Monitoring and Antiepileptic Drug Safety

L. James Willmore, MD, FAAN, FANA

ABSTRACT

Treatment of patients with epilepsy strives for complete seizure control without intolerable drug side effects. Independent of blood drug levels, toxic effects allow titration to efficacy; however, allergic reactions, metabolically or genetically determined drug-induced illnesses, and idiosyncratic effects of drugs, while rare, may be life-threatening.

Monitoring is an attempt to detect serious systemic toxic reactions of antiepileptic drugs in time to intervene and protect patients. The process begins with the disclosure to patients and family members of all information required for an informed decision delivered within the framework of risks and benefits. This review provides guidance regarding designing a monitoring strategy for patients requiring chronic treatment with antiepileptic drugs.

Continuum (Minneap Minn) 2013;19(3):801–805.

Case

A 20-year-old man was transferred from pediatric to adult neurologic care when he was 18 years old. He had a seizure disorder that began when he was 5 years old. He would stare, have myoclonic movements on the left side of his mouth, stiffen, and become still, followed by several minutes of confusion. Over time he developed generalized tonic-clonic seizures. His EEG as a child was reported to show 3-Hz generalized spike-and-wave discharges. He had good seizure control with valproate, which was discontinued when he was 16 years old. He remained seizure free for 2 years but then had recurrent complex partial seizures occurring 2 to 3 times each week, with occasional tonic-clonic seizures. Valproate was reinitiated, and seizures abated. In preparation for reinstitution of the medication, he had screening hematologic and hepatic studies, which were normal. The patient and his mother were advised about symptoms and signs of toxicity and the adverse effects of valproate. He remained under good control for 2 years but then developed vomiting after eating fatty foods. Screening blood studies showed mild elevation of hepatic transaminases. His gastroenterologist performed a liver biopsy, which showed microvesicular steatosis. After starting lamotrigine, which was increased to a therapeutic dose, valproate was tapered.

Address correspondence to Dr L. James Willmore, Saint Louis University School of Medicine, 1402 South Grand Boulevard (C-130), St Louis, MO 63104-1004, *willmore@slu.edu*.

Relationship Disclosure:
Dr Willmore holds stock greater than 5% of the company or greater than $10,000 in value in Pfizer Inc.

Unlabeled Use of Products/Investigational Use Disclosure:
Dr Willmore reports no disclosure.

DISCUSSION

All drugs used for the treatment of epilepsy can cause adverse effects; some are severe and even fatal. Treatment requires patients to tolerate some side effects because all drugs used for seizure control may cause symptoms that range from cloudy thinking to fatigue or drowsiness. The degree to which these side effects can be tolerated varies from patient to patient. It is important to discuss possible side effects with the patient, including a review of the rare and idiosyncratic life-threatening allergic reactions and metabolically or genetically determined drug-induced illnesses.

The best available evidence should be used to guide these discussions, including evidence-based guidelines, peer-reviewed primary articles and review articles, textbooks, and (lastly) expert opinion. References such as the *Physicians' Desk Reference* (*PDR*) can also provide helpful prescribing information.

States have tended to use source documents, including the *PDR*, in several ways. Some states consider the *PDR* and package insert as establishing the standard of care. In other states, the package insert and *PDR* are considered evidence of standard of care and a case for negligence may be established if a physician does not follow the prescribed directions.[1] Physicians may present their reasons for using a medication that does not fit the description in the *PDR* and package insert (Mulder rule and echo of Mulder;[1] Thompson v Carter, 518 So2d 609, 613 [Miss 1987]). Mulder v Parke-Davis, 181 NW2d 882 (Minn 1970) requires physicians to document their reasoning for deviation in the medical record. In other states, the *PDR* and package insert cannot be used without supporting expert testimony. This is known as the echo of the Mulder rule (Spensieri v Lasky, 723 NE2d 544 [NY 1999]).[1] It is good practice to always document the rationale for any treatment plan. Publications of discussions regarding what is considered appropriate treatment, along with legal references and disclaimers, have been reviewed in detail.[2]

Critical discussions with patients must be documented by noting their timing and content in the medical record. Further, for antiepileptic drugs (AEDs), a plan for ongoing monitoring needs to be designed to detect serious systemic toxicity in time to intervene and prevent patient harm. These discussions are part of the informed consent process that should include the risks and benefits of the treatment (**Practice Table 1**). Patients and their advocates need to understand that monitoring requires their vigilance and commitment to communicate with the physician.[3]

Evidence-based scientific criteria fail to support routine monitoring, and the resulting archival data rarely predict development of serious drug reactions.[3] Prospective studies of routine blood and urine testing in patients having long-term AED treatment found no serious reactions from phenobarbital, phenytoin, carbamazepine, or valproate. Routine monitoring provides no useful information and may prompt unwarranted action, such as discontinuation of an otherwise useful drug. Prospective studies of adults repeatedly show that routine laboratory monitoring is not cost-effective or valuable for protecting asymptomatic patients. Treatment of 480 patients with either carbamazepine or valproate in a double-blind controlled trial also demonstrated the lack of usefulness of routine laboratory monitoring.[4,5] However, measuring biochemical function and

PRACTICE TABLE 1 **Documentation Checklist**

- ▶ **Inform the patient about indicators of success**
- ▶ **Discuss trial-and-error nature of treatment**
- ▶ **Review serious or even fatal adverse effects**
  - Hepatotoxic
  - Hematologic
  - Dermatologic
  - Renal
- ▶ **Discuss symptoms or signs of a serious reaction**
- ▶ **Provide contact instructions and information**
- ▶ **Obtain baseline laboratory studies**
  - Hematologic
  - Hepatic
- ▶ **Conduct scheduled monitoring for patients at high risk**
  - Biochemical disorder
  - Neurodegenerative disease
  - Prior adverse drug reactions
  - Treatment with valproate
  - Without an advocate
  - Multiple disabilities, institutionalized
  - Han Chinese
  - Treatment with a recently approved drug that has US Food and Drug Administration monitoring requirements
- ▶ **Provide explicit warnings about personal safety**
  - Deep tub baths
  - Swimming without supervision
  - High places
  - Open machinery
  - Burn risks
  - Using common sense
- ▶ **Provide instructions and information about pace of ascension dosing (lamotrigine)**
- ▶ **Caution the patient about any change in mood or suicide ideation and actions that need to be taken**
- ▶ **For women**[15]
  - Caution patients of childbearing potential about teratogenicity
  - Discuss and obtain baseline bone health screening[16]
  - Discuss treatment with vitamin D and calcium (endocrine consultation)
  - Inform the patient about potential failure of hormonal contraception
- ▶ **Discuss state-specific rules that govern driving**
- ▶ **Inform the patient about sudden unexplained death**

structural circulating elements in blood at baseline before starting treatment with a new drug is good medical practice.[3]

One way to minimize risk is to identify high-risk patients by using clinical information from reports of idiopathic drug reactions.[6] For example, the risk of hepatotoxic reactions from valproate is nonspecific,[7] but those at risk are younger than 2 years of age, treated with several AEDs, and known to have metabolic disease with developmental delay.[8] Patients of Han Chinese background and patients from the Pacific Rim nations may harbor the *HLA-B**1502 allele of the human leukocyte antigen[9] and be at risk of hypersensitivity, including Stevens-Johnson syndrome and toxic epidermal necrolysis. The US Food and Drug Administration (FDA) has advised screening of Asian patients for this allele prior to prescribing carbamazepine and consideration of the risk in using phenytoin or fosphenytoin in these patients.[9] Cross-reactivity and sensitivity between carbamazepine, phenytoin, phenobarbital, lamotrigine, and oxcarbazepine may occur.

Some examples of specific adverse reactions include transient leukopenia in 10% to 12% of patients treated with carbamazepine; fatal reactions, such as aplastic anemia, are rare.[3,5] Before felbamate is prescribed, manufacturer recommendations must be reviewed[10] and a plan for hematologic and liver function screening must be developed. Written consent is required. Levetiracetam has been associated with behavioral changes in children and adults, including aggression, emotional lability, oppositional behavior, and psychosis.[11] Topiramate is associated with nephrolithiasis in up to 2% of patients, and dose-related weight loss should be discussed; glaucoma and oligohidrosis with hyperthermia both require caution.[12,13] Vigabatrin causes loss of peripheral vision.[14]

Prescribing physicians must be aware of the various AED-related side effects, educate their patients accordingly, and institute an appropriate monitoring program as recommended in the materials developed by the manufacturer in concert with the FDA. Because new drugs have been used on a selected and limited number of patients, their use should be initiated cautiously as their side effects and drug interactions may not be fully known. Depression and suicidal ideation are risks associated with epilepsy and with medications used in treatment.[11] It is important to be sure that patients, families, and caregivers are alert to changes in mood. Open communication is crucial for safe drug use, and the patient should always be instructed to contact his or her physician with any concerns.

REFERENCES

1. Bradford GE, Elben CC. The drug package insert and the PDR as establishing the standard of care in prescription drug liability cases. J Mo Bar 2001;57:233–242.
2. Willmore LJ, Pickens A, Pellock JM. Monitoring for adverse effects of antiepileptic drugs. In: Wyllie E, editor. *The treatment of epilepsy*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006:735–745.
3. Pellock JM, Willmore LJ. A rational guide to routine blood monitoring in patients receiving antiepileptic drugs. Neurology 1991;41(7):961–964.
4. Mattson RH, Cramer JA, Collins JF, et al; Department of Veterans Affairs Epilepsy Cooperative Study, No.264 Group. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. N Engl J Med 1992;327(11):765–771.

5. Blackburn SC, Oliart AD, Garcia Rodriguez LA, et al. Antiepileptics and blood dyscrasias: A cohort study. Pharmacotherapy 1998;18(6):1277–1283.
6. Glauser TA. Idiosyncratic reactions: new methods of identifying high-risk patients. Epilepsia 2000;41(suppl 8):S16–S29.
7. Willmore LJ, Wilder BJ, Bruni J, Villarreal HJ. Effect of valproic acid on hepatic function. Neurology 1978;28(9 pt 1):961–964.
8. Dreifuss FE, Langer DH, Moline KA, Maxwell JE. Valproic acid hepatic fatalities. II. US experience since 1984. Neurology 1989;39(2 pt 1):201–207.
9. Ferrell PB, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics 2008;9(10): 1543–1546.
10. Pellock JM, Faught E, Leppik IE, et al. Felbamate: consensus of current clinical experience. Epilepsy Res 2006;71(2–3):89–101.
11. Glauser TA. Behavioral and psychiatric adverse events associated with antiepileptic drugs commonly used in pediatric patients. J Child Neurol 2004;19(suppl 1):25–38.
12. Sankar PS, Pasquale LR, Grosskreutz CL. Uveal effusion and secondary angle-closure glaucoma associated with topiramate use. Arch Ophthalmol 2001;119(8):2110–2111.
13. Cerminara C, Seri S, Bombardieri R, et al. Hypohidrosis during topiramate threatment: a rare and reversible side effect. Pediatr Neurol 2006;34(5):392–394.
14. Willmore LJ, Abelson MB, Ben-Menachem E, et al. Vigabatrin: 2008 update. Epilepsia 2009;50(2):163–173.
15. O'Connor SE, Zupanc ML. Women and epilepsy. J Pediatr Pharmacol Ther 2009;14(4):212–220.
16. Meier C, Kraenzlin ME. Antiepileptics and bone health. Ther Adv Musculoskel Dis 2011;3(5): 235–243.