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Medication-Related Problems in Older Adults and the Importance of Comprehensive Medication

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Abstract

Objective: Older adults are at greater risk for medications-related problems due to age-related changes in drug disposition. Therefore, it is important to properly identify and mitigate the use of inappropriate medication(s) in this population. The purpose of this case is to demonstrate the importance of identifying and evaluating the medication-related problems in older adults via pharmacist-led comprehensive medication reviews.

Case: A 69-year old female patient with a past medical history of hypertension, myocardial infarction, atrial fibrillation, and hyperlipidemia has reported to her medical team with chief complaints of increased blurry vision, yellow-brown deposits within her eyes, and gradual hair loss over the last two to three months. The clinical pharmacist conducted a comprehensive medication review and noted that these symptoms were likely adverse drug reactions caused by amiodarone, and recommended discontinuation of the amiodarone in an effort to mitigate toxicities. One month later, the pharmacist followed-up with the care team, and was notified that the patient noticed improvement in her vision and continues to deny symptoms related to atrial fibrillation. The pharmacist recommended continuation of close monitoring of the patient for the next few months.

Conclusion: This case sheds light onto the importance of pharmacist-led comprehensive medication reviews to identify medication-related problems in older adults. Careful prescribing and continuous reviews of medication regimens can help to mitigate and prevent medication-related problems such as adverse drug effects and drug-drug interactions.

Keywords: Medication-related problems • Comprehensive medication reviews • Pharmacokinetic • Pharmacodynamics • Atrial fibrillation • Drug-drug interactions • Adverse drug reactions

Abbreviations: MRPs: Medication-Related Problems; PK: Pharmacokinetic; PD: Pharmacodynamics; CMRs: Comprehensive Medication Reviews; Afib: Atrial Fibrillation

Introduction

A medication-related problem (MRP) is defined as any undesirable event or situation experienced by a patient that is caused by drug therapy [1]. Examples of MRPs include drug interactions, improper drug selection, and adverse drug reactions [1]. Evidence indicates that older patients are at greater risk for MRPs due in part to Pharmacokinetics (PK) and Pharmacodynamics (PD) changes that occur with aging [2]. PK changes in older adults can include a decline in renal function, resulting in the accumulation of drugs and leading to toxicity [2]. Another PK change that can occur with aging is a reduction in first-pass metabolism, which is caused by a decrease in liver mass and blood flow. Therefore, the bioavailability of medications that undergo extensive first-pass metabolism (e.g., propranolol) can be increased in older adults, which may put them at an increased risk for Adverse Drug Events (ADEs) [2]. PD changes in older adults can be caused by alterations in drug sensitivity (e.g., decreased or increased response upon substrate binding to a receptor) and by impaired homeostasis (e.g., decreased blood pressure or temperature), resulting in an increased risk for ADEs [2,3]. Additionally, the presence of polypharmacy further increases the risk for drug interactions leading to ADEs and to non-adherence in older adults [4]. Several tools, such as the Beers Criteria, Screening Tool of Older Persons' Prescriptions (STOPP), and Medication Appropriateness Index (MAI), can aid in the identification of MRPs, such as potentially inappropriate medication use [5]. These tools can be particularly useful for pharmacists when performing CMRs to identify and prevent ADEs. Evidence suggests that pharmacist-led CMRs result in reduced occurrence of MRPs and can prevent inappropriate medication use in the geriatric population [6,7]. The following case demonstrates the importance of pharmacist-led CMRs in older adults in order to identify and mitigate MRPs.

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Case Report

A 69-year-old female, with a past medical history of myocardial infarction, hypertension, Atrial Fibrillation (Afib), and hyperlipidemia has reported to her medical team with chief complaints of increased blurry vision, yellow-brown deposits within her eyes, and gradual hair loss over the last two to three months. The patient's care team decided to have a clinical pharmacist review her medication list (Table 1) in order to identify if medications were the root cause for these adverse effects. During the CMR, the clinical pharmacist noted that these events could be the result of amiodarone toxicity and inquired about the duration and history of amiodarone therapy [8]. The patient had been prescribed amiodarone 200 mg daily for her Afib, and her condition had been maintained on it for nearly one year. The patient reported no palpitations, irregular heartbeats, or episodes of syncope compared to when her Afib was first diagnosed. Per the electronic health record and discussions with her care team, the patient was in normal sinus rhythm based on her latest EKG.

The clinical pharmacist knew that, while amiodarone is indicated for Afib, it is considered a potentially inappropriate medication for older adults due, in part, to the altered PK of amiodarone in this population [8]. Amiodarone can cause various ADEs (e.g., toxicities in the eye, pulmonary toxicities, thyroid disorders), some of which are seen in this patient. The clinical pharmacist also recognized that amiodarone could interact with the patient's warfarin,

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

Acetaminophen 25 mg: take one to two tablets by mouth every 4-6 hours as needed for pain (do not exceed ten tablets in 24 hours unless directed by a doctor)
Amiodarone 200 mg tablet: Take one tablet by mouth once daily at bedtime for heart
Atorvastatin 80 mg: Take one tablet by mouth once daily in the morning for cholesterol
Clopidogrel 75 mg: Take one tablet by mouth once daily in the morning for blood thinner
Furosemide 40 mg: Take one tablet by mouth once daily as needed for water retention
Lisinopril 10 mg: Take one tablet by mouth once daily in the morning for blood pressure
Metoprolol succinate 100 mg, extended release: take one tablet by mouth once daily in the morning for heart
Vitamin D3 50 mcg: Take one tablet by mouth once daily in the morning for supplement
Warfarin 10 mg: Take half a tablet by mouth once daily in the morning on Monday and Friday for blood thinner
Warfarin 7.5 mg: Take one tablet by mouth once daily in the morning on Sunday, Tuesday, Wednesday, Thursday, and Saturday for blood thinner

potentially resulting in an increased risk for bleeding, and could interact with metoprolol, leading to reduced heart rate, decreased Atrio-Ventricular (AV) conduction and AV block, dizziness, and light-headedness [9]. However, the patient's International Normalized Ratio (INR) was stable and she did not report any dizziness or light-headedness.

The clinical pharmacist who conducted the CMR recommended discontinuation of amiodarone, in an effort to mitigate potential drug-drug interactions and toxicities. The clinical pharmacist advised the care team to monitor the INR closely during the next several weeks to reduce the risk of stroke. One month later, the clinical pharmacist followed-up and learned that the patient was no longer complaining of blurry vision or corneal deposits and has noticed a reduction in the rate of hair loss without any noticeable symptoms of Afib. Knowing that full resolution of symptoms may take an additional one to two months because amiodarone and its active metabolite have a long elimination half-life (~61 days) [10], the clinical pharmacist advised continued monitoring of the patient's vision, EKG, INR, heart rate, and symptoms of Afib.

Discussion

This case study demonstrates the impact of a pharmacist-led CMR in identifying and mitigating one particular MRP (i.e., inappropriate medication). In older adults (>65 years old), various changes occur with agin [11]. Age-related physiological changes can result in altered PK of many drugs, including amiodarone [12,13]. Amiodarone is a class III antiarrhythmic medication, which was used by 8-11% of patients with median age of 70 years old enrolled in The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) a multicenter, double-blind randomized control trial (n = 14,264) [14,15] for the treatment of life-threatening ventricular arrhythmias and Afib [8]. Prevalence of adverse effects with the use of amiodarone ranges from 15% in the first year of treatment to 50% in cases of prolonged treatment [16].

This medication has unpredictable absorption and is very lipophilic, resulting in a large volume of distribution and a long half-life [17]. These PK parameters are altered in older adults; for example, the volume of distribution of amiodarone will be further increased due to increased body fat in older adults, which results in longer half-life [17]. Subsequently, older adults are at increased risk for ADEs and toxicities (e.g., visual problems, thyroid problems, pulmonary toxicities) with amiodarone. The mechanism behind the most common visual problem experienced by this medication, corneal deposits, can be explained by the cationic amphiphilic structure of amiodarone [18]. This structure allows the medication to cross the cell membrane, which can lead to phospholipid accumulation and subsequently, corneal deposits [18]. In addition, amiodarone's high iodine content and its tendency to accumulate in different organs in the body are responsible for the toxic effects of this medication on the thyroid and lungs [19,20]. Due to concerns over these ADEs, amiodarone is listed in the Beers Criteria as a medication to be avoided as first-line therapy in older patients [21].

Amiodarone inhibits multiple cytochrome P450 (CYP) enzymes, including *CYP2D6* and *CYP2C9*, and is extensively metabolized through *CYP3A4*. As a result, it can alter the metabolism of many drugs that are metabolized via these enzymatic pathways [8]. Metoprolol and warfarin, both of which were prescribed to the patient in the case, interact with amiodarone. Amiodarone inhibits the metabolism of metoprolol at *CYP2D6*, which leads to increased concentrations of metoprolol. Werner et al. report that the mean plasma concentration of metoprolol was nearly doubled (from 40 ± 19 to 70 ± 34 mcg/L; $P<0.01$) after a loading dose of amiodarone [22]. The study also showed that the area under the plasma concentration-time curve (AUC) of metoprolol increased from 767 ± 355 before to 1,387 ± 615 mcg x hours/L ($P < 0.005$). As a result, patients taking metoprolol and amiodarone can be at increased risk for ADEs including reduced heart rate, dizziness, and light-headedness [8,9].

Similarly, concomitant administration of warfarin, given for stroke prevention in patients with Afib, and amiodarone will cause increased levels of both the S and R enantiomers of warfarin due to complete inhibition of the *CYP2C9* and *CYP3A4* enzymes [23]. This will result in prolongation of INR, which will put the patient at increased risk for bleeding [9,23]. A retrospective cohort study in the Swedish population investigated the effect of amiodarone on the anticoagulant effect of warfarin and showed that initiation of amiodarone in warfarin users increased the INR from 2.6 to 3.1 [24]. In addition, one in three patients experienced supratherapeutic INR within 3 weeks after initiation of amiodarone, which necessitated the dose reduction of warfarin (mean decrease of 25%) to avoid ADEs (e.g., bleeding) [24].

Several other alternatives that are safer than amiodarone are available and effective for managing Afib in this population; however, older patients are still being prescribed amiodarone. Amiodarone is often initiated in the hospital setting due to its efficacy and the ability for around-the-clock monitoring of cardiac and hemodynamic status [1,25]. Upon hospital discharge, patients who are not closely monitored often continue amiodarone [25]. Rate-control medications, such as metoprolol, are often preferred over rhythm control therapy (e.g., amiodarone) due to mortality benefits [26]. Results from randomized clinical trials including Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE), have demonstrated an advantage of rate-control over rhythm control therapy in older adults with stroke risk factors [27]. However, for patients who did not receive the benefits from rate-control therapy, have symptomatic heart failure or are still symptomatic (e.g., palpitation, light-headedness) after being treated with beta-blockers, amiodarone should still be considered [28,29].

The patient discussed in this case presented with asymptomatic Afib and did not have any complaints of palpitations, lightheadedness, or dizziness. She did not have a history of heart failure, and she was also in a normal sinus rhythm, per her latest EKG results. In addition, she was experiencing ADEs from amiodarone (e.g., blurred vision) and there were potential drug-drug interactions between amiodarone and her other medications; therefore, the discontinuation of amiodarone was implemented.

Conclusion

Pharmacist-led CMRs can help in identifying and mitigating the MRPs commonly seen in older patients. Pharmacists are uniquely trained to identify medication-related problems and their potential to cause ADEs in older adults, through consideration of drug-specific PK factors. In the case discussed, the

pharmacist was able to speak with the healthcare team, gather information, and make appropriate recommendations to optimize the patient's regimen. The noted improvement in the patient's symptoms highlights the importance of CMRs to identify MRPs, such as the use of inappropriate medications.

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