Pharmacogenomics and reducing the frequency of adverse drug events

‘Application of pharmacogenetic and pharmacogenomic information should allow the potential for ADEs to be premanaged in the out-patient setting.’

Drug toxicity and adverse drug events Pharmacogenomics, as applied to medical practice, offers the promise of reduction in adverse drug events (ADEs), enhanced drug efficacy and selection of patients able to respond to specific agents. This editorial will focus on the history and evolving role of pharmacogenetics and pharmacogenomics as it moves from the basic research laboratory into clinical practice to reduce the occurrence of ADEs. In 1994, 2,216,000 patients either reported to the hospital or were in the hospital as a result of ADEs. Of these, 106,000 patients experienced fatal ADEs [1]. In 2000, 2,168,248 toxic events due to all forms of poisons and drugs were reported in the US. Toxin-related events in 2000 affected 8% of the US population. Of these events [2]:

- 1,418,573 were unintentional
- 748,094 were drug related
- 152,000 represented therapeutic errors

In 2001, there were 669,559 reports of ADEs due to drugs of abuse, including alcohol. There were 220,289 AD Es due to prescription psychotherapeutics, 99,317 due to prescription narcotics, 39,165 due to over-the-counter acetaminophen, 22,663 due to over-the-counter non-steroidal anti-inflammatory drugs and 14,642 due to prescription antiepileptics [101]. Data outlined in these three different national reporting schemas demonstrate a high degree of concordance and are consistent with other reports [3,4]. The estimated annual cost of drug-induced illness in the US is US$136 billion [5], and ADEs were estimated to be the fourth to sixth leading cause of death in the US [1].

Proof of principles Historically, much of the evidence that pharmacogenetics and pharmacogenomics facilitates individualized drug therapy has involved ADEs. Over 40 years ago it was recognized that life-threatening toxicity associated with the muscle relaxant succinylcholine resulted from inherited impairment in the hydrolysis of this drug by a genetically ‘atypical’ form of butyrylcholinesterase (pseudo cholinesterase). Those observations helped to stimulate the development of pharmacogenetics and pharmacogenomics. Subsequently, two decades ago, pharmacogenetic variations in drug metabolism catalyzed by a Phase I enzyme, cytochrome P450 (CYP) 2D6, and a Phase II enzyme, thiopurine methyltransferase (TPMT), were described. These two genetically polymorphic drug-metabolizing enzymes became ‘prototypic’ examples of the potential importance of pharmacogenetics-pharmacogenomics for understanding and avoiding ADEs. As a result, TPMT and CYP2D6 pharmacogenetics have played important roles in the evolution of this field and have helped to demonstrate the potential value of pharmacogenomics in the clinic. It is now evident that the one in 300 Caucasian subjects homozygous for alleles for extremely low levels of TPMT activity is at greatly increased risk for potentially fatal myelosuppression when treated with ‘standard’ doses of thiopurine drugs such as 6-mercaptopurine and azathioprine. Those observations are now so clear and convincing that the FDA recently held public hearings to discuss the possibility of modifying thiopurine drug ‘labeling’ to reflect this risk [6].

Challenges for today Despite the success of pharmacogenomics as demonstrated by TPMT, it is appropriate to ask if the greatest impact for pharmacogenetics will be obtained from applications to drugs that are used to treat relatively few patients. The answer, of course, is no. The present challenge is to broaden the application of the principles demonstrated by the butyrylcholinesterase and TPMT polymorphisms to a larger number of drugs and ADEs. Ultimately, a cost–benefit calculation that integrates ADE frequency with the costs generated will need to be performed in each case. Reversing the effects of ADEs often
requires in-patient hospital stays associated with appreciable cost. Application of pharmacogenetic and pharmacogenomic information should allow the potential for ADEs to be pre-managed in the out-patient setting, a much less expensive environment.

‘Genotyping or haplotyping alone will be insufficient to avoid adverse drug events.’

Of the top ten selling prescription drugs in the US in 2002 [7], olanzapine, sertraline and paroxetine, the eighth, ninth and tenth best selling drugs, respectively, are prescription psychotherapeutic agents that are associated with high rates of ADEs. Focusing pharmacogenetic efforts on identifying variations that predispose a patient to an ADE with these psychotherapeutic agents would be one example of a reasonable and cost-effective step toward minimizing ADEs while maintaining these patients in the outpatient setting. Paroxetine is metabolized mainly by CYP2D6, a highly polymorphic gene [102]. Like a number of other selective serotonin re-uptake inhibitors (SSRIs), paroxetine inhibits CYP2D6. Consequently, individuals who have polymorphisms that result in enzyme deficiencies are at increased risk for ADEs due to elevated SSRI levels as a result of deficient and/or inactivated CYP2D6. Conversely, individuals with CYP2D6 gene duplications may be at lower risk for ADEs but they may not receive the full benefit of drug therapy. Knowledge of the CYP2D6 genotype permits the prediction of metabolic phenotype to a first approximation. Individuals who are homozygous or compound heterozygous for inactivating polymorphisms and mutations are poor metabolizers and individuals with gene duplications are ultrarapid metabolizers. However, what risk should be assigned for heterozygous individuals? The answer to that question depends in part on the nature of the other drugs administered to this patient. CYP2D6 is inhibited by a wide variety of xenobiotics. Consequently, a heterozygous individual can be at high risk for an ADE if they are simultaneously taking other drugs that inactivate or inhibit CYP2D6 even if the SSRI dose has been adjusted downward.

However, genotyping or haplotyping for a drug-metabolizing enzyme alone is not a substitute for a thorough patient history that includes a list of prescription and non-prescription drugs that the individual is taking, including ‘nutriceuticals’. This clinical information must be integrated with the genotypic information to assess risk for ADEs. Furthermore, it will not be sufficient for the physician to merely understand drug-drug and drug-genotype interactions within their own specialty. Rather, it will also be necessary to understand predisposition to risk for ADEs involving other disease/organ systems. For example, paroxetine inhibits not only CYP2D6 but also CYP2C9, the predominant enzyme that metabolizes the anticoagulant S-warfarin. 30% of the Caucasian population is heterozygous for one or more CYP2C9 polymorphisms that affect S-warfarin metabolism [8]. Individuals with these polymorphisms can experience increased risk of bleeding if administered standard doses of S-warfarin, and their time to achieving stable dosing is usually prolonged [9]. Knowledge of these polymorphisms will help guide dosing in patients starting on anticoagulant therapy to reduce morbidity and improve outcome [10]. Polypharmacy must also be considered when prescribing S-warfarin. In summary, genotyping or haplotyping alone will be insufficient to avoid ADEs toxicology, pharmacology, pharmacogenetics and clinical status must be functionally integrated with the total clinical scenario for successful patient management. What is presently lacking is a database of knowledge to connect dose to genotype that takes into account gender, body mass, age, genotype as well as coadministered drugs, herbal and nutriceuticals.

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Challenges for tomorrow
ADEs as multigenetic traits
The focus on drug metabolism was a necessary initial simplification to make it possible to begin to define genetic components contributing to ADEs. However, it is likely that increased risk for ADEs can also occur as a result of variations in drug disposition that occur at multiple levels. Polymorphic variation in drug adsorption, distribution and excretion will also affect circulating drug concentrations and the incidence of ADEs. Understanding the pharmacogenomics of epithelial drug transporters, such as ATP binding cassette (ABC) proteins, is under intense investigation at this time. Key drug
transport proteins such as the organic anion transporter known as multiple resistance-associated protein isoform 2 (MRP2) and the organic cation transporter p-glycoprotein (pg), among others, control entry and export of drugs from epithelial cells [11-13]. These transporter proteins are also genetically polymorphic; significant sequelae have been associated with ABC protein polymorphisms and digoxin [14], cyclosporin [15], tacrolimus [16], fexofenadine [17], and protease inhibitors [18]. These polymorphisms contribute to significant variation in drug disposition, response to therapy and ADEs.

Improving prediction of phenotype from genotype

A fundamental precept of pharmacogenetics is predictability of phenotype from genotype or haplotype. In some instances, genotype-phenotype correlation is adequate for use in clinical interpretation. N-acetyltransferase haplotyping is highly accurate for predicting 'acetylator status'. TPM T genotype is used clinically to identify patients at risk for ADEs when treated with thiopurines. CYP2D6 and CYP2C9 genotyping can distinguish poor metabolizers from extensive and ultrarapid metabolizers. However, genotyping for only the coding regions and intronic splice sites is not optimal for predicting phenotype. It is well known that post-translational modifications affect protein function. Several studies indicate a focus on coding regions is inadequate for a complete picture of the relationship between DNA sequence variation and phenotype. For example, TPM T genotyping within the open reading frame of the gene makes it possible to categorize patients into broad treatment dosage cohorts. However, to truly individualize therapy with the goal of optimizing efficacy while minimizing toxicity, additional factors such as protein functionality must be considered. While the TPM T gene does not have a conventional TATA box, a complex promoter VNTR in the 5′-flanking region participates in the regulation of the level of enzyme activity. Repeat length appears to correlate inversely with enzyme activity [19]. This may add another dimension of complexity to the analysis of TPM T pharmacogenomics and for making decisions with regard to individualized drug dosing. Protein functionality may be important when using thiopurine drugs to treat an expanding disease population base that now includes patients with gastrointestinal and dermatologic diseases in addition to patients suffering from neoplasias.

An additional example of variation in drug disposition is at the level of gene expression. This factor has been considered for inducible genes, such as those encoding members of the CYP3A family, but it has often been ignored in other systems (e.g., CYP2D6). Recent evidence indicates that the level of expression of CYP2D6 may be indirectly influenced through regulation of the expression of hepatocyte nuclear factor 4 by nitric oxide (NO) [20]. As a result, therapeutic agents that affect the levels of coregulatory factors, such as those liberating NO (nitrate-containing drugs), may need to be considered in assessing the potential risk for ADEs from drugs metabolized by this enzyme.

'Pediatric adverse drug events are a significant public health issue.'

Preventing pediatric ADEs

ADEs in the adult population have received significant attention. However, pediatric ADEs are also a significant public health issue [21]. A recent example involves concern over acetaminophen labeling and the chance of inadvertent overdoses in the pediatric setting [103]. Acetaminophen is hepatotoxic and undergoes biotransformation through two routes: i) glucuronidation and sulfation to produce non-toxic excretable metabolites; and ii) production of hepatotoxic compounds through the action of CYP450 including CYP2E1. Polymorphic variations exist for all the genes involved. The hepatotoxic metabolite is further conjugated with glutathione. Glutathione synthesis involves γ-glutamylcysteine synthase, which is genetically polymorphic. Several glutathione-S-transferases are involved in conjugation reactions with glutathione and are also polymorphic or have common null alleles. The association of these polymorphisms with ADEs from acetaminophen overdoses in children has not as yet been established but deserves investigation. If such associations can be documented, then, at the very least, siblings of children who have experienced an ADE with acetaminophen should be evaluated and tested.

Expert opinion

Pharmacogenomics offers the promise of improving medical care through selection of patients who will respond more effectively to
drug therapy, optimizing efficacy and decreasing the frequency of ADEs. Many ADEs have an underlying identifiable genetic component. Pharmacogenomics is now poised to move into the clinic from a strong base of support built upon research studies on polymorphic drug metabolism. To successfully reduce the frequency of ADEs, pharmacogenetics and pharmacogenomics must broaden its focus to include not just a consideration of polymorphic drug metabolizing enzymes, but also additional pathways that contribute to polymorphic drug disposition such as drug-transporter and receptor polymorphisms and drug-drug interactions. A new level of complexity involving management of many bits of information is essential to move the prediction of phenotype from genotypic analyses into patient care.

Bibliography

18. Huisman MT, Smit JW, Schinkel AH et al.: Association of P-glycoprotein expression with the frequency of ADEs. Many ADEs have an underlying identifiable genetic component. Pharmacogenomics is now poised to move into the clinic from a strong base of support built upon research studies on polymorphic drug metabolism. To successfully reduce the frequency of ADEs, pharmacogenetics and pharmacogenomics must broaden its focus to include not just a consideration of polymorphic drug metabolizing enzymes, but also additional pathways that contribute to polymorphic drug disposition such as drug-transporter and receptor polymorphisms and drug-drug interactions. A new level of complexity involving management of many bits of information is essential to move the prediction of phenotype from genotypic analyses into patient care.

Websites

104. www.fdaadvisorycommittee.com/FDC/ AdvisoryCommittee/Committees/ NonprescriptionD Rugs/ 091902, acetaminophen/ 091902, Acetaminophen.htm
105. FDA Advisory Committee: Acetaminophen Labeling Should Warn About Liver Damage From Higher Than Recommended Doses.