The effects of pharmacogenetics on adverse drug reactions

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i. Introduction

Today's medicine is based on several diagnostic judgments. These diagnoses involve physicians observing the patient's signs and symptoms as well as listening to his or her story in order to arrive at an appropriate diagnosis. After making a diagnosis and administering appropriate medications, it was found that some patients are able to respond positively to the prescribed drug treatment, whereas others aren't able to respond as expected. Reasons for not responding as expected are due to diseases being caused by a variety of things, such as bacteria or viruses, which may lead the patient to require different drug treatments for a therapeutic effect. Another reason may be that not all patients respond the same way to the drug treatment. Different responses to drug treatment likely results from inherited genetic differences in drug metabolic pathways, affecting the patients' reactions to treatment[1]. This study is called pharmacogenetics.

Although the field of pharmacogenetics is quite new, the topic is important to be aware of due to differences in patient responses to medicine; the responses to medications can range from responding positively to treatment whereas others aren't effectively responding. Those who don't respond effectively to treatment are called adverse drug reactions.

Adverse drug reactions develop unpleasant reactions in the patient that can further injure him or her. Such reactions can range from nausea, blurry vision, and drowsiness to being fatal at some doses. One study showed that adverse drug reactions resulted from

[1] Kalow W. (2002). Pharmacogenetics and personalized medicine. *Fundamental & Clinical Pharmacology, 16:* 337-342. doi: 10.1046/j.1472-8206.2002.00109.x

genetic variants of other drug-metabolizing enzymes[2]. Furthermore, several other studies suggest that genetic polymorphisms, mutant genes, could explain why a small proportion of the population poses a high risk of drug toxicity[3,4].

It was found that adverse drug reactions are classified into six groups: dose-related, non-dose related, dose-related and time-related, time-related, withdrawal, and failure of therapy[5]. Dose-related reactions are predictable when the pharmacological properties of the drug are known and are dose-dependent. Non-dose related reactions are unpredictable and doesn't show any dose-related response. Although they represent a small proportion of the population, they are often serious and account for many drug-related deaths; such reactions aren't observed in animal testing. Time-related reactions deals with how much and how long will the patient rely on drug treatment in order to get better. The last classifications are withdrawal and failure of therapy. Withdrawal is when the patient is already dependent on the drug and suffers from the side effects when he or she is taken off from the drug. Failure of therapy deals with the patient not responding effectively to such treatment. This last group may also lead to drug-related deaths as the patient's health hasn't improved from the treatment[5]. Timing, illness, medical observations and lab results can all contribute to a suspected drug adverse reaction[6].

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[2] Meyer U. (2000). Pharmacogenetics and adverse drug reactions. *Adverse Drug Reactions, 356:* 1667-1671

[3] Ingelman-Sundberg M., Oscarson M., McLellan R. (1999). Polymorphic human cytochrome P450 enzymes: An opportunity for individualized drug treatment. *Trends in Pharmacological Science, 20*: 342-349.

[4] Roses A. D. (2000). Pharmacogenetics and future drug development and delivery. *The Lancet, 355*: 1358-1361. doi: http://dx.doi.org/10.1016/S0140-6736(00)02126-7

[5]Park B. K., Pirmohamd M., Madden T. S. & Kitteringham N. R. (1994). Bioactivation and bioinactivation of drugs and drug metabolites: relevance to adverse drug reactions. *Toxicology In Vitro, 8*(4): 613-621. doi: 10.1016/0887-2333(94)90029-9

[6] Edwards I. R., Aronson J. (2000). Adverse drug reactions: definitions, diagnosis, and management. *Adverse Drug reactions, 356*(9237): 1255-1259. Doi: 10.1016/S0140-6736(00)02799-9

According to a study done by Chyka (2000), death rates, gender, age, and drug categories associated with adverse reactions were analyzed. In 1995, it was found that 206 patients' deaths were due to adverse drug reactions in the United States. Furthermore, the majority of deaths were among patients' 60 years or older, and the gender ratio was equal[7].

Based on all prior information given, there appears to be a relationship between pharmacogenetics and adverse drug reactions. The relationship between the two variables is genetic susceptibility[8]. One study showed that genetic factors could determine susceptibility to dose-dependent and dose-independent adverse drug reactions. Susceptible determinants include pharmacokinetic and pharmacodynamics factors[9].

The importance of pharmacogenetics has opened up a new field in medicine. The variability of patients' responses to drug efficacy and safety will change the practice and economics of medicine. Tests that are specific to certain gene-causing diseases can easily help determine the onset of the disease in the individual. For example, those who are susceptible to late-onset Alzheimer's disease are likely to be carriers of the susceptibility gene, ApoE, on chromosome 19q13 or in the gene locus on chromosome 12q[10]. Although there may be current ethical implications for genetic testing, it is important to note that

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[7] Chyka P. A. (2000). How many deaths occur annually from adverse drug reactions in the United States? *The American Journal of Medicine, 109*(2): 122-130. doi: 10.1016/S0002-9343(00)00460-5

[8] Pirmohamed M. & Park B. K. (2001). Genetic susceptibility to adverse drug reactions. *Trends in Pharmacological Sciences, 22(*6): 298-305. doi: 10.1016/S0165-6147(00)01717-X

[9]Hoffmeyer S., Burk O., von Richter O., Arnold H. P., Brockmoller J., Johne A., Cascorbi I., Gerloff T., Roots I., Eichelbaum M. & Brinkmann U. (2000). Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and our relation of one allele with P-glycoprotein expression and activity in vivo. *Proceedings of the National Academy of Sciences USA, 97*(7): 3473-3478. doi: 10.1073/pnas.050585397

[10] Roses A. D. (2000). Pharmacogenetics and the practice of medicine. *Nature, 405:* 857-865. doi: 10.1038/35015728

pharmacogenetics can be applied to drug development and can help improve adverse drug reactions by decreasing drug-related deaths.

ii. Methods

The research of this paper was completed with the help of several research engines that includes Google Scholar, PubMed and the Penn State LionSearch. Terms that were used in this paper were 'pharmacogenetics', 'adverse drug reactions', 'drug treatment' and 'genetics'.

Requirements of papers to be used in this systematic review were that they must have full text papers available through the PSU library subscription. Primary research articles must also include the topic of pharmacogenetics and adverse drug reactions, must have a research design that involves cohort studies for risk factors in adverse drug reactions and randomized clinical trials for intervention studies. Furthermore, articles must have studies on cytochrome P450 enzymes and its role in adverse drug reactions, preferably in how the drug affects patient responses. Research subjects are to be focused on adults of 21 years or older. Lastly, articles must be published within the past 30 years.

iii. Results

Author: U. Meyer

Article: "Pharmacogenetics and adverse drug reactions"

Summary: The purpose of this retrospective cohort study was to assess the etiology and frequency of adverse drug reactions. Although adverse drug reactions affects a small number of the population, at least 6-7% of patients in U.S. hospitals have suffered from serious adverse reactions and 0.32% have fatal reactions (causing at least 100,000 deaths a year in America). To find out the mechanism behind these reactions, researchers

performed analytical methods to find out which CYP450 enzyme plays a role in adverse reactions. Compared to the CYP450 family, further investigations led researchers to believe that CYP2D6 is the enzyme that causes the most severe therapeutic failure. Researchers found that the enzyme would interfere with metabolizing enzymes, drug receptors and several other drug transport systems, all of which causes severe therapeutic issues, such as toxicity and tardive dyskinesia[2].

Author: A. D. Roses

Article: "Pharmacogenetics and future drug development and delivery"

Summary: The main objective of this prospective cohort study was to foresee the role of pharmacogenetics in drug development and delivery. It carried out a study in 829 middle-aged men who were homozygous carriers of Gly16/Gly16 and Arg16/Arg16, and also had moderate to severe asthma. Results show that it was found that homozygous Gly16/Gly16 carriers were more prone to be desensitized to the medication than Arg16/Arg16, leaving Gly16/Gly16 carriers to not achieve a therapeutic affect from drug treatment[10].

Author: M. Ingelman-Sundberg et al.

Article: "Polymorphic human cytochrome P450 enzymes: An opportunity for individualized drug treatment"

Summary: This clinical trial examined the relationship between CYP450 enzymes and personalized drug treatment. There were 450 subjects with neuropathy disorder in the trial and it was predicted that carriers of poor genetic variation in CYP2C9, CYP2C19 and CYP2D6 resulted in therapeutic failure and adverse effects of the drug. Furthermore, it was found that those who carried the CYP2D6 gene, in particular, were more likely to

be affected with adverse reactions; this gene copy was mostly observed in African (Ethiopian) and Middle Eastern (Saudi Arabian) descent[3].

Author	Year	Design	Population	Sample Size	Predictor	Outcome	Results
Meyer	2000	Retrospective cohort study	Caucasians, Asians and Black Africans who have had suffered from non-fatal adverse reactions in the past	206	Poor metabolites	Therapeutic failure, adverse effects	Poor genetic variation in CYP2D6 led to people suffering from adverse reactions such as tardive dyskinesia, drug dependence and toxicity
Roses	2000	Prospective cohort study	Middle-aged men who are carriers of common disease susceptibility and carriers of single-gene mutations and rare diseases	829	Formoterol	Moderate to severe asthma	Homozygous carriers of Gly16/Gly16 were prone to being unaffected by the medications than Arg16/Arg16 carriers
Ingelman	1999	Clinical trial	Americans of European, Asian, Middle Eastern and African descent in the Los Angeles county	450	CYP450 polymorphisms in patients with neuropathy disorder	Therapeutic failure, adverse effects and toxicity	Carriers of CYP2C9, CYP2C19 and CYP2D6 who were treated with a disease suffered from adverse effects of the medication

iv. Discussion

The main findings of the results prove to be corresponding with each other in that CYP450 enzymes play a vital role in drug adverse reactions. Compared to other CYP450 enzymes, two of the three articles confirmed that poor genetic variations in CYP2D6 provides the most serious adverse drug reactions in patients. These adverse reactions

include, but not limit to, tardive dyskinesia, poor metabolism of drugs which can lead to toxicity and become fatal and tachycardia[2]. Among the three studies, one study didn't look into what enzymes caused the adverse reactions, but rather, focused on a population that was diagnosed with a certain illness and focused on the genes that were associated in helping cause adverse reactions to a specific medication[4].

The results agree with other review articles on this topic that genetic susceptibility does play a role in the relationship between pharmacogenetics and adverse drug reactions. For example, it was found that people of Middle Eastern (Saudi Arabians) or African (Ethiopian) descent were likely to have a high gene expression of CYP2D6 which increases their susceptibility to adverse reactions[3,2].

Reviewing the field of pharmacogenetics and its effect on adverse drug reactions can impact the medical and scientific research field immensely. This will not only lead to further progressing the idea of personalized medicine, but will also lead to lower rates of drug-related deaths, drug dependence and other drug-related complications that may impact an individual's health in a harmful manner. Unfortunately, there are implications that may prevent pharmacogenetics from progressing in its field. For example, pharmacogenetics requires obtaining samples from an individual in order to gain access and interpret his or her genotype and phenotype. Depending on how to gain access to these results, some patients aren't very trusting if results are handed over the internet or over the counter. Another concern is in regards to the confidentiality of storage and how genetic information will be used for research. Lastly, it is questionable as to whether or not patients would have control over being tested for certain[11]. To acquire access to one's

[11] Corrigan O. (2005). Pharmacogenetics, ethical issues: Review of the Nuffield council on bioethics report. *Journal of Medical Ethics, 31*(3): 144-148

own personal results, it would be beneficial to provide some kind of official documentation to confirm the patient's identity. Results should also be stored in a confidential and secured room and should not be handed out to anyone else but the patient and the medical team, unless judicial courts grant access to such documents of an individual.