CLINICAL VIGNETTE

Drug-Drug Interactions in Patients Requiring Anticoagulation for Atrial Fibrillation and Atrial Flutter

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Abstract

Drug-drug interactions are increasing as patients use larger numbers of medications for chronic medical conditions. We present a patient taking primidone for a seizure disorder which prevented him from starting direct acting oral anticoagulant due to primidone's induction of the cytochrome P (CYP) systems.

Case Presentation

An 84-year-old male with recurrent seizures on primidone and atrial flutter not on anticoagulation was admitted after syncope. His cardiac evaluation included multi-day ambulatory EKG showing atrial flutter. His CHA_2DS_2-VASc score was four. Although his arrhythmia was unlikely the cause of his syncopal episode, the risks and benefits of anticoagulation were discussed with the patient and a shared decision was made to initiate anticoagulation. On prior visits, the patient had declined anticoagulation due to bleeding risk.

Anticoagulation agents were discussed with the team pharmacist. Primidone was a substrate and inducer for multiple cytochrome P (CYP) enzymes, including a strong inducer for CYP3A4.[1-3] Because of this interaction, it was not safe to prescribe any of the direct acting oral anticoagulants. Although warfarin also had interactions with primidone it was safe to use with careful monitoring. More frequent INR testing was needed to closely monitor drug levels. After further discussion, the patient elected to defer any anticoagulation given his concern for interaction with primidone and fear of recurrent seizures. He continued to declined anticoagulation at subsequent visits.

Discussion

In patients with atrial fibrillation, providers routinely consider the risks and benefits of anticoagulation for stroke prevention. The CHA_2DS_2-VASc score is commonly used to assess stroke risk. This takes into account multiple co-morbidities and approximates a yearly risk of stroke for individual patients. In adults with a CHA_2DS_2-VASc score greater than or equal to two, anticoagulation clearly shows a reduction in stroke risk with both warfarin and direct acting oral anticoagulants.[4] Although atrial flutter has a lower risk of stroke than atrial fibrillation, there is still an elevated risk compared to sustained normal sinus rhythm.[5] Guidelines recommend the same risk-based evaluation and consideration of anticoagulation in appropriate patients.[6] This patient met criteria for anticoagulation. Direct acting oral anticoagulants are recommended as first line therapy in patients with non-valvular atrial fibrillation and flutter. However, in patients with multiple drug-drug interactions, choosing a safe and effective anticoagulant remains a challenge.

Primidone was identified as causing drug-drug interactions. Primidone is a potent inducer of the CYP system, which rivaroxaban and apixaban both utilize for degradation.[7,8] In addition, primidone has a significant interaction with both dabigatran and edoxaban given its interaction with p-glycoprotein.[3,9,10] Initiating one of these direct acting oral anticoagulants with careful monitoring of drug levels is a potential option in some health systems. However, monitoring drug levels was not available to this patient. Even when drug level monitoring is possible, there is no consensus on how often to check levels and how to adjust dosing.[11] Another oral option was warfarin, but given the drug-drug interaction with primidone it would also require significantly more frequent initial lab testing. This patient was already apprehensive about taking a new medication. Frequent testing and office visits were significant factors in his decision to refuse anticoagulation. Changing seizure medications, was considered but given his complex seizure history and stability on primidone was not pursued. Although direct acting oral anticoagulants are often convenient for patients and better tolerated, numerous drug-drug interactions exist and should be assessed prior to prescribing new medications. Providers should discuss these interactions and risks with the patient, and use shared decision making to come up with a plan that meets the patient's goals. This patient decided the risk of interactions outweighed the benefits of therapeutic anticoagulation. Such decisions can have a significant and lasting impact on a patient's health.

This case also illustrates the importance of a thorough medication reconciliation and consultation with pharmacy when starting patients on new medications. Active medication review by pharmacists reduces the incidence of adverse drug events by identifying significant drug-drug interactions that are often

missed by providers.[12] With increasing use of chronic medications, the number of drug-drug interactions increases. Assistance from a pharmacist helps ensure new medications are added safely. This case highlights the importance of frequent medication reconciliations and the importance of assistance from pharmacy in assessing drug-drug interactions, especially with patients on medications known to induce the CYP system.

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