Pharmacogenetics and pharmacogenomics in pharmacy practice biology essay

The study of the interaction between genetics and therapeutic drugs is variously called pharmacogenetics or pharmacogenomics. The differences between the two are the initial approach of the science:

Pharmacogenetics starts with an unexpected drug response result and looks for a genetic cause.

Pharmacogenomics, on the other hand, begins with looking for genetic differences within a population that explain certain observed responses to a drug or susceptibility to a health problem (The Australasian Genetics Resource Book, 2007).

Pharmacogenetics refers to the study of inter-individual specific genetic variation (Zika et al. 2006). The term ‘ pharmacogenetics’ is occasionally used in a limiting sense to describe how different gene variants affect drug-response but it can also be defined more broadly as the study of the effect of heredity on human drug-response (Newton et al. 2007).

Factors that influence how an individual responds to medication include their external and internal environments and overall health, as well as their genetic make-up. The goal of pharmacogenetics is to understand the role that an individual’s genetic make-up plays in how well a medicine works, as well as what side effects are likely to occur in the individual’s body.

Understanding this can help tailor drugs in the future best suited for a particular individual (personalised medicine) or group (The Australian Genetics Resource Book, 2007). The small differences in the genes between different population groups, or some families within a population group, that

have built up over the generations can mean that they react differently to medicines.

However, some diseases, notably cancers, develop in cells which have an altered genetic constitution, so that the genetic make-up of the diseased tissue is no longer the same as that of the person in which it is present. Specific genes present in the diseased tissue may play a critical role in determining the optimum treatment. To establish this, it will therefore be necessary to identify the genetic make-up of the cancer itself: testing the patient before a cancer has developed is of no use, because the genetic changes are only present in the cancer cells and not in the normal host tissues (Nuffield Council on Bioethics, 2003).

Some potential benefits of pharmacogenetics include the following:

More powerful medicines: Drugs may be developed targeting specific health problems that will maximise therapeutic effects but decrease damage to nearby healthy cells

Safer drugs the first time: Doctors could have an idea which drug to use based on a genetic profile versus trial and error, decreasing the likelihood of adverse reactions

More accurate methods of determining dosages: Instead of dosages being based on body weight and age, it would be based on an individual’s genetics. This would decrease the likelihood of an overdose.

Better vaccines: Vaccines made of genetic material could activate the immune system to have all the benefits of existing vaccines but with reduced risks of infections (The Australasian Genetics Resource Book, 2007).

Implications of pharmacogenetics in practice are vast and encompass broad areas such as:

Drug response – the effects of angiotensin converting enzyme inhibitors have been found to be greater in people of European or UK ancestry than African-Americans.

Pre-treatment genetic screening of patients will eventually enable this knowledge to be applied in clinical practice. Moreover, variation in the genes that code for receptors (drug targets) may mean that some people may produce receptors that do not interact well with the drug. For example, some people have a lack of response to the drug salbutamol, used in the treatment of asthma, due to genetic variation in the gene that codes a receptor on the surface of smooth muscle cells lining airways of the lungs.

Drug targets – Genes may also determine how many of the receptors are produced on or within cells and genetic variation may mean that some people produce more of these sites than others. The action of the widely used antipsychotic drug haloperidol (Haldol) depends on its ability to bind to the dopamine (D2) receptor site. In one study, 63% of patients whose genetic make-up caused a large number of these receptor sites to be produced had a response to treatment with haloperidol. About 29% of patients with a smaller number of dopamine (D2) receptor sites responded well to the drug.

Drug metabolism – Pain relief medications such as codeine require an enzyme produced in the liver called CYP2D6 for the drug to be used by the body, break it down and remove it. Variations in the information contained in the CYP2D6 gene determine how much of this enzyme is produced in the liver (The Australasian Genetics Resource Book, 2007). The implication of variations in genotype on the metabolism of the immunosuppressant azathioprine is also an example. Polymorphisms in the gene encoding for the enzyme thiopurine S-methyl transferase (TPMT) lead to changes in the activity of the enzyme and rate of metabolism of azathioprine. Changes in the activity of the enzyme present clinically as an increased risk of neutropenia or a decreased chance of responding to azathioprine, at normal dose ranges. A genetic test for the polymorphism can identify individuals who are more likely to develop neutropenia. Thus, the aim of a pharmacogenetic test here is to minimise an adverse effect, although in other cases, a pharmacogenetic test may be able to predict an effective responseto a medicine by correlating an individual’s genotype with the observed pharmacological actions of medicines (phenotype) (Clemerson et al. 2006).

Drug development – Excluding from clinical trials those people whose genetic makeup would make the drug being tested harmful or ineffective for them will increase the chance that a drug will show itself useful to a particular population group. This would increase the chance that the same drug will make it into the marketplace. Undertaking pre-genetic screening of those patients taking part in a clinical trial should also make the clinical trials smaller, faster, and therefore less expensive. For example, as seen in clinical

trials for developing drugs for Alzheimer disease and other forms of dementia (The Australasian Genetics Resource Book, 2007).

The application of pharmacogenetics has two main aspects: improvements in the safety and efficacy of medicines. In improving safety, pharmacogenetics works in the following ways:

Pharmacogenetic tests reveal genetic variations already known to be associated with adverse reactions, allowing physicians to avoid exposing patients to medicines that would put them at risk. The majority of adverse reactions are caused because of an exaggerated effect of a medicine in the body. Less often, an adverse reaction may be an idiosyncratic response to the medicine.

Adverse reactions to medicines have significant costs, in both human and monetary terms. However, it is difficult to ascertain the impact of genetic variation in response to medicines because data concerning adverse reactions often include problems caused by errors in prescription, and because information about other causes such as interaction between different medicines may be non-existent.

Results from pharmacogenetic tests may also inform physicians in selecting the medicine most likely to benefit a particular patient. Many medicines are effective in only a proportion of patients treated. Sometimes, for a medicine to be effective, different doses are required for different patients. In the absence of a pharmacogenetic test for efficacy, the most appropriate medicine or dose is conventionally found by trial and error, although in some cases, tests of renal function may be used to predict the appropriate dose. It

has been suggested that a ‘ trial and error’ approach to prescription may reduce compliance for medicines that do work, since patients acquire a general aversion to taking medicines because of the unpleasant side-effects which they might experience. This therefore helps in improving efficacy of medicines (Nuffield Council on Bioethics, 2003).

A potential barrier to the development of pharmacogenetic tests concerns the application of intellectual property rights. Pharmacogenetic tests may be developed in a number of ways. The pharmaceutical company which is developing the medicine may also develop the pharmacogenetic test. Alternatively, a third party, such as another company or researchers from the public sector may develop the test independently. Furthermore, while the effect of pharmacogenetics may be to reduce some of the costs of developing new medicines, it would be imprudent to infer from this that the cost of purchasing medicines will necessarily fall (Nuffield Council on Bioethics, 2003).

Pharmacogenomics

Pharmacogenomics is the study of genetic variations that influence individual response to drugs. Knowing whether a patient carries any of these genetic variations can help prescribers individualise drug therapy, decrease the chance for adverse drug events, and increase the effectiveness of drugs (AMA, 2013). Pharmacogenomics holds the promise that drugs might be tailor-made for individuals and adapted to each person’s own genetic makeup. Environment, diet, age, lifestyle, and state of health all can influence a person’s response to medicines, but understanding an

individual’s genetic makeup is thought to be the key to creating personalised drugs with greater efficacy and safety.

Pharmacogenomics combines traditional pharmaceutical sciences such as biochemistry with annotated knowledge of genes, proteins, and single nucleotide polymorphisms (Human Genome Project Information, 2011).

The field of pharmacogenomics is still in its infancy. Its use is currently quite limited, but new approaches are under study in clinical trials. In the future, pharmacogenomics will allow the development of tailored drugs to treat a wide range of health problems, including cardiovascular disease, Alzheimer disease, cancer, HIV/AIDS, and asthma (Genetics Home Reference, 2013). The cytochrome P450 (CYP) family of liver enzymes is responsible for breaking down more than 30 different classes of drugs. DNA variations in genes that code for these enzymes can influence their ability to metabolise some drugs. Less active or inactive forms of CYP enzymes that are unable to break down and properly eliminate drugs from the body can cause drug overdose in patients. Clinical trials researchers use genetic tests for variations in cytochrome P450 genes to screen and monitor patients. In addition, many pharmaceutical companies screen their chemical compounds to see how well they are broken down by variant forms of CYP enzymes.

Another enzyme called TPMT (thiopurine methyltransferase) plays an important role in the chemotherapy treatment of common childhood leukemia by breaking down a class of therapeutic compounds called thiopurines. A small percentage of Caucasians have genetic variants that prevent them from producing an active form of this protein. As a result,

thiopurines elevate to toxic levels in the patient because the inactive form of TMPT is unable to break down the drug. Today, doctors can use a genetic test to screen patients for this deficiency, and the TMPT activity is monitored to determine appropriate thiopurine dosage levels (Human Genome Project Information, 2011).

Similarly to pharmacogenetics, pharmacogenomics has the potential to provide tailored drug therapy based on genetically determined variation in effectiveness and side effects (AMA, 2013). This will mean:

More powerful medicines – Pharmaceutical companies will be able to produce therapies more targeted to specific diseases, maximising therapeutic effects while decreasing damage to nearby healthy cells.

Better, safer drugs the first time – Recovery time will go down and safety will go up as the likelihood of adverse reactions goes down or is eliminated altogether. Improvements in drug discovery, design, and development are obvious applications for pharmacogenomics. A deeper understanding of the genetic factors which cause variance in drug metabolism can aid in the design of drugs with improved potency, reduced toxicity, and fewer side effects. For example, pharmacogenomics can identify potential drug targets (targets are typically enzymes or other proteins), and determine which targets are least prone to genetic variance. By selecting drug targets which are not prone to genetic variance, drug designers can create drugs which are more likely to have standard, expected, and safe reactions in people who take it.

More accurate methods of determining appropriate drug dosages – Current methods of basing dosages on weight and age will be replaced with dosages based on a person’s genetics – how well the body processes the medicine and the time it takes to metabolise it.

Pharmacogenomics can also be useful in clinical trials for drugs which have passed through the approval process sufficiently that human trials are possible.

Using this approach, a technique called genostratification can be used in selecting participants for clinical trials. This means that clinicians use genetic typing to select participants who are genetically more likely to react positively to the treatment which is under study.

This can potentially allow for an improved level of treatment success, and means that “ proof of concept” can be achieved sooner. This technique can also allow for a reduction in the required sample size for the trial, or shortened trial duration. Ultimately, a drug which may help save or improve lives can be used in the general public more quickly than otherwise would be possible.

Economic issues from molecule to marketplace – Pharmacogenomics eventually can lead to an overall decrease in the cost of health care because of decreases in:

the number of adverse drug reactions,

the number of failed drug trials,

the time it takes to get a drug approved,

the length of time patients are on medication,

the number of medications patients must take to find an effective therapy, and

the effects of a disease on the body (through early detection).

Applying pharmacogenomics to patient treatment can help devise individualised treatment regimes, to ensure that patients receive the drugs which are most appropriate for their genetic makeup.

In particular, this approach has significant potential in treating cancer, because there is a great degree of variance in the way people react to chemotherapy drugs. Tumors themselves are highly variable in genetic terms, and this partially accounts for the variance in drug responses. Using an approach which individualizes treatment regimes, to accommodate for this variance could improve cancer treatments significantly.

Pharmacogenomics is useful in general for patient treatment because it has the potential to identify on an individual basis the drugs which might cause adverse reactions. A person who might experience such a reaction can then be prescribed an alternative drug (Lloyd, 2008).

However, there are several potential barriers to pharmacogenomics which have to be overcome before the above discussed benefits of pharmacogenomics can be realised (Human Genome Project Information, 2011). These include the following:

Complexity of finding gene variations that affect drug response – Single nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered. SNPs occur every 100 to 300 bases along the 3-billion-base human genome, therefore millions of SNPs must be identified and analyzed to determine their involvement (if any) in drug response. Further complicating the process is our limited knowledge of which genes are involved with each drug response. Since many genes are likely to influence responses, obtaining the big picture on the impact of gene variations is highly time-consuming and complicated.

Limited drug alternatives – Only one or two approved drugs may be available for treatment of a particular condition. If patients have gene variations that prevent them using these drugs, they may be left without any alternatives for treatment.

Disincentives for drug companies to make multiple pharmacogenomic products – Most pharmaceutical companies have been successful with their “ one size fits all” approach to drug development. Since it costs hundreds of millions of dollars to bring a drug to market, will these companies be willing to develop alternative drugs that serve only a small portion of the population?

Educating healthcare providers – Introducing multiple pharmacogenomic products to treat the same condition for different population subsets undoubtedly will complicate the process of prescribing and dispensing drugs. Physicians must execute an extra diagnostic step to determine which drug is best suited to each patient. To interpret the diagnostic accurately and

recommend the best course of treatment for each patient, all prescribing physicians, regardless of specialty, will need a better understanding of genetics.

Conclusion

Despite the various potential barriers to both pharmacogenetics and pharmacogenomics, these fields are rapidly evolving with the promise that someday a simple and rapid DNA test will determine potential risks of adverse effects with a certain drug, and thus turning to another drug which would be more suitable for the patient.