IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

31st EDITION

Possible interaction between Clopidogrel and Proton Pump Inhibitors

Clopidogrel is an antiplatelet drug authorised for the prevention of atherothrombotic events in patients suffering from myocardial infarction, ischaemic stroke or acute coronary syndrome, or those at risk of these problems.

Published reports have suggested that clopidogrel (marketed as Plavix) is less effective in some patients than it is in others.[1-5] Differences in effectiveness may be due to genetic differences in the way the body metabolises clopidogrel, or due to co-administration of drugs that can interfere with the metabolism of clopidogrel.

Clopidogrel is metabolised by the liver to an active molecule that inhibits platelet aggregation; however evidence is emerging that some Proton Pump Inhibitors (PPIs) inhibit this pathway. This means that PPIs may reduce the effect of clopidogrel, resulting in an increased risk of heart attack. This interaction is more pronounced in patients who, for genetic reasons, are less able to convert clopidogrel into its biologically active form – so-called 'CYP2C19 poor metabolisers'.

The Journal of the Canadian Medical Association[6] has published the results of a population-based study that aimed to assess the clinical importance of the interaction between PPIs and clopidogrel. This research reviewed database records for 13,636 patients who were started on treatment with clopidogrel after an acute myocardial infarction between 2002 and 2007. 782 of these patients were readmitted within 90 days with a second event. Of this latter group, 734 patients were matched with 2,057 controls and analyses were performed for associations between usage of a PPI and cardiac events. Patients who were readmitted were more likely to have co-morbidities such as heart failure, diabetes and renal failure. Despite this additional disease burden they were less likely to be prescribed ACE inhibitors, beta-blockers or statins.

After correcting for many factors, this analysis found an increased risk in readmission related to cardiac events in current users of PPIs (adjusted odds ratio 1.27, 95% CI 1.03-1.57). Further analysis found no correlation between readmission and H2-receptor antagonists or in readmission among non-users of clopidogrel.

Notable limitations of this study are the lack of data for some important cardiac risk factors including smoking status, blood pressure and lipid levels. Non-prescription medication data were also unavailable for the analysis. The authors conclude that, "*concomitant treatment with clopidogrel and proton pump inhibitors should be minimised*".

In addition, several other published studies,[7-9] including pharmacokinetic studies, clinical trials and observational studies, also suggest a clinically significant interaction between clopidogrel and PPIs. As a class, PPIs share many pharmacokinetic features and in vitro studies have found that PPIs exhibit competitive inhibition for CYP2C19, albeit to varying degrees.[10] The available studies suggest that this clinically significant interaction affects all PPI products.

IMB Advice for Healthcare Professionals

- Healthcare professionals should be aware of this interaction and its potential to increase cardiac events such as acute myocardial infarction.
- Healthcare professionals should re-evaluate the need for starting or continuing treatment with a PPI in patients taking clopidogrel. The risk-benefit of continuing treatment with a PPI should be considered by the prescribing physician and the concomitant use of these medicines should be avoided unless essential.
- Healthcare professionals should continue to prescribe clopidogrel in line with its licensed

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indications and patients should continue to take clopidogrel as directed.
- PPIs should be prescribed strictly in line with their licensed indications.
- Healthcare professionals should continue to report suspected adverse reactions associated with clopidogrel/PPIs to the Irish Medicines Board.

1 Kim KA, *et al.* Nature 2008; 84: 236.
2 Mega JL, *et al.* N Engl J Med 2009; 360: 354.
3 Simon T, *et al.* N Engl J Med 2009; 360: 363.
4 Desta Z, *et al.* Clin Pharmacokinet 2002; 41: 913.
5 Xie HG, *et al.* Pharmacogenetics 1999; 9: 539.
6. Juurlink D, *et al.* CMAJ 2009; 180:713–18.
7. Pezalla E, *et al.* J Am Coll Cardiol 2008; 52: 1038.
8. Ho M, *et al.* JAMA 2009; 301: 937.
9. SCAI statement on "A national study of the effect of individual proton pump inhibitors on cardiovascular outcomes in patients treated with clopidogrel following coronary stenting: The Clopidogrel Medco Outcomes Study"
10. Li X-Q, *et al.* Drug Metab Dispos 2004; 32: 821

Alli (orlistat): recommendations for safe over- the-counter use

Alli is a medicine that contains the active substance orlistat (60 mg). It is licensed for use in adults who are overweight (body mass index, BMI ≥ 28kg/m2) and should be taken in conjunction with a low calorie, low-fat diet. Following an EU based assessment and recommendation, Alli can now be obtained in pharmacies without a prescription. Before this recommendation, orlistat was, and remains, available as 120mg capsules on prescription only (under the brand name Xenical).

How should Alli be used?
Alli should only be used strictly in accordance with its licensed indications and should be taken as one capsule with water just before, during, or up to one hour after each main meal, three times a day. If a meal is missed or contains no fat, Alli should not be taken. The patient should be on a diet in which about 30% of the calories come from fat. The food in the diet should be spread over three main meals. Patients taking Alli should start a diet and exercise regime before beginning treatment. If patients taking Alli have been unable to lose weight after 12 weeks, they should speak to their doctor or pharmacist. Treatment should not exceed 6 months, and thereafter users should continue with a reduced-calorie, lower-fat diet and activity plan to maintain weight loss. Patients should be aware that Alli is not a quick fix to weight loss: it can be used to help someone aim for steady weight loss of 1–2 lbs per week in conjunction with a sustained reduced-calorie, lower-fat diet; increased physical activity will also aid weight loss, and behavioural support should be recommended.

Interaction and warnings for safe use:
Like Xenical, Alli decreases fat absorption and can affect the absorption of fat-soluble drugs and vitamins. Therefore, the actions of the following drugs may be affected:

- Ciclosporin
- Warfarin/oral anticoagulants - these drugs are contraindicated with Alli treatment because of potential for decreased vitamin K absorption.
- Amiodarone – patients should see their GP before starting Alli as it may be necessary to adjust their amiodarone dose.

Alli may indirectly reduce bioavailability of the oral contraceptive pill. Patients should be advised to use additional contraception if they have severe diarrhoea.

Those who are taking medicines for high blood pressure or high cholesterol should visit their GP while taking Alli. Such consultations will ensure patients are taking the correct dose of these medicines.

Before starting Alli, patients with diabetes should see a GP. Alli is not recommended for use by patients who are taking acarbose for diabetes because interaction studies have not been done.

Alli can reduce absorption of fat-soluble vitamins (i.e. A, D, E, and K): patients should take a multivitamin supplement at bedtime.

Patients should be reminded that being overweight increases the risk of developing several serious health problems such as diabetes and heart disease. It should be highlighted to patients that these conditions may not cause someone to feel unwell and patients should be encouraged to continue to visit their GP for regular monitoring of chronic conditions. Further advice for healthcare professionals and patients about Alli is available through the product information and from the European Medicines Agency (EMEA), at www.emea. europa.eu.

Healthcare professionals and consumers should continue to report suspected adverse reactions to Alli or Xenical to the Pharmacovigilance Unit of the Irish Medicines Board.

Use of ACE inhibitors and Angiotensin II receptor antagonists during pregnancy and breastfeeding

Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists are licensed for a range of conditions including hypertension and may be particularly suitable for young patients with high blood pressure (but not those of black ethnic origin) and those with some comorbidities such as diabetic nephropathy. While methyldopa is considered to be the antihypertensive of choice during pregnancy and breastfeeding, it will not be suitable for some women and other options may need to be explored.

Use in pregnancy

Angiotensin II is essential for normal kidney development, and the use of ACE inhibitors and angiotensin II receptor antagonists in late pregnancy has been associated with adverse effects on the kidney and other congenital anomalies. During the 2nd and 3rd trimesters of pregnancy, the use of angiotensin II receptor antagonists is contra-indicated. Some data have also suggested an increased risk of congenital anomaly after exposure during the first trimester of pregnancy.[1] This study[1] reported an increase in congenital malformations, particularly cardiac, following exposure to ACE inhibitors in the first trimester of pregnancy. Therefore, ACE inhibitors and angiotensin II receptor antagonists should not be used at any stage of pregnancy unless absolutely necessary, and only then after the potential risks and benefits have been discussed with the patient. It is recommended that female patients of childbearing age be informed of the fetotoxic effects of angiotensin II receptor antagonists and ACE inhibitors and of the need to alter antihypertensive treatment if they are planning a pregnancy.

Use during breastfeeding

ACE inhibitors

In general, ACE inhibitors have a small molecular size and so their transfer to breast milk is possible. With the exception of captopril, the active metabolites of ACE inhibitors have long elimination half-lives; however, these metabolites are poorly absorbed orally. Data on the use of ACE inhibitors in breastfeeding are sparse and relate mostly to captopril, enalapril, and quinapril; findings indicate that drug is transferred to breast milk.[2-4] Although the levels transferred to an infant via breastfeeding are unlikely to be clinically relevant, there are insufficient data to exclude a possible risk of profound neonatal hypotension, particularly in preterm babies.

Angiotensin II receptor antagonists

No data on the use of angiotensin II receptor antagonists during breastfeeding are available. These agents are small enough to pass into breast milk, and some unpublished studies have found them in the milk of lactating rats. However, most angiotensin II receptor antagonists are highly bound to maternal plasma proteins, which can substantially limit their transfer into breast milk. The effects of potential exposure on a nursing infant are unknown.

Advice for healthcare professionals:

Use in pregnancy:

ACE inhibitors and angiotensin II receptor antagonists **should not be used at any stage of pregnancy unless absolutely necessary**, and only then after the potential risks and benefits have been discussed with the patient.

Use during breastfeeding

ACE inhibitors:

Captopril, enalapril, or quinapril:

Use in breastfeeding is not recommended in the first few weeks after delivery because of the possibility of profound neonatal hypotension; preterm babies may be at particular risk. Use may be considered when the infant is older if an ACE inhibitor is necessary for the mother. Healthcare professionals may prescribe these medicines during breastfeeding if they consider that this treatment is essential for the lactating mother but careful follow-up of the infant for possible signs of hypotension is recommended.

Ramipril, lisinopril, fosinopril, trandolapril, moexipril, or perindopril: use in breastfeeding is not recommended. Alternative treatments with more established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm baby.

All angiotensin II receptor antagonists:

Use in breastfeeding mothers is not recommended. Alternative antihypertensive treatments with more established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm baby.

1 Cooper WO, *et al.* N Engl J Med 2006; 354: 2443–51.
2 Devlin RG and Fleiss PM. J Clin Pharmacol 1981; 21: 110–13.
3 Redman CW, *et al.* Eur J Clin Pharmacol 1990; 38: 99.
4 Begg EJ, *et al.* Br J Clin Pharmacol 2001; 51: 478–81.

Aliskiren (Rasilez) – Recommendations for safe use

Aliskiren (Rasilez) is the first in a new class of medicine that directly inhibits rennin. Aliskiren is licensed for the treatment of essential hypertension with a recommended dose of 150 mg once daily. In patients whose blood pressure is not adequately controlled, the dose may be increased to 300mg once daily. The antihypertensive effect is substantially present within two weeks (85-90%) after initiating therapy with a dose of 150mg once daily. Aliskiren may be used alone or in combination with other antihypertensive agents and should be taken with a light meal once a day, preferably at the same time each day. As is the case with some other antihypertensive medicines, aliskiren should not be taken with grapefruit juice.

Angioedema
Angioedema can occur as a rare and serious side-effect of treatment with aliskiren.

Acute renal failure
There have been reports of acute renal failure in patients with risk factors for renal dysfunction (including hypovolaemia, heart disease, liver disease, or kidney disease). Furthermore, there is an increased risk of renal insufficiency, including acute renal failure, when patients with renal artery stenosis are treated with aliskiren.

Use with NSAIDs
As in the case of some other antihypertensives, Non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the antihypertensive effect of aliskiren. In some patients with compromised renal function (e.g. dehydrated or elderly patients) aliskiren given concomitantly with NSAIDs may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible when treatment is stopped.

Advice for healthcare professionals:
Aliskiren should not be used for the management of high blood pressure in patients who have previously experienced angioedema during treatment with aliskiren.

Patients should be advised that they should stop aliskiren and seek medical advice immediately if they develop symptoms of angioedema, such as swelling of the face, eyes, lips or tongue (or both), hands and feet, or difficulty breathing or swallowing.

Extreme caution is required if aliskiren is used in patients with renal artery stenosis or conditions predisposing to kidney dysfunction (such as hypovolaemia, heart disease, liver disease, or kidney disease) because of a risk of acute renal failure. If any signs of renal failure occur, aliskiren should be promptly discontinued.

NSAIDs may reduce the antihypertensive effect of aliskiren. Elderly patients or patients with compromised renal function may be at risk of further deterioration of renal function if NSAIDs and aliskiren are used in combination.

Erlotinib: new safety information

Erlotinib (Tarceva) is indicated for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer, and for patients with metastatic pancreatic cancer (in combination with gemcitabine).

As part of continued intensive monitoring of this medicine, the IMB wishes to communicate new safety information about the following risks:

Gastrointestinal Perforation: Patients receiving erlotinib are at increased risk of developing gastrointestinal perforation. In particular, patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. Tarceva should be permanently discontinued in patients who develop gastrointestinal perforation.

Bullous and exfoliative skin disorders: Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal. Tarceva treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

Ocular Disorders: Very rare cases of corneal perforation or ulceration have been reported during use of Tarceva. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with Tarceva treatment which are also risk factors for corneal perforation/ulceration. Tarceva therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain.

Further information is available in the Dear Healthcare Professional Communication distributed by Roche and available on the IMB website.