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The Utility of Pharmacogenetics in a Patient with Terminal Illness: A Case Report

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Abstract

Pharmacogenetics (PGx) is an emerging science which looks at genetic factors (pharmacogenes) that can influence drug tolerability and efficacy, depending upon variations in the resulting proteins function or structure. Variants of certain pharmacogenes can increase the risk of side effects, affect drug exposure and help predict likelihood of efficacy or inefficacy. The prevalence of such genetic mutations varies by ancestry and is not equally distributed in populations. Commercial PGx assays typically evaluate both pharmacokinetic (PK) and pharmacodynamic (PD) genes. Pharmacokinetic genes, such as those coding for the cytochrome P450 enzyme superfamily, have been shown to affect drug exposure and influence the absorption and metabolism of many drugs used across multiple disease states. Pharmacodynamic genes typically encode for proteins that are more often drug targets, such as receptors. They are more related to drug sensitivity or response without providing any dosing guidance. In general, PK genes are considered more actionable than PD genes. We present a complex case in which multiple genetic variants provided insights into the patients previous care and future management.

Keywords: Pharmacogenetics • Opioids • ADHD • Anxiety • Depression

Introduction

Case report

A 61-year-old Caucasian woman presented to her primary care physician with intractable pain and anxiety due to metastatic adenocarcinoma of the colon. She stated that "several" medications she had tried for pain and anxiety had not provided relief. She also complained of insomnia and lassitude. Her colon carcinoma had been treated with multiple bouts of chemotherapy over a four-year period and she was aware of her terminal prognosis.

She had a past medical history of type 2 diabetes mellitus, carcinoma of the left breast, vitamin B12 deficiency, iron deficiency anemia and gastroesophageal reflux, in addition to generalized anxiety disorder. She had previously been prescribed methylphenidate for "brain fog", without relief. She inquired about pharmacogenetic testing as she had not obtained relief for pain and anxiety with past medications. She was unsure what anxiolytics she had tried, but had failed a trial of tramadol for pain and had experienced constipation from other opioids. Current medications included eszopiclone 2mg HS, empagliflozin 25mg daily, losartan 50mg daily, insulin aspart and rivaroxaban 20mg daily (for a clot associated with her chemotherapy port).

The patient lived alone, did not smoke and used alcohol occasionally. Relevant family history included a maternal history of Alzheimer's disease, leukemia and breast cancer. Her father had Parkinson's disease and coronary artery disease. Her brother had developed an addiction to oxycodone following surgery for back pain. Psychiatric exam revealed a normal affect and mood and no evidence of hallucinations or psychosis.

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The patient was offered and received a 24 gene commercial PGx assay (Genomind, King of Prussia, PA). Pharmacokinetic gene results revealed that she was a CYP2C19 ultrarapid metabolizer, a CYP2D6 and UGT2B15 intermediate metabolizer and had decreased function of ABCB1. Pharmacodynamic gene variants revealed that she was SLC6A4 LS (long short), COMT VAL/VAL, ADRA2A C/C and OPRM1 G/G. The remaining genes were wild type.

Following pharmacogenetic testing she was prescribed celecoxib 100mg daily prn pain, Adderall (amphetamine and dextroamphetamine mixed salts) 20mg daily prn for "chemo fog" and hydroxyzine 50mg TID prn anxiety.

The patient experienced improvement in all symptoms, including her cognitive symptoms and reported that she was "shocked to find out that my body would not metabolize morphine" (sic).

Results and Discussion

Several features of this patient's genetic results are noteworthy. She is a CYP2D6 intermediate metabolizer (*1/*4). CYP2D6 is responsible for the metabolism of dozens of commonly used drugs, including the conversion of tramadol to its active metabolite, O-desmethyltramadol. Therefore, having genetic variants in CYP2D6 could impact the serum levels of certain medications and their metabolites. For example, CYP2D6 poor metabolizers (PMs) have been shown to experience decreased analgesic effects from tramadol due to having reduced serum levels of its active metabolite. Because studies have consistently shown decreased analgesia in CYP2D6 PMs, the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend avoiding tramadol in this patient population [1]. While the guidelines still suggest using the label-recommended starting dose in CYP2D6 intermediate metabolizers, they do mention that "patients should be monitored closely for a less than optimal response and should be offered an alternative analgesic if warranted". This patient had failed treatment with tramadol, possibly due to her CYP2D6 genotype and/or having variants in genes that have been shown to impact opioid sensitivity, such as OPRM1 and COMT.

OPRM1 encodes for the μ opioid receptor and patients carrying the G allele may have decreased sensitivity to opioids, therefore requiring larger than expected doses to achieve adequate pain relief [2,3]. The patient was homozygous for the G allele of OPRM1, (rs1799971), which may have

contributed to her poor response to opioids. The PGx report for this patient stated “non-opioid analgesics may be used if clinically indicated”. Given these results and the patient’s poor response and/or tolerability to opioids, the patient was initiated on celecoxib, a non-steroidal anti-inflammatory drug (NSAID) that is indicated for acute pain, which subsequently led to significant improvement in pain.

COMT encodes for catechol-o-methyltransferase, responsible for the catabolism of dopamine in the frontal cortex. This individual’s genotype for COMT (rs4680) was Val/Val, which has been associated with increased COMT enzyme activity and decreased sensitivity to opioids [4]. VAL/VAL genotype is also associated with an increased likelihood of response to dextroamphetamine for executive function. Therefore, she was empirically started on Adderall (mixed amphetamine salts) for chemotherapy-related cognitive impairment, or “chemo fog”, with significant improvement. Interestingly, the patient’s genotype for ADRA2A (rs1800544) was C/C, which has been associated with decreased response to methylphenidate, which she had previously failed [5].

A limitation of applying the results of these studies to this patient is that COMT studies with dextroamphetamine were performed in healthy adults and ADRA2A studies with methylphenidate were performed in individuals with attention-deficit/hyperactivity disorder. However, there is generally limited data on pharmacologic interventions used to improve chemotherapy-related cognitive impairment.

Conclusion

This case illustrates the utility of PGX in an individual with a complex medical history and concurrent serious medical illnesses. In particular, the results helped elucidate this patient’s poor response to opioids for cancer-related pain and prompted the use of a non-opioid, highlighting the role of PGx testing in individualizing treatment decisions. Additionally, gene-drug and drug-drug or drug-drug-gene interactions, also known as phenoconversion, are a common cause of adverse drug reactions. Polypharmacy is common and most such individuals will have at least one actionable genetic variant. PGx can inform on efficacy and tolerability and has been shown to decrease resource utilization and improve outcomes.

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