Hyponatremic Cognitive Dysfunction Resulting from Drug-Drug-Gene Interaction between Sertraline and Cannabidiol in an Intermediate CYP2C19 Metabolizer Patient

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Abstract

Background: *Pharmacogenomics (PGx) can provide more precision in determining causation of adverse drug reactions (ADRs) from drug-drug-gene interaction clinical application.*

Case Summary: *Patient was an intermediate CYP2C19 metabolizer on stable therapy taking a low but therapeutic dose of sertraline for depression and anxiety over a period of 20 years. The patient then became hyponatremic and cognitively impaired after addition of cannabidiol (CBD) to this sertraline regimen. The proposed mechanism was drug-drug-gene interaction of CBD further inhibiting the CYP2C19 metabolism of sertraline and increasing drug exposure to produce moderate to severe hyponatremia and subsequent cognitive dysfunction.*

Practice Implications: *Pharmacogenomics (PGx) testing may assist in etiology of patient symptoms from adverse drug reactions (ADRs) or drug-drug interactions by combining these with detection and application of drug-gene interactions. This case shows inhibition of CYP2C19 by CBD to further increase sertraline exposure, producing hyponatremia and subsequent cognitive dysfunction through CYP2C19 phenoconversion by CBD.*

Keywords: CYP2C19, Hyponatremia, Drug-drug-gene interaction, pharmacogenomics, cannabidiol, PGx

Background

Sertraline is a common selective serotonin reuptake inhibitor (SSRI) used to treat a variety of anxiety disorders and depression. Its metabolism is mediated by the cytochrome P450 system, with the highly polymorphic CYP2C19 specifically at the forefront via N-demethylation.[1-2] SSRIs and other classes of antidepressants such as the tricyclics (TCAs) are a known cause of hyponatremia, especially in elderly patients.[3,4] Hyponatremia, defined as a serum sodium below 135 mmol/L, has been linked to cognitive dysfunction in a number of studies.[5-7]

Cannabidiol (CBD) is one of many phytocannabinoids present in cannabis plants, from which many over-the-counter products are derived. CBD has many proposed indications from chronic pain to insomnia, but it has only been FDA-approved in one product for rare seizure disorders.[8] The majority of CBD products are sold as supplements and are easily accessible to the general public.[9] CBD has been established as both a substrate and a potent inhibitor of CYP2C19, one of the top four most common enzymes involved in drug metabolism.[10-16]

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Drug-mediated inhibition or induction of a metabolic enzyme resulting in significant changes in exposure to the substrates of that enzyme is referred to as phenoconversion. CYP2C19 has been shown to be susceptible to this phenomenon and it has been noted in other cases that CBD may influence sertraline, in particular, via phenoconversion. This case report provides an example of possible CBD-induced phenoconversion of CYP2C19 resulting in increased exposure to sertraline and subsequent hyponatremia.[17-18]

Sertraline and CYP2C19

One of sertraline's primary metabolites observed in vitro and in vivo is N-desmethylsertraline, an N-demethylation product generated largely by CYP2C19. [1-2,19-20] The CYP2C19 gene is highly polymorphic - to date, there are 39 known allele variants. Phenotype is based on the patient's specific diplotype or presence of star variants of differing function. Table 1 shows examples of genetic diplotypes and their predicted phenotypes.

In vitro studies have demonstrated altered exposure and pharmacokinetic parameters of sertraline in poor metabolizers versus extensive metabolizers in the form of increased area under the plasma concentration versus time curve and half-life (T1/2). The only actionable phenotype result for CYP2C19 is poor metabolizer, in which case a dose reduction or alternative drug is recommended. All other phenotypes do not warrant therapy adjustment. [1-2, 21]

DOI: https://doi.org/10.24926/iip.v13i3.4890

Practice Setting

The practice setting is an outpatient pharmacotherapy consultant service run by ambulatory care pharmacists. Patients are referred to this service by medical specialty clinicians when medication related problems are suspected, and more in-depth medication therapy management is warranted. The practice model at Mayo Clinic Florida integrates a team-based approach in which physicians routinely refer patients to the pharmacotherapy service in order to answer medication questions, confirm their clinical thoughts, or augment their own knowledge gaps about medications and supplements when it comes to ADRs and drug interactions, especially in niche areas such as pharmacogenomics.

Case Summary

The patient is a 78-year-old male who was referred to the pharmacotherapy service after his neurologist became concerned about his persistent cognitive decline. The pharmacotherapy service was tasked with evaluating the patient's medication regimen in relation to his pharmacogenomic testing results and cognitive dysfunction because the provider wanted more information on pharmacological or supplemental contribution to any drug interactions and the patient agreed. The patient's past medical history is significant for herpes zoster, bilateral vestibular dysfunction, sleep apnea, pulmonary nodule, atrial fibrillation, essential hypertension, gastroesophageal reflux disease, benign prostatic hyperplasia, hyperlipidemia, atherosclerosis, spondylitis with radiculopathy, hyponatremia, vertigo, deep vein thrombosis, anxiety, major depression, and cognitive impairment. At the time of consult, his medication list included apixaban, omeprazole, sertraline, and CBD.

The patient's depression and anxiety were well-controlled on sertraline 50mg once a day for 20 years with no notable ADRs and no serum electrolyte abnormalities. In March of 2021, the patient began taking an over-the-counter CBD supplement daily for additional treatment of his chronic pain. Over the next year, the patient's serum sodium fell to hyponatremic levels, and he was referred to a neurologist due to concerns for decreased cognitive function in the form of short-term memory loss and attention deficits. The neurologist did not note any significant changes on the patient's brain MRI or other clinical cause for the patient's decreased cognition. The neurologist did note that the patient's hyponatremia could have been related to his antidepressant medication. In January of 2022, the patient's serum sodium level fell to an all-time low of 120 mmol/L. The decision was made to discontinue the sertraline, and over the course of the next two months the patient's sodium level gradually trended upward, eventually reaching 132 in March of 2022 when he was referred to the pharmacotherapy service for evaluation. Cognition improved as sodium levels increased after the CBD, then sertraline, were removed.

Pharmacogenomic testing was recommended in order to rule-out genetic metabolism deficits as a cause for the patient's symptoms. The testing was an outside, CLIA-certified lab. The patient's pharmacogenomic results revealed that he carries the heterozygous CYP2C19 *1/*2 genotype, making him a phenotypically intermediate metabolizer. There is no significant evidence to warrant dose adjustments of SSRIs for patients who are CYP2C19 intermediate metabolizers. However, there is evidence to support a dose reduction or alternative medication in poor metabolizers.[2] The patient's recent incorporation of CBD into his medication regimen and his subsequent hyponatremia and neurological symptom onset infer the possibility of phenoconversion to potential poor metabolism that resulted in higher exposure of sertraline and therefore increased risk of ADRs, specifically cognitive decline. There is good correlation of increasing sertraline-induced hyponatremia with the start and continued use of CBD. Patient reported his provider was contemplating reinitiation of sertraline at a lower dose or another antidepressant but future therapy was unclear at the time of the pharmacist consult.

Discussion

CBD products are sold over-the-counter without FDA approval, with the exception of Epidiolex®. An examination of CBD products by the FDA revealed that some of them are contaminated with THC, the psychoactive component of cannabis with its own metabolism and pharmacogenomic interactions.[22] This is a potential external factor in this patient's case, as the CBD product he was taking was an over-the-counter supplement. Unlike prescription and over the counter medications, cannabis products, herbal and dietary supplements are not strictly regulated by the FDA.[23]

Hyponatremia is not considered a dose-dependent ADR.[24] However, differences in exposure due to patient variability in individual pharmacogenomic and pharmacokinetic parameters could explain why some patients experience this effect and others do not.

CYP2C19 genotype does not always translate to the corresponding phenotype that is predicted based on allele function.[17] Other factors, such as concomitant use of CYP2C19 inhibitors or inducers, also play a role in enzymatic activity. When evaluating a patient's medication therapy for appropriateness and predicted response, pharmacogenomic testing is just one factor that needs to be considered. As in this case, the patient's pharmacogenomic results did not reflect what the patient was experiencing clinically. It was the discovery of an additional therapeutic agent with evidence of CYP2C19 inhibition that contributed to a more complete clinical picture.

DOI: https://doi.org/10.24926/iip.v13i3.4890

Conclusion

Pharmacogenomic testing combined with close provider and pharmacist collaboration can be an important patient-specific parameter to utilize when evaluating a patient's medication regimen for potential causes of ADRs. This case serves as an example of a drug-drug-gene interaction that possibly contributed to the patient's development of hyponatremia and accompanying cognitive dysfunction.

The opinions expressed in this paper are those of the authors.

Conflicts of Interest

We declare no conflicts of interest or financial interests that the authors or members of their immediate families have in any product or service discussed in the manuscript, including grants (pending or received), employment, gifts, stock holdings or options, honoraria, consultancies, expert testimony, patents, and royalties.

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DOI: https://doi.org/10.24926/iip.v13i3.4890

Table 1: CYP2C19 Phenotypes and Selected Diplotype Examples

Likely Phenotype	Genotype	Diplotype Examples
Ultrarapid Metabolizer (~2-5% of patients)	An individual carrying two increased function alleles	*17/*17
Rapid Metabolizer (~2-30% of patients)	An individual carrying one normal function allele and one increased function allele	*1/*17
Normal metabolizer (~35-50% of patients)	An individual carrying two normal function alleles	*1/*1
Intermediate metabolizer (~18-45% of patients)	An individual carrying one normal function allele and one no function allele or one no function allele and one increased function allele	*1/*2, *1/*3, *2/*17
Poor metabolizer (~2-15% of patients)	An individual carrying two no function alleles	*2/*2, *2/*3, *3/*3

Reference [25]

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