Case Studies in Optimizing Antiepileptic Treatment

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Abstract

- *Objective:* To review 3 cases drawn from the clinic that highlight difficulties in epilepsy management and illustrate an approach to treatment and its rationale.
- *Methods:* Case presentations and literature review.
- *Results:* Epilepsy is a chronic disease, and as such presents challenges to patients and physicians in a variety of settings. Patients with epilepsy face the same health risks as the general population, such as heart disease, stroke, and infection. However, treatment for these conditions must be tailored to minimize impact on seizure control as well as interactions with antiseizure medications. In addition to these risks, patients with epilepsy are at high risk of depression and other psychiatric comorbidities, which should be recognized and treated as part of a comprehensive management plan. In addition, patients with epilepsy will face the same life events as nonepileptic patients, such as pregnancy and childbirth, but with optimal management will have relatively few adverse outcomes. The challenge to physicians is to determine optimal management, which sometimes means changing, minimizing, or discontinuing antiepileptic therapy.
- *Conclusion:* Treatment decisions must take into account individual patient characteristics, patient and physician preferences, cost and tolerability of available therapies, and must be balanced between the risk of seizures and the risks of therapy.

The treatment of epilepsy can be regarded as both a science and an art. With myriad drug choices as well as alternative therapies, treatment decisions must take into account individual patient characteristics, patient and physician preferences, and cost and tolerability of available therapies. Treatment decisions must be balanced between the risk of seizures and the risks of therapy. Current data on antiepileptic drugs (AEDs) and guidelines for the use of AED therapy were reviewed in our article in the October 2009 issue of *JCOM* to provide a framework for tailoring antiepileptic therapy to the individual patient [1]. Issues that commonly arise include questions on initiation of treatment, AED choice, drug monitoring, side-effect management, drug-drug interactions, and special considerations such as pregnancy. In this article, we review 3 cases drawn from the clinic that serve to highlight difficulties in epilepsy management and to illustrate an approach to treatment and its rationale. It must be appreciated that the ideal treatment choice may not exist and that treatment decisions often must be made with limited data.

CASE 1

Mr. M is a 62-year-old man with past medical history of hypertension and hyperlipidemia. Four weeks prior to initial presentation, he underwent routine dental cleaning. Two days following this procedure, he developed persistent low-grade fevers but otherwise felt well. Three days later, Mr. M developed acute right hemiparesis and aphasia and was admitted to the hospital for acute stroke. Brain imaging showed multiple hemorrhagic infarcts predominantly in the left middle cerebral artery territory. Further workup revealed *Streptococcus viridians* bacteremia and vegetation on the mitral valve. He was started on appropriate antibiotics. His hospital course was significant for fluctuating language deficits ranging from following simple commands to complete receptive aphasia. Electroencephalogram (EEG) showed left greater than right-sided slowing but no epileptiform activity. He was started on levetiracetam 500 mg twice per day for concern of possible partial seizures. He was discharged to rehabilitation on antibiotics and levetiracetam.

Discussion

Mr. M suffered multiple embolic strokes from endocarditis, and these included cortical regions with hemorrhagic

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conversion. Any of these infarcts or bleeds, particularly more cortically located lesions, could be an epileptogenic focus. Although there was no definite clinical or electrographic evidence of seizure, the risk and consequences of possible seizure were felt to outweigh those of AED therapy in the short term. In this case, levetiracetam was chosen as initial antiepileptic therapy given its availability in oral and intravenous (IV) forms, rapid titration schedule allowing starting doses to be therapeutic, relatively benign side-effect profile, and lack of significant interactions with other medications. Levetiracetam is gaining popularity in monotherapy, although it is not approved by the U.S. Food and Drug Administration or backed by the American Academy of Neurology (AAN) for monotherapy in either partial or generalized seizures. Currently, there is 1 randomized controlled trial showing similar seizure-free rates at 6 months and 1 year compared with carbamazepine (1 of the agents accepted as typical first-line therapy for patients with partial seizures) with a nonsignificant difference in treatment failure due to side effects [2].

Case 1 Continued

Two days later, Mr. M suffered a witnessed generalized tonic-clonic seizure lasting 2 minutes and aborting without treatment. He was transferred back to the neurology ward where he recovered to his baseline over the course of several hours. A repeat head computed tomography scan revealed no new findings and a levetiracetam level was drawn, which later returned at 30 μg/mL. His levetiracetam dose was increased to 1000 mg twice per day. Two days later, he had another witnessed tonic-clonic seizure lasting 1 minute followed by a second seizure prior to regaining consciousness. He was given lorazepam 2 mg IV and loaded with fosphenytoin 20 PE/kg IV. Subsequently, he was maintained on phenytoin at a goal level of 10 to 15 μg/mL. Over the next few days, Mr. M's clinical condition improved to the point that he could say his name and respond with yes or no to simple questions. He was again discharged to rehabilitation, and 2 weeks later levetiracetam was tapered off.

Discussion

Although levetiracetam is regarded as a broad-spectrum AED (approved as adjunctive therapy in partial and generalized myoclonic epilepsy) and is used in a variety of settings, as noted above, there are insufficient data to support its use in monotherapy. In this case, a levetiracetam level was drawn due to the increased seizure frequency despite therapeutic dosing. Although serum levels have not been correlated with seizure prophylaxis (as they have with older AEDs such as phenytoin), the International League Against Epilepsy guidelines on therapeutic drug monitoring suggest that it is appropriate to monitor drug levels in the setting of persistent seizures despite therapeutic dosing [3]. This may be useful to predict toxicity with increases in dosage. However, serum levels of levetiracetam are best used in patients who have been clinically stable on the drug for a period of time and in whom a therapeutic level has been established. In contrast, phenytoin levels should be monitored following dosage changes, since they follow nonlinear kinetics and it can be difficult to predict the serum level for a given dosage change. Phenytoin is also indicated for monotherapy and serum levels are correlated with seizure protection. Finally, treatment with a single AED (monotherapy) is the preferred treatment regimen when possible, and therefore levetiracetam was discontinued once seizures were controlled.

Case 1 Continued

Mr. M continued to improve clinically, and 2 months later he was able to walk with a cane, follow complex commands, and communicate basic concepts to family and friends. He underwent mitral valve replacement requiring initiation of warfarin treatment. His primary care physician monitored and maintained the international normalized ratio (INR) and phenytoin levels in therapeutic range (2.5–3.5 and 10–20 μg/mL, respectively). However, 6 months after discharge from rehabilitation Mr. M developed symptoms of an upper respiratory infection, during which time he experienced two 30- to 60-second episodes of witnessed unresponsiveness. Following these episodes, there was a several-hour period of decline in his ability to communicate with his family. The phenytoin level was 11 μg/mL at that time. The patient's serum phenytoin goal was increased to 15 to 20 μg/mL, without further events. Lifelong AED therapy was recommended to the patient, and lamotrigine was offered for chronic therapy instead of phenytoin. However, the patient preferred to continue phenytoin, with reluctance to make any changes. He received calcium and vitamin D supplementation and plans were made for regular bone density tests and dental care.

Discussion

For Mr. M, lifelong AED therapy was recommended based on his history of having 4 or more seizures, an abnormal EEG (regardless of whether epileptiform features were found), and neurological deficits. Based on the MESS trial data [4], Mr. M is in the highest risk stratification group for future seizures. In his case, treatment significantly increases the likelihood of reaching a 2-year seizure-free remission. Mr. M was comfortable with lifelong therapy, but the prescriber must be aware of the short- and long-term complications of therapy. Phenytoin is an effective AED but has several therapeutically limiting side effects. These side effects are more likely to be seen at higher serum levels, such

as those required for adequate seizure prophylaxis in Mr. M. Long-term side effects of chronic use include osteoporosis, cerebellar atrophy with resulting ataxia, gingival hyperplasia, coarsening of facial features, and peripheral neuropathy. Since Mr. M's gait is already impaired, further ataxia might be crippling. Furthermore, phenytoin increases the risk of osteoporosis, making ataxia an increasingly risky iatrogenic complication. For these reasons, Mr. M was advised to take calcium and vitamin D supplementation and continue regular dental care, and his primary physician was advised to monitor bone density.

Mr. M was also offered an alternate therapy with a newer AED, but he preferred not to switch medications. In this case, he was offered lamotrigine, although other agents including carbamazepine or oxcarbazepine could also be considered. All AEDs have side effects, and these should help guide therapy. Common and serious side effects of common AEDs are listed in **Table 1** [1]. Data suggest that carbamazepine, oxcarbazepine, or lamotrigine are optimal first-line agents in the treatment of partial epilepsy in terms of seizure control and tolerability [5,6], although phenytoin is also effective [7]. Ultimately, Mr. M's decision to remain on phenytoin was an informed one, and this is an important factor in AED choice. Nevertheless, revisiting this issue over the course of his care would be reasonable.

As a final note, the prescriber must be aware of possible drug-drug interactions. In this case, it is notable that phenytoin induces multiple hepatic enzymes and is highly protein bound. Therefore, it could decrease the levels of hepatically metabolized enzymes or could cause an abrupt rise in the free level of other protein-bound enzymes. However, in this case the patient's primary care physician had been closely monitoring the patients INR while changing phenytoin doses, as the warfarin concentration may be reduced due to the increased hepatic clearance induced by phenytoin. Conversely, other drugs may influence phenytoin levels; for example, certain fluoroquinolones (eg, ciprofloxacin) may decrease phenytoin levels, while chloramphenicol inhibits hepatic enzymes responsible for phenytoin metabolism and leads to increased levels. This may be of particular concern with concomitant use of fluoroquinolones, since these medications may reduce seizure threshold independently of their effects on AED levels, and the combined effect could lead to increased seizure likelihood. The principles of drug-drug interactions are not limited to phenytoin, as outlined in **Table 2** [1].

CASE 2

Mr. C is a 52-year-old man from Brazil with a history of bipolar disease and poorly controlled seizures. His first seizure occurred at age 33 years, after he had been drinking heavily and stayed up late one night. Although he has no recollection of the event, witnesses described generalized convulsions. During the course of his workup, he was found to have 2 calcified lesions, 1 in the left frontal lobe and 1 in the right insula, which were consistent with neurocysticercosis. He was started on carbamazepine but was lost to follow-up shortly thereafter.

Discussion

Neurocysticercosis is the leading cause of epilepsy in developing countries. In the natural lifecycle of this tapeworm (*Taenia solium*), humans ingest pork infected with larval cysts. Normally, tapeworm eggs found in fecal matter would be ingested by swine and the hatched larvae disseminate into muscle tissue, which would be consumed by humans who would then excrete more eggs to complete the tapeworm lifecycle. However, human ingestion of the *T. solium* eggs through sources contaminated with fecal matter leads to larval dissemination just as it would in swine. These larvae can migrate to any organ, but the most common locations include connective tissue, the eyes, and the brain. Dissemination is typically asymptomatic, but degenerating or calcified cysts in the brain may serve as a nidus for seizures. Cysts can be treated medically with antihelminthic medications (eg, albendazole or praziquantel). In terms of seizure control, the only double-blind randomized trial comparing antihelminthic treatment with symptomatic treatment alone demonstrated no statistically significant difference in outcome for partial onset epilepsies [8] but a significant reduction in generalized epilepsies. Antihelminthic treatment is not indicated for calcified granulomatous remnants seen in this patient.

Case 2 Continued

The patient was reconnected with the medical system during a psychiatric hospitalization for paranoid delusions and alcohol detoxification. He reported continued frequent (at least weekly) convulsive events over 19 years in the setting of alcohol abuse and poor medication compliance. An interictal EEG performed during the hospitalization demonstrated continuous left frontal slowing without epileptiform discharges. The patient was counseled about medication compliance and restarted on carbamazepine, initially 200 mg twice daily, eventually uptitrated to 400 mg in the morning and 600 mg in the evening. He reported good compliance since discharge and routine drug levels remained in the therapeutic range between 10 and 12 µg/mL. In follow-up, the patient reported some mild vertigo associated with uptitration of the medication but was able to tolerate the side effect. The patient reported going more than 1 month without known convulsive episodes, but he did report occasionally awakening with confusion, odd behavior, and paranoid delusions of thieves pursuing him. Overall, the patient had poor memory of these events. On

Table 1. Common and Serious Side Effects of Antiepileptic Drugs and Contraindications to Use

Generic Name	Common Side Effects	Serious Side Effects
Carbamazepine	Hyper/hypotension, N/V, dizziness, nystagmus, diplopia, somnolence	AV block, CHF, syncope, SJS/TEN, hypocalcemia, hyponatremia, acute intermittent porphyria, aplastic anemia, hepatitis, acute renal failure, angioedema
Clonazepam	Excessive salivation, dizziness, ataxia, somnolence, seizures, abnormal behavior, respiratory depression	
Ethosuximide	Decreased appetite, abdominal symptoms, ataxia, dizziness, headache, somnolence, hiccoughs	Aplastic anemia, SJS, SLE, seizures
Felbamate (requires patient registration to prescribe)	Decreased appetite and weight loss, abdominal symptoms, purpura, photosensitivity, dizziness, headache, insomnia	Aplastic anemia and hepatic failure (both may be fatal), SJS, seizures
Gabapentin	Peripheral edema, myalgias, dizziness, nystagmus, somnolence, abnormal thoughts/behavior. Rarely, myoclonus	SJS, coma, seizures
Lacosamide	Diplopia, dizziness, headache	Syncope, suicidal behavior, hypersensitivity reactions
Lamotrigine	Ataxia, dizziness, asthenia, abdominal symptoms, tremor, diplopia, dysmenorrhea, rash	Rare life-threatening SJS (higher risk with fast titration, age < 16, or use with VPA), hepatic failure, renal failure, DIC
Levetiracetam	Decreased appetite, vomiting, asthenia, dizziness, headache, somnolence, abnormal behavior, irritability, cough	Pancytopenia, liver failure, suicidal behavior
Oxcarbazepine	Abdominal symptoms, ataxia, dizziness, nystagmus, vertigo, diplopia, URI	Hyponatremia (> elderly or on diuretics), SJS/TEN, angioedema
Phenobarbital	Somnolence, dizziness, irritability, headache, constipation, N/V. In children, hyperactivity.	Thrombophlebitis, scaling eczema, SJS, agranulocytosis, megaloblastic anemia, thrombocytopenia, liver failure, osteopenia, rickets
Phenytoin	Lethargy, abnormal movements, confusion, headache, nystagmus, ataxia, dysarthria, encephalopathy, N/V, constipation, pruritus, rash Chronic use: gingival hyperplasia, "dilantin facies," osteoporosis, hirsutism, cerebellar atrophy, peripheral neuropathy	Hepatic failure, aplastic anemia, lupus erythematosus, SJS/TEN, scaling eczema, purpuric rash, bullous dermatosis
Pregabalin	Peripheral edema, increased appetite and weight gain, constipation, xerostomia, ataxia, dizziness, somnolence, blurred vision, diplopia, euphoria	Angioedema
Primidone	N/V, ataxia, dizziness, somnolence	Thrombocytopenia, megaloblastic anemia
Rufinamide	Shortened QT interval, nausea/vomiting, dizziness, headache, lethargy	Suicidal behavior
Tiagabine	Pruritus, incresed appetite, abdominal symptoms, confusion, ataxia, dizziness, paresthesias, pharyngitis	Seizures, status epilepticus, sudden death
Topiramate	Decreased appetite and weight loss, abdominal symptoms, confusion, decreased psychomotor performance, cognitive impairment, diplopia, nystagmus, fatigue	Renal stones, metabolic acidosis, open angle glaucoma, liver failure, SJS/TEN, hyperammonnemia, hypohydrosis, hyperthermia, suicidal behavior
Valproic acid	Increased appetite and weight gain, alopecia, peripheral edema, rash, abdominal symptoms, asthenia, dizziness, ataxia, diplopia, nystagmus, respiratory symptoms, somnolence, tremor	Hyperammonemia, pancreatitis, liver failure, palpitations, thrombocytopenia (dose-related), ototoxicity
Zonisamide	Abdominal symptoms, ataxia, confusion and memory impairment, dizziness, nystagmus, diplopia, fatigue, decreased appetite and weight loss, renal stones	Aplastic anemia, SJS/TEN, schizophreniform disorder

AV = atrioventricular; CHF = congestive heart failure; DIC = disseminated intravascular coagulation; MAOI = monoamine oxidase inhibitor; N/V = nausea and vomiting; SJS = Stevens-Johnson syndrome; SLE = systemic lupus erythematosus; TCA = tricyclic antidepressant; TEN = toxic epidermal necrosis; URI = upper respiratory infection; VPA = valproic acid. (Reprinted from reference 1.)

Contraindications
Bone marrow suppression, use of MAOI within 14 d, use of nefazodone, TCA hypersensitivity, +HLA-B*1502 allelic variant
Acute narrow angle glaucoma, significant liver impairment
History of blood dyscrasia or liver disease
Relative: severe hepatic impairment, AV block, severe cardiac disease
Porphyria, significant liver impairment, respiratory disease (dyspnea or obstruction)
Porphyria, barbituate hypersensitivity
Familial short QT syndrome
Urea cycle disorders, significant liver impairment
Sulfonamide hypersensitivity

one occasion, he awoke with a sore shoulder and a chipped tooth. Because of concern for further seizures, lamotrigine was started. Serum levels of both carbamazepine and lamotrigine were closely monitored and therapeutic levels were achieved for both. The patient remained seizure-free without further awakenings associated with confusion or injuries and no further paranoid delusions over 3 months. A decision was made to slowly taper carbmazepine to off and to continue lamotrigine monotherapy.

Discussion

Carbamazapine is a good choice for partial-onset epilepsies as suspected in this patient with known calcified cysts. There is extensive experience with carbamazepine in neurocysticercosis due to its worldwide availability and relatively low cost. Based on the results of the SANAD trial, carbamazepine is an effective agent for partial-onset seizures, although lamotrigine is better tolerated [5]. Based on cost and the patient's history of poor compliance, carbamazepine was felt to be the best initial choice. Unfortunately, seizure control remained suboptimal at the maximum dose of carbamazepine this patient was able to tolerate. The confusion on awakening and his report of injury without explanation suggested continued ictal events. Although rare, the odd behavior and paranoid delusions could also represent postictal psychosis following frontal lobe seizures given his known frontal lesion; however, the patient also has known bipolar disorder, which would be another explanation. Therefore, the decision was made to start lamotrigine therapy because it is a good AED in partial-onset seizures and is approved for mood stabilization in bipolar I disorder. Carbamazepine is a broad-spectrum inducer of hepatic enzymes, and therefore will induce metabolism of lamotrigine. Lamotrigine was initiated at dosing suggested for combination with an enzyme-inducing drug.

Because seizure control was achieved after adding lamotrigine, carbamazepine was slowly tapered to off, again requiring close monitoring of lamotrigine levels to avoid toxicity. Ideally, drug monotherapy is the preferred strategy for seizure control. If a patient fails a first drug, a second and possibly third agent should be tried in monotherapy before using adjunctive agents. Monotherapy is successful in approximately 70% of patients with epilepsy [9,10].

CASE 3

Ms. A is a 34-year-old woman who experienced her first seizure at age 26 years. At that time she had no known past medical history and was only taking oral contraceptives. She had been awake for a prolonged period of time after consuming a large quantity of alcohol when, without aura or warning, she suffered a prolonged convulsion of all extremities requiring emergency intubation and

Table 2. Antiepileptic Drug (AED) Metabolism and Effects on Hepatic Enzymes

Generic Name	Serum Protein Binding, %	Metabolism	Excretion	Effect on CYP Isoenzymes
Carbamazepine (CBZ)	75	Hepatic, autoinduces own metabolism; CYP3A4, metabolite by epoxide hydrolases	> 70% renal; dialyzable	Broad-spectrum inducer including CYP1A2, CYP2C9, CYP2C19, CYP3A4, UGT, epoxide hydrolases
Clonazepam (CZP)	85	Hepatic; CYP3A4	Renal	None
Ethosuximide (ESM)	0	Hepatic; CYP3A4	Renal	None
Felbamate (FBM)	25	50% hepatic (other unchanged); inducible CYP isoforms	90% renal	Induces CYP3A4 (weak/tissue-specific) Inhibits CYP2C19
Gabapentin (GBP)	0	None	Renal	None
Lacosamide (LCM)	< 15	60% hepatic (other unchanged); CYP2C19	Renal; dialyzable (~50% removed)	None
Lamotrigine (LTG)	55	Hepatic; glucuronyl transferase (UGT1A4 > 1A3)	95% renal	Induces UGT (weak)
Levetiracetam (LEV)	0	25% hepatic (other unchanged); enzyme hydrolysis	Renal; dialyzable (~50% removed)	None
Oxcarbazepine (OXC)	40	> 50% hepatic (other unchanged); glucuronyl transferase	> 95% renal	Induces CYP3A4 (weak/tissue-specific) Inhibits CYP2C19 (weak)
Phenobarbital (PB)	55	Hepatic; CYP2C9, CYP2C19	Renal; dialyzable	Broad-spectrum inducer including CYP1A2, CYP2C9, CYP2C19, CYP3A4, UGT, epoxide hydrolases
Phenytoin (PHT)	90	Hepatic; CYP2C9, CYP2C19	Renal	Broad-spectrum inducer including CYP1A2, CYP2C9, CYP2C19, CYP3A4, UGT, epoxide hydrolases
Pregabalin (PGB)	0	< 10% hepatic (other unchanged)	Renal; dialyzable (~ 50% removed)	None
Primidone (PM)	10	Hepatic, metabolized to PB and PEMA by CYP450	Renal	Broad-spectrum inducer including CYP1A2, CYP2C9, CYP2C19, CYP3A4, UGT, epoxide hydrolases
Rufinamide (RFM)	34	Hepatic; carboxylesterase hydrolysis	Renal; dialyzable (~ 30% removed)	Induces CYP3A4 (weak) Inhibits CYP 2E1 (weak)
Tiagabine (TGB)	96	Hepatic; CYP3A4	Fecal > renal	None
Topiramate (TPM)	15	30% hepatic (other unchanged); inducible CYP isoforms	Renal; dialyzable	Induces CYP3A4 (weak/tissue-specific) Inhibits CYP2C19 (weak)
Valproic acid (VPA)	90	Hepatic; mitochondrial oxidase, glucuronyl transferase, minor CYP450	> 70% renal; dialyzable (~ 20% removed)	Inhibits CYP2C9, UGT, epoxide hydrolases
Zonisamide (ZNS)	50	> 50% hepatic (other unchanged); CYP 3A4, N-acetyl transferase	> 95% renal	None

Reprinted from reference 1.

Common Drugs That Affect This AED	Common Drugs That Are Affected by This AED
↑ CBZ: diltiazem, verapamil, clarithromycin, erythromycin, fluoxetine, INH, omprazole ↓ CBZ: FBM, PB, PHT, RFM, CBZ (autoinduction)	↓: FBM, LTG, TGB, TPM, ZNS, OCPs, antipsychotics, CCBs, cyclosporine, protease inhibitors, theophylline, warfarin
↑ CZP: cimetidine, erythromycin, omeprazole ↓ CZP: CBZ, PB, PHT, rifampin	Generally does not affect other drugs
↑ ESM: possibly VPA, INH ↓ ESM: CBZ, PB, PHT	Generally does not affect other drugs
↑ FBM: VPA ↓ FBM: CBZ, PB, PHT	↑: CBZ epoxide, PB, PHT, VPA ↓: CBZ, OCP
↓ GBP 20%: antacids	None
None	None
↑ LTG: sertraline, VPA ↓ LTG: CBZ, OXC, PB, PHT, PRM, OCPs, rifampin	↓: VPA 25%
None	None
↓ Active metabolite: CBZ, PB, PHT	↑: PHT ↓: OCPs (at high doses)
↑ PB: FBM, VPA ↑ or ↓ PB: PHT	↓: CBZ, FBM, LTG, PHT, RFM, TGB, TPM, VPA, ZNS, antipsychotics, CCBs, OCPs, protease inhibitors, steroids, theophylline, tricyclics, warfarin
↑ PHT: FBM, OXC, PB, TPM, VPA, amiodarone, cimetidine, diltiazem, fluconazole, fluoxetine, isoniazid, omeprazole, ritonavir ↓ PHT: CBZ, PB, antacids, ciprofloxacin, sucralfate	↓: CBZ, FBM, LTG, RFM, TGM, TPM, VPA, ZNS, anitpsychotics, CCBs, cyclosporine, narcotics, OCPs, statins, steroids, theophylline, tricyclics, ↑ or ↓ warfarin
None	None
Similar to PB	Similar to PB
↓ RFM: CBZ, PB, PHT	↑: PB, PHT, PRM, VPA ↓: CBZ, LTG, OCPs
↓ TGB: CBZ, PHT, PB	None
↓ TPM: CBZ, PHT, PB	↑: Metformin, PHT 25% ↓: OCPs (at high doses)
↑ VPA: FBM, ASA, fluoxetine, isoniazid ↓ VPA: CBZ, LTG, PB, PHT, ritonavir	↑: CBZ epoxide, FBM, LTG, PB, free PHT, CCBs, tricyclics, warfarin, zidovudine
↓ ZNS: CBZ, PB, PHT	None

sedation. The patient had no memory of the event. Workup revealed normal neurologic examination, but brain magnetic resonance imaging (MRI) was abnormal with a T2 hyperintensity in the left temporal lobe, suspicious for a focus of cortical dysplasia. An EEG obtained several days after the initial event was normal. She was treated with phenytoin without further known seizures. Two years later, she was switched to carbamazepine due to gingival hyperplasia.

Discussion

Based on the patient's initial presentation, starting AED therapy was felt to be most prudent because of the severity of her initial seizure (requiring intubation and sedation) and the abnormality on brain MRI, possibly suggesting a source for seizures. Although the MESS trial data [4] might classify the patient as low risk for epilepsy, clinical judgment must always be applied first. In this case, both the patient and clinician agreed that the benefits of AED therapy outweighed the risks. However, the use of phenytoin comes with increased risks in the young patient. Long-term phenytoin use may lead to significant cosmetic changes such as coarsening of facial features, hirsutism, and gingival hyperplasia. Furthermore, chronic use may lead to irreversible cerebellar atrophy. Finally, AEDs that induce hepatic enzymes can decrease the efficacy of oral contraceptives. This includes both phenytoin and carbamazepine as well as primidone, phenobarbital, felbamate, oxcarbazepine, and higher doses of topiramate. Therefore, women taking these medications should be encouraged to use additional methods of birth control.

Case 3 Continued

Ms. A did well on carbamazepine, but at age 30 years became pregnant for the first time. This was an unplanned but desired pregnancy. She was started on prenatal vitamins including high-dose folic acid 4 mg/day and continued on carbamazepine at 300 mg twice per day. Fetal ultrasound demonstrated normal fetal development.

Discussion

Epilepsy in young women poses unique challenges, particularly in regard to contraception and pregnancy. Convulsive maternal seizures pose significant traumatic risk to the fetus, including the potential for intracranial hemorrhage [11]. However, AEDs also have demonstrated risk of teratogenicity. In the general population, there is an approximate 2% risk of major birth defects (including cardiac, orofacial, urogenital, or skeletal defects). In contrast, the risk for pregnant women with epilepsy taking a single AED has been estimated to be 4.5%, and for multiple AEDs

to be 8.6% [12]. Ultimately, the risks and benefits of such therapy must be discussed with patients, who are often unaware of the potential risks to the fetus [13]. Based on data from several pregnancy registries tracking use [14] of the older antiepileptic agents (phenytoin, carbamazepine, valproic acid, and phenobarbital), carbamazepine has the lowest teratogenic potential [15–17]. Based on the North American registry, patients taking carbamazepine had a 2.5% incidence of major birth defects (relative risk of 1.6) [15]. These results are comparable to other registries: 2.2% in the United Kingdom registry and 3% in the Australian registry [18,19]. In contrast, valproic acid had the highest risk of major birth defects—10.7% in the North American Pregnancy Registry but ranging from 6.2%–13.3% in other registries [20]. Newer AEDs (developed since 1993) may have reduced teratogenic risk, but data is lacking. In the North American, United Kingdom, and Australian registries, data for lamotrigine is comparable to carbamazepine [14]. The AAN guidelines for treatment of pregnant women with epilepsy recommend optimizing treatment to the lowest effective dose of a single AED. Furthermore, the guidelines recommend considering preconception folic acid supplementation, although they note that there is a lack of evidence regarding benefit or appropriate dosing [21]. It is frequent practice to recommend 1 mg daily for all women of childbearing potential and to recommend dosages of 3 to 5 mg per day starting preconception and continued throughout pregnancy, since neural tube defects may occur prior to recognition of pregnancy. Some physicians also advocate providing prenatal vitamin K supplementation for mothers taking enzyme-inducing AEDs. However, there is no specific AAN guideline on this due to insufficient evidence [21].

Case 3 Continued

At 25 weeks into her pregnancy, the patient developed occasional feelings of "disconnectedness," inability to concentrate, and sensations of hearing conversations "everywhere." The episodes lasted 1 to 2 minutes followed by minutes to hours of confusion and headache. The patient was noted to have a blood pressure of 105/90 mm Hg. Urinalysis, serum chemistries, and liver function tests were unremarkable. Serum carbamazepine level was 4.8 mg/L, compared with 6 to 9 μg/mL prior to her pregnancy. An MRI demonstrated no new abnormalities. Magnetic resonance venography demonstrated no venous sinus thrombus. A lumbar puncture was unremarkable. The patient's carbamazepine dose was increased to 500 mg twice per day.

Three days later, the patient experienced an episode of aphasia and right facial twitching. Repeat laboratory studies, including another lumbar puncture, were unremarkable. A serum carbamazepine level was 7.1 mg/L. Continuous EEG monitoring captured numerous seizures originating from the left temporoparietal cortex. Seizures were electrographically terminated with lorazepam 1 mg IV. Carbamazepine was increased to 500 mg 3 times per day, and levetiractetam 750 mg twice per day was added. The patient returned to baseline over the course of the next 2 days and experienced no further spells during her pregnancy. She delivered a healthy baby girl at 39 weeks' gestation.

Discussion

In patients with epilepsy, a change in seizure pattern warrants further clinical investigation. In this patient, eclampsia, infection, and venous sinus thrombosis were considered. However, the ultimate etiology of her seizures was most likely related to pregnancy-induced changes in pharmacokinetics, which are complex and difficult to predict. Pregnancy induces certain hepatic enzymes including CYP3A4, a major contributor to carbamazepine metabolism [20] but inhibits others. Furthermore, other factors contributing to pharmacokinetics are affected: plasma volume increases, serum albumin concentration decreases, renal blood flow increases, and total body weight and fat content increase. Taken together, these changes can result in variable drug effects, which can change depending on trimester.

In addition to increasing the patient's carbamazepine dosing, levetiracetam was added as adjunctive therapy. Levetiracetam is a broad-spectrum AED that is not hepatically metabolized and has no interaction with carbamazepine. However, there are limited data for levetiracetam in pregnancy, and it is classified as category C (causes harm to animal fetuses, but not studied in humans). In this case, however, given the relatively late gestational age, the theoretical risk to the fetus was felt to be outweighed by the benefit of aborting seizures in the patient, indirectly imparting a benefit to the fetus as well.

Case 3 Continued

Three months after delivery, levetiracetam was gradually tapered to off, and the patient continued on carbamazepine monotherapy. Three years later, the patient continued to be seizure-free on carbamazepine. She returned to neurology clinic for consideration of possible AED discontinuation. A repeat EEG was normal and brain MRI demonstrated stability of the left temporal abnormality.

Discussion

The decision to discontinue AED therapy is often a difficult one for patients and physicians. Some patients argue for lifelong AEDs due to fear of recurrent seizures. Conversely, some patients prefer to taper medications as soon as possible, often related to side effects, cost, or complexity. Such

decisions must be made carefully and with knowledge of potential risks of both continuing and discontinuing therapy. An AAN practice parameter put forth in 1996 outlines 4 criteria for AED discontinuation: (1) seizure freedom for 2 to 5 years, (2) single seizure type (either partial or generalized), (3) normal neurological examination and IQ, and (4) normalized EEG with therapy [22]. These recommendations were based on meta-analysis of 17 studies, although only 1 of these was a randomized clinical trial [23]. However, data supporting EEG normalization in adults was mixed in these studies, and the value of EEG normalization remains controversial [24]. Nevertheless, an abnormal EEG at the time of discontinuation may have a negative impact on the likelihood of successful withdrawal [23]. Based on analysis of the pooled data, approximately 61% of adults withdrawn from AED therapy remained seizure-free, while 39% had seizure recurrence. This risk of recurrent seizure is highest immediately following medication withdrawal [25]. It is worth noting that even in patients continuing AED therapy following seizure freedom for several years, about one third have subsequent seizures [23]. However, the longer a patient remains seizure-free on AED therapy, the greater the likelihood they will remain seizure-free without medication. Since the risk of death or intractable epilepsy as a result of medication withdrawal is very low [25], adults who meet the AAN practice parameter criteria listed above and would be able to tolerate the risks of recurrent seizures in the short term (including a potential temporary driving suspension) should be offered the option of withdrawing therapy.

CONCLUSION

Epilepsy is a chronic disease, and as such presents challenges to patients and physicians in a variety of settings. Patients with epilepsy face the same health risks as the general population, such as heart disease, stroke, and infection. However, treatment for these conditions must be tailored to minimize impact on seizure control as well as interactions with antiseizure medications. In addition to these risks, patients with epilepsy are at particularly high risk of depression and other psychiatric comorbidities, which should be recognized and treated as part of a comprehensive management plan. Finally, patients with epilepsy will face the same life events as nonepileptic patients, such as pregnancy and childbirth, but with optimal management will have relatively few adverse outcomes. The challenge to physicians is to determine optimal management, which sometimes means changing, minimizing, or discontinuing AED therapy.

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Financial disclosures: None.

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