PHARMACOLOGIC TREATMENT OF EPILEPSY

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Case Presentation

A 64-year-old man had a first generalized seizure. He was seen in an emergency room where magnetic resonance imaging revealed a right parietal meningioma with a diameter of 2.5 cm. He was seen by the neurosurgery team and a craniotomy was performed. He was discharged from the hospital on phenytoin. Three weeks later he reported drowsiness and unsteadiness to his neurologist. In addition, he described episodes of transient sensory disturbance in his left arm, sometimes with twitching movements of the left hand and wrist. These episodes could last ≤3 minutes, and his hand and arm would be weak afterward for several hours. A phenytoin level was measured at 17. Lamotrigine was added to his regimen, and on 400 mg/day the lamotrigine level was 3.8. The dose was increased gradually to 400 mg BID and seizures stopped. Two hours after each dose, however, the patient would become dizzy, nauseated, and encephalopathic for a period of 60–90 minutes.

Introduction: *Salient Features of the Case*

The patient presented with a convulsive seizure due to a meningioma and developed simple partial sensory-motor seizures arising in the region of the meningioma after its resection. The seizures persisted with phenytoin at a moderately high serum level but responded to lamotrigine as a second agent at just above the maximum tolerated dose. This case illustrates a common course of events for otherwise healthy adults who have seizures due to structural brain disease and are placed on phenytoin and lamotrigine.

Principles of Antiepileptic Drug Therapy

General principles for using antiepileptic drugs (AEDs) suggest that it is important to maximize the first AED before adding a second. Typically, this means increasing the dose of the AED until either seizures come under control or side effects are induced at just above the maximum tolerated dose. This was illustrated in this patient when phenytoin was increased until it caused side effects, and lamotrigine was increased until seizures stopped, also to the point of causing side effects, rather than stopping at an arbitrary lower dose. The next action should be to reduce the dose to the maximum tolerated dose. Some AEDs are so well tolerated that a maximum tolerated dose is often not achievable, in which case dosing stops at the level above, which few patients benefit from; 5,000 mg/day for levetiracetam and 4,000 mg/day for gabapentin. However, even among these drugs, if a patient is getting progressively more benefit from higher doses, then higher dosing is occasionally pursued. A second principle of AED use is to add a second drug, lamotrigine in this case, which is increased until effectiveness is demonstrated and then the first drug is withdrawn. Or, if the second drug does not prove effective, it can be withdrawn instead. This will prevent accumulating unnecessary AEDs. Overlapping the drugs will keep the patient "covered" with at least one drug at a reasonable dose, as opposed to withdrawing the first drug while escalating the second drug, which might leave the patient in the position of having ineffective doses of two drugs.

Drawbacks to Phenytoin

Phenytoin was the first AED selected for this patient, which is typical, as phenytoin remains the most commonly prescribed AED. Phenytoin is a traditional favorite of primary care physicians because it is familiar, available in intravenous form, can be dosed QD, and is inexpensive. However, phenytoin has many acute and chronic problems and it should no longer be recommended as initial monotherapy for most patients. Phenytoin induces hepatic enzymes, interacts with AEDs and other drugs, and is less well tolerated in the elderly; therefore, it is an especially poor choice in the elderly. Elderly patients and others often suffer from neurotoxicity, including ataxia, blurry vision, and sleepiness. A fall from ataxia in the elderly can be fatal. Phenytoin is predisposed to acute toxicity because it has a narrow therapeutic index. This means that small increases in the dose can cause large increases in toxicity.

Phenytoin causes cumulative side effects, a disadvantage unique among the AEDs. Long-term use of phenytoin occasionally causes peripheral neuropathy and cerebellar degeneration that adds to the risk for falling. Careful questioning about foot numbness and other symptoms of peripheral neuropathy and close inspection for loss of ankle jerk reflexes are important to detect peripheral neuropathy. Symptoms of peripheral neuropathy usually stop progressing when phenytoin is withdrawn but the peripheral neuropathy usually persists. Induction of hepatic enzymes increases vitamin D metabolism, which often leads to osteoporosis; therefore, patients on phenytoin should have vitamin D levels checked regularly and be treated for vitamin D deficiency when it is detected. Osteoporosis may be present even when vitamin D levels are normal, so periodic bone mineral density tests (dual-energy x-ray absorptiometry [DXA] scans) should

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be performed. Daily vitamin D and calcium should be recommended for all patients on enzyme-inducing AEDs to prevent osteoporosis, even if vitamin D levels and DXA scans are normal.

Comparative Effectiveness Studies

If phenytoin is not a good first choice in the elderly, then what is? Carbamazepine replaced phenytoin as the drug of choice for initial monotherapy of focal onset seizures or when the seizure type is unknown because of the previously noted problems with phenytoin. Thus, the few comparative studies performed have assumed that carbamazepine is the standard therapy and have not included phenytoin. There are no large, placebo-controlled, blinded, randomized controlled trials (RCTs) of multiple AEDs in the elderly. However, there are small comparative trials. The seminal RCT of carbamazepine versus lamotrigine using an individualized titration scheme in 150 elderly patients did not find a difference in efficacy as measured by time to next seizure.[1] However, this study found more people seizure free on lamotrigine, which was better tolerated than carbamazepine. A study of ~600 elderly patients randomized to lamotrigine 150 mg/day, gabapentin 1,500 mg/day, or carbamazepine 600 mg/day did not find a difference in efficacy but did find that lamotrigine and gabapentin were better tolerated than carbamazepine.[2] These studies have several limitations, but if we assume that phenytoin is at least as poorly tolerated as carbamazepine, then these studies suggest that lamotrigine or gabapentin are better choices than the other drugs in the elderly.

Lamotrigine

Lamotrigine as a second choice for this patient is complicated because phenytoin significantly affects the metabolism, and consequently the dosing, of lamotrigine. The half-life of lamotrigine is ~25 hours when given alone, but reduced to ≤12 hours when given with hepatic enzyme–inducing drugs like phenytoin. This means the target dose for lamotrigine given with phenytoin is about twice that when given alone. The typical dose needed is 500–800 mg/day when given with enzyme inducers, although this must be approached cautiously in the elderly because of increased risk for side effects as illustrated in this case.

Lamotrigine and phenytoin levels were checked in this patient and had some value. However, obtaining serum drug levels of AEDs on a routine basis is of limited or no value. A prospective study randomized 180 patients to have AED doses adjusted based on routine serum blood levels in one group to achieve typical blood levels and adjusted entirely on clinical grounds in another group.[3] There were no differences in efficacy measurements such as time to first seizure or 12-month remission rate, fairly definitively demonstrating the lack of utility for routinely obtaining AED levels. On the other hand, this does not mean that blood levels are never useful. Blood levels obtained for a specific purpose can be very useful. As in the current case, the blood level may help detect impending toxicity for AEDs with a narrow therapeutic index such as phenytoin and carbamazepine. Blood levels may help substantiate suspected noncompliance or fast metabolizers of phenytoin or lamotrigine who occasionally require surprisingly high doses. A prospective observation of AED levels used in this way found that ~25% of the time the levels altered management.[4] The value of blood level monitoring is even less for second-generation AEDs because they have a wide therapeutic index and there are almost no studies of the relationship between efficacy or tolerability and serum level.[5]

The timing of side effects in the current case (2 hours after dosing), the transient nature over 1–1.5 hours, and the characteristic symptoms of "drunkenness" (dizzy, nauseated, and encephalopathic) suggest that the symptoms are due to peak dose side effects. This occurs when the serum level exceeds the patient's threshold for AED side effects. Lamotrigine, and most AEDs, have peak levels 1–2 hours after oral dosing and then the levels progressively fall until the next dose. Peak dose side effects can be prevented by avoiding high peak serum levels. This can be done by frequent dosing or using extended-release preparations. The extended-release formulation of lamotrigine avoids the drug level fluctuations that accompany peaks and troughs of the serum level in immediate-release lamotrigine.[6]

Lamotrigine was probably selected in this case because it is well tolerated in the elderly but it does have drawbacks. Rash occurred in ~1:1,000 adults and almost 1:50 children in early clinical trials of lamotrigine, which led to a black box warning. However, serious rashes (Stevens-Johnson syndrome and toxic epidermal necrolysis) were less common in clinical trials and are very uncommon in clinical practice today. This is probably because lamotrigine was given at high doses and escalated quickly in clinical trials but is escalated slowly in clinical practice now. This seems to have avoided the frequent occurrence of rash, although patients and physicians must remain vigilant for it. Common dose escalation paradigms may require months to achieve a target dose, especially when lamotrigine is given with valproate because valproate inhibits lamotrigine metabolism, escalating blood levels. Thus, lamotrigine is not a good choice when a drug must be added quickly.

Alternative Second AEDs

Other AEDs could have been considered as a second AED in this patient. There are few other AEDs specifically examined in the elderly. A placebo-controlled, RCT of topiramate in 77 patients >60 years old with partial seizures found low dose (50 mg) as effective as a higher dose (200 mg) when needed as monotherapy, but that the 200 mg dose was more effective when added as adjunctive therapy.[7] Importantly, the adverse event rate was similar with both doses and relatively low. This is not a comparative effectiveness study and does not inform us as to whether topiramate is any more efficacious than other AEDs, but demonstrates that it is effective to some degree at relatively low doses that are likely to be used in the elderly.

When efficacy studies do not strongly suggest one drug over another, as is often the case, then AEDs are selected based on their characteristics that might treat comorbid conditions or characteristics that might pose special problems for certain patient populations. Lamotrigine is a good choice for depressed patients because it reduces depression in a statistically significant manner in analysis of a subset of depressed older patients enrolled in placebo-controlled efficacy studies of lamotrigine.[8] Gabapentin and pregabalin are good choices when there is comorbid chronic pain. Topiramate is a good choice in patients who experience migraines because it is an effective migraine prophylactic and is approved by the United States Food and Drug Administration for the treatment of migraines. It also causes weight loss, which can be a benefit for obese patients but may be a problem for underweight ones. Zonisamide can also cause weight loss.[9] Levetiracetam is easy to use and is usually well

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tolerated, although it occasionally causes irritability. In a study of 34 older patients with poststroke epilepsy, levetiracetam rendered 82% seizure free, whereas 20% had side effects.[10] Oxcarbazepine is related to carbamazepine and is likely to replace it in the future because it does not require serum level monitoring or surveillance blood work; however, it can cause hyponatremia. It has some mood-stabilizing properties that can be advantageous and was moderately well tolerated in a prospective open-label study of a small subgroup of elderly patients.[11]

Although they did not investigate efficacy in the elderly, there are a few comparative efficacy studies in the adult population that help select among AEDs. The seminal Veteran's Administration Cooperative Study[12] found carbamazepine and phenytoin to be better tolerated and generally more effective for partial seizures than phenobarbital and primidone (a drug rarely used now). While it is unlikely that one of these AEDs would be selected as a first choice today, it substantiates the contemporary wisdom that phenobarbital is less well tolerated. The Standard and New Antiepileptic Drugs (SANAD) study is the only large prospective study of multiple AEDs for treatment of partial seizures, although it is an open-label study.[13] Lamotrigine was generally the most efficacious with regard to time to treatment failure (defined as time to switching drugs for side effects or ineffectiveness) compared to carbamazepine, gabapentin, oxcarbazepine, and topiramate, but carbamazepine had the shortest time to a 1-year remission. This is generally interpreted to suggest that lamotrigine is the most efficacious drug. An alternative interpretation is that it might be logical to start with carbamazepine because those who tolerate it have the shortest time to remission; however, this requires great vigilance for side effects and, if present, to quickly move to lamotrigine. A complementary SANAD study of valproate, lamotrigine, or topiramate for generalized or unclassified seizures found valproate had a better time to treatment failure than topiramate, and shorter time to 1-year remission than lamotrigine, thus concluding that valproate is generally preferable for generalized seizures.[14] The SANAD studies have several limitations but these are somewhat ameliorated by the large number of patients in each trial; 1,721 patients in the partial seizure study and 716 in the generalized seizure study.

Summary

Treating seizures and epilepsy seems more intimidating today because there are so many AEDs to choose from. However, most second-generation AEDs are well tolerated, have few drug interactions, and are seemingly nearly equally efficacious, thereby making it more difficult to choose the wrong AED. Knowing a few principles of AED treatment will allow clinicians to select the appropriate AED based on a few comparative effectiveness studies, and the knowledge of unique properties of AEDs, which suggest certain specific AEDs are better in patients with specific characteristics, especially based on age, comorbid depression, migraine, chronic pain, and obesity. A logical next step in management of the current case is to reduce lamotrigine to a tolerated dose. If seizures do recur, select another agent from among those previously reviewed.

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QUESTION-AND-ANSWER SESSION

Q: Would it make sense in this case to simply substitute an extended-release lamotrigine preparation rather than moving on to an alternative drug given that the toxicity described is clearly a peak level effect?

Dr. Fountain: Switching to an extended-release preparation of lamotrigine would be a logical strategy, although I suspect the patient is very close to the maximum tolerated dose of lamotrigine because "encephalopathy" for 90 minutes is a somewhat severe degree of side effect.

Q: Is there any evidence for choosing between gabapentin and pregabalin?

Dr. Fountain: Some patients in efficacy trials of pregabalin responded to pregabalin but had not previously responded to gabapentin, so pregabalin was more effective for these patients.[1] However, there are no head-to-head comparisons, and it is likely the reverse would be true for some patients. Gabapentin is also less expensive, and affordability may be a concern for some patients.

Q: Are there circumstances in which you add a second medication and achieve seizure control, but then leave the first medication in place rather than withdrawing it?

Dr. Fountain: Patient preference certainly plays a role in this. Seizures are sometimes so persistent that once control is achieved it is reasonable to continue on two medications because the risk for side effects is less than the risk from recurrent seizures.

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