ABSTRACT

Antiepileptic drugs are increasingly being used in the nursing home environment. Their function is not only to control seizures but also to treat numerous psychiatric conditions. Because each drug has a unique spectrum of metabolic interactions and cognitive effects, it is critical to carefully monitor the cognitive and behavioral baseline of patients and compare it with follow-up measures. Four case studies are described in this article, illustrating some of the potential confusion arising from drug intolerance, misdiagnosis, and complex drug interactions. The importance of laboratory tests and up-to-date knowledge of the properties of antiepileptic drugs is emphasized. Ultimately, the patient's quality of life rests on the ability of the healthcare system to not only prevent seizures or treat psychiatric conditions but to do so while maintaining cognitive function, activities of daily living, and patient dignity. (Adv Stud Pharm. 2007;4(3):72-76)

INTRODUCTION

As the population of nursing home patients rises, an increasing number of patients will be prescribed anticonvulsant drugs. These drugs are not just being used for controlling seizures. More and more, other applications for these drugs are being discovered, specifically for other disorders of mood and cognition. Given the current emphasis toward decreasing unnecessary drug use, care must be taken to ensure that target behaviors and adverse effects are appropriately monitored. The following 4 case studies illustrate some of the potential confusion arising from drug intolerance, misdiagnosis, and complex drug interactions.

CASE STUDY 1

Background

ML is a 78-year-old woman with a history of schizoaffective disorder and neuroleptic malignant syndrome associated with the use of haloperidol and olanzapine.

Medical History

ML was admitted to a long-term care facility (LTCF) 2 years ago after an extended hospitalization for neuroleptic malignant syndrome caused by clozapine. Given the serious adverse effects she experienced with antipsychotic therapies, ML was then treated with the anticonvulsants valproate and clonazepam. Over the past 18 months, she experienced a gradual decline of mental status, in addition to tremor and other gait disturbance problems. Her ability to perform activities of daily living (ADLs) deteriorated, she required increased assistance, and she became wheelchair bound.

Imaging and Laboratory Studies

ML's laboratory tests were normal. Salient measurements include a valproic acid (VPA) trough serum...
concentration of 93 µg/mL, serum ammonia of 46 µg/dL, and albumin at 3.7 g/L. On the mini–mental status exam that was performed, she scored 13 out of a possible 30, which indicates dementia. The Unified Parkinson's Disease Rating Scale was applied to ML, which resulted in a score of 75, indicating Parkinson's disease.

**Treatment Plan**

Antipsychotics had been ruled out and ML had also failed on lithium. A crossover from VPA to lamotrigine (LMT) was performed by first titrating the LMT according to the manufacturer's guidelines to 100 mg per day, the dose recommended for treatment of bipolar-associated dementia. VPA was then tapered at a rate of 500 mg every 7 days. Once the VPA dose had fallen below 500 mg and stopped, the LMT dose was doubled to 200 mg per day, resulting in similar plasma levels as was seen at 100 mg per day in the presence of VPA.

**Treatment Course**

ML tolerated the crossover quite well. Her mini–mental status exam score improved to 19 and her gait problems have also improved.

**Discussion**

ML's case is difficult because she is among a small population of patients who develop neuroleptic malignant syndrome to multiple antipsychotics. When a steady decline in function is seen with the addition of medications such as VPA, laboratory tests may be useful because they sometimes reveal underlying causes. Serum ammonia, for example, is measured to check for a metabolic encephalopathy that is associated with elevated ammonia levels. This is sometimes caused by VPA effects on the citric acid cycle.Albumin is measured to better assess the free plasma concentration of highly protein-bound drugs. If the serum albumin is significantly depressed, the brain may be experiencing higher concentrations of unbound VPA than reflected in the proposed therapeutic concentration range of 50 µg/mL to 125 µg/mL. Given ML's response to the removal of VPA, her dementia and Parkinson's disease were likely caused by VPA. It can be difficult to diagnose VPA-induced dementia and Parkinson's disease because it occurs much like the disorders themselves: slow, insidious, and hard to differentiate.

LMT was chosen as an alternative therapy primarily because of the presence of case reports describing the use of LMT to treat dementia, in addition to its approved use in bipolar disorder. There was some degree of risk associated with the decision to transition to LMT because the incidence of rash with LMT is significantly higher in the presence of VPA. Despite this concern, it was thought that ML would be better served attempting to maintain some degree of psychiatric stability. Additionally, it has been observed that although initial instances of hypersensitivity during crossover were on the order of 40%, the titration was relatively rapid. Slowing down the titration greatly reduces the incidence of this adverse effect.

An interesting complication arising from drug interactions between VPA and LMT is that VPA blocks the metabolism of LMT, effectively increasing the plasma concentration by as much as double. Thus, theoretically, to keep LMT plasma levels constant, as VPA is tapered, the dose of LMT must be increased. However, this effect is maximal at approximately 500 mg of VPA daily. Because ML was at 1500 mg of VPA daily, the increase in LMT dose does not need to be taken into consideration until the VPA dose decreases below 500 mg. For this reason, the dose of LMT remained constant until VPA had decreased to a non-saturating level.

Ultimately, the decision to transition ML to LMT was correct as evidenced by the improvement in her cognitive and motor abilities. This underscores the usefulness of some of the newer antiepileptic drugs (AEDs) in psychiatric conditions.

**CASE STUDY 2**

**Background**

MJ is a 74-year-old man who was brought to the emergency department after his second generalized seizure. Phenytoin (PHT) was administered intravenously at a dose of 18 mg/kg, followed by a maintenance dose of 2 mg/kg twice daily.

**Medical History**

MJ had a cerebrovascular accident resulting in left hemiparesis and has been residing in an LTCF for 6 months. Six weeks after the emergency department visit, MJ complained of fatigue, was taking frequent naps, and was not participating in the LTCF daily activities.
**Imaging and Laboratory Studies**

During the emergency department visit, an electroencephalogram and magnetic resonance imaging were performed but were uninformative. Trough plasma concentration of PHT was examined and found to be 15 μg/mL. Serum albumin was found to be 4.0 g/dL.

**Treatment Plan**

Because the laboratory values were within acceptable norms, it was concluded that MJ was intolerant to PHT. Out of concern for possible changes in mental status, risk to bone health, possibility of gum disease, and the potential for drug-drug interactions, it was decided to convert MJ to LMT. The standard LMT titration rate was used to reach a target dose of 200 mg twice daily. One week after the target dose was reached, the serum concentration of LMT was measured. The dose was then slowly adjusted as recommended until the serum concentration of LMT was greater than 4 μg/mL. At this point, PHT was tapered at a rate of 100 mg every 5 days.

**Treatment Course**

MJ was titrated to 200 mg twice daily without side effects. One week after achieving the target dose, serum concentration of LMT was measured and found to be 3.2 μg/mL. LMT was increased to 250 mg twice daily and PHT was then tapered by 100 mg every 5 days. MJ returned to baseline ADL and remains seizure-free.

**Discussion**

Patients admitted to the emergency department with new-onset seizures are commonly given PHT 1 g intravenously, which is not the correct dose. To achieve a therapeutic concentration of 10 to 20 μg/mL, loading doses should be calculated based on the patient’s weight, with a range of 15 to 20 mg/kg. In the case of MJ, the correct loading dose of 18 mg/kg PHT was given intravenously. The maintenance dose was then adjusted from the standard initial dose of 2.5 mg/kg twice daily to 2.0 mg/kg twice daily, allowing for the changes in metabolism associated with the patient’s age.

Gabapentin and LMT would have been appropriate choices for this patient; however, LMT was decided upon because of its unusual indication that it can be used in monotherapy in patients who are initially taking one of the older drugs. Thus, LMT was added and, subsequently, PHT was tapered. The LMT titration is performed slowly as suggested by the manufacturer’s instructions. This limits rash and other side effects because the patient now has time to adapt. Ultimately, in the presence of an enzyme inducer such as PHT, it may be necessary to ramp up to a dose of 400 to 800 mg daily to reach the appropriate serum concentration. Historically, PHT tapers were done at a rate of 100-mg capsule every 3 to 4 weeks. Currently, a rate of 100 mg every 5 days is common. This may seem like a rapid decrease in PHT; however, it has been shown that LMT plasma levels do not change appreciably until virtually all PHT is removed from the system. Thus, we have found that drug transitions can be much more rapid in these patients than previously appreciated. This avoids extended periods of the inducer drug at subtherapeutic doses while awaiting a rise in plasma concentration of the induced drug. The applicability of this to other drug-drug interactions remains an important question.

**CASE STUDY 3**

**Background**

BB is a 66-year-old male, previously diagnosed with Wernicke-Korsakoff syndrome and chronic daily headaches, who presented with new-onset epilepsy.

**Medical History**

BB has a history of headaches treated with beta blockers and nonsteroidal medications.

**Imaging and Laboratory Studies**

All laboratory values were normal, including computed tomography and magnetic resonance imaging results.

**Treatment Plan**

At the time, BB’s medications included a multivitamin, a calcium supplement (600 mg daily), propranolol (80 mg daily), and ibuprofen (600 mg 3 times daily as needed). Vitamin D3 was added (2000 U daily). Because of the patient’s history of headaches, topiramate was chosen as the appropriate AED because it is approved to treat seizures and migraine. Dosing began at 25 mg daily and was increased weekly to a target of 100 mg twice daily.

**Treatment Course**

At the 3-month follow-up, the patient was...
seizure-free and had a significant reduction in headaches. However, BB had also experienced a decrease in long-term memory and his ADL quotient was also reduced. Following a neurology consult, it was decided not to abandon topiramate but rather to attempt to reduce the dose to 50 mg twice daily. The dose reduction was successful. At 6 months, BB remained seizure-free, his headaches were well controlled, and his ADL and long-term memory returned to baseline.

Discussion

This case demonstrates the value of attempting to establish the minimum effective dose for an AED. The target doses established in clinical trials may be greater than necessary for many older patients. Monitoring seizure frequency can assist in determining an individual's dose; however, this measure can be difficult if the seizures are infrequent or if they are subtle in affect and easily missed. Serum concentration monitoring of AEDs may be overvalued. However, a once-a-year measurement of those AEDs with established therapeutic ranges allows the facility to monitor for changes caused by alterations in serum binding or clearance rates. A second reason for attempting to find a minimum dose comes from recent data suggesting that resistance may be a function of the time and degree of exposure to an AED.16 Minimizing the dose may minimize the possibility of developing resistance.

CASE STUDY 4

Background

VM is a 68-year-old man with a diagnosis of mental retardation, schizophrenia, and partial seizures.

Medical History

VM’s medications include fluphenazine (5 mg 3 times daily), benztropine (2 mg twice daily), docusate (200 mg twice daily), PHT (400 mg daily at bedtime), a multivitamin (once daily), and calcium (600 mg with vitamin D twice daily with meals). Every 2 to 3 months, VM had an episode of fixed upward gaze lasting approximately 2 minutes. The psychiatrist’s diagnosis was oculogyric crisis associated with fluphenazine. Diphenhydramine (50 mg intramuscular) was administered during oculogyric episodes. VM would then nap for several hours, after which he would return to baseline.

Imaging and Laboratory Studies

A neurology consult and electroencephalogram showed that VM exhibited multifocal epileptiform discharges consistent with a mixed seizure disorder not completely treated by the PHT. It was recommended that VPA be added to VM’s regimen.

Treatment Plan

VPA was titrated to a target serum concentration of 75 µg/mL. VPA has a significant interaction with PHT, which induces the expression of metabolic enzymes, requiring a greater dose of VPA. Meanwhile, VPA preferentially displaces PHT from its plasma protein binding sites. To account for these interactions, unbound PHT was measured with a target therapeutic range of 1 to 2 µg/mL and the PHT dosage adjusted accordingly.

Treatment Course

VM remained seizure-free for 2 years under this regimen. Then, a trial of monotherapy was attempted to see if PHT was no longer needed. PHT was tapered as described above; however, VM began to experience seizures again. PHT therapy was resumed and VM has remained seizure-free for 6 years.

Discussion

Oculogyric crisis is an acute dystonic reaction most often seen soon after initiation of an antipsychotic drug or an increase in the maintenance dose of that drug.18 The typical antipsychotics, such as fluphenazine, are most commonly associated with this side effect. However, numerous other drugs, in addition to stress and fatigue, have been known to precipitate oculogyric crises in susceptible individuals. The diagnosis implicating fluphenazine was most likely incorrect because VM was experiencing complex partial seizures. This is supported by the addition of VPA, eliminating these events with no change in fluphenazine dosage.

CONCLUSIONS

Evaluating medication histories in a LTCF environment has been likened to detective work. Often, there is little or no medical history available to assess the patient who may also be unable to assist. Disease symptomology can be subtle or misleading and may represent adverse drug reactions. Pursuit of laboratory tests and accurate histories derived in
part from family and friends can be invaluable diagnostic tools.

The goals of AED therapy are no seizures and no side effects. Rendering the patient seizure-free at the expense of cognitive function or motor function can result in a diminution in quality of life rather than an improvement. Given the number of available treatment options at this time, it is well worth the effort to attempt rational therapy adjustments based on the most recent data.

REFERENCES