Adding Pharmacogenetics to the Clinical Laboratory

Narrow Therapeutic Index Medications as a Place to Start

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Although pharmacogenetics is a new discipline, it is anticipated to have applications in many fields, including drug development, therapeutic dosing guidance, and disease risk stratification. Rai has suggested that pharmacogenetic testing during drug development trials could create a large number of drug compounds targeted to particular pharmacogenetic phenotypes. This approach in turn would necessitate clinical pharmacogenetic testing as a requirement for therapy with that drug. Specific pharmacogenetic dosing guidelines would advance the science of prescribing drugs toward truly individualized drug therapy. It is anticipated that in turn, individualized drug therapy will enable physicians to predict and, ideally, to prevent many adverse drug reactions (ADRs), which are a leading cause of morbidity and mortality in this country, estimated to be the fifth leading cause of death among hospitalized patients (see Table 1).

The aim of pharmacogenetic testing is to describe how people will respond differently to medicines a priori because of their genetic profile. The term “pharmacogenetics” has been pieced together from the words “pharmacology” (the study of how drugs work in the body) and “genetics” (the study of how traits are inherited). Pharmacogenetic testing in a clinical setting links genotype to phenotypic differences in the pharmacokinetics or pharmacodynamics of medications. Through the application of pharmacogenetic information, extreme phenotypic differences in the pharmacokinetics (the body’s action on the drug) or pharmacodynamics (the body’s response to a drug) of drugs can be predicted. In addition, pharmacogenetic information reveals molecular mechanisms of drug action. It is anticipated that clinical pharmacogenetic testing will become routine and that more defined dose adjustments will soon become available to translate the results into clinical practice. This will increase demands on the clinical laboratory for high-throughput genetic testing. This article describes 1 entry approach to narrow the field of possible pharmacogenetic tests to those that can be tied with existing therapeutic drug monitoring (TDM) testing.

The Basics of TDM, Including Narrow Therapeutic Index

Therapeutic drug monitoring in the hospital has traditionally been a collaboration between the clinical laboratory, which provides serum concentrations, and the clinical pharmacists. The pharmacists work with the general medicine teams, surgery, subspecialty services, and the intensive care unit team to evaluate the appropriateness of drug therapy and interpretation of serum concentrations. In general, it is most important to conduct serum concentration monitoring in drugs with a narrow therapeutic index (NTI). The US Food and Drug Administration identifies a medication as having a narrow therapeutic index if very small changes in the dosage level could cause either subtherapeutic or toxic results. Offering serum or whole-blood TDM of NTI medications is a service that is well known in many clinical laboratories. Unfortunately, TDM is often a reactive process, and the first serum concentration obtained for many NTI medications comes days after initiation of therapy. By this time, levels could be well outside the therapeutic range in cases of genetic polymorphisms. To move from therapeutic drug monitoring to therapeutic drug management will likely require greater service from the clinical laboratory, including conducting or at least interpreting pharmacogenetic testing.

How Do TDM and Pharmacogenetics Fit Together?

Combining TDM and pharmacogenetics in a hospital setting would take advantage of the inherent cooperativity of the 2 fields. By linking the 2 approaches prior to dose optimization in the critically ill patient, as well as the 2 groups involved in dose management, the TDM laboratory and the pharmacist, the safest and most cost-effective TDM could be achieved. In a survey of physicians, NTI, also known as critical dose, medications were responsible for a high incidence of adverse events. Four of the medications listed in Table 2, carbamazepine, phenytoin, furosemide, and digoxin, in particular were reported by physicians to have...
been involved in ADRs. These reactions included increased pain and suffering; emergency room visits, hospitalization, and even death; increased health care costs; changed or additional prescriptions; and additional laboratory testing. These 4 NTI medications as well as others listed in Table 2 have clinically relevant genetic variants that have been shown to affect dosing.

For example, P-glycoprotein, the protein product of the human MDR1 (ABCB1) gene is 1 factor controlling bioavailability of many medications, including digoxin. In the intestine MDR1 decreases bioavailability by keeping digoxin in the intestinal lumen. In the kidney MDR1 increases excretion by transport of digoxin into the urine. This transporter has 2 clinically relevant polymorphisms, at amino acids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids 2677 and 3435, that if present produce a protein with lower aminoacids. A study by Kurata et al9 conducted in healthy volunteers genotyped for MDR1. They found the bioavailability of digoxin in wild-type and homozygous variant subjects were significantly different, 67.6% ± 4.3% and 87.1% ± 8.4%, respectively (P < .05). The MDR1 variants were also associated with differences in disposition kinetics of digoxin, with the renal clearance almost 32% lower in homozygous variant subjects (1.9 ± 0.1 mL/min/kg) than subjects with the wild-type genotype (2.8 ± 0.3 mL/min/kg), and with heterozygous subjects having an intermediate clearance value (2.1 ± 0.6 mL/min/kg). MDR1 transports many other medications as well, including cyclosporine and disopramide. Therefore, a one-time test for polymorphism in MDR1 prior to initiating therapy with any of these medications could at least provide additional support to begin dosing and may even prevent adverse events, including overdosing, in homozygous variant patients. However, as noted by many authors prospective studies to test this approach have yet to be published.

An example of pharmacogenetics affecting TDM in our own hospital can be illustrated by the following case. A 23-year-old white man was admitted to the emergency department for a closed head injury. After surgery to remove a subdural hematoma, the patient was prophylactically given phenytoin, an antiseizure medication, with a standard dosage of a 1-g bolus followed by 100 mg every 8 hours. Total serum phenytoin on day 3, assuming steady state had been achieved, was 46 µg/mL (therapeutic range, 10–20 µg/mL). No clinical signs of toxicity were observed, but the patient was comatose. The patient was being given no other medications known to inhibit metabolism of phenytoin, and renal and liver functions were good. The phenytoin was in a range considered to be potentially toxic, and this value initiated a call to the clinical chemistry fellow covering the TDM/toxicology service for the hospital. Consultation with the clinical pharmacist caring for this patient indicated no explanation for the high serum phenytoin (other than an inappropriately high dose). The enzyme primarily responsible for phenytoin metabolism is CYP2C9. The gene that produces this enzyme may contain 1 or both of 2 common genetic variants, CYP2C9*2 and CYP2C9*3. The enzymes produced by these variant genes have 5% and 12%, respectively, of the activity of the wild-type enzyme.10 This severe phenytoin toxicity has been observed...
in patients with variant alleles of the CYP2C9 gene, with total serum levels reaching 79 mg/L.11 and elimination half-life as long as 103 hours. Standard elimination half-life is 22 hours.12 At least 1 of these alleles is present in approximately 35% of the white population. This information was shared as part of the pharmacogenetics consultation, and as a result, the pharmacists requested the genetic testing on this patient through the hospital ordering system. The testing took 2 days, and the patient was reported to have an intermediate metabolizer genotype CYP2C9*1*2. The literature supports a 25% to 30% dose reduction in this case.13,14 This information along with the genotype was provided in the clinical genotyping results. Although the phenytoin was discontinued after this toxic phenytoin value, the patient was placed back on phenytoin later in the hospital course on a 30% dose reduction.

How could drug monitoring have been changed to drug management in this case? Earlier serum monitoring could have prevented the initially supertherapeutic phenytoin level, aided perhaps by the use of pharmacokinetic computer models.15 Also, if results of pharmacogenetic testing had been available prior to the accident, a reduced phenytoin dose would have been indicated initially. In our case, the genotyping results could have been available on day 2, perhaps preventing the high drug level seen. Faster turnaround times would make pharmacogenetic testing even more useful in the care of the critically ill patient. It is unclear whether testing all hospital patients to be placed on phenytoin would improve care or be cost effective.

There is an active and ongoing debate on if or how much pharmacogenetic testing can decrease health risk or health care costs.16-18 It is safe to say at this time that the jury is still out, because the field is too new to provide a definitive answer. The most important information for medications already on the market will be obtained from prospective clinical trials of pharmacogenetic testing. Outside of HIV genotyping, there are very few publications in this field. Feasibility data may also emerge from studies of new drug entities where pharmacogenetics testing was included in phase 1 and phase 2 trials to assess the effect of genetic variance.

If studies do indicate that pharmacogenetic testing should become standard practice, is widespread testing feasible? The technical feasibility of performing pharmacogenetic testing in a clinical setting in a timely, cost-effective manner for all patients who may benefit is still an evolving field. No single technology has emerged as a leader in the testing market.19 Pioneers in pharmacogenetic testing have up to this point been either using a “home-brew assay” approach or using the analyte-specific reagents that have been made available. As of January 2004 there is no Food and Drug Administration–approved diagnostic device for pharmacogenetic testing. Many clinical laboratories are already involved in some form of genetic testing. Guidelines have been released that particularly address clinical pharmacogenetic testing (see Table 3). Laboratories must also obtain Clinical Laboratory Improvement Amendments of 1988 certifications as well as state licenses. At our own laboratory, the Pharmacogenetics Diagnostic Laboratory, we are using a combination of home-brew and analyte-specific reagent kits for testing clinical samples. This approach has a direct impact on turnaround times in the clinical laboratory. Whereas the analytic limit to genotyping turnaround times is currently hours, the low test volumes in the current environment translates many times to actual turnaround times of days due to batching of samples. In our experience, as the demand for testing increases (we have seen a 300% rise in test volumes in the last 12 months), our turnaround times have actually decreased to less than 4 days on average.

A recent article by Suther and Goodson20 found that many primary care physicians believe genetics to be a low practice priority. However, this may be because of a lack of knowledge of the potential impact of genetics. Most currently practicing physicians are exposed to fewer than 30 hours of training in genetics, and it is probable that pharmacogenetics was not part of that training.21 Therefore, the biggest barrier to pharmacogenetic testing is probably not a technologic but an educational barrier. It is important that comprehensive reviews of the subject be made available and that practice guidelines be developed from prospective clinical trials using pharmacogenetic testing.

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