To Medical Practitioners,
Pharmacists
and Non-Medical Prescribers
working in NHS Grampian

Proton pump inhibitors and clopidogrel

The following is proposed as interim advice:

1. Clopidogrel should be prescribed as at present for its usual indications.

2. PPIs should not be prescribed concurrently as a matter of routine.

3. If patients on clopidogrel (often clopidogrel and aspirin) require acid-suppressant therapy, it is recommended that an H₂-antagonist such as ranitidine be used at a dose of 300mg twice daily (unlicensed dose).

4. Some patients are at greater upper GI risk – for example those with previous peptic ulcer or upper GI bleeding. In those circumstances discussion with Cardiology or Gastroenterology may be appropriate.

5. It is not recommended that pantoprazole be used routinely as a replacement for omeprazole. The evidence that pantoprazole is superior to other PPIs is not overwhelming and it is ten times more expensive than omeprazole.

6. The Formulary Group sees no reason to believe that the action of the generic clopidogrel will be different from the branded product and would therefore recommend that generic clopidogrel be used in preference to Plavix®. This will result in considerable cost-savings. Note: Due to possible stability issues Plavix® will continue to be used in compliance aids.

Yours sincerely

[Signature]

Professor John Webster
Chairman Formulary Group

For more information see Appendix 1
Appendix 1: NHS Grampian Formulary Group - Proton pump inhibitors and clopidogrel

Background

Proton pump inhibitors (PPIs) and the antiplatelet drug clopidogrel are amongst the most widely prescribed (and co-prescribed) drugs worldwide. In Grampian alone in 2008, the spend on PPIs was approximately £3M and on clopidogrel £1.8M.

The implications were therefore very considerable when it was suggested that a significant drug-drug interaction might occur between PPIs and clopidogrel.

The evidence for such an interaction is at three levels:

1 Pharmacological studies have established that clopidogrel is a pro-drug that is converted to an active metabolite which then binds irreversibly to the platelet P2Y12 receptor. This metabolic conversion is mediated by hepatic cytochrome P450, in which the 2C19 isoenzyme plays a key role\(^1\). Evidence suggests that PPIs may act as powerful inhibitors of P450 2C19, reducing the conversion of clopidogrel to its active metabolite.

2 Omeprazole has been shown in a double-blind study in 124 patients to significantly decrease the effect of clopidogrel on platelet activation\(^3\). The clinical effects of this observation were not evaluated.

3 A number of observational studies have suggested that the co-administration of PPI with clopidogrel may lead to adverse clinical outcomes:

- In a small series of patients taking clopidogrel, the risk of acute myocardial infarction was much higher in those patients who were taking regular PPIs than in those who were not\(^4\).

- In a large retrospective, population-based case-control study in Canada\(^5\), 734 patients discharged from hospital on clopidogrel after acute myocardial infarction (AMI) and who were readmitted because of AMI within 90 days were compared with controls who did not suffer recurrent AMI within that time. Current use of PPI was associated with an increased risk of recurrent MI [adjusted OR 1.27 (1.03 – 1.57)]. In a subgroup analysis pantoprazole differed from other PPIs in showing no increase in risk, though numbers were very small and confidence intervals wide.

- In a further retrospective cohort study from the 127 Veterans Administration hospitals in the USA, 8205 patients were studied after discharge from hospital on clopidogrel for acute coronary syndrome (ACS)\(^6\). Compared with the use of clopidogrel alone, the use of clopidogrel with PPI was associated with an increased risk of death or readmission to hospital [adjusted OR 1.25 (1.11 – 1.41)].

- The MEDCO outcomes study investigated retrospectively a cohort of patients who had undergone coronary stent placement during 2005-2006\(^7\). Patients who took clopidogrel alone (N=9682) were compared with those who took clopidogrel and PPI (n=4521). Those on combination therapy showed an increased risk of major cardiovascular events (hospitalisation for stroke, myocardial infarction, angina or coronary revascularisation) [adjusted OR 1.79 (1.62 – 1.97)].

- The CREDO study investigators undertook a retrospective analysis of their original study database in 2116 patients undergoing coronary stenting\(^8\). This analysis showed no adverse effect of clopidogrel plus PPI versus clopidogrel alone. PPI, whether used with clopidogrel or placebo, was associated with a slight increase in cardiovascular endpoints

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at 1 year [HR 1.5 (1.1-2.1)]. This raises the possibility of a potentially confounding variable – that “open label” PPI use may in itself identify a subgroup of patients at increased risk.

All of these studies suffer from the limitations of retrospective analyses and are subject to a number of very significant sources of potential bias and confounding. Detailed inspection of the cohorts reveal a number of very significant imbalances in risk factors and a considerable amount of information is not available for analysis. Even with extensive use of statistical adjustment, it can be difficult to compensate fully for these and additional considerations may apply that have not been allowed for. The data do have a certain external consistency and should not be lightly dismissed. However, there is general agreement that the issue will not be resolved until the necessary prospective randomised studies have been undertaken. This is the missing piece of the jigsaw.

However, as such data will not be available for some time, an interim policy is required in order to advise the many thousands of patients on these drugs.

References:

6 Ho PM, Maddox TM, Wang L et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009; 301(9): 937-44.

John Webster, Clinical Pharmacology Unit