Clinical Pearl: CYP450 genotyping

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Attempts to use genotyping for the purposes of "personalizing" the pharmacotherapy of patients with mental illness is a growing clinical practice. As a group of specialists within a healthcare discipline that has an evolving patient care role, it is necessary for psychiatric pharmacists to understand when pharmacogenomics should be considered during clinical care, and how best to use this type of information. While literature reports detail the typing of genes which code for the production of a wide range of proteins, today, psychiatric practitioners are predominantly genotyping CYP450 enzymes.

While not all psychotropic medications are metabolized by the CYP450 system, most are. When the CYP450 system is involved in metabolism, many psychotropics are substrates for CYP2D6 and 3A4. A few key psychotropic drugs, however, have metabolic routes that involve other CYP450 enzymes (Table 1). When significant DNA variability within a CYP450 enzyme gene occurs, the activity of the produced enzyme can be substantially different from enzyme produced by the same gene that has no DNA variability. In such patients who are treated with conventional doses, concentrations of medications metabolized by a polymorphic enzyme can be either much greater or much lower when compared with a similar patient who has normal genes. For each CYP450 enzyme, a person has an inherited metabolizer status which can be any one of the following: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM) and ultra-rapid metabolizer (UM).

In order to rationalize the CYP450 genotyping of a patient, it makes most sense to first consider patients who have a protracted treatment history of either not responding to, or not tolerating several medications. This is especially true when the primary metabolic routes of those medications occur through similar CYP450 enzymes. In the case of a poor response history to medications despite the use of acceptable doses, it may be appropriate to reason that the patient is a UM. In the case of poor tolerability history to medications, it may be appropriate to reason that the patient is a PM.

The following two cases were presented in part at the 2011 Annual Meeting of the College of Psychiatric and Neurologic Pharmacists in Phoenix, AZ. The first case is meant to demonstrate one line of thinking that may lead a practitioner to decide to have a patient's CYP450 enzymes genotyped. The second case illustrates a scenario in which a patient's CYP450 enzymes have already been genotyped and how the information can be used to guide a dosing recommendation.

CASE #1

Patient details: at the time when CYP450 genotyping was being considered, the patient was a 20 year old male patient of Indian descent with velo-cardio-facial syndrome (VCFS). VCFS is genetic disorder in which there is a deletion of a small segment of the long arm of chromosome 22, it is also known as "22q11 deletion syndrome". While there can be many signs and symptoms associated with this disorder, psychosis can be prominent in affected individuals. The patient's psychiatric presentation was significant for schizophrenia, paranoid type and he was being treated with: risperidone 6 mg/day, ziprasidone 160 mg/day, divalproex (dose unknown, most recent vpa level = 83), lorazepam 0.5 mg/day and benztropine 1.5 mg/day. Despite this aggressive antipsychotic treatment, the patient was not responding well (e.g., exhibiting signs of paranoid behavior) and he was also experiencing parkinsonism and central obesity. Because of persistent sub-optimal responsiveness and because the patient had a genetic disorder (the CYP2D6 gene also resides on chromosome 22), a decision was made to genotype the patient's CYP2C9, 2C19 and 2D6 enzymes. Results of the testing revealed the following: 2C9 *1/*3, 2C19 *1/*1 and 2D6 *2a/*2. Interpretation: these results indicate that the patient is a 2C9 intermediate metabolizer (i.e., a *1 gene codes for normal enzyme activity, a *3 allele codes for decreased enzyme activity), a 2C19 extensive metabolizer (i.e., a *1 gene codes for normal enzyme activity) and a 2D6 extensive metabolizer (i.e., the *2 and *2a genes code for normal enzyme activity). Application: in this case, the genotyping results did not immediately

Table 1: Psychotropics as Substrates for the CYP450 System

CYP	Antianxiety	Antidementia	Antidepressant	Antipsychotic	Hypnotic	Misc.	Mood Stabilizer	Stimulant
1A2			Amitriptyline Duloxetine Fluvoxamine Imipramine Mirtazapine	Clozapine Haloperidol Olanzapine	Melatonin Ramelteon	Propranolol		
2B6			Bupropion Sertraline					
2C9/19	Diazepam (19)		Amitriptyline (19) Citalopram (19) Fluoxetine (9) Imipramine (19) Sertraline (9)		Doxepin (19)	Benztropine (9)?		
2D6		Donepezil Galantamine	Desipramine Duloxetine Fluvoxamine Mirtazapine Nortriptyline Paroxetine Venlafaxine	Aripiprazole Fluphenazine Iloperidone Perphenazine Risperidone	Doxepin	Benztropine Clonidine Propranolol		Atomoxetine Dextroamphetamine
3A4	Alprazolam Buspirone Clonazepam Diazepam	Donepezil Galantamine	Citalopram Mirtazapine Nefazodone Sertraline	Aripiprazole Clozapine Iloperidone Lurasidone Quetiapine Ziprasidone	Eszopiclone Quetiapine Trazodone Triazolam Zolpidem	Guanfacine	Carbamazepine Tiagabine	Modafinil

contribute to understanding any of the patient's clinical findings including whether or not to modify the dosing of any of the patient's medications being taken at that time. It is important to note that only three of the patient's CYP450 enzymes were genotyped, and so there was incomplete information for the patient's other CYP450 enzymes. Genotyping the CYP3A4 enzyme may have also had clinical value.

CASE #2

Patient details: at the time of the consult, the patient was a 10 year old female with a diagnosis of ADHD and eating disorder NOS. The psychiatrist had recently received CYP450 genotyping results that described the patient's CYP2D6 gene as "null" (i.e., inactive enzyme, a 2D6 poor metabolizer). Prior to getting the genotyping results, the psychiatrist had been treating the patient with atomoxetine using conventional dosing. While it was not optimally controlling the patient's ADHD symptoms, it was helpful for the patient's over eating behaviors and weight gain. Upon learning the results of the CYP2D6 genotyping, the atomoxetine was discontinued. The consultation requested involved the following questions: 1) If a patient with inactive 2D6 enzyme is treated with atomoxetine, how is it metabolized?, and 2) what are the safety risks of using atomoxetine in a patient with an inactive 2D6 enzyme system? Discussion: these results indicate that the patient has an inactive 2D6 enzyme system. Several alleles described in the literature code for the production of inactive enzyme. The frequencies of these alleles vary. While the patient's 2D6 enzyme is inactive, it is likely that other CYP enzymes will "pick up" the metabolism of 2D6 substrates like atomoxetine. Specifically, atomoxetine used in 2D6 poor metabolizers will likely be metabolized by other CYP450 enzymes, but at a slower rate. The Strattera® product label states that, compared with 2D6 EMs, atomoxetine dosed in 2D6 PMs will have a greater bioavailability (94% vs 63%), a 10 fold greater AUC, a 5 fold greater $C_{ss,max,}$ and a longer elimination half-life (21.6 v. 5.2 hours). Dosing recommendations for 2D6 PMs in the Strattera® product label state that patient's begin at a daily dose of 0.5 mg/kg and remain there for 4 weeks. Dose increases should only be considered if target symptoms are not improved and the initial dose is tolerated. The maximum daily dose in 2D6 PMS is 1.2 mg/kg. If a child is over 70 kg, then dosing is set at 40 mg/day initially, and then a dose increase to 80 mg if target symptoms are not improved and the 40 mg/day is being tolerated after 4 weeks of treatment. The product label also states that the following adverse effects occur more frequently in PMs

than in EMs: insomnia, weight decreased, constipation, tremor, excoriation, conjunctivitis, syncope and mydriasis. Despite the guidance from the product label, the dosing recommendation made for the patient was to begin with 10mg qod or 10 mg qd if atomoxetine treatment was desired. The rationale being that response and tolerability should be tested at the lowest possible dose, since these doses were likely to generate atomoxetine concentrations comparable to, or higher than, patients who were CYP2D6 EMs taking 40 mg/day. The patient's atomoxetine treatment was initiated and maintained by the psychiatrist at 10 mg/day with successful efficacy and tolerability.

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