PostScRxipt - ExtRa

NHS Greater Glasgow

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ASPIRIN 75 mg, WHICH FORMULATION?

- **Low dose aspirin is indicated for the primary and secondary prevention of vascular events.**
- **Endoscopy studies in healthy volunteers suggest that the use of enteric-coated aspirin incurs a lower risk of GI injury compared with dispersible or plain formulations. However, endoscopy studies are poor predictors of serious upper GI complications e.g. bleeds.**
- **Three well conducted epidemiological studies and two meta-analyses contradict this, suggesting that the risk of serious upper GI complications is similar for plain and enteric-coated aspirin.**
- **The lack of evidence for enteric-coated formulations to reduce clinically significant upper GI complications and their greater cost in comparison with the dispersible formulations means their routine use cannot be justified.**
- **Therefore, dispersible aspirin is the formulation of choice in NHS Greater Glasgow.**

Introduction

Who should get prophylactic low-dose aspirin?

A recent meta-analysis demonstrated that aspirin is protective in most types of patient at increased risk of occlusive events, including those with an acute myocardial infarction (MI) or ischaemic stroke, unstable or stable angina, previous MI, stroke or cerebral ischaemia, peripheral arterial disease or atrial fibrillation (AF).[1] Low dose aspirin 75-150 mg daily was found to be as effective as higher doses, the effects of doses lower than 75 mg were uncertain. For most healthy individuals for whom the risk of a vascular event is likely to be less than 1% a year, daily aspirin is probably inappropriate.[1] The recently revised NHS Greater Glasgow antiplatelet guideline recommends dispersible aspirin 75 mg daily (300 mg for AF) as the antiplatelet of choice in the above patient groups and for primary prevention in high risk individuals (10 year coronary heart disease risk >20%).[2]

What is the theory behind enteric-coated aspirin and GI complications?

Gastrointestinal (GI) disturbances such as nausea, dyspepsia, and vomiting are the most common adverse effects of aspirin.[3] These symptoms may be minimised by giving aspirin with food, minimising the dose and co-prescribing an acid suppressant. Peptic ulceration and GI haemorrhage can occur with aspirin probably through a combination of direct damage to the gut mucosa and systemically via the inhibition of prostaglandin synthesis.[4]

Enteric formulations are coated with a combination of cellulose, silicon or other inactive ingredients providing resistance to disintegration in the stomach; this property allows dissolution of the drug in the higher pH of the duodenum.[5] In theory, this should protect the gastric mucosa from local irritation although duodenal damage can still occur.[4] Results from several endoscopic studies in healthy volunteers support this hypothesis, gastric erosion[6-10] and micro-bleeding[6-8] being less in those who used the enteric-coated preparation. It is known that these lesions are not good predictors of major upper gastro-intestinal complications[11] and it is unclear what the clinical importance of such studies is in patients taking aspirin in the long-term.[4]

Dispersible aspirin is more rapidly absorbed than standard aspirin and produces about half as much occult bleeding, probably by minimising high localised concentrations and therefore direct mucosa damage.[4]

Evidence

Is there any evidence to support enteric-coated aspirin?

In 1997, the Drug and Therapeutics Bulletin concluded that there was no convincing evidence that enteric-coated aspirin at a dose of 75 mg reduced the risk of major GI bleeding compared with soluble aspirin.[4] Here, we review recently published literature.

A large case control study (550 incident cases of upper GI bleeding) compared the relative effect of plain, enteric-coated and buffered aspirin on major upper GI bleeding.[5] In doses of less than 325 mg/day there were no significant differences in the relative risk of major upper GI bleeding between preparations: plain 2.6 (95% CI 1.7-4.0), enteric-coated 2.7 (95% CI 1.4-5.3) and buffered 3.1 (95% CI 1.3-7.6). Furthermore, there were no important differences in risk between the formulations and site of bleeding (gastric vs. duodenal) for doses ≤325 mg/day.

A second case controlled study conducted using the UK General Practice Research Database identified 287 cases of upper GI complications (bleeding or perforation) amongst "current" users of aspirin.[11] The relative risk of an upper GI complication compared with 837 controls was 2.0 (95% CI 1.7-2.3). Enteric-coated aspirin was associated with a risk similar to plain aspirin, 2.3 (95% CI, 1.6-3.2) vs. 1.9 (95% CI 1.6-2.3) respectively. The relative risks were similar when analysed separately by bleeding and perforation, or gastric and duodenal sites.

A Danish observational cohort studied the association of low-dose aspirin (100-150mg per day) use with hospitalisation for upper GI bleeding based on record linkage between a population-based prescription database and a hospital discharge registry.[12] Incidence rates of upper GI bleeding in 27,694 users of low-dose aspirin were compared with the incidence rates in the general

population over a 5 year period. The standardised incidence rate ratio was: all patients 2.6 (95% CI, 2.2 to 2.9). The risk was similar among users of plain aspirin, 2.6 (95% CI, 2.2 to 3.0) and users of enteric-coated aspirin, 2.6 (95% CI, 1.8 to 3.5). Authors conclude that use of an enteric-coating did not seem to reduce the risk of GI bleeding.

Two meta-analyses (one of randomised controlled trials the other of epidemiological studies) concluded that there was insufficient evidence to suggest that modified/enteric-coated formulations of aspirin reduce the incidence of upper GI complications, compared with standard formulations.[13,14]

Safety

Will patients come to harm if switched?

Patients may complain of a recurrence of their dyspepsia when switched from an enteric formulation. Such patients should have their dose minimised, advised to take aspirin with food and prescribed an antacid if required. Other contributory factors should be addressed (e.g. excess alcohol intake, NSAID use); if GI symptoms do not respond then omeprazole 20 mg daily should be added.[2]

Patients may have been commenced on an enteric-coated formulation because they are considered to be at risk of a GI event and the enteric-coated formulation was perceived to offer some protection. These patients should be reviewed as they may require gastro-protection with omeprazole. However, the use of enteric-coated aspirin in patients taking a PPI is illogical. The raised pH in the stomach brought about by acid suppression will result in disintegration of the enteric-coating and thus dissolution of the drug within the stomach as happens with dispersible and plain formulations.

Place in Therapy

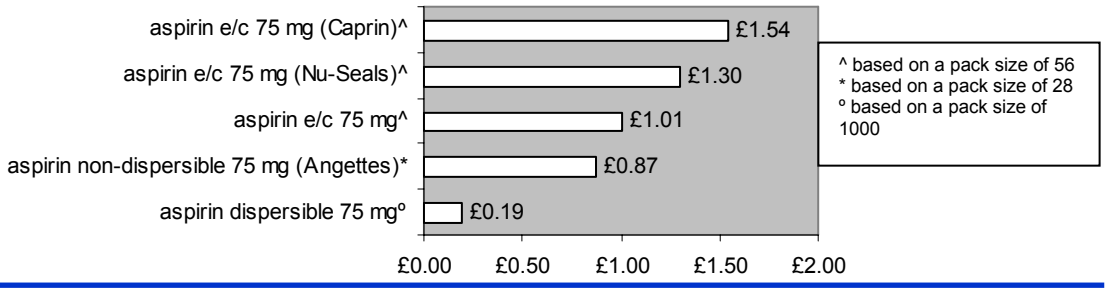
Endoscopy studies in healthy volunteers suggest that the use of enteric-coated aspirin incurs a significantly lower risk of GI injury compared with dispersible or plain formulations. However, endoscopy studies are poor predictors of serious upper GI complications e.g. bleeds.

The lack of evidence for enteric-coated formulations to reduce clinically significant upper GI complications and their greater cost in comparison with the dispersible formulations means their routine use cannot be justified.

Therefore, dispersible aspirin is the formulation of choice in NHS Greater Glasgow.

How much do they cost?

Cost for 28 days treatment (Scottish Drug Tariff/MIMS November 2005)



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