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Identifying Adverse Drug Effects of Amiodarone through a Pharmacist-Led Comprehensive Review

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Abstract

Purpose: Amiodarone is a medication often utilized in the critical care setting for acute arrhythmic episodes and may be inappropriately continued post-discharge, leading to an increased risk of adverse drug events. The gap in transition of care upon discharge and subsequent failure to discontinue medications initiated during hospitalization can lead to increased healthcare utilization and costs. The presented case serves as an example of the consequences that can result from failure to discontinue amiodarone after hospitalization and demonstrates the role of clinical pharmacists in identifying inappropriately continued therapy to reduce the risk of adverse events.

Case: A 66-year-old female presented to her primary care physician complaining of worsening bilateral hand tremors. Unable to determine the origin of this symptom, the physician asked a clinical pharmacist to perform a comprehensive review of the patient's medications. The clinical pharmacist discovered that the patient was hospitalized a year prior for sepsis with infective endocarditis. During that hospital stay, she was started on amiodarone for an acute episode of atrial fibrillation. The pharmacist determined that the tremors were likely an adverse drug reaction from amiodarone and also recognized amiodarone as a potentially inappropriate medication for this particular patient. The amiodarone was subsequently discontinued. Within several weeks of discontinuation, the patient's tremors improved significantly.

Conclusion: This case demonstrates the importance of medication review after initiation of amiodarone during hospitalization. Due to the high potential for toxicity, the use of amiodarone should be reviewed and re-evaluated routinely. Clinical pharmacists can contribute their expert pharmacological knowledge to evaluate the appropriateness of amiodarone during and after transition of care to prevent future adverse outcomes.

Keywords: Transitions of care • Amiodarone • Tremor • Pharmacy • Adverse drug event

Abbreviations: CVA: Cerebrovascular Accident; COPD: Chronic Obstructive Pulmonary Disease; GERD: Gastroesophageal Reflux Disease; TSH: Thyroid Stimulating Hormone

Introduction

Amiodarone, a class III antiarrhythmic drug, is commonly administered as short-term treatment for acute episodes of atrial fibrillation in the critical care setting. However, it is frequently continued in the post-acute setting without re-evaluation of therapy or referral to a specialist [1]. According to one study, amiodarone is continued inappropriately after discharge in more than 80% of patients who develop new onset of atrial fibrillation as a result of critical illness [1].

While amiodarone is an effective treatment option for the management of atrial fibrillation, this medication is not without risk. The American Heart Association/American College of Cardiology/Heart Rhythm Society guideline for the management of patients with atrial fibrillation recommends avoiding the use of amiodarone for sinus rhythm maintenance due to the potential risk of toxicities and drug-drug interactions [2]. Amiodarone is associated with common adverse drug effects such as nausea, vomiting, headache, and fatigue; and several adverse drug reactions have been reported that include neurological, thyroid, hepatic, pulmonary, and ocular toxicities [2-4].

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Amiodarone inhibits various Cytochrome P450 (CYP) enzymes including CYP2D6, CYP2C9, and CYP1A2, as well as P-glycoprotein drug transporter, increasing the risk of toxicity with other medications that require these pathways for elimination [2-4]. Given these risks, oral amiodarone is not recommended as a first-line drug for chronic management of uncomplicated and well-tolerated atrial fibrillation. Oral amiodarone should be reserved for patients with life-threatening arrhythmias and for those who do not tolerate or respond to beta-blockers or non-dihydropyridine calcium channel blockers [2-4]. The following case presentation describes a situation in which amiodarone was continued inappropriately in one patient resulting in a preventable adverse drug reaction.

Case Presentation

A 66-year-old community-dwelling female with a past medical history of chronic diastolic heart failure, coronary artery disease, history of Cerebrovascular Accident (CVA), hypothyroidism, hyperlipidemia, hypertension, chronic kidney disease, type II diabetes with complications (peripheral neuropathy, retinopathy, history of big toe amputation), Chronic Obstructive Pulmonary Disease (COPD), and Gastroesophageal Reflux Disease (GERD), presented to her prescriber with complaints of worsening tremors.

The symptoms began as intermittent bilateral hand tremors that worsened at night. One month later the patient complained of increasing symptoms, with tremors in both hands and arms. As the tremors progressed, it became more difficult for her to sleep, eat, and perform activities of daily living. The patient's primary care physician contacted her clinical pharmacist to determine if the tremors could be caused by any of the patient's medications (Table 1). The

Table 1. Comprehensive list of the patient's medications.

Acetaminophen 500 mg tablet: 2 tablets by mouth once daily
Albuterol HFA 90 mcg/inhalation: 2 puffs by mouth 4 times daily as needed
Amiodarone 200 mg tablet: 1 tablet by mouth once daily
Aspirin 81 mg tablet: 1 tablet by mouth once daily
Atorvastatin 20 mg tablet: 1 tablet by mouth once daily
Cetirizine 10 mg tablet: 1 tablet by mouth once daily
Calcium carbonate 500 mg tablet: 1 tablet by mouth twice daily
Duloxetine 60 mg delayed release capsule: 1 capsule by mouth twice daily
Fluticasone/umeclidinium/vilanterol 100 mcg-62.5 mcg-25 mcg/inhalation powder: 1 puff by mouth once daily
Furosemide 80 mg tablet: 1 tablet by mouth once daily
Insulin glargine 100 units/mL solution: 36 units subcutaneously once daily
Isosorbide mononitrate 120 mg extended release tablet: 1 tablet by mouth once daily
Levothyroxine 125 mcg tablet: 1 tablet by mouth once daily
Magnesium 400 mg tablet: 1 tablet by mouth once daily
Methocarbamol 500 mg tablet: 1 tablet by mouth once daily
Pantoprazole 40 mg delayed release tablet: 1 tablet by mouth once daily
Potassium gluconate 550 mg tablet: 1 tablet by mouth once daily
Pregabalin 300 mg capsule: 1 capsule by mouth twice daily
Ropinirole 1 mg tablet: 1 tablet by mouth 3 times daily
Telmisartan 40 mg tablet: 1 tablet by mouth once daily

clinical pharmacist conducted a medication reconciliation and comprehensive review of the patient's history, medication profile, and electronic health record, and subsequently identified risk mitigation opportunities.

The clinical pharmacist found no clear indication for amiodarone. Upon further investigation, it was discovered that amiodarone had been initiated in the hospital over a year prior, during an episode of atrial fibrillation secondary to sepsis with infective endocarditis and septic emboli to the brain. Since this hospitalization, no other episodes or symptoms associated with atrial fibrillation were noted. Amiodarone was identified by the pharmacist as a potentially inappropriate medication and discontinued.

In addition, the pharmacist noted that the patient was on the maximum recommended daily dose of duloxetine, 60 mg twice daily. The pharmacist recommended a dose reduction, as the risks may outweigh the benefits of daily doses higher than 60 mg. These risks increase the likelihood of falls in older adults and include adverse effects such as dizziness, drowsiness, neuromuscular weakness, and tremors. Per recommendations, duloxetine dosage was reduced to 60 mg once daily. Within approximately four weeks of medication changes, the patient reported that her tremors decreased significantly. No signs of tremors were observed by medical staff during the day and the patient reported a significant reduction in shaking. Upon further follow-up six months later, symptoms had not returned and the patient was tremor-free.

Discussion

Inappropriately continuing medications that were initiated in the acute setting upon discharge from the hospital is a common issue encountered in the geriatric patient population [5], the consequences of which include adverse drug events, polypharmacy, and decline in health status, emergency department visits and re-hospitalizations [5]. An estimated 19% of hospital patients experience adverse events after discharge and two-thirds of these events are medication-related [6]. Involvement of clinical pharmacists in the transition of care process can reduce patient mortality, emergency department visits, and cost [7], as well as readmission rates [8]. The presented case highlights just one example of the consequences that may result due to a lack of medication review during transition of care. This example is one of an individual in a high-risk age group taking amiodarone, a medication commonly associated with toxicity and drug interactions, and presenting with tremors that prompted a polypharmacy review.

A plethora of evidence suggests that amiodarone is a common perpetrator of drug-induced tremors and other forms of neurotoxicity in cardiac patients [3,9-11]. However, the incidence has decreased over time, as lower doses are used in practice today [10,12], suggesting a dose-dependent effect. Although the specific mechanism of amiodarone-induced tremor is unknown, several potential mechanisms have been suggested. It has been postulated that the ability of amiodarone to penetrate the blood-brain barrier plays a major role in the development of these adverse drug reactions. Another proposed mechanism of amiodarone-induced tremor is indirectly linked to its potential to cause hyperthyroidism [3]. Amiodarone is structurally similar to thyroid hormone and contains 37% iodine, which is required for endogenous thyroid hormone production in the thyroid gland. In patients without thyroid dysfunction, excess iodine inhibits thyroid hormone synthesis through autoregulation. However, in patients with thyroid dysfunction, this feedback mechanism can fail and lead to hyperthyroidism. Besides excess iodine, the amiodarone molecule itself has direct cytotoxic effects on the thyroid follicular cells, leading to thyroiditis, which may cause tremors [13].

Amiodarone-induced thyroid toxicity only occurs in three percent of patients [14], while neurotoxic effects with amiodarone have been reported in more than one-third of patients [10,15]. Specifically, tremor has been reported in up to 30% of those on long-term amiodarone therapy [15]. Most cases of amiodarone-induced tremor result in enhanced physiological tremor, which is caused by sensitization of muscle spindles [16]; however, further research is required to learn more about this mechanism. Some data suggests the risk of experiencing amiodarone-induced tremors increases with duration of treatment [10], which highlights the importance of timely discontinuation of amiodarone or switching to appropriate chronic therapy post-discharge from the critical care setting.

The length of time between discontinuation of amiodarone and reduction in amiodarone-induced tremors, in this case, was approximately four weeks. This delay is expected given amiodarone's long elimination half-life (58 days on average). Amiodarone-induced toxicity and drug-drug interactions can persist for weeks to months following discontinuation. Elimination is even further prolonged in older adults over the age of 65 years due to pharmacodynamic and pharmacokinetic changes associated with aging and the use of multiple medications [11]. Additive adverse effects of duloxetine may have also played a role in causing or worsening tremors. Duloxetine has been associated with extrapyramidal symptoms such as dyskinesia [17,18]. While no formal pharmacokinetic studies have been conducted with concomitant use of duloxetine and amiodarone, the potential for a drug interaction exists, further increasing the likelihood adverse effects. Amiodarone inhibits CYP1A2 and CYP2D6 [4], two major metabolic pathways of elimination for duloxetine [19]; concomitant administration of these medications may increase the plasma concentrations of duloxetine. Previous pharmacokinetic studies have

demonstrated that, in the presence of CYP1A2 and CYP2D6 inhibitors, the area under the curve for duloxetine has increased by 460% and 60%, respectively [19,20]. Therefore, a similar result may be expected with the combination of duloxetine and amiodarone.

Like many older adults, this patient had a multitude of co-morbidities, including hypothyroidism and COPD. Among the adverse effects associated with amiodarone, thyroid hormone fluctuations and pulmonary toxicity are of great concern, and the latter is included as a boxed FDA warning for amiodarone. Despite the patient's pre-existing conditions, amiodarone was continued post-discharge.

Conclusion

This case serves to demonstrate the need for medication review and clinical pharmacist involvement in transition of care after initiation of amiodarone during hospitalization. Long-term continuation of amiodarone without re-evaluation of therapy can result in unrecognized adverse drug reactions and may contribute to increased healthcare utilization. In the presented case, a complaint from the patient regarding worsening tremors prompted a thorough polypharmacy review by a clinical pharmacist, leading to the resolution of an adverse drug reaction and prevention of further amiodarone toxicity. Due to the high potential for toxicity and drug interactions, amiodarone therapy should be reviewed and re-evaluated routinely to determine its appropriateness given the diagnosis and the availability of alternative therapy. Clinical pharmacists can contribute their expert pharmacological knowledge to properly evaluate medication regimens post-hospitalization.

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