The effects of pharmacogenetics on adverse drug reactions

Jennifer Ramon

Abstract

Drug treatment provokes a variety of responses in patients – some are able to respond effectively to the treatment while others aren't. The study of patient responses to medications is called pharmacogenetics. Pharmacogenetics focuses on the inherited genetic differences that affect the drug metabolic pathway. This explains how and why patients respond differently to drugs. Adverse drug reactions are the results of how the patient responds negatively to the treatment. The purpose of this literature review is to understand the role of pharmacogenetics in understanding adverse drug reactions. While this paper only serves as an introduction, the final paper will further emphasize the role of pharmacogenetics and its efficacy in adverse reactions.

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Pharmacogenetics on adverse drug reactions: Why is This Important?

Today's medicine is based on several diagnostic judgments. Medical 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. This study is called pharmacogenetics.

Pharmacogenetics is the study of genetic differences in metabolic pathways, focusing on how and why patients respond differently to drugs[1]. Although the field of pharmacogenetics is quite new, the topic is important to be aware of due to differences in patient responses to medicine. Because patients' respond to drug treatments differently, some respond positively 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

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[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[6]. 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 pattern, 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 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., Pirmohamed 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.