

Management of Two New-Onset Seizures Within Two Hours

Unprovoked seizures pose a dilemma for clinicians.
Here's a look at the evidence for and against medical intervention.

By Niranjan Siva, MD
and Amit Verma, MD

A 24-year-old male had a first-time witnessed generalized tonic-clonic seizure without aura lasting about one minute. Two hours later, while being evaluated in the emergency room, he had a second witnessed generalized tonic-clonic seizure without aura lasting about one minute. Blood chemistry was normal. A CT scan of the brain was normal. He was intravenously loaded with Cerebyx in the emergency room and discharged on Dilantin. He was seen in neurological consultation a few weeks later with no side effects of Dilantin. A Dilantin serum level was therapeutic. An MRI scan of the brain and an EEG were normal.

Questions: For the purpose of prognosis, has he had one seizure or two? How often do patients with new-onset epilepsy have two seizures within a couple of hours of each other? For long-term therapy, should he be continued on Dilantin or switched to one of the newer drugs?

Expert Opinion

The case presented reveals the dilemma that many physicians encounter regarding management of new onset seizures. A variety of factors are to be considered prior to initiating antiepileptic medications.

The decision to initiate antiepileptic drugs in an individual experiencing seizure must be made on a case-by-case basis in conjunction with the patient. This decision to initiate an AED is based on the assumption that the use of such medicines will reduce the chance that the

patient will go on to have subsequent seizures. In addition, the benefit of initiating such therapy should outweigh the possible risks of the treatment. Although most neurologists would generally not treat a "first seizure" in an individual who presents with a normal exam and imaging based on the relatively low risk of recurrence, such a decision should be based on each individual's unique situation.

Large numbers of case series have shown that many individuals presenting with what is felt to be a "first" generalized tonic-clonic seizure, on further questioning, describe a variety of episodes suggestive of complex partial or partial seizures. Such a history would suggest that these patients would in all likelihood have an increased risk for subsequent seizures.

In addition, factors such as remote symptomatic etiology, abnormal EEG, being asleep at the time of first seizure, history of prior febrile illness and Todd's paralysis at the time of the first witnessed seizure all increase the risks of recurrence of seizures.¹ These unique risk factors in an individual experiencing a single unprovoked seizure may provide support for initiation of AEDs on a case-by-case basis. Therefore, each patient's unique circumstances should be reviewed prior to initiating antiepileptic medications.

The decision to treat is thus based on an individual's presumed increased risk for subsequent seizures. What then is a patient's risk for recurrence? Various studies have tried to determine the precise of risk of recurrence following a single unprovoked seizure. Overall rates of reoccurrence have ranged from 25 to 70

percent in a broad range of studies of children and adults. After carefully excluding individuals with prior seizures, recurrence risk has been found to range between 30 to 50 percent.¹⁻³ A 1991 meta-analysis of case series of new onset seizures showed that the risk of recurrence after a first unprovoked seizure is 42 percent over the next two years.⁴ As a majority of individuals with a single unprovoked first seizure will not go on to have subsequent seizures, an argument has been made to not initiate treatment following a first seizure.

Controversy has existed regarding treatment of a first seizure not only due to the presumed low risk of recurrence but also based on the idea that early treatment does not alter the long term prognosis. The Italian First Seizure Trial group conducted a randomized controlled study of antiepileptic medication vs. placebo following a first generalized tonic-clonic seizure. The study found that although the recurrence rate was lower in the treated group compared to the untreated group (24 percent vs. 42 percent) in early follow up, both groups had similar long-term outcomes at five years. The study has provided further support not initiate AED therapy till a patient is found to truly have recurrent seizures.

While recurrent rates following a first seizure ranges from 30 to 50 percent, most studies suggest that the risk of recurrence following a second seizure jumps to 70 percent, with most recurrences occurring early.^{3,5} Meta-analysis of case series suggests that 60 to 70 percent of recurrent seizures occur within six months of the initial seizure.^{2,4} As most

individuals with a new onset seizure will present with subsequent seizures in a relatively short period of time, the generally accepted paradigm for the management of individuals with a single unprovoked seizure with a normal exam and clinical workup has been a 'wait and see' approach to determine if a diagnosis of epilepsy would truly declare itself. With an onset of a second seizure, it has been customary to initiate treatment due to the relatively high risk of recurrence (70 percent).

For the patient in the above scenario, the treating practitioner must decide whether the patient should be started on antiepileptic drugs (AEDs). This decision to acutely treat the patient described may be based not only on the duration of the witnessed seizures (*i.e.*, status epilepticus or prolonged seizure) but also on the idea that these events are indeed two separate seizures, suggesting that the patient may now be at a higher risk for subsequent seizures necessitating the initiation of a drug.

Thus, what is the evidence that two independent seizures occurring within a short interval (within 24 hours) have an increased risk for recurrence when compared with a single seizure over the same time period? Do the two independent seizures in the above example occurring with an interval of a few hours represent one seizure, suggesting a lower risk of recurrence or two independent seizures suggesting a higher risk of reoccurrence?

Pros and Cons

Most studies looking at recurrent seizures have considered multiple seizures occurring within a 24-hour period as a single seizure. The International League Against Epilepsy, an organization dedicated to the prevention, diagnosis and treatment of epilepsy, in their Guidelines for Epidemiological Studies on Epilepsy in 1993, created a rigorous definition of epilepsy for the purposes of diagnosis of seizure.⁵ Their definition of a new onset seizure did not differentiate

multiple seizures within a 24-hour period from a single seizure. As a result, most subsequent studies of new onset seizures did not make this differentiation. Little data is thus available regarding long-term prognosis of multiple seizures within a 24-hour period.

Two studies published in 2000 took opposing views regarding prognosis of multiple seizures occurring within a 24-hour period.

Camfield and Camfield reviewed new onset seizures in 490 children in the Nova Scotia epilepsy database from 1977-1985.⁸ Of the 490 children studied 70 children had two or more seizures within a 24-hour period ("same-day seizures"). The remaining 420 children had their initial seizures separated by at least 24 hours ("different day seizures"). The study found that 80 percent (56/70) of the "same-day seizures" eventually went on to have one or more seizures whether they were treated or not. This compared with 80.9 percent (340/420) of patients with "different day" seizures who went on to have more seizures.

The findings of this study supported the authors' view that prognostically, at least in children, multiple seizures carried a higher risk of recurrence despite the interval between seizures. That is, a single seizure had a lower risk of recurrence when compared with multiple seizures occurring within a relatively short interval.

Despite the findings of the study, criticisms have been raised surrounding differences between the two groups studied. Criticism has involved the younger age and increased likelihood of remote symptomatic etiology in "same day" group, which might have increased the risk of recurrence in this group. In addition, the study design was a retrospective one with a review of enrolled patients with two or more seizures rather than a prospective study of first seizure.

Another study by Shinar et al, a prospective study of 407 children fol-

lowed for a mean period of 9.6 years from the time of first unprovoked seizure, concluded that the cumulative risk for a second seizure was 29 percent, 37 percent, 43 percent and 46 percent at one, two, five and 10 years respectively.¹ The study found that after more than one seizure within a 24-hour period (which was not further defined) there was no significant increased risk for a second, third or 10th seizure, although there was a borderline significant value for increased risk of a fourth seizure. The authors concluded that two or more unprovoked seizures within a 24-hour period should be considered a single event and thus be treated accordingly. Although the data regarding prognosis for multiple seizures within a 24-hour period is not conclusive, the generally accepted management of these seizures has been to treat them as a single seizure.

Worth the Risks

The patient in the above example was started on phenytoin at the time of discharge from the emergency room to follow up with a neurologist. The neurologist seeing the patient is now placed in the position of deciding if the patient should be continued on phenytoin, tapered off phenytoin, or switched to another antiepileptic medication. If decision is made to continue antiepileptic medications, one must decide to either continue phenytoin or switch to one of the newer AEDs.

Since its introduction in 1938, phenytoin has been shown effective for the treatment of both partial and generalized epilepsy. However, its long-term use has resulted in identification of such side effects as neuropathy, osteoporosis, gingival hyperplasia and hirsutism. Therefore, there has been an increasing shift towards selection of one of the newer antiepileptic medications early in the course of diagnosis to minimize the long-term sequelae of the older antiepileptics.

Over the last 15 years, 10 new medications for the treatment of epilepsy have become available. With the exception of felbamate, the newer AEDs at this time appear to have improved tolerability and better adverse effect profile. Although numerous studies have shown that the newer antiepileptic medications do not have superior efficacy when compared to the older AEDs, the new AEDs do appear to have improved side effect profile as well as improved tolerability as seen by lower withdrawal rates in various studies.⁹⁻¹¹

Although selection of an appropriate AED is beyond the scope of this article, selection should be based on efficacy, a good long-term side effect profile, and a low interaction potential with various other medications the patient may be receiving. The newer AEDs appear to provide an efficacious alternative to the older AEDs with an improved side effect

profile and thus appear to be an acceptable, if not superior alternative to the older AEDs. With the information available to the practitioner, each patient's specific circumstance must be taken into consideration before a decision is made to initiate or continue antiepileptic medications. **PN**

1. Fishbain D, Cutler R, Rosomoff H, Rosomoff R. (1999). Chronic Pain Disability Exaggeration/Malingering and Submaximal Effort Research. *The Clinical Journal of Pain*, 15, 244-274.
2. Gervais R, Green P, Allen L, & Iverson G. (2001). Effects of Coaching on Symptom Validity Testing in Chronic Pain Patients Presenting for Disability Assessment. *Journal of Forensic Neuropsychology*, 2(2), 1-16.
3. Aronoff GM, Tota-Faucette M, Phillips L, Lawrence CN. Are Pain Disorder and Somatization Disorder Valid Diagnostic Entities. *Current Review of Pain* 2000 4:309-312.
4. Ruocco A, Swirsky-Sacchetti T, Raines D, Mandel S. Neuropsychological Malingering and Psychological Symptom 1. Shinnar et al. Predictors of multiple seizures in a cohort of children prospectively followed from the time of their first unprovoked seizure. *Annals of Neurology* 2000; 48: 140-147.
2. Camfield et al. Epilepsy after a first unprovoked seizure in childhood. *Neurology*. Neurology 1985;35: 1657-60.
3. Hauser et al. Risk of recurrent seizures after two unprovoked seizures. *New England Journal of Medicine* 1998; 338:429-34.

4. Berg et al. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. *Neurology* 1991; 41:965-72.
5. Commission on Epidemiology and Prognosis, International League against Epilepsy. Guidelines for epidemiologic studies on epilepsy. *Epilepsia* 1993; 34: 592-596.
6. First Seizure Trial Group. Randomized clinical trial on the efficacy of antiepileptic drugs in reducing the risk after a first unprovoked tonic clonic seizure. *Neurology* 1993; 43: 478-83.
7. Musicco et al. First Seizure Trial Group. Treatment of the first tonic clonic seizure does not improve the prognosis of epilepsy. First Seizure trial Group. (First Group). *Neurology*, Oct 1997, 49: 991-998.
8. Camfield and Camfield. Epilepsy can be diagnosed when the first two seizures occur on the same day. *Epilepsia*, 41(9): 1230-1233, 2000.
9. Kwan, P and Brodie, M. Clinical trials on antiepileptic medications in newly diagnosed patients with epilepsy. *Neurology* 2003; 60:S2-S12.
10. Marson et al. New antiepileptic drugs: a systematic review of their efficacy and tolerability. *BJM* 1996; 313: 1169-74
11. Marson et al. Levetiracetam, oxcarbazepine, remacemide and zonisamide for drug resistant localization-related epilepsy: a systematic review. *Epilepsy Res* 2001; 46:259-70.

Magnification: One and the Same? *Archives of Clinical Neuropsychology*, 20(7), 2005.

Niranjan Siva, MD is a resident and Amit Verma, MD is Assistant Professor at the Peter Kellaway Section of Neurophysiology, Department of Neurology at Baylor College of Medicine in Houston.