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Case Report

Adverse Effects: Considering Cytochromes P450, Plasma Levels, and Permeability Glycoproteins Altogether

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Abstract

Patients taking psychotropic medications sometimes experience unexpected adverse effects with low doses. While these have classically been attributed to a genetic poor metabolic status, permeability glycoproteins may also be culprits. Described herein is a case series of patients with and without negative outcomes supporting this possibility.

Keywords: Depression; Genomics; Cytochrome P450; Permeability Glycoproteins; Clomipramine; Plasma Levels.

Introduction

Adverse effects represent a significant challenge in the realm of pharmacotherapy as they can lead to the development of clinically relevant comorbidities and/or to treatment discontinuation [1]. As such, it is important to be aware of the factors influencing not just patient response but tolerability and the emergence of adverse effects. Genetic polymorphisms and their associated phenotypes are an example of a measurable factor, which impacts both these parameters. Classically, pharmacogenomics has focused mostly on cytochrome P450 variations; however, we came across a clinical case, which highlights the importance of considering other genetically influenced elements of psychopharmacology.

Permeability glycoproteins (p-GPs) are one of the most extensively studied ATP-binding cassette (ABC) transporter that function as a biological barrier by expelling toxins and xenobiotics out of cells [2]. As such, it contributes to a reduction in toxicity and has broad substrate specificity [3]. It is coded by the ABCB1 (ATP-binding cassette subfamily B member 1) gene, also known as MDR1 (multidrug-resistance gene 1). It is differentially expressed in specialized epithelial cells of secretory/excretory organs (liver, kidneys, small intestine) and in endothelial cells of capillary blood vessels at blood–tissue barriers, such as the blood–brain barrier or the placenta [4-6]. Genetic polymorphisms of ABCB1 can lead to variations in p-GP expression or function, thereby contributing to inter-individual variability in drug absorption and disposition [7,8]. The most studied polymorphism is the single nucleotide polymorphism rs1045642, also known as C3435T, which is a transition in exon 26 of the ABCB1 gene that can influence p-GP activity [9].

Case Presentation

One of our patients, Mr. A was a 56 year old male with major depressive disorder (MDD) of moderate intensity accompanied by severe anxiety. A complete blood work up had not revealed any clinically relevant anomalies. He had not improved and/or tolerated a variety of medications indicated for MDD, including adjunctive strategies as per Canadian Guidelines [10]. He was then prescribed a very low starting dose of clomipramine (25 mg at bedtime). He experienced a major improvement in mood and anxiety (Clinically Useful Depression Outcome Scale score decreased from 38 to 21 and Generalized Anxiety Disorder-7 score decreased from 16 to 5 [11,12]) approximately three weeks after starting the medication. However, soon after initiation of clomipramine he experienced sexual dysfunction, severe dizziness, and two fainting spells with

falls. Orthostatic hypotension was noted on follow-up twenty days later: blood pressure was 117/69 with a regular heart rate of 64 when sitting, which decreased to 95/69 with a heart rate of 80 when standing, whereas it was 132/77, pulse 52 at baseline, and regular throughout. This was unlikely due to adrenergic hypo-functionality as he had not had such a reaction to noradrenegic medications before. Blood levels of clomipramine and desclomipramine were then requested, but unexpectedly were found to be at and below the threshold of detection, respectively see (Table 1). In light of the favorable response, the patient was counselled to continue the clomipramine at 25 mg daily while being careful with positional changes; however, the persistence of the side effects led him to discontinue the medication before the next appointment. A few weeks later, the clomipramine was re-introduced at the lower dose of 10 mg daily as the patient's mental state had deteriorated again. The patient experienced an improvement in mood and anxiety but also the same side effects as when he was on 25 mg daily, though these were less severe (postural dizziness, sexual dysfunction). The patient was eventually advised to try alternating 10 mg of clomipramine with 20 mg the following day; however, this led to a resurgence of side effects and the dose was lowered once more to 10 mg daily. The patient discontinued the medication on his own before the next appointment as the adverse effects had become intolerable.

In light of the puzzling findings from the abovementioned case, we asked four other patients who were prescribed clomipramine in our unit to submit a sample for genetic testing (Optimum Plus, Dynacare, Ottawa Canada). All five patients signed a consent. Out of these patients, only Mr. A and Ms. B had the genetic polymorphism of rs1043642, which would confer reduced p-GP expression/activity and thus lead to a higher chance of tolerability issues. Just like our index patient, Ms. B's genetic cytochrome enzymes profile was normal. This patient had received a single dose of 50 mg of clomipramine and experienced severe adverse effects (nausea, sweating, passing out) and never took clomipramine again. These adverse events were not likely to be attributable to adrenergic hyperactivity as she did not that type of adverse events with prior adrenergic medications for MDD. The three other patients did not have tolerability issues, one has a single CYP450 anomaly, and plasma levels above the usual therapeutic range. Two achieved sustained remission for years with adjunctive medications to clomipramine.

The ABCG2 (rs2231142), another p-GP, as well as for another SNP of ABCB1 (rs2032583) were also provided on the commercially available panel that was used, but only the polymorphism at rs1043642 resulted in intolerable side effects from clomipramine. Indeed, Mr. E, had anomalies at both rs2032583 and rs2231142; however, as can be seen in (Table 1) his plasma clomipramine and norclomipramine levels were normal to high and were well tolerated.

Patient/ age	Dose of clomipramine	Plasma level of clom./ desclom.*	CYP1A2	CYP2D6	CYP3A4	p-GP (C3435T) (rs*1045642*)
Mr. A 56	25 mg/day	85/<83 nmol/L	Normal	Normal	Normal	↓ function
Ms. B 38	50 mg X 1	N.D.	Normal	Normal	Normal	↓ function
Mr. C 76	125 mg/day	1888/555 nmol/L	Normal	Poor met.	↑ function	Normal function
Ms. D 40	150 mg/day	1232/855 nmol/L	Normal	Normal	↓ function	Normal function
Mr. E 30	150 mg/day	1521/1868 nmol/L	Normal/ ↑ function	Normal	Normal	Normal function

Table 1: Doses, plasma levels and genetic profile for the five patients

Usual therapeutic range: total level 450-1500, with 83 nmol/L being the detection threshold; met. For metabolizer status; desclom. For desmethyl-clomipramine; ↑ for increased function and ↓ for decreased function; N.D: not determined. Plasma levels were obtained 12 hours after the last dose using Dynacare, Ottawa.

Discussion

Classical pharmacogenetics have sought to address the problems of individual variability of plasma levels of various medications. Indeed, genetic tests are being used to determine cytochrome phenotype variations that can a significant impact on pharmacokinetics and pharmacodynamics to prescribe more judiciously. However, the cases presented herein remind us that the cytochromes are not the only elements impacting the distribution of specific medications. Though some meta-analyses found no significant effect of p-GP polymorphisms on response and tolerability [13, 14], the two problematic cases described above illustrate an important difficulty that clinicians can encounter in their practice, when a patient responds well to a medication but experiences intolerable adverse effects, even at low doses.

The literature on p-GP and their clinical significance is very heterogeneous, in both methodology and outcomes. Results have varied in different studies but it has been suggested that the higher the number of T alleles present, the lower the function or expression of p-GP [15]. Thus, patients with a higher number of T alleles would show higher levels of p-GP substrate drugs, because of reduced elimination. The higher tissue drug level may then lead to increased susceptibility to side effects. For example, one study found an increased risk of venlafaxine-induced akathisia [16]. On a more positive note, this increased drug concentration may also lead to a greater response. Indeed, some studies have shown an association between the TT genotype carriers, who may accumulate higher levels of the drug in their brain, and earlier remission than with the wild type genotype [17].

The most likely possibility to account for the major adverse events experienced by our two patients, in comparison to the others who had expected pharmacokinetic profiles of the same medication, is that there may have been preferential accumulation in the central nervous system. More specifically, it has long been know that clomipramine and desclomipramine have regional brain differences in distribution and accumulation upon acute and chronic administration, with concentration ratios varying as much as six fold in the rat cerebellum versus the cortex and/or the hypothalamus [18, 19]. Though we would still not recommend routine genomic testing [10], it is important to keep in mind lesser-known elements that may influence our patients' response to treatment and their tolerability when faced with cases that are more complex.

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