Schizophrenia Research 149 (2013) 1–14

Contents lists available at SciVerse ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Review

CYP450 Pharmacogenetic treatment strategies for antipsychotics: A review of the evidence

Dana Ravyn [a], Vipa Ravyn [b], Robert Lowney [a], Henry A. Nasrallah [c,*]

[a] CMEology, West Hartford, CT, United States
[b] Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Denver, CO, United States
[c] Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH, United States

ARTICLE INFO

Article history:
Received 27 March 2013
Received in revised form 3 June 2013
Accepted 19 June 2013
Available online 17 July 2013

Keywords:
Schizophrenia
Antipsychotic
Cytochrome
Metabolism
Pharmacogenetics

ABSTRACT

Although a number of first- and second-generation antipsychotics are available, achieving optimal therapeutic response for patients with schizophrenia can be challenging. The presence of polymorphic alleles for cytochrome P (CYP) 450 may result in lack of expression, altered levels of expression, or altered function of CYP450 enzymes. CYP2D6, CYP1A2, and CYP3A4/5 are major enzymes in the metabolism of antipsychotics and polymorphisms of alleles for these proteins are associated with altered plasma levels. Consequently, standard dosing may result in drug plasma concentrations that are subtherapeutic or toxic in some patients. Patient CYP450 genotype testing can predict altered pharmacokinetics, and is currently available and relatively inexpensive. Evidence-based guidelines provide dose recommendations for some antipsychotics. To date few studies have demonstrated a significant association with genotype-guided antipsychotic use and clinical efficacy. However, many studies have been small, retrospective or cohort designs, and many have not been adequately powered. Numerous studies have shown a significant association between genotype and adverse effects, such as *CYP2D6* polymorphisms and tardive dyskinesia. This review summarizes evidence for the role of CYP450 genetic variants in the response to antipsychotic medications and the clinical implications of pharmacogenetics in the management of patients with schizophrenia.

1. Introduction

Antipsychotics accounted for over 14 million US treatment visits in 2008 (Mark, 2010). There is significant interindividual variation in response to antipsychotics, much of which remains unexplained (Stroup, 2007). Antipsychotics are one of the most highly individualized classes of medications. Despite the fact that a number of first- and second-generation antipsychotics are available, achieving optimal therapeutic outcomes can be challenging for some individuals. The majority of patients with schizophrenia do not experience complete therapeutic benefit with antipsychotic therapy, which can lead to polypharmacy, a practice poorly supported by clinical evidence and associated with risk of adverse effects (McEvoy et al., 2006; Zink et al., 2010). Further, risk of discontinuation and relapse can result from treatment-limiting adverse effects and long-term side effects such as weight gain and metabolic syndrome (Cha and McIntyre, 2012).

Variability in response to antipsychotics can be influenced by an array of factors, including age, sex, ethnicity, nutritional status, smoking, and alcohol use. There is strong evidence for the role of genetic variability in individual responses to antipsychotic therapy. Advances in pharmacogenetic research have led to discovery of many polymorphisms strongly linked to the metabolism and pharmacodynamics of antipsychotic medications. The goal of clinical pharmacogenetics is to use individual-level genetic data to predict and optimize the response to antipsychotics while preventing or minimizing adverse events. Use of pharmacogenetics has demonstrated the ability to improve patient outcomes in many therapy areas, and is generally cost effective (Crews et al., 2012). Nevertheless, evidence-based guidelines for pharmacogenetics remain scarce, and there are numerous barriers to its clinical implementation (McCullough et al., 2011; Mrazek and Lerman, 2011; Schnoll and Shields, 2011).

1.1. Methods

This review summarizes evidence for the role of genetic variants of CYP450 enzymes in the metabolism of antipsychotic medications and the clinical implications of pharmacogenetics of cytochrome P (CYP) enzymes in the management of patients receiving antipsychotics. A literature search was conducted to examine the impact of CYP450 variants on antipsychotic pharmacology and any known

* Corresponding author at: Psychiatry & Neuroscience, University of Cincinnati College of Medicine, Department of Psychiatry and Behavioral Neuroscience, 260 Stetson Street, Suite 3200, Cincinnati, OH 45219, United States. Tel.: +1 513 558 4615; fax: +1 513 558 4616.
E-mail address: henry.nasrallah@uc.edu (H.A. Nasrallah).

0920-9964/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.schres.2013.06.035

clinical outcomes. The search strategy [(pharmacogenetic* OR "cytochrome P*") AND (antipsychotic* OR neuroleptic*)] was used to identify relevant literature in PubMed and OVID. The search was conducted for all articles from inception to April 30, 2013. Eligible studies included pharmacologic characteristics of antipsychotics relevant to CYP metabolism in vitro, in healthy volunteers, or in patients, or reports of efficacy or adverse effects that defined patients according to CYP genotype or phenotype. Relevant literature was used to identify any additional primary studies. Research abstracts, unpublished studies, articles with non-English abstracts, commentaries, letters to the editor, and editorials were excluded. As discussed in detail below, study quality was limited by small study size, poorly defined populations and ethnicity, and scarcity of outcomes studies.

2. Pharmacogenetic studies of antipsychotics

2.1. Overview

The term pharmacogenetics was coined by Vogel in 1959, and refers to the interaction between an individual's genetics and his or her response to drugs, often on the basis of a single gene polymorphism (Vogel, 1959). In contrast, pharmacogenomics is a relatively recent term used in association with studies of the human genome and focuses on complex, multifactorial interactions. While pharmacogenetics seeks to individualize therapy, pharmacogenomics identifies targets for drugs, and characterizes drug responses in populations.

Studies of the pharmacogenetics of antipsychotics evaluate the association between genetic variations with either the pharmacokinetics or pharmacodynamics of individual agents. In pharmacokinetic studies, pharmacogenetics aims to predict antipsychotic drug responses by identifying variants in genes associated with the metabolism of specific agents. Such genetic variations affecting metabolism may lead to alterations in the bioavailability of certain antipsychotics, resulting in loss of efficacy (decreased plasma levels) or increased toxicity (elevated plasma levels). In pharmacodynamic studies, pharmacogenetics evaluates the association of genetic polymorphisms in drug targets with therapeutic outcomes or adverse effects. These targets may be receptors postulated to have a role in the etiology of disease, targets in the mechanism of action of the therapeutic agent, transporters, or intermediates in signaling pathways involved in efficacy or side effects of the drug.

2.2. Pharmacogenetic testing

Pharmacogenetic testing of drug metabolism consists of two approaches (Sheffield and Phillimore, 2009). Biochemical tests are used to evaluate the rate of metabolism by a patient after he or she takes a probe drug, which is a well characterized target of a recognized metabolic pathway. The excretion of the parent drug and its metabolite are then measured at regular intervals and a rate of metabolism calculated. The result is often referred to as an individual's phenotype, although the use of the term to describe functional aspects of drug metabolism differs from its connotation in genetics. Although the activity of a patient's metabolic enzymes can be measured directly, this is not practical, particularly for CYP450 enzymes, which would require a liver biopsy.

The other approach to pharmacogenetics is the use of molecular genetic testing to characterize the alleles of a patient's gene related to metabolic enzymes, the drug target, or receptors. The genes of interest often have a number of alleles, and polymorphisms present in these alleles may result in lack of expression, altered levels of expression, or altered function.[1]

[1] In this article, unitalicized capitals are used to indicate a protein and italicized capitals are used to indicate a gene. Alleles are indicated by an asterisk, followed by the allele number. In most cases, *1 represents the wild type; for example, CYP2C9 is the enzyme and *CYP2CP*1* is the most common allele.

3. Pharmacokinetics and genetic variations in CYP450 enzymes

Historically, pharmacogenetics has focused on drug metabolizing enzymes as a result of their wide variation in comparison to allelic polymorphisms of pharmacodynamic drug targets (Brosen, 2004). Further, outcomes of genetic variation are easier to measure because drug metabolism assays are standardized, and interpretation is relatively straightforward. For example, a low steady-state concentration indicates rapid metabolism and a high concentration indicates slow metabolism. Numerous enzymes associated with drug absorption and elimination have been the subject of pharmacogenetic studies, which are recommended or required by the US Food and Drug Administration (FDA) for certain therapies. The FDA requires information related to pharmacogenetic biomarkers in the labeling of over 100 drugs, 27 of which are for agents with a primary indication in psychiatry (US Food and Drug Administration, 2012).

Association of an enzyme with metabolism of a drug is necessary but not sufficient justification for pharmacogenetic testing, as many drugs may be metabolized by alternative pathways. Further, pharmacogenetic results should be interpreted in context of the physician's knowledge of other factors that influence efficacy and toxicity of antipsychotic agents, such as comorbidities, adherence, body weight, and smoking (Rostami-Hodjegan et al., 2004). In addition to pharmacogenetic considerations, CYP isoforms can be induced and inhibited by certain drugs, which can substantially alter metabolism of other drugs through drug–drug interactions.

Oral antipsychotics are substrates of CYP450 enzymes, which are crucial to their metabolism and elimination (Fig. 1). The efficacy and toxicity of antipsychotic agents is affected by factors that induce or inhibit CYP450 expression and function, such as drug–drug interactions. Additionally, the multiallelic nature of CYP450 enzyme genetics can result in various phenotypes. These polymorphisms reflect gene insertions and deletions, gene duplications, copy number variations, and single nucleotide polymorphisms (SNPs), which can lead to decreased or elevated metabolism. The resulting phenotypes associated with these genetic variants are usually classified as one of four groups: poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM) or normal, and ultra-rapid metabolizers (UM) (Fig. 2) (van der Weide et al., 2005).

The clinical consequences of variations in metabolism depend on whether the drug taken is pharmacologically active or is a prodrug that needs to be converted to an active metabolite. If the antipsychotic is pharmacologically active, the PM phenotype will result in increased plasma concentration. Many antipsychotics have a narrow therapeutic window and reduced metabolism can result in concentration-dependent adverse effects, as illustrated in Fig. 2 (van der Weide et al., 2005). Patients with the IM phenotype are also likely to have increased exposure to drugs compared with EMs. However, the degree to which plasma levels are elevated and their clinical significance is often unclear. The UM phenotype can result in subtherapeutic drug levels when conventional doses are administered as the antipsychotic will be metabolized before it has a pharmacologic effect. The PM is most extensively studied for antipsychotics, particularly in those agents with a narrow therapeutic index. UM phenotype is clinically significant because of its wide distribution (Sistonen et al., 2009). In contrast to pharmacologically active agents, a prodrug must be metabolized to an active form. For some antipsychotics, the parent drug and its metabolite will both have activity, and variations in metabolism can have complex outcomes.

3.1. CYP variations and dose recommendations

The human *CYP2D6* gene is polymorphic and the resulting CYP2D6 isozymes have significant implications in clinical medicine (Zhou, 2009). Of 121 drug labels that included pharmacogenetic information from 1945 to 2005, 35% pertained to CYP2D6 (Frueh et al., 2008). The majority of antipsychotics are metabolized primarily or secondarily by CYP2D6 (Fig. 1). Additionally, CYP2D6 variability is a significant