Practical Application of Pharmacogenetics and Pharmacodynamics for the Anesthetist and ICU Practitioner*

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Introduction:

The composition of the human genome was published in 2002. The estimated cost was $100 million.

Through subsequent advances in technology, in 2018, comparable testing can be done for ~ $100. Increasingly the development of so-called “personalized medicine” envisioned at the time the genome was described is becoming a reality. As the cost has gone down , the description of genetic differences as an explanation for heretofore unexplained variations in drug effects has grown. Examples of this can be readily found – for example the use of the BRCA1 (Breast Cancer 1 gene) to help define response to various forms of chemotherapy in women with breast cancer. This paper will provide some background detail so that practicitioners may be better informed about what the literature they are becoming increasingly exposed to and provide some practical examples of the application of pharmacogenetics and pharmacogenomics to clinical practice.(1)

Definitions:

To provide for a common understanding of study details, a list of commonly used terms and their definitions follows.

- Pharmacogenetics – the study of the differences among individuals with regard to clinical response to a particular drug – “one drug, many genomes”
- Pharmacogenomics – The study of differences among compounds with regard to the gene expression response in a single normative genome “Many drugs, one genome”
- Allele – Variant forms of a gene at a specific location in the genome
- Deletion – a mutation caused by the removal of DNA from the chromosome
- Exon – Region of a gene encoding for a particular portion of the complete protein
- Genotype – an individual’s two alleles at a specific loci
- Locus – The physical location of a gene (or gene segment) on a chromosome
- Mutation – Permanent and structural alteration in DNA
- Phenotype – A patient’s observable clinical and physiological characteristics as a result of inherited genotype interacting with their environment e.g. blue eyes
- Polymorphism – The existence of multiple genotypes in a population, at one locus

- SNPs – Single nucleotide polymorphisms – The difference of a single-base pair at a specific position in the genome between two different individuals in a population
- Variant – same as polymorphism

Current Approach

The current approach to drug therapy is frought with difficulty. It is based on a “one size fits all” strategy and inevitably this leads to some patients being under-dosed and some over-dosed. This is based on a variety of covariables including gender (most initial dosing studies exclude women of child-bearing potential), age (drug effect and metabolism varies across the age spectrum), ethnicity (population differences exist in response to drugs e.g., hypertension in subjects of African descent) not examined in sufficient detail during the premarketing phase of drug utilization and which often take years to be appropriately recognized. The advent of “personalized medicine” whereby the individuals response to a drug could be predicted based on the contribution of their genetic profile allows for more appropriate dosing strategies to be employed.(2)

Factors to consider when examining the impact a genetic condition may have on drug response

In order for a genetic defect to have a meaningful contribution to drug effect some of the following should apply:(3)

- The genetic alteration should have a major effect on the total active drug moiety
- There is a clear concentration vs response relationship
- There are severe concentration-dependent adverse effects
- There is a narrow therapeutic index

Genomic Variants

Based on their allele distribution, various types of genomic variants have been described.(4)

Variant	Allele Distribution	Effect on Active Drug	Effect on Metabolite formation
Usual (UM)	N/N	None	None
Poor Metabolizer (PM)	Abn/Abn	Increased	Reduced
Intermediate Metabolizer (IM)	Abn/N	Increased	Reduced
Extensive Metabolizer	N/N + N/N	Reduced	Increased

(EM)			

Factors influencing the application of genetic information in the ICU/OR environment

The application of pharmacogenetics to the ICU/OR environment is hampered by the lack of availability of rapid testing for allele type at the bedside. However, as the cost of performing a enetc analysis comes down and technology improves, this is increasingly less of a problem. Although to date largely market driven, bedside technology now exists for example to predict an individuals response to clopidogrel based on their genotyping.

In addition, the degree to which other covariables interact with the genetic abnormality may significantly influence the observed clinical effect. These factors include such things as disease, drug-drug interaction, substance abuse etc. For the genetic defect to be manifest phenotypically in an important manner, the following apply: 1) the frequency of the abnormal allele is significant; 2) The SNP can be identified with sufficient sensitivity and specificity and 3) the SNP predicts a reliable response – efficacy, toxicity, or failure.

Gene Identification

There are two general methods for identifying genetic variants. The first is the candidate gene approach whereby identification of variability in drug response is identified e.g., failure to inhibit platelet aggregation and resultant recurrent myocardial infarction. After ruling out other factors e.g., effect of weight and altered volume of distribution, genetic samples are obtained from affected and non-affected individuals and variation in genetic profile of genes involved in the metabolic process identified. In the case of clopidogrel this would involve variation in the CYP2C19 allele (candidate gene - CYP2C19*2). Confirmation as to whether the candidate gene is the most responsible is then examined in a separate cohort. This has eveolved to the point wher point of care testing devices for bedside use are becoming available.(5)
The second approach is the genome wide method whereby the entire genome of normal vs affected individuals is examined – so called gene-expression profiling (e.g. septic vs nonseptic patients) and the distribution and alteration of alleles is compared. This approach tends to identify a number of potential associations which must again be confirmed by examining a second cohort to see if the assumptions are correct.

Practical Examples:

CYP2C19 – Observations that a significant proportion of patients treated with clopidogrel following percutaneous coronary intervention (PCI) had a recurrent MI led to investigations designed to discover why this was occuring including the effect of dose increases. Eventually it was discovered that genetic alterations in the metabolic pathway involving the metabolism of clopidogrel. Clopidogrel is a pro-drug and as such requires metabolism to form the active moiety. While several metabolic pathways exist

including esterification to an inactive compound (85%), a large proportion of the metabolism occurs through the cutochrome P450 pathway – specifically CYP2C19. Patients with the variants CYP2C19*2 had reduced ability to metabolize the prodrug. Meta-analysis of several studies involving different assay techniques have confirmed that carriers of the CYP2C19*2 allele are at increased risk for inadequate antiplatelet effect pre-disposing then to increased risk of recurrent MI.(6)

CYP2D6 – The metabolism of a number of drugs uses in pain management e.g., codeine, hydromorphone occurs through this isozyme. Poor Metabolizers have an inability to metabolize the drug and at least one death has been directly attributed to this effect.(7)

CYP3A4/5 – This enzyme system is responsible in whole or in part for the metabolism of >50% of administered drugs including fentanyl, sufentanil, and midazolam. Midazolam is metabolized exclusively by this enzyme system and it has been used as a probe to examine drug interactions involving the CYP3A4 enzyme system. CYP3A4/5 is subject to genetic variability and the CYP3A4*3 allele is associated with reduced ability to metabolize midazolam. Skrobik et al examined the genetic contribution to the development of coma and delirium in patients admitted to the intensive care unit and receiving midazolam and/or fentanyl. They were unable to demonstrate a difference in the incidence of either complication attributable to the genetic profile.(8)

Butyrcholinesterase – Anesthesiologist have long been aware that some individuals have prolonged neuromuscular blockade following administration of succinylcholine, atracurium and mivacurium. The genetic defect lies in a point mutation at chromosome 3. There are many variants for this defect and a classification scheme has been developed.(9) Other affected drugs of interest to anesthesiologists and metabolized by butyrlcholinesterase are remifentanil and esmolol.

Alterations in receptor function:

While genetic alterations in metabolic function are important, it must also be recognized that genetic influenced alterations in receptor function may also occur. Malignant hyperthermia is due to alterations in the receptor function of the ryanodine receptor located on the sarcoplasmic reticulum and responsible for intracellular calcium mobilization. More than 30 different SNPs have been identified as genetic variants leading to the syndrome.(10)

Gene therapy:

Recognition that a genetic defect may play a seminal role in disease suggests that development of gene replacement therapy may have therapeutic potential. Hemoglobinopathies are associated with significant morbidity and mortality worldwide. Recent developments in gene therapy suggest it may be possible to significantly alter the course of transfusion dependent $\beta thalassemia$. (11)

Conclusions:

- Genetic variants are common causes of important differences in drug effect
- Bedside diagnostic tests for common variant genes are now available and will influence drug choices
- Personalized medicine is evolving and recognition of the role that altered pharmacogenetics and pharmacogenomics plays in any disease process is rapidly expanding
- Gene therapy will shortly become a reality
- Anesthesiologists and Critical Practitioners need to be aware of changes in therapeutics which will occur as a result

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