IRISH MEDICINES BOARD

Clopidogrel and Proton Pump Inhibitors - Updated recommendations on interaction potential

Background:
Clopidogrel is indicated for the prevention of atherothrombotic events in patients who have had a myocardial infarction or ischaemic stroke, or who have established peripheral arterial disease. The combination of clopidogrel (brand name Plavix) and aspirin may be used to prevent atherothrombotic events in patients with acute coronary syndrome.

Proton pump inhibitors (PPIs) are indicated for the treatment of oesophageal reflux disease, dyspepsia, or gastric ulcers, and are frequently co-prescribed with clopidogrel.

Updated recommendation:
Previous advice on concomitant use of clopidogrel with proton pump inhibitors has been modified in the context of additional data. Use of either omeprazole or esomeprazole with clopidogrel should still be discouraged. However, the current evidence no longer supports extending this advice to other PPIs.

Previous advice regarding interaction potential:
Following assessment of available data in May 2009, the EU Committee for Medicinal Products for Human Use (CHMP) concluded that concomitant use of any PPIs with clopidogrel should be avoided unless considered essential. The product information for clopidogrel was consequently updated on the basis of data, which demonstrated that omeprazole competitively inhibits the CYP2C19 isoenzyme (which metabolises clopidogrel to its active metabolite), reduces the ability of clopidogrel to inhibit platelet aggregation and reduces the beneficial effect of clopidogrel in patients. Although evidence for a similar effect on clopidogrel metabolism with the other PPIs was relatively sparse, a precautionary approach for the whole class was adopted in light of the findings of some clinical outcome studies suggesting an attenuation of the cardioprotective effect of clopidogrel by PPIs other than omeprazole. This issue was highlighted in the August 2009 issue of MIMS Ireland.

New evidence supporting updated recommendations:
Since the 2009 review, new evidence has become available which, although having some methodological limitations, casts some doubt on the clinical relevance of possible interactions between clopidogrel and PPIs as a class effect. However, the evidence supporting an interaction with omeprazole and esomeprazole remains valid.

Findings from clinical studies for the different PPIs have shown some inconsistency, possibly because there is true variation in the extent to which they interact with clopidogrel. This inconsistency may also reflect several variables including an individual's pharmacogenetics, medication compliance, and comorbidities; the doses of clopidogrel and the relevant PPI; and study design.

In light of the most recent evidence, the previous advice (to avoid all PPIs unless absolutely necessary for patients taking clopidogrel) is no longer considered necessary. Nevertheless, concomitant use of clopidogrel with omeprazole or esomeprazole should be discouraged. The current evidence does not support extending this advice to other PPIs. However, because it is not possible to completely exclude a possible interaction with these PPIs on the basis of available data, the potential risk of a slight reduction in efficacy of clopidogrel should be considered in the context of the potential gastrointestinal benefit of the PPI.

Advice to Healthcare Professionals:
- Concomitant use of clopidogrel and omeprazole or esomeprazole is to be discouraged unless considered essential.

- Consider PPIs other than omeprazole or esomeprazole in patients who are taking clopidogrel. Other gastrointestinal therapy such as H2 blockers (except cimetidine) or antacids may be more suitable in some patients.

- Discourage concomitant use of other known CYP2C19-inhibiting medicines with clopidogrel because these are expected to have a similar effect to omeprazole and esomeprazole (CYP2C19 inhibitors include fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine, and chloramphenicol).

Further information on assessment of the study data is available in the IMB's Drug Safety Newsletter 37th Edition, June 2010 and a list of references is available on request from the Irish Medicines Board.

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