DOSAGE SPECULATIONS IN THE TREATMENT OF EPILEPSY IN DIALYSIS PATIENTS: NEW OR CLASSICAL MEDICATION?

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Summary

The aim of our study was to to assess the knowledge on treatment of epilepsy in haemodialysed patients whose therapy involves a series of peculiarities.
Case presentations: Three patients of our unit were receiving antiepileptic drugs. Two of them were under classical antiepileptic medication (phenytoin). The third patient changed his medication from a classical (phenytoin) to a modern antiepileptic drug (lamotrigine) due to insufficient drug levels. The two patients under classical antiepileptic therapy were well treated for a long time. The third patient after changing his therapy to the new one exhibited side effects of insufficient dosing (recurrent episodes of generalized seizures for a period of 17 days) before managing to estimate the right drug dosage.
There is a lot of research to be done so that we can be more positive about modern antiepileptic medication in haemodialysed patients.

Keywords: Antiepileptic drugs; Lamotrigine; Phenytoin; Generalized seizures.

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Introduction

Epilepsy is a chronic neurological condition with a prevalence of 4-8 per 1000. Treatment of epilepsy usually involves long-term medical treatment. Initiation of antiepileptic drug therapy needs awareness about the choice of the minimum effective dose of an appropriate monotherapy. In choosing between different anti-epileptic drugs, consideration should be given to the efficacy of the drug for an individual patient and the tolerability of the drug (1).

Over the past decade, there has been a proliferation of new therapies for the treatment of epilepsy. Faced with this growing list of options, clinicians must decide what therapy, or combination of therapies, is best for a given individual. Although controlled clinical trials exist for each treatment option, the answer to these questions may remain unclear (2).

Few patients with severe renal impairment have been evaluated during chronic treatment with new antiepileptic drugs (lamotrigine et al). Because there is inadequate experience in this population, these medications should be used with caution in such cases.

Case presentations

We report 3 cases of haemodialysed (HD) patients of our unit receiving antiepileptic therapy due to generalized seizures after celebrovascular episodes. First patient was a male, 48 years old, diabetic (type I) for 30 years, being on haemodialysis for 9 years and suffering from generalized seizures after a stroke. He was receiving phenyntoin treatment for 15 years without complications. Second case was a male, 55 years old, with Fabry disease, being on haemodialysis for three years and receiving therapy with phenytoin (for one year), after generalized seizures that followed a stroke. No recurrent episodes of epilepsy had been mentioned during all these three years. Third case was also a male, 55 years old, diabetic (type II) for 15 years, being on haemodialysis for three years. After a stroke he had an episode of generalized seizures and began antiepileptic medication with phenytoin. Althought substantial alterations, drug levels were hypotheurapeutic for almost two months. In the end medication was changed to lamotrigine. In the beginning a dosage of 100 mg was given daily. One week later an episode of generalized seizures was mentioned during the last hour of haemodialysis. An increase in dosage to 150 mg was prescribed. Three days later seizures reappeared during the last hour of dialysis. Then we made a new dosage increase to 200mg. One week later seizures reappeared and a 400mg dosage was finally given. Since this alteration seizures never reappeared. The total period of tome for dosage estimation was 17 days during which 3 seizure relapses were mentioned.

Discussion

There are a few data available in national bibliography to determine effectiveness of treatments for haemodialysed patients with generalised seizures with new (lamotrigine et al) compared with older antiepileptic drugs (AEDs) (3). Lamotrigine is a drug of the phenyltriazine class chemically unrelated to existing AEDs (4). In Table 1 we describe drug's dosage according to bibliography for patients older than twelve (5).

Table 1

Initial dose lamotrigine	Usual increment	Maximum
25 mg /day	25 mg/week	300 mg

Following oral absorption, maximum plasma concentrations are rapidly achieved. Absorption of lamotrigine is linearly related to dose. Lamotrigine undergoes extensive metabolism, primarily by conjugation, and exhibits autoinduction that is complete within 2 weeks and can be associated with a 17% reduction in lamotrigine blood concentrations. Its elimination half-life depends on AED co-medication. Thus, in patients taking hepatic- enzyme-inducing AEDs (phenytoin, carbamazepine, phenobarbitone and primidone) it is substantially reduced, while co-medication with sodium valproate prolongs its half-life. On the other hand, patients taking a

combination of an enzyme-inducing AED and sodium valproate will exhibit intermediate lamotrigine half-life values (6).

The quoted "therapeutic" range of blood levels for AED's is a compromise between toxicity and efficacy. In fact, therapeutic means seizure control. A therapeutic plasma concentration range has not been established for lamotrigine. Dosing of lamotrigine should be based on theurapetic response (7).

There are controversial researches about lamotrigine levels and renal failure. Some researches suggest that impaired renal function will have little effect on the plasma concentrations of lamotrigine achieved for a given dosing regimen (8). Some other indicate that haemodialysis shortened the elimination half-life of lamotrigine from 59.6 +/- 28.1 h during the interdialysis period to 12.2 +/- 6.4 h during the dialysis period; 17% of the dose was extracted by haemodialysis (9).

There is a meaning to ordering drug concentrations only for those antiepileptic drugs for which a relation between blood concentration and therapeutic and/or toxic effects has been established. These include carbamazepine, phenytoin, valproic acid, henobarbital, primidone, and ethosuximide. There is currently no evidence for a therapeutic range or that monitoring concentrations improves treatment outcome for clobazam, clonazepam, lamotrigine, gabapentin, topiramate, or vigabatrin. So every decision we must take about dosage to begin therapy with a new AED has to do only with doctors' experience and theurapetic response. This is much more difficult as far as haemodialysed patients are concerned.

In our patients as far as classical antiepileptic drugs are concerned a few problematic situations should be mentioned. When we have to do with modern antiepileptic medication, things become complicated. We should refer to our case receiving lamotrigine. Although the initial dose of lamotrigine and current alterations were above pharmacological indications for the general population, drug levels were not sufficient to suppress neurological symptoms for a long time until a final dose of 400 mg was given with a rapid increment. This was also in the upper dosage limit according to drug introductions.

In conclusion, when it comes to choosing a possible antiepileptic drug for patients on haemodialysis, basically all the pharmacological treatments for these medical diseases must be considered. This is because of the possible interactions that may reciprocally alter the effectiveness of the two types of drugs and, similarly, their pharmacokinetics, pharmacodynamic behaviour and preferred choice of pathways (10). As far as new AEDs are concerned we must be more cautious because farther experience is needed.

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