INTENSIVE CARE MEDICINE

2008 ANNUAL UPDATE

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Common Abbreviations

ALI  Acute lung injury
ARDS Acute respiratory distress syndrome
BAL Bronchoalveolar lavage
CBP Cardiopulmonary bypass
CNS Central nervous system
COPD Chronic obstructive pulmonary disease
CT Computed tomography
CVP Central venous pressure
DIC Disseminated intravascular coagulation
DO₂ Oxygen delivery
EEG Electroencephalogram
EKG Electrocardiogram
HIV Human immunodeficiency virus
ICU Intensive care unit
IL Interleukin
LPS Lipopolysaccharide
MAP Mean arterial pressure
MOF Multiple organ failure
MRI Magnetic resonance imaging
NF-κB Nuclear factor-kappa B
NO Nitric oxide
NOS Nitric oxide synthase
PAC Pulmonary artery catheter
PAF Platelet activating factor
PAI Plasminogen activator inhibitor
PAOP Pulmonary artery occlusion pressure
PARP Poly(ADP-ribose) polymerase
PEEP Positive end-expiratory pressure
RBC Red blood cell
ROS Reactive oxygen species
ScvO₂ Central venous oxygen saturation
SIRS Systemic inflammatory response syndrome
SOFA Sequential organ failure assessment
SvO₂ Mixed venous oxygen saturation
TLR Toll-like receptor
TNF Tumor necrosis factor
VILI Ventilator-induced lung injury
VO₂ Oxygen uptake
I Genetic Factors
Are Pharmacogenetics and Pharmacogenomics Important for Critically Ill Patients?

C. Kirwan, I. MacPhee, and B. Philips

Introduction

Drugs are administered to patients using dosing regimens established from animal data, clinical trials, and population studies. However, there may be enormous variation in dose requirement, efficacy, and adverse effects between individuals within a given population. Although this may partly be attributed to factors such as age, concomitant drug interactions, co-morbidities, and the underlying disease itself, genetic factors are estimated to account for 15–30% of between individual differences and for some drugs the impact of genetics may be much higher [1,2]. Genetic variation may influence all aspects of pharmacokinetics and pharmacodynamics and although the clinical relevance of pharmacogenetics remains uncertain, the idea is developing that some drug therapies may be individualized in the future.

Historically genetic variations have needed to be dramatic to be noticed. For example, the inherited deficiency of glucose-6-phosphate dehydrogenase results in severe hemolysis if such patients are exposed to primaquine. This was clearly inherited as large population variation was observed between African (deficiency is common) and Caucasian (deficiency rare) patients. With the development of the Human Genome Project it has become possible to look for less dramatic genetic variations which if understood may have significant impact on the use and administration of drugs to individuals.

This chapter will define pharmacogenetics and pharmacogenomics, describe how the science has evolved over the last few years, and attempt to highlight the possible impact the developments will have in the management of critically ill patients.

Pharmacogenetics or Pharmacogenomics?

Historically, pharmacogenetics is the older term and emerged as individual variation in the pharmacokinetic and pharmacodynamic response to drugs became apparent [3–5]. In general, pharmacogenetics identifies gene polymorphisms, which generate phenotypes of clinical importance. To be clinically relevant, these polymorphisms need to be either sufficiently common in the population or, if rare, of sufficient medical impact (e.g., the deletion of expression for pseudo-cholinesterase and the metabolism of succinylcholine) to alter clinical management.

The development of the Human Genome Project [6] has coined the new term, pharmacogenomics. This term incorporates pharmacogenetics but has a rather broader meaning, describing the wider influence of DNA sequence variation on phenotype and the effect on drug handling and efficacy. Pharmacogenomics also includes
Table 1. Areas of pharmacology in which genetic polymorphism may alter a patient's risk of toxicity or therapeutic benefit

<table>
<thead>
<tr>
<th>Process</th>
<th>Target</th>
<th>Drug Example</th>
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<td>Absorption</td>
<td>ATP-binding cassette B1 (ABCB1)</td>
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<td>Metabolism [Phase 1]</td>
<td>CYP2D6</td>
<td>Codeine</td>
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<tr>
<td></td>
<td>CYP2C9</td>
<td>Warfarin</td>
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<td>Metabolism [Phase 2]</td>
<td>Uridine diphosphate-glucuronosyltransferase (UGT1A1)</td>
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<td>Thiopurine S-methyltransferase (TPMT)</td>
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<td>Excretion</td>
<td>Sodium lithium countertransport (SLC) transporters</td>
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<td>DNA repair</td>
<td>XRCC1</td>
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<tr>
<td>Cellular target</td>
<td>β2-adrenoreceptor</td>
<td>Asthma therapy</td>
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</table>

the application of genomic technologies to new drug discovery and further characterization of older drugs. Unlike other factors influencing drug response, inherited determinants generally remain stable throughout a person's lifetime (Table 1).

Pharmacogenetics, Pharmacogenomics, and Drug Metabolism

Phase I reactions (oxidation, reduction, and hydrolysis) and phase II conjugation reactions (acetylation, glucuronidation, sulfation, and methylation) are influenced by a number of genetic polymorphisms. Early discoveries include the metabolism of drugs such as succinylcholine and isoniazid or hydralazine. Four allelic genes coding for plasma cholinesterase cause wide variation in activity and therefore rate of hydrolysis of succinylcholine [7] and a common genetic variation in the phase II, N-acetylation, pathway causes large differences in the half-life and plasma concentrations of drugs metabolized by N-acetyltransferase including isoniazid, hydralazine, and procainamide.

Currently, more than 30 families of enzyme complexes responsible for drug metabolism have been described in humans and numerous variations exist in the genes encoding the many enzymes and proteins. Several reviews illustrate the ways these variants may be clinically important [2, 8–10] but the real clinical significance for most remains unstudied and uncertain. A clinical effect is most likely to be notable for drugs metabolized under predominately monogenic control and for those which possess narrow toxic or therapeutic ratios [2, 11–13], although significant haplotypes and frequent linkage disequilibria are also recognized.

Although a number of different types of polymorphisms have been shown to influence drug response, single nucleotide polymorphisms (SNPs) are likely to be the most profitable in terms of pharmacogenomics analysis. SNPs are the most common variant class in the human genome with one occurring at approximately every 1000 base pairs. It is because these genetic variations are so common and technology exists for their rapid genotyping that SNPs are capable of revealing genomic variation on a scale which is not yet possible with other types of DNA polymorphism. One important clinical example found by this technique concerns the thiopurine methyltransferase (TPMT) gene. Approximately 100 SNPs have been identified on the TPMT gene but four in particular markedly increase the risk of bone marrow
failure after administration of 6-mercaptopurine or azathioprine [14]. Other examples where data from SNP studies has suggested a clinical effect are found in the fields of gastroesophageal reflux, epilepsy, and human immunodeficiency virus (HIV) [15–17].

**Clinically Relevant Genetic Polymorphisms in Critical Care**

Pharmacogenetics is a new science to critical care. The heterogeneity of patients and complexity of drug regimens makes investigation fraught with difficulty. The following is a selection of some of the more important systems that may have clinical significance.

**The Cytochrome P450 Isoenzymes**

Approximately 12 cytochrome P450 (CYP) isoenzymes of families CYP1, CYP2, CYP3 are collectively responsible for most phase I reactions in the human liver. Collectively they account for over 60% of all drug elimination [18]. Alleles of the CYP enzymes are allocated a number. The wild type is allocated the number *1 and the terminology for an individual homozygous for the wild type allele (e.g., CYP3A4) would be CYP3A4 *1/*1.

**CYP3A**

Midazolam, a benzodiazepine commonly used in anesthesia and intensive care medicine, is exclusively metabolized by CYP3A. Enzymes in the CYP3A sub-family (CYP3A4 and CYP3A5) are the most abundant CYPs in the human liver. CYP3A4 is the most predominant form expressed in liver cells but CYP3A5 may contribute to more than 50% of the hepatic CYP3A activity in the one third of the population that express both enzymes [19]. There is a large genetic variability in both of these enzymes and many different alleles have been described. A number are rare and many alleles of CYP3A4 have little or no significance on endogenous substrate metabolism [20, 21]. CYP3A5 is, however, more significant. Polymorphic CYP3A5 expression is strongly correlated with a single nucleotide change, designated CYP3A5 *3 [22]. Volunteers who are homozygous (CYP3A5 *3/*3) for the CYP3A allele showed marked loss of enzyme activity and thus midazolam clearance, when given midazolam in the presence of itraconazole (CYP3A4 and CYP3A5 inhibitor) [19, 23] and can be considered functional non-expressers. For patients undergoing solid-organ transplant, the CYP3A5 *3/*3 genotype confers a lower dose requirement of tacrolimus for both loading and maintenance. Patients with CYP3A5 *1/*1 or *1/*3 have a delay in achieving target blood tacrolimus concentrations and genotyping may help in the initial dosing of tacrolimus after transplantation [24].

**CYP2B6**

CYP2B6 is one of the most polymorphic CYP genes in the liver with over 100 SNPs described, numerous complex haplotypes, and distinct ethnic frequencies. Its expression in the liver is highly variable with some individuals expressing more than 100 fold more enzyme than others [18]. CYP2B6 has not been extensively investigated but clinical substrates include cyclophosphamide, anti retrovirals, synthetic opioids (e.g., methadone), and propofol [25].