Amlodipine, clopidogrel and CYP3A5 genetic variability: effects on platelet reactivity and clinical outcomes after percutaneous coronary intervention.

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Abstract

To test the effect of a loss-of-function variation of the cytochrome P450 (CYP) 3A5 on drug-drug interaction between amlodipine and clopidogrel. Amlodipine is a well-known inhibitor of CYP 3A4, an isoenzyme of CYP3A that activates clopidogrel. However, controversy exists regarding whether amlodipine adversely affects clopidogrel response and clinical outcome after percutaneous coronary intervention (PCI). In the presence of CYP3A4 inhibitors such as amlodipine, the genetic variation of CYP3A5, the isoenzyme responsible for the backup CYP3A activity, may play an important role in clopidogrel activation.

Design:

Post hoc analysis of a prospectively enrolled cohort.

Patients:

Patients enrolled in the CROSS-VERIFY cohort from June 2006 to June 2010, with successful genotyping of CYP3A5.

Main Outcome Measures:

The pharmacodynamic analysis end point was clopidogrel on-treatment platelet reactivity (OPR) and the clinical analysis end point was the composite of cardiac death, non-fatal myocardial infarction, ischaemic stroke and stent thrombosis at 12 months post-PCI.

Results:

1258 patients had successful genotyping and were categorised as CYP3A5 non-expressers (749 patients) and expressers (509 patients) according to the CYP3A5 genotype. Amlodipine users showed higher OPR versus non-users only in CYP3A5 non-expressers (249±83 vs 228±84 P2Y12 reaction units, p=0.013). These findings was corroborated by clinical outcomes, in which amlodipine users had a higher incidence of events compared with non-users only in CYP3A5 non-expressers (4.6% vs 0.6%, HR 7.731, CI 2.042 to 29.264, p=0.004).

Conclusions:

Treatment with amlodipine is associated with increased clopidogrel OPR and increased risk of thrombotic events after PCI, which is dependent on the CYP3A5 genetic status.

Commentary:
Amlodipine is well-known to sedationist practitioners, as many patients get calcium channel blockers for hypertension or angina. It is said that amlodipine also potentiates the effect of midazolam so less midazolam should be given for sedation when patients are on this drug. It should not be a problem as long as drugs are titrated to effect.
What is more interesting is the fact that when amlodipine and clopidogrel (Plavix®) are used together there is a higher incidence of thrombotic effects. This is an important consideration as more and more patients are on anticoagulants. It is not always clear or easy whether to stop or carry on with these drugs when doing procedures under sedation.

When patients qualify for sedation outside the operating, antihypertensive therapy must be continued. So what about clopidogrel then? There are two possibilities - i) contact the cardiologist and find out whether the drug before can be stopped before sedation, but ii) usually the clopidogrel will be continued.

The important point here is that it is essential to know about this interaction. Maybe we should alert our colleagues not to prescribe the two drugs together, or at least they should be aware of this possibility when doing a case where the patient takes the two drugs together.