PAIN MEDICINE CASE REPORTS

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UNRAVELING THE MYSTERY OF PAIN: A UNIQUE CLINICAL ENCOUNTER AND CASE REPORT

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Background: The Clinical Pharmacogenetics Implementation Consortium published an updated guideline for opioids and CYP2D6, OPRM1, and COMT in December 2020. These guidelines include recommendations to avoid key opioids in patients who are ultrarapid or poor metabolizers of CYP2D6 to avoid toxicity and optimize efficacy.

Case Report: An older woman encountered a letter to the editor in a family magazine regarding genomically based responses to opioids. She reached out for more information and assistance, attesting to continued lack of analgesia to opioids prescribed during occasions of severe pain over the course of many years. A pharmacogenomic analysis proved to be the key to solving her mystery.

Conclusion: Pharmacogenomic results may provide life-altering information transforming a patient's perspective on health care. Personalized medicine may be a key component in providing objective evidence for opioid treatment efficacy. There is a critical need for both provider and patient education to increase awareness of pharmacogenomics and how it can be applied to effective pharmacotherapy. Research is needed to explore appropriate, effective educational methods.

Key words: Case report, pharmacogenomics, pharmacogenetics, opioid, CYP2D6

BACKGROUND

Pain is a debilitating condition that affects the quality of life for many people. In 2021, approximately 51.6 million adults in the United States experienced chronic pain and 17.1 million experienced high-impact chronic pain (1). Pain has a significant economic impact; substantial health care costs and loss of productivity are correlated with pain (1). Addressing pain and improving people's quality of life has been a public health challenge (2).

Opioid analgesics are frequently prescribed to manage pain. In 2023, the overall opioid prescription rate in the United States was 37.5 prescriptions per 100 people (Centers for Disease Control and Prevention). Although the prescription rate in 2023 decreased from 46.7 prescriptions per 100 people reported in 2019, it remains exceptionally high.

Additionally, the response to pain with opioid analgesics is highly variable and may be attributed to genetic polymorphisms (3-5).

Adverse side effects resulting from opioid treatment are very common (6). Administering codeine to a 2-year-old toddler after an adenotonsillectomy resulted in the death of the young boy. Postmortem cytochrome P-450 2D6 (CYP2D6) genotyping indicated that the toddler was an ultrarapid metabolizer of codeine (7). Because of the postoperative deaths of children who were prescribed codeine, preemptive pharmacogenomic testing for prescribing codeine has been routinely implemented at St. Jude Children's Research Hospital (8).

Although the benefits of pharmacogenomic testing for mitigating adverse side effects are clear, patient awareness of pharmacogenomic testing remains limited.

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We report on a case in which a patient learned about pharmacogenomic testing to inform pharmacotherapy from a weekly magazine.

CASE DESCRIPTION

On March 12, 2024, an article entitled, "Smoke Screen," was published (9). It documented a true account of a young adult's medical crisis following years of vaping. The narrative recounts, "Levi was in so much pain from the [chest] tube that he could barely eat or sleep. They had tried morphine, Toradol, IV Tylenol, and oral oxycodone by this point, but nothing seemed to ease the many pieces to the discomfort of the chest tube."

A pharmacist reader of the magazine took note and penned a letter to the editor addressing the possibility that a patient's genomic phenotype could lead to a diminished analgesic response to opioids metabolized via the CYP2D6 pathway (10). The pharmacist related, "if you or someone you know suffers from pain that is not alleviated by common opioids, this may be due to a genetic variation of the CYP450 2D6 enzyme involved in the metabolism of many opioids. Poor metabolizers of this enzyme would not be able to convert those opioids to their active metabolite in the liver and hence wouldn't experience analgesia. A genetic test could determine one's 2D6 metabolizer status and enable the health care team to utilize opioids not metabolized by this pathway" (10).

Nearly 8 months later, in November of 2024, the pharmacist received an email from the administrative office at the magazine requesting permission to connect her with a woman who read the letter and wanted help. The pharmacist acquiesced, setting the stage for an unexpected clinical pharmacogenomics consultation.

Patient Information

Patient SW reached out to the pharmacist a short while after receiving contact information from the magazine. She self-identified as an older, White woman who preferred not to share her exact age or further identifying details. SW shared her pertinent medical history related to pain control, although she was somewhat guarded as she was uncertain she could trust a medical provider to nonjudgmentally listen and believe her narrative. She related an incident involving a tooth extraction during young adulthood followed by extreme agony for days afterward with the oral surgeon dismissing her claims that the narcotic he prescribed didn't work. SW recalled being prescribed codeine at that time. More recently, she experienced acute onset back pain after years of chronic back pain. She underwent an MRI which revealed 2 fractured discs. She was told the treatment was pain control and time, but her pain was, "terrible" for weeks. She was essentially bedbound and unable to function. She did not remember the exact narcotics attempted but again named codeine and hydrocodone. She was unwilling to allow the author to consult with her doctor or pharmacy to verify the precise analgesics attempted or a timeline. SW remembered having short-term relief with a ketorolac injection, but otherwise recalled her experience as, "a nightmare," with doctors, friends and family telling her she was overreacting, that the codeine her doctor prescribed was a very strong narcotic, and that she should carry on.

She was in a haze of pain and guilt, thinking maybe everyone was right and it was all in her head. When she saw the pharmacist's letter to the editor in the magazine, although the back pain incident had been a decade earlier, she read the letter and immediately proclaimed out loud, "that's me! That's exactly me!" She related feeling a deep relief and validation, that she's not crazy and that lack of response to narcotics is real and even in print with scientific rationale.

After further validating the possibility that a patient might not experience analgesia from narcotics, the pharmacist recommended SW undergo genomic testing.

Diagnostic Assessment

Four months later, almost a year after the publication of the initial article, SW had her genomic results. SW reached out to share her results with the pharmacist, sending a screenshot of her laboratory records via cell phone. The pharmacist reviewed the images and provided counseling to SW on the interpretation of her genotype results and its implications regarding her potential future use of opioids. Regarding the CYP2D6 enzyme, SW displayed a *4/*41 genotype. This corresponds to an intermediate metabolizer phenotype. Based on the CPIC Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy recommendations, use label-recommended age- or weight-specific dosing for codeine or tramadol. If no response and opioid use is warranted, consider a non-tramadol or non-codeine opioid (11).

Notably, SW had attempted codeine use previously and did not achieve a response. Thus, should SW encounter a scenario requiring opioid use, opioids not

metabolized via the CYP2D6 pathway would be recommended. These may include methadone or fentanyl (12).

In addition, SW was counseled regarding sharing her genomic results with the appropriate healthcare provider should the need arise. She was reassured that her lack of response to codeine was not all in her head but rather an intrinsic part of her genetic makeup leading to her reduced ability to metabolize codeine to its active metabolite, morphine, and experience analgesia.

Once again, SW verbalized the life-changing implications of her results. Perhaps even more important to her than knowing which opioids to avoid was the proof that her previous experiences with opioids were supported by objective evidence, which left her with a sense of relief and trust in herself, confidence and empowerment to be a self-advocate in the future.

DISCUSSION

Patient awareness of pharmacogenomics and a fundamental knowledge of how it can be applied to effective pharmacotherapy are becoming key objectives in implementing personalized medicine. However, direct research on pharmacogenomic patient counseling is currently very limited. Brewer et al (13). embedded a sub-study in a pharmacogenomics clinical trial that was designed to examine patients' beliefs regarding CYP2D6 genotyping use in assessing tamoxifen efficacy in breast cancer patients. The study demonstrated that the participants understood that genotypes would affect rate of recurrence when prescribed tamoxifen.

Knowledge gaps among healthcare professionals present a barrier hindering pharmacogenomic implementation (14). In addition, pharmacogenomic experts tend to practice at large academic medical centers while the community healthcare settings lack knowledge and expertise (14).

Efforts have been made to increase education and competence, such as NHGRI's Genomic Education Center (GenomeEd) (15). Cincinnati Children's Hospital Medical Center has been a leader in educating and communicating the benefits of pharmacogenomic testing to patient caregivers (16). St. Jude Research also has a strong program focused on communicating with patients and patient caregivers (17).

Despite these efforts, recent survey data reveal that providers have low confidence in their ability to integrate pharmacogenetics into practice (18). While an online pharmacogenomics education program was useful in providing a positive learning experience (19), there is a substantial research gap in evaluating educational modalities to guide the development of effective, efficient, and appropriate programs.

There remains a critical need to broadly communicate to the public the potential for pharmacogenomics in medication management. In this report, we describe how communication in a magazine led to a patient's understanding of her response to opioid treatment. In addition, based on the patient's narrative, there was also a critical need to educate her providers.

This case study illustrates the delivery of person-centered care (PCC). We endeavored to adhere to the preferences of the patient. The patient was guarded in sharing medical information. As a result, the patient did not permit verification of dates or the medication list. At the provider level, empathy and respect are key characteristics of PCC. PCC is based on relational ethics, viewing the patient as a key collaborator in their own pharmacotherapy, predicated on the patient's needs, history, and capabilities. Relational ethics, including mutual respect and knowledge, can be influenced by a patient's medication experience. In concert with pharmacogenomic testing, a patient's medication experience can be influenced by their unique genomic profile. Hillman et al. (20) suggest that a patient's attitude and behavior regarding medications are defined by how the patient relates to health conditions that have affected them and by their own experiences with medications. Privacy of the patient's medication experience relates to the patient's perceived risk and concerns transcending the biomedical realm into the social realm. Importantly, this case study illustrates a pharmacist educating a patient regarding PGx testing. The pharmacist was aware of relational ethics and counseled the patient on the potential benefits of PGx testing in the context of the patient's medication experience.

Patient SW presented with a CYP2D6 genotype *4/*41, which is defined as an intermediate metabolizer phenotype. While avoidance of codeine is recommended with a strong recommendation classification for patients with CYP2D6 poor metabolizer phenotype, the CPIC Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy recommendation for codeine use in patients with an intermediate metabolizer phenotype is considered a moderate recommendation. This moderate recommendation indicates that "there is close or uncertain balance" regarding whether the evidence is high quality and whether the desirable effects clearly outweigh the undesirable effects (11).

Vevelstad and colleagues examined the metabolism of codeine by measuring levels of metabolized morphine in the urine of patients who were normal and intermediate metabolizers of CYP2D6 (21). The authors concluded that the amount of morphine generated by the metabolism of codeine may be insufficient for effective pain relief. A more recent study conducted by Radford et al. (21) and published in 2019 investigated whether urine samples to measure codeine metabolism in patients who completed a pain assessment could predict 2D6 phenotype . The authors found that all poor and intermediate metabolizers were codeine nonresponders. In line with these studies, our patient with an intermediate metabolizer phenotype reported lack of analgesia to codeine.

In comparison to the CPIC Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy (12), the Centers for Disease Control and Prevention (CDC) Clinical Practice Guideline for Prescribing Opioids for Pain addresses whether to initiate opioids for pain, selecting opioids and determining dosages, deciding duration of opioid prescriptions with appropriate follow-up, and assessing risk and addressing potential harms of opioid use (23). The guidelines do not offer recommendations concerning pharmacogenomic testing or the use of pharmacogenomic results to guide opioid selection and dosage.

Similarly, the World Health Organization (WHO) published two guidelines addressing opioid use, including Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence (24) and Community Management of Opioid Overdose (25). These guidelines do not address pharmacogenomic testing nor offer recommendations regarding applying pharmacogenomic results to patient care. There appears to be an opportunity for both the CDC and WHO to expand guidance on implementation and utilization of clinical pharmacogenomics.

The Gender Pain Gap represents the phenomenon of women's pain being dismissed and undertreated compared to men's pain (26). Women's pain is more likely to be considered psychological or hysterical, influencing patient care (27). This gap is also evident when comparing opioid use by sex: women were significantly more likely than men to report lifetime opioid use (28). Moreover, experiencing dismissal of pain by health care providers may lead to feelings of guilt, inadequacy, and helplessness and impact future help-seeking behavior (29). SW described her experiences as, "a nightmare," being accused of overreacting and being told to, "carry on," leading to guilt and fear that perhaps the pain was all in her head. Obtaining irrefutable evidence of her genomic polymorphism translating to a lack of analgesic response to opioid narcotics confirmed what has been described in the literature: objective diagnostics greatly influence the healthcare experience, quality of life, and emotional state (30).

CONCLUSION

Pharmacogenomic results may provide life-altering information transforming a patient's perspective on health care. Personalized medicine may be a key component in providing objective evidence for opioid treatment efficacy. There is a critical need for both provider and patient education to increase awareness of pharmacogenomics and how it can be applied to effective pharmacotherapy. There is a need for research exploring appropriate effective educational methods.

Author Contributions

SB identified the patient case, interacted with the patient, obtained informed consent from the patient, and drafted the patient case portion of the manuscript as well as portions of the introduction and discussion.

ZL provided guidance for the pharmacogenomic analysis and drafted the introduction, background, discussion, and conclusion of the manuscript.

Both authors were involved in contributing to and reviewing multiple drafts of the manuscript and approved the final version for submission.

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