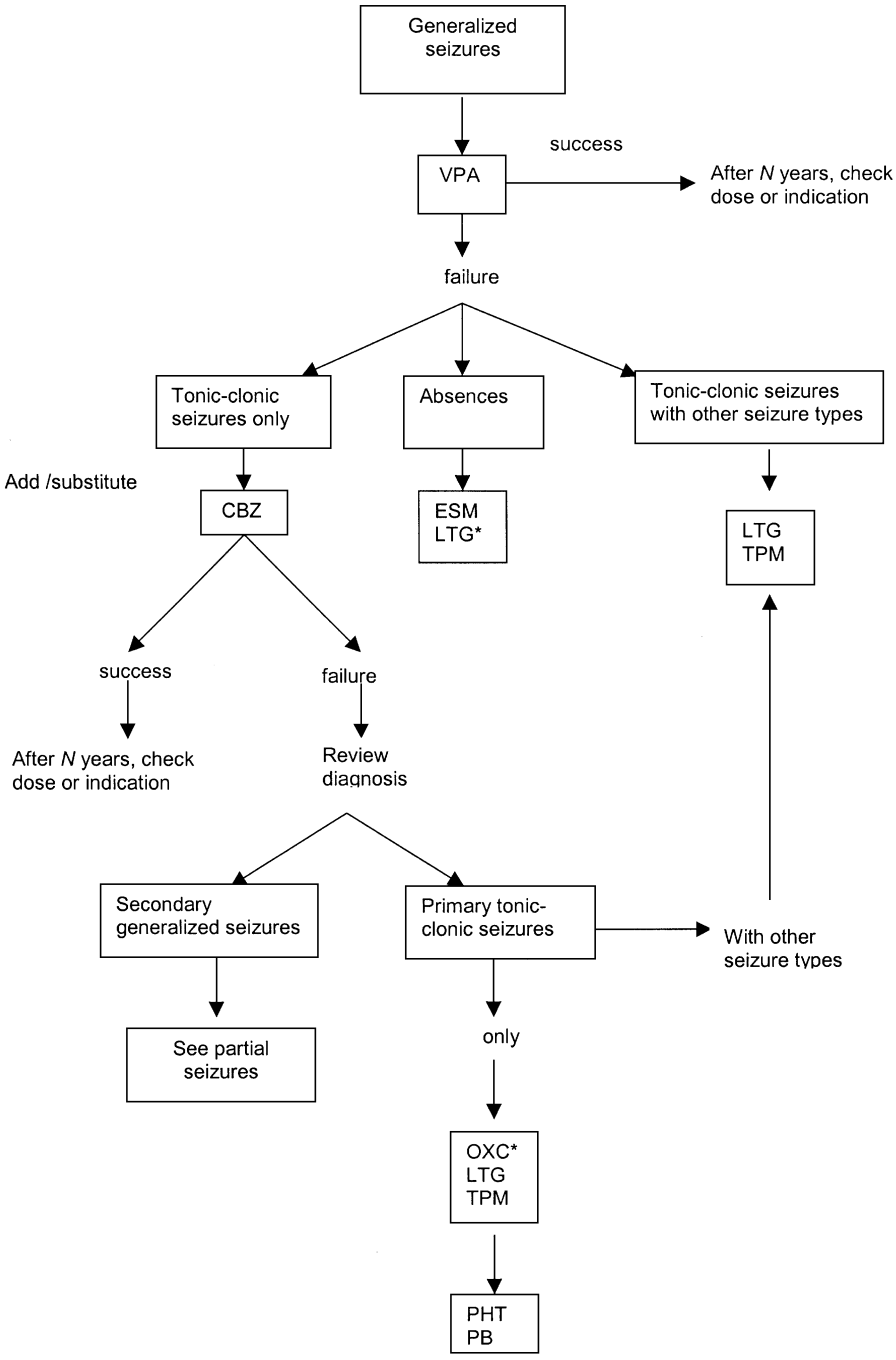

FIG. 1. — Decision tree for generalised seizures
* not reimbursed nor registered in this indication in Belgium

to be reassessed after a variable period according to the epileptic syndrome.

If the treatment is not efficacious or not well tolerated, the second choice will depend on the seizure type and the epileptic syndrome.

– *Tonic-clonic seizures only* : A second AED will be added to VPA : CBZ, LTG, oxcarbazepine (OXC), topiramate (TPM) and when available in Belgium levetiracetam (LEV) (Perucca, 1999). Phenytoin (PHT) and phenobarbitone (PB) should be considered as a third choice in specific cases because of chronic side effects. After successful bitherapy, the first AED may be downtitrated in order to achieve monotherapy. However, in Belgium, OXC and LEV are not reimbursed in this indication.
– *Typical absences only* : In case of failure or intolerance to VPA, ethosuccimide (ESM) or LTG (Culy and Goa, 2000) are the second choice treatment. However, LTG is not registered in Belgium in this indication. Other AEDs such as TPM (Yeung *et al*., 2000) or LEV have not been tried in controlled studies in this seizure type, but open studies or anecdotal cases have shown some efficacy in refractory cases.
– *Tonic-clonic seizures combined with other seizure types such as myoclonic or absence* : In

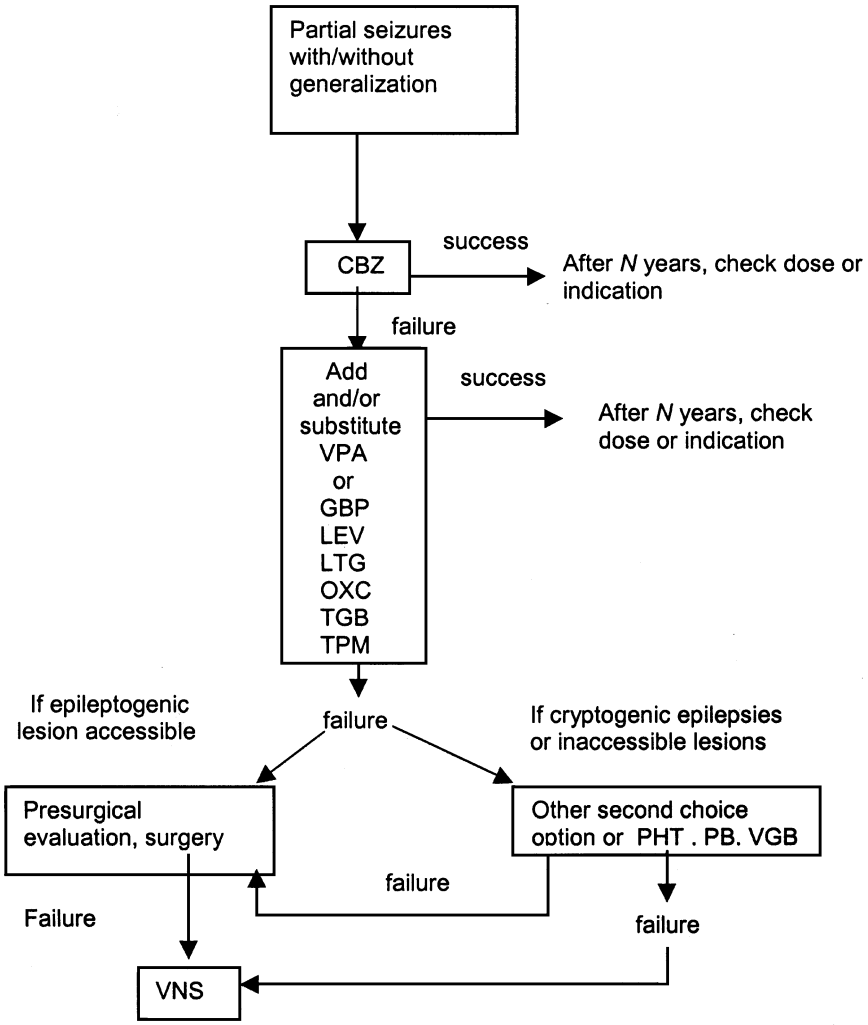

FIG. 2. — Decision tree for partial seizures with/without secondarily generalized seizures

syndromes, such as Juvenile Myoclonic Epilepsy, the second choice should be LTG or TPM (Wheless, 2000). Controlled studies with LEV are ongoing in this indication. Open studies have been published showing good efficacy, but LEV is not yet registered in these epileptic syndromes (Genton and Gelisse, 2000).

– *Tonic-clonic seizures of undetermined origin* : As for idiopathic generalised epilepsies, VPA is the first choice avoiding the risk of worsening the patient. If VPA is ineffective or not tolerated, the diagnosis must be re-evaluated. If the diagnosis remains undetermined, LTG or TPM should be tried. If tonic-clonic seizures seem to be the only seizure type, other AEDs could be tried as explained previously.

TREATMENT OF PARTIAL SEIZURES (Fig. 2)

In case of partial seizures, with or without secondary generalisation, CBZ remains the first choice. If the patient becomes seizure free, after a period of 2 to 4 years, the indication and/or the dose of the AED should be reassessed according to the clinical data of the specific case.

If seizures are not controlled or if CBZ is not well tolerated, a second AED becomes necessary, at least temporarily. At the present time, according to the Belgian regulations of reimbursement (Fiche de Transparence n° 22), VPA is the optimal second line AED. However, according to the International Guidelines, the best choices are TPM, LTG, LEV, OXC, GBP or TGB (Devinsky and Cramer, 2000).

Again, if the patient becomes seizure free, the first AED could be progressively downtitrated to achieve monotherapy. If seizures persist and/or if there is a resectable epileptogenic lesion, the patient should be referred to a surgical center for presurgical evaluation. If the epilepsy is cryptogenic or multifocal, or if the lesion is not accessible, other AEDs should be tried as explained previously. PHT and PB can be tried if the other AEDs are unsuccessful. Vigabatrin (VGB), widely used in the past few years in the treatment of refractory partial seizures, should not be used, with a few exceptions, because of visual field constriction (Eke *et al.*, 1997).

Finally, in refractory cases which cannot be operated or after failure of surgery, vagus nerve stimulation (VNS) remains a helpful option, 30

to 50% of the patients being significantly improved, the efficacy growing with time (De Giorgio, 2000).

This discussion about idiopathic generalised epilepsies and partial seizures can be applied for most patients, regardless of their age.

Special cases related to the paediatric population

- Neonatal seizures : PB remains the first drug and PHT is the second choice in case of persistent seizures.
- West syndrome or infantile spasms : VGB appears to be the first choice, in spite of the adverse events on visual fields. If VGB works, results are fast. VGB has to be stopped if epileptic spasms remain uncontrolled. Corticoids remain a second option. ACTH, prednisone or hydrocortisone have well known acute and subacute adverse events. Some cases successfully treated with TPM have been published. TPM could be an option in case of persistent spasms or in case of severe adverse events with previous treatments (Thijs *et al*., 2001 ; Glauser *et al*., 2000).
- Lennox-Gastaut syndrome : VPA remains the first choice (for reimbursement in Belgium) while LTG, felbamate (FBM) or TPM are a good second option. However, according to the International Guidelines, only these new AEDs are the first option. For decades, all older AEDs have proved their inefficacy (Schmidt and Bourgeois, 2000).

Place of benzodiazepines (BZDs)

BZDs should be reserved for acute and subacute treatment of seizures, and not for chronic treatment. There is a problem of tolerance with loss of efficacy after weeks or months. There is also a risk of withdrawal seizures and adverse events are multiple and may be both severe and insidious.

However, for some specific paediatric syndromes, when a fast answer is mandatory, BZDs can be added at the beginning of the treatment, and then progressively withdrawn when the other AEDs become effective.

Conclusion

The first choice of an AED becomes more difficult with the growing number of drugs available to practitioners.

VPA and CBZ remain the first choice in most patients and epileptic syndromes. PHT and PB, because of their chronic side effects, are only considered as a third option.

BZDs should be reserved for acute or subacute use, with few exceptions.

If seizures persist after the first trial, we propose simple decision trees according to the seizure type and to the syndrome classification.

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Abbreviations

Benzodiazepines	→	BZDs
Carbamazepine	→	CBZ
Ethosuccimide	→	ESM
Felbamate	→	FBM
Gabapentin	→	GBP
Lamotrigine	→	LTG
Levetiracetam	→	LEV
Oxcarbazepine	→	OXC
Phenytoin	→	PHT
Phenobarbital	→	PB
Sodium valproate	→	VPA
Tiagabine	→	TGB
Topiramate	→	TPM
Vigabatrin	→	VGB

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