Case Report
Volume 10:7, 2020
DOI: 10.37421/jccr.2020.10.1368

Clinical Case Reports

ISSN: 2165-7920 **Open Access**

Angiotensin Converting Enzyme (ACE) Inhibitor-Induced Cough Resulting in Prescribing Cascade

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Abstract

Objective: Prescribing cascade usually results from the misdiagnosis of a drug-related adverse event or condition. Although the prevalence of prescribing cascade remains unknown, it likely increases the risks associated with polypharmacy (e.g., adverse drug events). Furthermore, consequences of prescribing cascade are more likely to be detrimental for the elderly population due to the presence of multiple chronic diseases and the complexity of the derived medication regimen. This case aims to shed light on a particular prescribing cascade due to Angiotensin-Converting Enzyme (ACE) inhibitor-induced cough.

Case: A 101-year-old male with a past medical hypertension, osteoarthritis, gastroesophageal reflux disease, atrial fibrillation, hyperlipidemia, muscle weakness, and mild intermittent asthma was experiencing worsening of cough. To manage his hypertension, the patient was previously prescribed lisinopril and amlodipine. To control the cough, the patient was then prescribed benzonatate (Tessalon Perles®) and budesonide-formoterol (Symbicort®). Lisinopril-induced cough was postulated; after the discontinuation of lisinopril and the initiation of losartan, the cough resolved. However, the use of the benzonatate and budesonide-formoterol was not re-evaluated.

Conclusion: This case is an example of prescribing cascade resulting from a misdiagnosis of an ACE inhibitor-induced cough. Misdiagnosis may result in inappropriate prescribing of medications that increase the risks resulting from polypharmacy, such as adverse drug events. Pharmacists are uniquely positioned to intercept and avoid such prescribing cascade.

Keywords: Prescribing cascade • Angiotensin converting enzyme inhibitors • Cough • Polypharmacy

Abbreviations: • ACE Inhibitor(s): Angiotensin-converting Enzyme Inhibitor(s) • MSR: Medication Safety Review • ACE: Angiotensin Converting Enzyme • ARB: Angiotensin Receptor Blocker • MRP: Medication Related Problem

Introduction

Many geriatric patients are treated for cardiovascular diseases for which they are prescribed Angiotensin-Converting Enzyme (ACE) inhibitors. In addition to antihypertensive effects, ACE inhibitors have the benefit of reducing complications caused by some diseases, such as coronary artery disease, heart failure, diabetes, and diabetic nephropathy [1]. Although ACE inhibitors are generally tolerable, almost 20 percent of patients discontinue treatment due to adverse drug effects, particularly the induction of a dry cough [1,2]. It is estimated that up to 35 percent of patients treated with an ACE inhibitor experience drug-induced cough [3,4]. The dry cough is predominantly seen among females and non-smokers, but its pathogenesis remains uncertain and is presumed to be multifactorial [5]. Due to lack of specificity, the identification of ACE inhibitor-induced cough remains a common challenge among clinicians [6,7].

The concept of prescribing cascade was originally coined by Rochon and Gurwitz in 1995 to describe a major geriatric problem [8]. Prescribing cascade remains a major problem within the healthcare system and is often an unrecognized contributor to polypharmacy, especially in geriatric populations [5,9]. Due to the complexity of chronic diseases that are common with advancing age, a new symptom may be misinterpreted as a new condition rather than an adverse event of a current medication; such an assumption leads to initiation of new medications, resulting in prescribing cascade [9].

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Received 18 June 2020; **Accepted** 25 June 2020; **Published** 02 July 2020

Case Presentation

A 101-year-old male with a past medical history of hypertension, osteoarthritis, gastroesophageal reflux disease, atrial fibrillation, hyperlipidemia, muscle weakness, and mild intermittent asthma presented five months ago with a chief complaint of persistent cough. At the time, the patient was already taking 21 medications, including lisinopril, for management of his chronic conditions. Clinical staff at his Assisted Living Facility (ALF) initiated budesonide-formoterol and benzonatate, as they believed the cough was due to uncontrolled asthma.

Five months after initiation of this treatment for asthma-related chronic cough, a clinical pharmacist conducted a comprehensive medication review (CMR) as the patient was still complaining of that persistent cough. The pharmacist advised the ALF that the cough may be induced by the ACE inhibitor, lisinopril, and recommended switching from lisinopril to an Angiotensin Receptor Blocker (ARB). Pursuant to the clinical pharmacist's recommendation, the ALF staff changed the patient's lisinopril to losartan. A few months later, on a follow up CMR, it was noted that the patient responded well to the change in therapy and the cough resolved. Subsequently, the clinical pharmacist questioned the continued need for benzonatate and budesonide-formoterol, as the patient was no longer presenting a cough or symptoms of asthma exacerbations. Recognizing the prescribing cascade, the ALF staff discontinued both of these medications per pharmacist recommendation. No harm resulted from the initiation of both therapies and the patient's medication burden and out-of-pocket costs decreased after discontinuation.

Discussion

This case serves as an important reminder of a clinical pharmacist's role in identifying and mitigating prescribing cascade. An ACE inhibitor-induced cough may occur within hours of the first dose of medication or its onset can be delayed for weeks, even months, after initiation of therapy [1-7]. While the cough usually resolves within one to four weeks after discontinuation of therapy, it may persist for up to three months in some individuals.

Although the etiology of ACE inhibitor-induced cough remains unclear, there are several proposed mechanisms. One such mechanism is suggested to be linked to the accumulation of bradykinin and prostaglandins, secondary to a decrease in angiotensin II production [6]. ACEs Amino Peptidase-P (APP) and Neutral Endopeptidase (NEP) are protease enzymes that are responsible for the degradation of bradykinin. However, the angiotensin-converting enzyme is thought to be the most effective at facilitating the degradation. ACE inhibitors are known to block the conversion of angiotensin I to angiotensin II, thereby impacting the degradation of bradykinin [1]. While bradykinin usually has a short half-life, it may prolong with the use of an ACE inhibitor. The presence of an ACE inhibitor can increase bradykinin concentration, which then stimulates prostaglandin synthesis, thereby inducing a dry, tickly, and often bothersome cough [3-6]. The only effective intervention for ACE inhibitor-induced cough is the discontinuation of the offending agent-in this case, lisinopril [4].

When discontinuing an ACE inhibitor, several alternatives may be considered. Among the most prescribed alternatives are ARBs. ARBs are unlikely to induce cough because their mechanism of action does not involve ACE inhibition. Thus, use of ARBs as ACE inhibitor alternatives avoids the elevation of bradykinin and substance P [3].

In this patient case, lisinopril was identified as the offending agent and was discontinued; however, the budesonide-formoterol inhaler and benzonatate were enduringly administered as chronic medications after the ACE inhibitor-induced cough diagnosis. During a second CMR with access to patient medical record, the pharmacist recommended re-evaluating the need for the subsequent cough suppressant and inhaler. Although there is limited evidence about the long-term safety of benzonatate, case reports demonstrate the drug having a narrow safety margin [10,11]. Even when administered at therapeutic doses, benzonatate still has the potential for adverse effects when administered incorrectly. Crushing or chewing benzonatate has resulted in bronchospasm, laryngospasm, seizure, and subsequent cardiovascular events [11]. With regards to budesonide-formoterol, studies demonstrate an increased risk of osteoporosis and fractures from long term use of inhaled corticosteroids; however, this association is inconsistent across the existing body of literature [12]. Most observational studies regarding these adverse effects are among individuals with chronic obstructive pulmonary disease [12,13]. Although the evidence is sparse, there may still be a risk with long-term use.

The pharmacist reviewed the patient's medication regimen during routine CMRs and, with collaboration from the facility providers, was able to uncover the history behind each medication and determine the need for discontinuation. Among individuals with multiple chronic conditions, identifying underlying problems may be difficult, thereby increasing the probability of the initiation of new agents and subsequent adverse effects. Previous studies show that Medicare beneficiaries with chronic conditions such as chronic heart failure, diabetes, respiratory conditions, and hypertension have significantly higher odds of incurring a Medication-Related Problem (MRP). MRPs were also found to be about twice as common among individuals taking eight or more medications, with chronic medications increasing risk by an additional 10 percent [14]. An interdisciplinary approach to care is essential to enable proper recognition of such prescribing cascade by clinicians. In this case, pharmacist collaboration with a clinic nurse and pharmacist access to complete medical records was necessary in order to identify and resolve the cascade.

Although the prevalence of prescribing cascade is currently unknown, its occurrence unequivocally leads to unnecessary polypharmacy. As a result, subsequent adverse drug events and their associated sequelae, such as hospitalizations and increased healthcare utilization (e.g., increased medical costs), can be reasonably expected. An essential element to prevent prescribing cascade is avoidance and early detection [8]. To mitigate these risks, pharmacists must identify the root cause of the cascade and determine if

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

Acetaminophen 500 mg tablet: 2 tablets by mouth twice daily
Vitamin D3 2000 units tablet: 1 tablet by mouth once daily
Omeprazole 20 mg delayed-release capsule: 1 capsule by mouth once daily
Guaifenesin 100 mg/5 ml syrup: 5 ml by mouth every 4 hours as needed
Albuterol sulfate 2.5 mg/3 ml (0.083%) solution for nebulization: Inhale 1 vial via nebulizer 4 times daily
Polyethylene glycol 3350 powder for solution: Mix 1 capful in 4 to 8 ounces of fluid by mouth daily as needed
Eliquis 2.5 mg tablet: 1 tablet by mouth twice daily
Amlodipine besylate 5 mg tablet: 1 tablet by mouth once daily
Artificial tears (Hypromellose) 0.3 % eye drops: Instill 1 drop in each eye twice daily
Fiber therapy 2 g/19 g powder for suspension: Mix 1 teaspoon in 4 to 8 ounces of fluid and take by mouth daily
Trazodone hydrochloride 50 mg tablet: 1 tablet by mouth once daily
Simvastatin 10 mg Tablet: 1 tablet by mouth once daily
Tessalon perles 200 mg liquid filled capsule: 1 capsule by mouth 3 times a day as needed
Symbicort 80mcg-4.5 mcg/actuation HFA aerosol inhaler: Inhale 1 puff by mouth twice daily
Losartan 50 mg tablet: 1 tablet by mouth once daily
Metoprolol succinate 50 mg extended-release tablet: 1 tablet by mouth once daily
Preservision AREDS 2 soft gel: 1 capsule by mouth twice daily
Zofran ODT 4 mg: Dissolve 1 tablet by mouth every 6 hours as needed
Torsemide 10 mg tablet: 1 tablet by mouth once daily
Melatonin 10 mg capsule: 1 capsule by mouth once daily
Calcium 600 mg tablet: 1 tablet by mouth twice daily

the offending medication of the cascade can be altered (Table 1). Thereafter, medications used to treat the adverse drug reaction should be immediately re-assessed for necessity. Healthcare provider education and recognition of prescribing cascade can reduce the risk of adverse events in this population [13,14].

Conclusion

While primary healthcare providers are largely responsible for the management of patients' chronic conditions, collaboration with pharmacists can supplement this responsibility. Additionally, clinical programs that implement CMRs aid in the identification of MRPs and produce actionable recommendations for providers. The collaborative approach and access to the patient medical record helps clinical pharmacists and prescribers select the most appropriate therapy based on several pertinent factors. More importantly, this approach enables clinicians to identify the appropriateness and indication of medication therapy.

Acknowledgements

The authors want to thank Dana Filippoli and Amy Haines for their comprehensive review and comments on the content of this paper.

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How to cite this article: Stacy-Ann Wright, Chandni Bardolia, David Bankes, and Nishita Shah Amin, et al. "Angiotensin Converting Enzyme (ACE) Inhibitor-Induced Cough Resulting in Prescribing Cascade." Clin Case Rep 10 (2020): 1368. DOI: 10.37421/jccr.2020.10.1368