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Second Generation AEDs: Characteristics, Guidelines and ED Patient Selection

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Case Presentation

A 65 year old woman retired teacher was brought to the ED by her husband. He reported that in the morning during breakfast his wife stared for several seconds then fell to the floor and shook for about 1 minute. After the event she was slightly disoriented.

By the time of presentation in the ED she was recovered completely but had no recollection of this episode. The patient's husband reported that over the past six months she experienced rare episodes of staring for few seconds during which time she did not respond.

In the ED, workup was conducted, including a CT scan and EEG. Both tests showed no abnormality. Blood tests revealed mild hyponatremia and elevated INR. Her past medical history is significant for a right nephrectomy. She donated one

kidney to her twin sister. She was recently diagnosed with atrial fibrillation and started on warfarin. She does not have any other medical problems. Her family history is remarkable for lupus in her twin sister. Neurological examination was normal.

The patient was loaded with 1gm of IV fosphenytoin and discharged home on oral phenytoin 300 mg/day with the recommendation to see a neurologist in outpatient clinic in 3-4 weeks.

She had no further convulsions but felt slightly dizzy and experienced some difficulty with concentration. She did blood tests 3 weeks after phenytoin initiation. The tests revealed sub-therapeutic INR which required adjustments of her warfarin dose. PHT level was within mid-therapeutic range. During the first clinic visit the patient told her neurologist about her cognitive problems and dizziness. The neurologist discussed with the patient several management options. Therapy with levetiracetam was suggested. Initial dose of Levetiracetam 250 mg BID was added to phenytoin. In one week dose was increased to 500 mg BID, phenytoin was tapered off over 3 weeks and then discontinued. Treatment with levetiracetam is well-tolerated and adverse effects seen while taking phenytoin have resolved. She has been seizure-free since the time of initiation of treatment with antiepileptic medications.

Key Clinical Questions and Learning Points

What kind of event did this patient have?

The description of the event is suggestive of an epileptic seizure most likely of partial onset with secondary generalization, although in a patient with this history, necessity of additional cardiac work up should be considered. A normal EEG and head CT are commonly seen in patients with epilepsy. MRI of the brain may identify structural lesion. Repeated EEGs may increase the diagnostic yield of this procedure.

Useful annotated reference follows.

Factors related to the occurrence of typical paroxysmal abnormalities in the EEG records of epileptic patients.
Ajmon M, Zivin LS. *Epilepsia* 1970;11:361-381

This study was performed in 308 patients with epilepsy. A first routine EEG was abnormal in 56%. The patients were followed for at least one year and additional EEGs were performed; 92% eventually had at least one abnormal record. The rate of abnormal EEG varies with age (young children – up to 80%; elderly - 33%).

Should treatment with antiepileptic medication be initiated after a first seizure?

This patient's history of episodic staring preceding the first convulsive event is highly suspicious for complex partial seizures. In addition she is on warfarin and at risk for severe bleeding in the event of fall and convulsion. In this setting initiation of AED was appropriate.

Useful annotated reference follows.

Seizure recurrence after a first unprovoked seizure.
HauserWA et al., *N Engl J Med* 1982;307;522-528

In this study the risk for recurrent seizure after a single generalized tonic-clonic event was 26% at 3 years. Risk for recurrence was higher in case of symptomatic

seizures, presence of bilateral spike and wave on EEG and in those who had siblings with epilepsy.

Are there specific considerations for AED selection in the patient with new onset seizures in ED?

Identification of seizure type, efficacy and adverse effects of AED, drug interaction and the patient's profile are factors in the choice of AED treatment. This patient's seizure presentation is consistent with partial onset seizures with secondary generalization.
All of the current AEDs (with the exception of ethosuximide) have an indication for the treatment of partial epilepsy.

Useful annotated reference follows.

Effectiveness of first antiepileptic drug.
Kwan P, Brodie M. *Epilepsia* 2001;42(10):1255-1260

More than 60% of patients with epilepsy will be seizure-free on a single AED, with nearly 50% achieving seizure freedom on the first AED used.

Should all new onset seizure patients be started on second generation AEDs based on the published guidelines?

Fosphenytoin is one of the few parenteral AEDs available. The risk of recurrent convulsion explains this treatment choice made by the ER physician. It is an appropriate AED for this patient's seizure type. At the same time chronic use of phenytoin caused adverse effects and drug interaction.

Change in AED management was performed in outpatient neurology clinic after discussion with patient of several treatment options. The older AEDs were not recommended due to unfavorable side effects and high probability of drug interaction. Zonizamide and topiramate, effective broad-spectrum AEDs, were avoided due to the possibility of kidney stones, particularly in this patient who has only one kidney. In addition, topiramate may cause cognitive adverse effects. Adequate seizure control with the use of gabapentin will require high doses which are commonly associated with somnolence. Use of lamotrigine, another broad spectrum, effective AED with minimal drug interaction, is limited by the necessity

of very slow dose titration in order to minimize the risk of developing serious rash. Oxcarbazepine, an effective AED for partial epilepsy, was avoided due to risk for hyponatremia in the patient with mildly diminished sodium level. Pregabalin, although effective for management of partial seizures, causes CNS adverse effects, weight gain and peripheral edema.

Levetiracetam was a good treatment option. This medication demonstrates broad spectrum efficacy, low potential for drug interaction and has excellent safety record. This is the only second generation AED now available for IV injection.

Useful annotated reference follows.

Efficacy and tolerability of the new antiepileptic drugs I and II: treatment of new onset epilepsy(I) and treatment of refractory epilepsy(II); report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society.
Neurology 2004; 62:1252-1273

This is the most recent AAN guideline created based on evidence-based data acquired from 23 expert reviews of 1462 articles published between 1987 and 2003. The guideline summarizes efficacy, tolerability and safety of seven new AEDs approved by the FDA over the last 10 years. The following recommendations were made:

- patients with newly diagnosed epilepsy can be initiated on standard AEDs (CBZ, PHT, VPA, PB) or on new AEDs (LTG, OXB, TPM, GBP)
- LTG can be included in treatment option for children with newly diagnosed absence seizures
- all new AEDs have demonstrated efficacy as add-on therapy and all of them are appropriate as add-on therapy in patients with refractory epilepsy
- for all AEDs, slower titration was better tolerated
- all AEDs are more effective in higher doses
- the side-effects of all AEDs increase in dose-dependent manner