

Pharmacogenomics Case: Unintentional Overdose from β -Blockers

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Background

While medications are a critical component of the care of PACE participants, they also can cause problems. A medication-related problem (MRP) is defined as any undesirable event experienced by a patient, involving or is suspected to involve his or her medication and potentially or actually interfering with a desired therapeutic outcome or leading to a deleterious outcome.

Medication-related problems cause hundreds of thousands of emergency department visits, hospitalizations, and deaths annually in the United States.¹⁻⁴ Additionally, the costs of MRPs rival the costs of leading diseases in the United States. Today, MRPs cost over \$200 billion in health care costs.⁵⁻¹⁰ As high users of medications, PACE participants are at high risk of MRPs.

Numerous factors are associated with MRPs. One of the most common, yet under-recognized, factors is unintentional overdose. According to a national study, two-thirds of hospitalizations of older Americans are due to unintentional overdose of medications.¹¹ There are myriad contributing factors to unintentional overdose, but one of the most significant factors is a participant's genetic makeup.

Pharmacogenomics (PGx) is the study of how genetic makeup influences medication response. Genetic variation in drug-metabolizing enzymes and drug transporters can significantly affect medication concentrations and, hence, increase the risk of MRPs. Many enzymes involved in medication metabolism carry genetic variants (polymorphisms) that can increase or decrease enzyme activity or, in

certain cases, even lead to the complete inactivation of the enzyme involved.¹² Such variation can lead to higher or lower concentrations of a medication and its metabolites during the initial steps in the metabolism of the medication, which are mostly mediated by the cytochrome P450 (CYP) enzyme family. The CYP2D6 enzyme, for example, is known to be involved in the metabolism of β -blockers. The CYP2D6 enzyme has been found to exhibit high individual variability in metabolic activity mainly caused by genetic polymorphisms.^{13,14} The purpose of this article is to provide a real-life example of how PGx can be applied to individualize the medication care plan for a PACE participant in order to reduce the risk for unintentional overdose from a β -blocker.

PGx Case

A 60-year old Caucasian male presented to a PACE program with a past medical history of cerebrovascular accident with left hemiparesis and dysarthria, as well as heart failure, coronary artery disease with stent placement, aortic stenosis, and atrioventricular block with a pacemaker. He had a history of very frequent falls (six in a four-month time period), which were assumed to be from his hemiparesis. He had occasional orthostatic hypotension, but not consistently, and he complained of constant dizziness, which was felt to be lightheadedness and not interpreted as vertigo. At the time of enrollment in the PACE program, the participant was already prescribed the β -blocker metoprolol tartrate 50mg twice daily. His condition continued to deteriorate, which led to response-guided dose reductions of metoprolol from 50mg twice daily to 37.5mg twice daily and

subsequently to 25mg twice daily. A PGx test was ordered by the participant's physician, and the results demonstrated that the participant had CYP2D6 genetic polymorphism. Specifically, the participant was a CYP2D6 intermediate metabolizer. Based on the newly-uncovered information about the participant's genetic makeup coupled with the CareKinesis pharmacist's recommendation, the physician weaned the participant off metoprolol and started alternative therapy with atenolol 25mg once daily. After switching to atenolol, the lightheadedness reportedly subsided and the frequency of the falls reduced. The participant continued on atenolol for approximately three months but, unfortunately, continued to fall.

Ultimately, the atenolol was discontinued and no alternative β -blocker was initiated. Confounding factors in this case included his pacemaker, which made it difficult to evaluate the chronotropic effect of the β -blocker, and the participant was also prescribed low-dose fludrocortisone about a month after starting atenolol.

The process involved in this case is depicted in the screen shot and described in detail below. As the first step (1), the pharmacist accessed the "precision prescribing" component of the CareKinesis Medication Risk Mitigation (MRM) system, which, in this case, included the results of the PGx test. As the second step (2), the pharmacist interpreted the results of the PGx test in the context of the participant's current medication regimen. As the third step (3), the pharmacist prepared a recommendation to send to the participant's physician. As the fourth step (not depicted), the pharmacist followed up with the participant's physician and other health care providers to obtain information about the participant's response to the metoprolol. As the fifth and final step, the pharmacist made a specific recommendation, based on the

aforementioned PGx test results and clinical status, to individualize the medication care plan for a PACE participant. In this case, the pharmacist recommended trying an alternative β -blocker (i.e., atenolol) to potentially mitigate the unintentional overdose causing hypotension in this participant.

Explanation & Summary

The medical impact of polymorphisms in CYP2D6 on the response to β -blockers is controversial.

While a detailed discussion of the controversy is beyond the scope of this article, it is worth some explanation in the context of this participant case.

Metoprolol metabolism is primarily mediated by CYP2D6, with approximately 60% of the oral metoprolol dose being metabolized by this cytochrome enzyme.¹⁵ There is ample evidence in the literature that reproducibly shows that CYP2D6 polymorphisms cause variation in metoprolol pharmacokinetics as well as affect the pharmacokinetics of other β -blockers such as carvedilol.^{16,17} However, whether these differences in metoprolol pharmacokinetics translate into variability in response (i.e., pharmacodynamics) is a subject of ongoing debate.¹⁸⁻²⁰ Fueling this debate are some studies showing that CYP2D6-related pharmacokinetic variation does not carry forward into pharmacodynamic variation.^{16,17}

In other words, while CYP2D6 polymorphisms affect β -blocker pharmacokinetics, the polymorphisms have shown no apparent effect on pharmacodynamics, namely blood pressure. There are numerous explanations for these study findings including, but not limited to, the following: response to β -blockers may also be modulated by genetic variation in β -adrenergic receptors (ADRB); in addition to CYP2D6, several cytochrome enzymes contribute to the metabolism of β -blockers, with possible contributions by CYP1A2,

CYP2C9, CYP2C19 and CYP3A4; even among the frequent CYP2D6 alleles (*1, *2, *9, *10, *17 and *35), there may be differences in enzyme expressions and metabolic activities; some β -blockers are metabolized to active metabolites, which contribute, in some cases significantly more than the parent medication, to their clinical effects; and, there appears to be great inter-individual variation in the affinity and maximum β -blocker effects.¹⁶

This ongoing debate should not detract from the clinical application of PGx. As demonstrated in this case, information about a participant's genetic makeup helped explain, at least in part, his poor response to β -blocker therapy. Learning that the participant was a CYP2D6 intermediate metabolizer helped inform the pharmacist's and physician's decision to switch the metoprolol to an alternative β -blocker. Although the participant continued to fall despite the therapy modification, the

frequency of his falling reduced and his lightheadedness subsided. It is plausible that the PGx-guided therapy change was a safer option than the continued response-guided dose reductions.

In summary, preventing and reducing MRPs is complex and successful interventions are often multilayered. Participants enrolled in PACE with complex medication regimens require a much more personalized approach. Central to this personalized approach is PGx testing to assess participants' genetic predisposition to safely and effectively respond to medications. The example provided by this case is part of CareKinesis services that provide multilayered, pharmacist-provided interventions using an innovative MRM platform, which incorporates PGx testing and application, to individualize medication care plans for PACE participants in order to mitigate unintentional overdose and optimize health outcomes.

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