Clopidogrel and the Concept of High-Risk Pharmacokinetics

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Four large trials, reported in the last several weeks, have identified loss-of-function alleles in the gene encoding cytochrome P450 2C19 (CYP2C19) as important risk factors predicting apparent failure of clopidogrel efficacy.1–4 Previous studies have shown that clopidogrel is a prodrug that requires bioactivation,5 mediated in part by CYP2C19, to achieve its antiplatelet efficacy.6 All 4 trials built on this knowledge and studied the effects of CYP2C19 variants on coronary events (including death, myocardial infarction, and in-stent thrombosis) in patients receiving clopidogrel. Hazard ratios for a single CYP2C19 variant allele ranged from 1.5 to 4, depending on the end point and the specific population. We describe here how this apparently surprising outcome could be anticipated from first principles in clinical pharmacology. We then discuss how considering this result within the context of a contemporary understanding of clinical pharmacokinetics and pharmacogenetics raises new hypotheses that require further testing.

Anticipating This Result: The Concept of High-Risk Pharmacokinetics

In an era of increasing attention on multiple genetic variants as mediators of variability in drug action (pharmacogenomics), it is a bit of a surprise to see such a spectacular effect of a single set of variants on clinically important outcomes for a very widely used drug. However, the new findings with clopidogrel are entirely consistent with a set of clinical pharmacokinetic findings that now extend back decades and define the concept of high-risk pharmacokinetics,7,8 a risk of serious drug toxicity when drug concentrations depend on variable activity of a single metabolic pathway.

The processes of absorption, distribution, metabolism, and excretion rely on specific proteins that metabolize drugs and move them into and out of cells. Although the activities of these processes vary among individuals, we now understand that genetic variation can result in near-complete absence of enzymatic activity in some individuals. It follows that drugs with a bioactivation that relies on a single pathway will display highly variable clinical effects if that pathway is inhibited or absent on a genetic basis. This is the issue with clopidogrel and a number of other drugs described here.

Variable Bioactivation of Other Prodrugs

Approximately 7% of the European American and African American populations lack functional alleles for another P450, CYP2D6.9 Codeine is bioactivated to its active metabolite (morphine) by this enzyme, and CYP2D6-poor metabolizers display decreased analgesic opioid effects of the drug.10 Tamoxifen is bioactivated by a number of pathways, including CYP2D6,11 and preliminary analyses of outcomes during tamoxifen therapy as a function of CYP2D6 genotype support the idea that poor metabolizers have an increased incidence of recurrent breast cancer during tamoxifen therapy.12–14

High-Risk Pharmacokinetics and Drug Elimination

A second high-risk situation is the administration of a drug that has the potential to cause serious toxicity at high concentrations and whose elimination depends on a single pathway. In this case, perturbation of that pathway, by genetic factors or by interactions, can lead to marked increases in drug concentrations (because alternate pathways for drug elimination are not present) and thus drug toxicity (see the Figure).

Warfarin is bioinactivated by CYP2C9-mediated metabolism. Common variants in this enzyme lead to a reduction of function (CYP2C9*2) or near-complete reduction of function (CYP2C9*3). Rare individuals who are homozygous for the loss-of-function allele (*3/*3, ≤1% of a white population) display striking reductions in warfarin dose requirement and may be at increased risk for complications during therapy.15,16 It is now apparent that warfarin dose requirements reflect variation in both CYP2C9 and VKORC1, which encodes a protein in the vitamin K receptor complex that is the target of the warfarin drug action. Because there is such a narrow margin between the dosages required for efficacy and those producing toxicity for this drug, adjustment of dose in the broad population exposed to the drug according to genotype, not simply identifying *3/*3 homozygotes, may be a preferred approach.17 Large trials testing this idea are now in the planning phase.18

Some drugs are markedly affected by genetic variation in metabolism, but because a wide range of concentrations is well tolerated, the clinical consequences are minor. Metoprolol and timolol undergo CYP2D6-mediated bioactivation. Toxicity is not a problem in poor metabolizers, however, because marked increases in β-blocker concentrations do not result in severe adverse effects; some data suggest that metoprolol cardiodoselectivity may be lost in poor metabolizers.19

Implications

Drug Interactions

An obvious possibility raised by the clopidogrel findings is that coadministration of CYP2C19-inhibiting drugs might
patients discharged on clopidogrel from 127 Veteran’s Administration Hospitals in 2003 to 2006 similarly found a higher event rate among those on PPIs, although specific agents of the class were not examined.28 However, database studies are not randomized controlled studies, and the problem of residual confounding resulting from baseline differences in patients receiving omeprazole can be difficult to exclude. Notably, the Clopidogrel and the Optimization of Gastrointestinal Events (COGENT-1) trial evaluating a clopidogrel-omeprazole combination product was terminated by the sponsor in early 2009.

Further retrospective analyses to weigh the risks and benefits of the combination are likely required because prospective randomized clinical trials to assess the effect this interaction on cardiovascular and gastrointestinal events are not available or planned. At this point, it seems clear that this potential interaction should be evaluated on a PPI-specific basis and that it is unlikely to represent an effect shared by all drugs in the class.

Other Drug Interactions Linked to High-Risk Pharmacokinetics

The concern about a clopidogrel-omeprazole interaction is the latest in a long line of serious adverse drug reactions based on the principles of high-risk pharmacokinetics.

Terfenadine is a very potent QT-prolonging agent but, in the vast majority of individuals, undergoes near-complete presystemic metabolism by a single enzyme, CYP3A. Although individuals absolutely lacking CYP3A activity have not been described, patients receiving potent CYP3A inhibitors such as certain azole antifungals or macrolide antibiotics displayed inhibited presystemic metabolism, accumulation of terfenadine in plasma, marked QT prolongation, and torsades de pointes and sudden death.29 Cyclosporin is also eliminated by CYP3A-mediated metabolism, and coadministration of the CYP3A inhibitor ketoconazole can increase cyclosporin concentrations and lead to toxicity unless the dosage is lowered.30

CYP2D6 activity can be inhibited by a number of agents, including quinidine, some tricyclic antidepressants, and some (but not all) selective serotonin reuptake inhibitors, notably fluoxetine and paroxetine. It is common to coprescribe selective serotonin reuptake inhibitors and tamoxifen to prevent flushing, a frequent side effect. The parallels to clopidogrel-omeprazole are striking; although this therapy may alleviate adverse effects, it may also increase the likelihood of failure of drug efficacy.11 Studies are underway to examine the role of concomitant therapy with CYP2D6-inhibiting selective serotonin reuptake inhibitors on the outcome of tamoxifen therapy.

Digoxin is eliminated not by metabolism but by biliary and renal excretion mediated by a specific drug transport molecule, P-glycoprotein, encoded by the MDR1 (also known as ABCB1) gene. A range of commonly used drugs such as amiodarone, verapamil, quinidine, and itraconazole inhibit P-glycoprotein, and they reproducibly and reliably produce digoxin toxicity by eliminating the major route of drug excretion.31
The distribution of loss-of-function alleles in CYP2C19 and many of the other genes involved in drug disposition described here varies across ethnicities. Loss-of-function CYP2C19 alleles are especially common in Asian populations, whereas CYP2D6 loss-of-function alleles are more common among European and African subjects, and the CYP2C9*3 allele is seen almost exclusively in European populations.\(^1\) Interestingly, omeprazole is a CYP2C19 substrate, and ulcer-healing efficacy was higher among Japanese subjects with loss-of-function alleles.\(^2\) An interesting question is the extent to which cardiovascular events in Asian subjects receiving clopidogrel reflect the prevalence of CYP2C19 variant alleles.

**What Now?**

It is almost inconceivable that clopidogrel represents the end of a long line of drugs with the potential to produce severe toxicity or suffer failure of efficacy as a result of high-risk pharmacokinetics. Furthermore, although the examples cited here focus on single variants producing important clinical effects, there is now little doubt that variation across many genes accounts for variability in response to widely used drugs such as warfarin and clopidogrel. An ongoing challenge is identification of these gene and pathways, validation of any findings, and ultimately translation to the bedside.

The idea of preprescription genotyping to identify patients at high risk for adverse effects has some appeal. However, it is important to establish that any change in drug therapy based on such results be evidence based. In the case of warfarin, algorithms to predict dosage requirements\(^3\) based on clinical features and CYP2C9 and VKORC1 genotypes are a key step to randomized trials. The situation is murkier for patients with variant CYP2C19 alleles in whom clopidogrel therapy is started because there is currently no basis for dose adjustment. One logical answer may be uniform tests of platelet aggregation during drug therapy.

Another approach is to prescribe alternative therapies for those at risk because of variant alleles. For both warfarin and clopidogrel, such alternative therapies, factor X inhibitors and prasugrel, are in late development. One strategy, which would require prospective evaluation, is to prescribe newer (and presumably more expensive and less well-studied) therapies in those subjects at risk of adverse drug effects because of DNA variants compared with treatment with older, cheaper drugs in those without the risk alleles. In the case of clopidogrel versus prasugrel, an informed decision requires consideration of the relative frequencies of adverse events with the 2 agents, the extent of gastroprotection conferred by PPIs, the extent of cardiovascular protection conferred by drug regimens that do or do not include PPIs, whether PPIs are clinically interchangeable in gastroprotection and in cardiovascular events, and the cost implications of a preprescription genotyping strategy. Clinical trials and further analyses of extant data sets may firm up some of the preliminary answers we are now getting.

**Disclosures**

None.

**References**

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