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EMERGENT COMPLICATIONS OF THE NEWER ANTICONVULSANTS

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□ **Abstract—Background: Multiple new anticonvulsants have been introduced recently and they are supplanting the older medications. Whereas the older drugs have well-recognized side effects, both in typical therapeutic doses and in overdosage, the properties of the newer ones are unique and largely unknown to all but sub-specialists. Objectives: This article gives a concise overview of the potential complications of these new medications in both therapeutic use and overdose. Discussion: Clinically significant side effects of the new anticonvulsants, such as metabolic acidosis from topiramate, autoimmune reactions from lamotrigine, hyponatremia from oxcarbazepine, or psychosis from levitiracetam can cause serious morbidity and mortality if unrecognized. The effects of these medications in overdose are also largely unknown to most emergency physicians. Conclusions: This article reviews the major potential side effects of the new seizure medications and the treatment of their overdoses for the practicing emergency physician.** © 2010 Elsevier Inc.

□ **Keywords—new anticonvulsants; complications; overdose; side effects; treatment**

INTRODUCTION

In recent years, many new medications have been approved for control of seizures. Each of them has a unique side-effect profile. Many side effects have become apparent in the post-marketing phase with more widespread use. When first introduced, felbamate (Felbatol®; Meda Pharmaceuticals Inc., Somerset, NJ) was received enthusiastically as an unusually effective anticonvulsant with a very low risk profile. Subsequently, it has been withdrawn from common use due to post-marketing discovery of a relatively high risk of aplastic anemia and liver failure. Although still used, it is limited to a select subset of seizure patients who do not respond to other medications. It also requires explicit consent and frequent laboratory monitoring (1). Similarly, vigabatrin is another new anticonvulsant, which has been highly restricted in its use due to the post-marketing recognition of permanent visual field defects (2). The picture is further clouded by the fact that many of these medications are used in combination for better seizure control. This review article will summarize the side effects or overdose patterns associated with these newer medications.

THE CLINICAL CHALLENGE

The newer anticonvulsants overall have more tolerable side-effect profiles, better efficacy, or are easier to maintain in a therapeutic range; they are replacing the old standard medications such as carbamazepine (Tegretol®; Novartis Pharmaceuticals Corporation, East Hanover, NJ), phenytoin (Dilantin®; Parke-Davis, Morris Plains, NJ), phenobarbital (Luminal®; Bayer, Leverkusen, Germany), or valproic acid (Depakote®; Abbott Laboratories, Abbott Park, IL) as first-line treatments. Some of these are also replacing the older antimanic medications like lithium and valproic acid. As they are more fre-

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quently prescribed, more patients will present to the Emergency Department (ED) or other health care providers with complications from their use. Whereas the older drugs and the complications of their use are familiar to practicing physicians, the newer medications are likely to be much less so.

The anticonvulsant hypersensitivity syndrome (AHS) is another phenomenon seen with many anticonvulsants that can cloud the clinical picture. AHS consists of a triad of fever, skin rash, and internal organ involvement. Symptoms typically start 2 to 8 weeks after medication initiation. Fever is usually seen first, followed by skin rashes and then internal organ pathology, especially hepatitis. The renal, hematologic, or pulmonary systems are potentially affected. Skin rash can progress to Stevens-Johnson syndrome (SJS.) Of the newer medications, lamotrigine in particular has a tendency to cause this problem.

Experience with overdoses of these medications is limited. Overdoses are expected to become more common as their use in psychiatric conditions, or seizure patients with co-morbid psychiatric conditions, increases. Epilepsy by itself is a risk factor for psychiatric co-morbidities, including suicidal behavior (3). Recently, the U.S. Food and Drug Administration (FDA) reported that patients taking anticonvulsants, including all those mentioned in this article, are more likely to experience suicidal ideation. It is difficult to determine if this is related to the medications or the conditions for which they are prescribed. A complicating factor is that, outside of a few academic centers, blood levels are not available for these drugs and are difficult to interpret. This is especially problematic in case of overdosage. In overdose, as a general rule, these drugs can cause lethargy, sedation, or increased seizure frequency (4). At this time, no specific antidotes exist for these drugs. Supportive care and activated charcoal are basic treatments for overdose with these agents. Fortunately, the toxicity of these medications is generally lower than that of the older anticonvulsants. A study of 164 patients who intentionally overdosed on new anticonvulsant medications showed no fatalities (3). A poison control center remains the best source for up-to-date information on treatment of these overdoses.

TOPIRAMATE (TOPAMAX®)

Indications for Use

Topiramate (TOPAMAX®; Ortho-McNeil-Janssen Pharmaceuticals Inc., Raritan, NJ) is becoming a popular anticonvulsant for many types of epilepsy and is used alone or in combination. It is also approved for migraine prophylaxis and is used off-label for the management of bipolar disorder, alcoholism, and even to facilitate weight loss, as it is anorectic.

Side Effects

Like most anticonvulsants, it can be sedating, and among the newer anticonvulsants, it seems to cause the greatest impairment of neurocognitive function (5). As a chemical relative of acetazolamide (Diamox®; Wyeth-Ayerst Laboratories, Philadelphia, PA), topiramate is a carbonic anhydrase-inhibiting diuretic that may cause a dose-dependant metabolic acidosis. Most often, this is not clinically significant (i.e., serum bicarbonate $<$ 17, seen in up to 11% of patients), but it may become so for select patients, especially those with renal failure or other predisposing conditions. In one study, 48% of patients had some degree of metabolic acidosis (6). Awareness of this side effect will help the clinician explain an abnormal laboratory value in patients taking this medication. It may present with a compensatory hyperventilation, irritability, or mental status changes. Sodium bicarbonate administration, with monitoring of the serum potassium level, may be considered in severe acidosis (7). Topiramate, as with other carbonic acid anhydrase inhibitors, is associated with an increased risk of kidney stones. Secondary angle closure glaucoma and acute myopia have also been reported, even in pediatric patients. It presents with a painful red eye, and is usually bilateral. Resolution is rapid after discontinuation of the medication (8). Oligohydrosis (decreased sweating) and hyperthermia have also been reported, particularly in children (9).

Overdose

Overdose may cause varying degrees of sedation, coma, status epilepticus, hypotension, and severe metabolic acidosis (10). This is presumably related to the carbonic anhydrase inhibition causing the same side effect as in therapeutic doses. At least one fatality apparently related to topiramate ingestion has been reported (11). No specific antidotes exist for this drug. Treatment should be primarily supportive for symptoms as needed. Bicarbonate may be required for severe metabolic acidosis. Activated charcoal seems to help with overdose, as it shows in vitro binding to this drug. Excretion is primarily renal. Hemodialysis is effective at removing this drug, but no clear indications exist at this time. It could be reserved for severe symptoms such as seizures, refractory hypotension, or significant metabolic acidosis.