Labels on Antiepileptics to Carry Suicidality Warning

BY BETSY BATES
Los Angeles Bureau

The Food and Drug Administration has directed physicians to inform patients taking anticonvulsant medications that the drugs have the potential to increase suicidal thoughts and behavior.

Families and caregivers should also be notified of this risk so that they can be attuned to changes in behavior in patients receiving the medications, according to the FDA's alert for health care professionals.

Based on an agency review of nearly 200 clinical trials of 11 antiepileptic drugs, the directive coincided with an FDA announcement that manufacturers of any medication in the class will be required to add warnings about suicidal thoughts or behavior in prescribing information or labeling and to develop medication guides for patients.

Revised labeling or an explanation "why they do not believe such labeling changes are necessary" must be submitted to the agency within 30 days.

Jack Cox, a spokesman for Pfizer Inc., said in a telephone interview his firm will comply with the order.

"Pfizer will work closely with the FDA to update the labeling of our antiepileptic medications Lyrica [pregabalin] and Neurontin [gabapentin], in a timely manner," he said.

"We have not heard directly from the FDA, but we will work to address any of the agency's concerns," said Tricia Geoghegan, a spokesperson for Ortho-McNeil Neurologics, makers of topiramate.

Ms. Geoghegan noted that the label for Topamax (topiramate) has always included "content about this topic," but added that revisions will be made should the FDA request them.

The agency's decision drew on data from placebo-controlled clinical trials that enrolled 43,892 patients aged 5 years and older taking the medications for epilepsy, psychiatric disorders, and other conditions.

The FDA meta-analytic review of 199 trials determined that patients receiving antiepileptic drugs were at a twofold risk of suicidal behavior or thoughts (0.43%), compared with patients receiving placebo (0.24%).

The difference translates to 1 additional case of suicidality per 530 patients treated with antiepileptic drugs.

The absolute rate of events was highest in psychiatric patients (8.5 suicidality reports per 1,000 patients who were receiving antiepileptic medications, compared with 5.7 per 1,000 for psychiatric patients who were taking placebo).

Among epilepsy patients, 3.4 events per 1,000 were reported for those receiving antiepileptic medications, compared with 1.0 for those assigned to receive placebo. ■

The FDA's health care alert is available at www.fda.gov/cder/drug/InfoSheets/HCP/antiepileptics200812.htm.

Intravenous Lorazepam Bests Rectal Diazepam for Seizures

BY SUSAN LONDON
Contributing Writer

SEATTLE — Intravenous lorazepam is more effective than rectal diazepam in stopping status epilepticus in children who present to the emergency department with seizures that began at home, judging from findings from an English study.

The finding challenges earlier reports that suggested the two agents are equivalent for this indication, especially given the contention that it is easier to administer rectal drugs than to start an intravenous line outside the hospital.

Most of the existing data on optimal treatment come from hospital-based research, which "doesn't take into consideration the different time periods: what happens in the community, what happens on arrival into hospital, what happens after failure of first-line treatment in hospital," Dr. Richard F. Chin said at the annual meeting of the American Epilepsy Society.

From May 2002 to April 2004, investigators in the ongoing North London Status Epilepticus in Childhood Surveillance Study prospectively collected population-based data at 22 North London hospitals about children who experienced community-onset convulsive status epilepticus.

During the study period, 240 episodes of community-onset convulsive status epilepticus were documented in 182 children, reported Dr. Chin, the study's lead investigator and a pediatric neurologist with the Institute of Child Health in London. The children had a median age of 3.2 years, and 52% were girls.

Overall, 2% percent of the episodes ended without any treatment. Another 61% were initially treated outside the hospital, and of these 22% were terminated before hospital arrival.

In multivariate analyses of the 203 episodes that were treated in the hospital, children were more than three times as likely to have termination of their seizures with first-line therapy in the emergency department if that therapy was intravenous lorazepam instead of rectal diazepam.

"That is very important because current guidelines, certainly within the [United Kingdom and other settings], suggest some degree of potential equivalence between a choice of rectal medication and [intravenous] medication," he said. "Some people think there is a bit of concern getting IV access and administering medication. Certainly, there doesn't seem to be any basis for this within our setting."

When first-line therapy failed, children were nearly nine times more likely to have seizure termination with second-line therapy if that therapy was intravenous phenytoin instead of rectal paraldehyde.

Dr. Chin had no relevant conflicts of interest to report. ■

EDITORIAL

Suicidality Report: More Harm Than Good?

For years, we've had scientifically sound data telling us that patients with epilepsy have an increased risk of depression. But the recent federal warning of an increased risk of suicidal ideation in patients on antiepileptic drugs is based on much less rigorous data, and could do more harm than good.

BY CARL W. BAZIL, M.D., PH.D.

After the initial Food and Drug Administration alert reporting increased suicidal ideation with anticonvulsant drugs, some of my patients asked if they should discontinue their medications. They did not realize, as I did, that although any risk of suicidal ideation was very small, the risk of stopping medications, with possible uncontrolled seizures, was much greater. I easily convinced them of this, but I have colleagues who report that some of their patients stopped medications.

On the surface, the alert does sound frightening: Patients receiving antiepileptic drugs (AEDs) had twice the risk of suicidal behavior or ideation than did those taking placebo. But even with this doubling, the risk remained very small—less than 0.5% of patients taking the drugs. Moreover, the FDA recommendation was based on a retrospective analysis of 199 separate AED trials. None of these trials was designed to examine the risk of suicidal ideation; instead, this information was collected during patient self-reports of adverse events.

These reports, determined by a series of open-ended questions posed by the investigator, have a notorious potential for bias. If the patient complains of one adverse event, say, depression, the investigator will automatically ask more questions, including questions about suicidality. And because it's known that drugs always evoke more adverse events than do placebos, once a patient reports an adverse event, investigators will have increased vigilance for others. Thus, an adverse effect—in this case suicidality—could be recorded more often in the drug group than in the placebo group, even if the rates were similar in the two groups.

Another potential bias—that of depression associated with clinical improvement—could have skewed the analysis. Paradoxically, a subset of epilepsy surgery patients become very depressed after successful surgery. It's a reaction to an enormous life change that requires a lot of adjustment. Similarly, patients who improve on drug therapy may also become depressed, but this doesn't mean that the drug caused the depression.

Finally, the meta-analysis lumped together all the classes of AEDs, making no attempt to categorize drugs by different mechanisms. There is no way to determine if a specific drug, or class of drug, was significantly associated with an increased risk of suicidality. From a scientific standpoint, it's hard to believe so many drugs with different methods of action could have the same effect. Information from other studies suggests that certain drugs do have the potential to increase depression, and therefore (possibly) suicidality, but the FDA alert covers this very diverse group as one class, with one risk.

The FDA has recently experienced significant criticism for its postmarketing monitoring of drug safety. It may be that this alert is at least partly a reaction to that criticism. But if the agency wants to firmly establish a link between AEDs and suicidal ideation, a retrospective study is not the way to proceed. Instead, a prospective study using specially validated psychological measures is warranted.

In the absence of such a study, physicians should make sure that patients understand this is not a high risk, and stress that these drugs are very safe when taken as directed. As depression is present in epilepsy patients, physicians should always be vigilant for its presence. If there is an upside to this alert, physicians may recognize and treat depression in more epilepsy patients, thereby improving their lives. But I am concerned that this action on the part of the FDA will cause inappropriate reluctance to use medications that, on the whole, are very safe and helpful to patients with epilepsy. ■

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