Treatment of Seizures in Patients with Significant Drug Interactions and Co-Morbidities

How can clinicians optimize treatment of seizures for individuals with cardiovascular disease or gioblastoma?

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A 66-year-old right handed male with history of coronary artery disease and hyperlipidemia managed with aspirin and simvastatin presents with recurrent episodes of blank stare, garbled speech with loss of consciousness for the past six weeks. Neurologic examination is unremarkable. MRI brain reveals moderate deep white matter disease, and an EEG reports epileptiform discharges emanating from the left fronto-temporal region.

What factors will influence choice of treatment for seizures in a patient with a history of cardiovascular disease?

Many patients who have cardiovascular disease (CAD) are managed medically based on clinical recommendations for lipid lowering and use of antiplatelet agents. Because development of epilepsy is common in the elderly, it is useful to be aware of potential interactions for medications utilized for the highly prevalent condition of coronary artery disease.

Review of basic pharmacology provides the framework to understand drug-drug interactions. Drugs undergo biotransformation primarily in the liver along with other tissues such as the intestines, skin, lungs and kidneys, typically aiming to change compounds into more hydrophilic molecules that can be more easily excreted by the kidneys.

The biotransformation processes include phase I (oxidation, reduction and hydrolysis) occurring in the subcellular structure of the microsomes and mediated by the cytochrome P450 family of enzymes. Environmental and genetic factors can significantly influence the activity and result in clinically relevant variations in a patient's metabolism of a drug.[1] Many first generation and several second generation antiepileptic drugs (AEDs) share a common feature of enzyme induction that can result in an increase in the metabolism of different substrates targeted by the particular cytochrome p450 enzyme along with a decrease in the action of the inducer. Additionally, co-administered drugs can be affected by the process with an acceleration of their own metabolism, a process known as autoinduction.[2]

Knowledge of these basic tenets of biotransformation assists in the selection of anticonvulsant therapy in the setting of multiple potential drug-drug interaction. Statins have become a mainstay of treatment for hyperlipidemia. The goal of management of hyperlipidemia is to utilize a statin to lower the low-density lipoprotein cholesterol level to 70 to 100mg per dL in patients with coronary artery disease.[3] Statins are metabolized by the cytochromic p450 system, in particular the 3A4 family, and would be expected to have reduced serum levels in the presence of an 3A4 enzyme inducing antiepileptic medication. This interaction has been demonstrated between atorvastatin and phenytoin where bioavailability of atorvastatin was reduced by phenytoin coadministration. It was observed that dose adjustment may be required to maintain adequate atorvastatin exposure when coadministered with phenytoin. It has also been proven in the combination of simvastatin and carbamazepine.

Atorvastatin and simvastatin are metabolized by the 3A4 iso-enzyme family of the cytochromic p450 system. Carbamazepine and phenytoin are inducers of 3A4. In contrast, lamotrigine is not an inducer or inhibitor of the 3A4 iso-enzyme family. No interaction between atorvastatin and lamotrigine was observed when both medications were co-administered.[4] A less effective statin, pravastatin is unaffected

by 3A4 induction. Because of the importance of statin use in patients with coronary artery disease and stroke, knowledge of the properties of the antiepileptic medications is essential for appropriate selection or alternatively, dosing of the statin to counteract the interaction.

Antiplatelet therapy is an important component of CAD management because platelet aggregation at atherothrombotic plaque sites can produce clinically significant thrombosis and resultant MI. The most common antiplatelet agents used in the United States are aspirin and clopidogrel.[5] Aspirin has several important interactions with antiepileptic medications with which a clinician should be aware. Of note, salicylates may enhance the adverse effect of zonisamide, topiramate, and acetazolamide, resulting in an increase in the metabolic acidosis that can be observed during use of these medications. All three anticonvulsants share carbonic anhydrase inhibition. Clinical symptoms of metabolic acidosis include drowsiness, hyperventilation, vomiting, confusion, and lethargy. The onset may take days to weeks to manifest.[6,7]

The mechanism of this interaction is unclear. Salicylates appear to reduce carbonic anhydrase inhibitor protein binding and decrease carbonic anhydrase inhibitor excretion by the kidneys. In addition, carbonic anhydrase inhibitor-induced decreases in plasma pH might result in a higher concentration of non-ionized salicylate, which can more readily enter the central nervous system, resulting in clinical symptoms.[8,9] While the effect appears to be dose dependent, so that cardiac patients taking low dose aspirin are at lesser risk, it is still advisable that the combination of aspirin and an antiepileptic medication containing the carbonic anhydrase inhibitory mechanism be avoided. If this is not possible, close monitoring of metabolic acidosis is warranted. Aspirin additionally can have effects on other anticonvulsant medications. In particular, the serum level of valproic acid can be increased resulting in clinical symptoms of toxicity.[10] It has been noted that aspirin may increase the serum level of phenytoin; however, little change in the free fraction of phenytoin is observed. Therefore, no symptoms of toxicity are observed. It is advisable to monitor both a free and total fraction when checking levels of phenytoin.[11]

It is notable that clopidogrel does not have any clinically significant interactions with any of the anticonvulsant medications. This absence of interactions is noted for both enzyme inducing and non-enzyme inducing antiepileptic medication.

A 45-year-old right-handed male presents to the emergency room after having a witnessed seizure described by his spouse as eye deviation to the left, head version to the left followed by a fall with a generalized seizure. The patient underwent brain MRI, which revealed a mass in the right frontal lobe described as a hyperintense lesion on T2 surrounded by vasogenic edema. A brain biopsy is performed and histology reveals glioblastoma multiforme. He is seen by a neuro-oncologist who plans for resection followed by radiochemotherapy.

What is the best selection of antiepileptic medication for the patient while he receives definitive treatment?

Glioblastoma multiforme accounts for 50-60 percent of all primary brain tumors in adults and carries a median life expectancy of 15 months.[12] Seizures occur in 30-50 percent of patients with glioblastoma multiforme, and they remain at increased risk of recurrent seizures.[13] Seizure control is an important issue in care in neuro-oncology and influences quality of life. Careful selection of an antiepileptic medication regimen can optimize clinical outcomes.

Current standard of care for glioblastoma multiforme consists of surgical resection (if possible) and radiation with adjuvant and concomitant treatment with temozolamide.[14-16] A retrospective study of glioblastoma patients (of which 35 percent were treated with temozolamide) noted that patients receiving non-enzyme inducing medications (primarily valproic acid) demonstrated both improved survival and greater hematologic toxicity as compared to those patients receiving enzymeinducing antiepileptic drugs.[17] The authors proposed that this difference could result from the lack of enzyme induction in the primarily valproic acid group or enzyme inhibition by valproate (i.e., increased chemotherapeutic agent concentrations and effects) or some combination of these effects. According to temozolomide prescribing information, temozolomide oral clearance is an average of five percent lower with concurrent valproic acid.[18]

A subsequent analysis was performed to assess whether antiepileptic drugs modulate the effectiveness of temozolomide and resulting survival. Patients receiving valproic acid had more thrombocytopenia and leukopenia than patients without an antiepileptic drug or patients taking an enzyme inducing antiepileptic drug only. The overall survival of patients who were receiving an antiepileptic drug at baseline versus not receiving any antiepileptic drug were similar. Patients receiving valproic acid alone appeared to derive more survival benefit from temozolomide and radiotherapy than patients receiving an enzyme inducing antiepileptic drug or patients not receiving any antiepileptic drug. The findings suggest that valproic acid may be preferred over an EIAED in patients with glioblastoma who require an antiepileptic drug during

(Continued on page 27)

(Continued from page 25)

temozolomide-based chemoradiotherapy.[19] Future studies are needed to determine whether valproic acid increases temozolomide bioavailability or acts as a sensitizer for radiochemotherapy.

The results conclude that selection of antiepileptic drug in patients with glioblastoma should be carefully considered because it may affect survival. The findings also favor the use of non-enzyme inducing antiepileptic medications to allow use of modern chemotherapy that often show increased hepatic metabolism if patients are given an antiepileptic drug which is an enzyme inducer. Common medications used in this setting include levetiracetam because of its availability in oral and intravenous formulation and comparatively a lack of drug interactions. Valproate is an alternate choice. ■

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