

Clopidogrel Considerations

A look at the black box warning, implications of generic options, the need for peripheral trials, and the potential for genetic testing.

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In 2010, clopidogrel was the third most commonly prescribed drug in the US. The US Food and Drug Administration (FDA) included a black box warning in the drug information for clopidogrel to aid precise drug delivery and to minimize complications. Clopidogrel recently became available in a generic version, so a significant increase in the use of this drug can be expected. This development plus a basic understanding of pharmacogenomic information, as recommended in its black box warning, may help decrease life-threatening thrombotic or hemorrhagic complications.

BACKGROUND

The liver is the major site of drug biotransformation, and the cytochrome P450 (CYP450) enzymes located in the membranes of the smooth endoplasmic reticulum are responsible for most drug metabolism. Genetic differences in humans affect the function of several of the CYP450

enzymes. Current knowledge of the genetic polymorphism affecting drug metabolism has increased exponentially in the last few years, leading to a whole new branch of science that is referred to as *pharmacogenomics*.

To a large extent, the plasma concentration of drugs is determined by the individual patient's metabolic status. The consequences of CYP450 polymorphisms range from serious toxicity to ineffective drug therapy. Genetically determined reductions in CYP450 enzyme activity (poor metabolizers [PMs]) for active drugs have important implications for narrow-therapeutic-index drugs, such as warfarin, in which increased plasma concentrations contribute to bleeding complications. On the contrary, for prodrugs (the therapeutic effect of a prodrug occurs only after conversion to an active metabolite [Figure 1]) such as clopidogrel, deficient enzyme activity (PMs) can prevent the attainment of therapeutic drug plasma concentrations and lead to thrombotic complications.

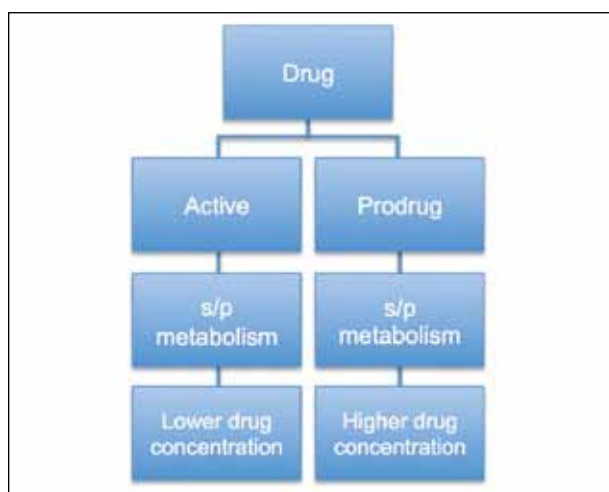


Figure 1. The differences between an active drug and a prodrug.

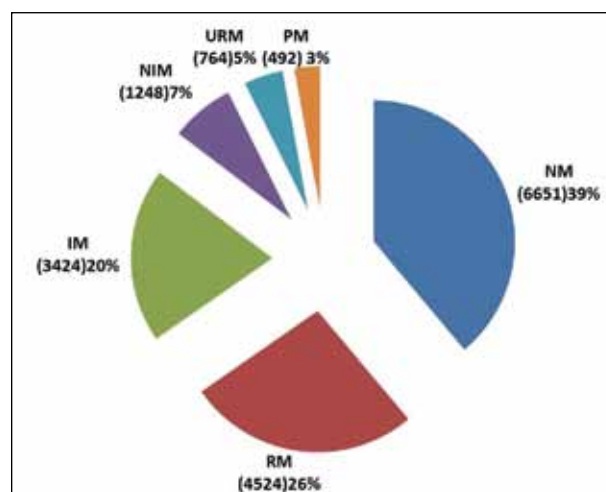


Figure 2. Types of metabolizers and their incidence in a 17,103-patient subset.

Clopidogrel efficacy dependent on conversion to active metabolite by CYP450 enzymes, principally CYP2C19; less active metabolite formed and smaller anti-platelet effect observed in CYP2C19 poor metabolizers on recommended clopidogrel doses; poor metabolizers w/ACS or undergoing PCI had higher cardiovascular event rates than in pts w/normal CYP2C19 function; CYP2C19 tests are available, and may assist in treatment strategy; consider alternative dosing strategies or other anti-platelet treatment in CYP2C19 poor metabolizers.

Figure 3. The black box warning for clopidogrel.

2C19 AND CLOPIDOGREL

The CYP2C19 enzyme is responsible for biotransformation of clopidogrel to its pharmacologically active thiol metabolite. Approximately 3% to 5% of whites and 20% of Asians and African Americans are PMs. In a series of 17,103 patients (Figure 2),¹ only approximately 39% were normal metabolizers (NMs), so only 39% of patients taking drugs metabolized by the 2C19 pathway are achieving the expected therapeutic plasma concentration for that drug. Overall, 10% of all prescribed drugs are metabolized via this pathway, which includes commonly used drugs such as esomeprazole (the number one prescribed drug in the US), omeprazole, diazepam, propranolol, and cilastazol.

A significant number of patients are intermediate metabolizers (IMs) and PMs (23%). Unfortunately, IMs and PMs produce approximately 30% to 50% less of the active clopidogrel metabolite compared with NMs, predisposing them to a higher thrombotic event rate in those requiring effective antiplatelet therapy.¹ This led to a black box warning in the clopidogrel prescribing information (Figure 3). The labeling was updated in March 2010 in response to reports of reduced efficacy with CYP2C19 IMs and PMs.² The label warns of reduced effectiveness in PMs and states that genetic testing is available. The label further advises health care professionals to consider alternative strategies in patients who are identified as PMs.

The need for dual-antiplatelet therapy with aspirin and clopidogrel in patients with peripheral arterial disease (PAD) is based on the MIRROR (Management of Peripheral Arterial Interventions With Mono or Dual Antiplatelet Therapy) and CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) studies.^{3,4} Based on the results

of CAPRIE, a single dose of clopidogrel has been approved as an effective alternative to aspirin for secondary prevention of atherosclerosis in PAD patients.^{3,5} The results of the MIRROR study, with endpoints evaluating clopidogrel resistance and 6-month clinical events, demonstrated that dual-antiplatelet therapy reduced peri-interventional platelet activation and improved functional outcome without higher bleeding complications. The study concluded that patient-tailored dual-antiplatelet therapy seems to be desirable for endovascularly treated patients with PAD. The study also demonstrated that patients with PAD had a 30% prevalence of resistance to clopidogrel. Other similar studies on patients with PAD have demonstrated a 9.8% to 35.2% resistance to clopidogrel.⁶⁻⁸

Although it is not recommended to extrapolate data from coronary studies to PAD patients, most current recommendations regarding antiplatelet management of PAD are derived from coronary data. In a meta-analysis by Mega et al,⁹ of nine clinical trials involving 9,685 patients, the hazard ratio for major adverse cardiovascular events was 1.55 (95% confidence interval, 1.11–2.17) in IMs and 1.76 (95% confidence interval, 1.24–2.5) for PMs (compared with NMs). Among patients who underwent coronary intervention with stent placement, the hazard ratio for stent thrombosis was 2.67 (95% confidence interval, 1.69–4.22) and 3.97 (95% confidence interval, 1.75–9.02) in IMs and PMs, respectively, compared with NMs.

On the contrary, the rapid metabolizers and ultrarapid metabolizers (URMs) are at a greater risk for bleeding complications due to higher plasma levels of the active metabolite. The risk for bleeding was greatest among URM, with an odds ratio of 3.27 (95% confidence interval, 1.33–8.1) compared with NMs.¹⁰

Recently, the National Institutes of Health–supported Clinical Pharmacogenetics Implementation Consortium published guidelines on genotype-guided antiplatelet therapy.¹¹ The first approach is to genotype all patients with elective stent procedures, as data are most valuable if

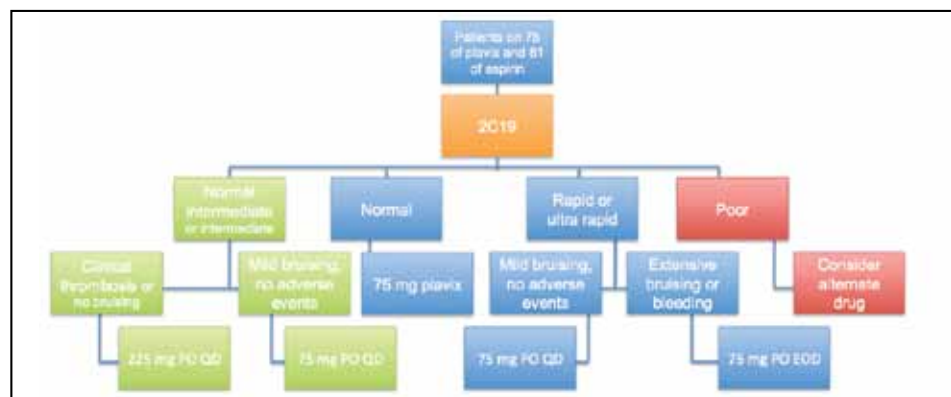


Figure 4. A genome-based dosing algorithm for clopidogrel.

The rapid and ultrarapid metabolizers are at a greater risk for bleeding complications due to higher plasma levels of the active metabolite.

available at preintervention. The second is to target moderate-to-high-risk patients, such as those with a history of stent thrombosis, diabetes, renal insufficiency, or high-risk angiographic features. A recent study helps to better define the dosing for clopidogrel based on genotype.¹² In this prospective, randomized, double-blinded study of 333 patients, tripling the maintenance dose of clopidogrel to 225 mg daily in IMs and normal intermediate metabolizers (NIMs) achieved levels of platelet reactivity similar to that seen with the standard 75-mg dose in NMs; in contrast, for PMs, doses as high as 300 mg daily did not result in comparable degrees of platelet inhibition. One possible algorithm incorporating clinical findings and based on the previously mentioned study can be seen in Figure 4.

DISCUSSION

Currently, the FDA recommends using genome-based drug dosing for approximately 120 drugs. A list of the drugs used in patients with vascular disease with a pharmacogenomics black box warning is provided in Table 1. Medicare and most other insurance carriers currently reimburse for 2C19 tests based on the FDA guidelines and in an effort to reduce complications. In 2000, the cost of drug-related adverse events exceeded \$177.4 billion.¹³ It is probably safe to assume that these costs have only increased. Interestingly, it has been demonstrated that the cost associated with adverse drug events exceeds the expenditure for the initial drug therapy.¹⁴ Hence, most health care providers are starting to recognize that drug-related complications are serious, expensive, and need to be addressed urgently, as they are a largely preventable medical problem. The question is, "To what degree are they preventable?"

The genetic test for 2C19 can be performed from tissue samples collected from the patients. These can be done either by a buccal swab test or by a blood test. For the buccal swab test, cotton swabs are rubbed inside the mouth to obtain cell samples. Cheek cells collected using the buccal swab included in the collection kit yield results with the same accuracy as blood samples because the DNA is the same regardless if it is collected from cheek cells or blood.

CONCLUSION

The patent protection for clopidogrel expired on May 17, 2012. Currently, clopidogrel is marketed worldwide in

TABLE 1. DRUGS WITH A BLACK BOX WARNING BASED ON PHARMACOGENOMICS

Drug	Biomarker
Carvedilol	CYP2D6
Clopidogrel	CYP2C19
Isosorbide and hydralazine	NAT1, NAT2
Metoprolol	CYP2D6
Prasugrel	CYP2C19
Pravastatin	ApoE2
Propafenone	CYP2D6
Propranolol	CYP2D6
Ticagrelor	CYP2C19

nearly 110 countries. It was the third top-selling drug in the US, with sales of \$4.7 billion, in 2010 and an expected significant growth spurt with generic versions that will be available in the US by late 2012. Given the high risk involved in performing interventions in patients with subtherapeutic or supratherapeutic levels of clopidogrel, it may be a prudent approach to genotype patients with the need for effective antiplatelet therapy. Continued study is needed to further gain information in this challenging arena. ■

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