Canterbury District Health Board
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Clinical Pharmacology Bulletin

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Drugs & Gastrointestinal Bleeding

Gastrointestinal (GI) bleeding is a major cause of morbidity and mortality. Commonly prescribed drugs may potentiate the risk of bleeding. This bulletin summarises the current evidence regarding some drugs less well known to increase the risk of GI bleeding including clopidogrel, selective serotonin reuptake inhibitors (SSRI's), tricyclic antidepressants & calcium channel blockers.

What is the risk of GI bleeding with clopidogrel?

Low dose aspirin (75mg) is known to double the risk of upper GI bleeding (1). Clopidogrel is recommended in US guidelines in patients with major GI intolerance of aspirin, from which it might be inferred that it is safer than aspirin. Clopidogrel is an antiplatelet drug that inhibits the platelet adenosine diphosphate receptor. In vivo, adenosine diphosphate receptor antagonists impair the healing of gastric ulcers by suppressing the release of platelet derived growth factors (2). There is evidence from a retrospective study that patients taking ticlopidine (action equivalent to clopidogrel) are almost as likely to have endoscopic evidence of mucosal damage as patients taking aspirin or NSAID's (3). The addition of clopidogrel to low dose aspirin is thought to increase the risk of major bleeding (including GI bleeding) by a factor of 1.3 (4,5). These studies suggest that clopidogrel does increase the risk of GI (and other) bleeding, although it is unclear how this compares with low dose aspirin.

Is clopidogrel as safe as aspirin plus a proton pump inhibitor (PPI) in patients with recent GI bleeding?

A recent 12-month prospective, double blind trial of 320 patients who presented with peptic ulcer bleeding on aspirin were randomly assigned to 75mg clopidogrel plus placebo daily or aspirin 80mg daily plus esomeprazole 20mg twice daily for 12 months (6). All patients were Helicobacter pylori negative (or had the infection successfully treated), and ulcer healing was confirmed endoscopically post acid suppression treatment. The end point of recurrent ulcer bleeding occurred in 8.6% of patients receiving clopidogrel, compared with one receiving aspirin plus esomeprazole (0.7%) (p=0.001). Recurrent ischaemic events did not vary significantly between the two groups.

- The evidence suggests that aspirin plus a PPI is a safer alternative to clopidogrel in high risk patients with GI bleeding.

Do Antidepressants increase the risk of GI bleeding?

Evidence suggests that there is an increased risk of GI (and other) bleeding with SSRI's. However, is this risk clinically important and in whom is it relevant? SSRI's and some tricyclic antidepressants limit the uptake of blood serotonin by platelets, leading to lower serotonin concentrations within the platelets. One of the functions of serotonin within platelets is to promote platelet aggregation. Therefore a decreased amount of serotonin in platelets may increase the risk of abnormal bleeding (7).

In a large study (n=64000) of new antidepressant users, a significant association was found between the degree of serotonin reuptake inhibition and risk of hospital admission with abnormal bleeding as the primary diagnosis (8). Antidepressants were classified according to their degree of inhibition of serotonin reuptake (high, intermediate, low). The odds ratio of bleeding (compared with the 'low' group with a value of 1.0) was 1.9 (CI 1.1-3.5) for the 'intermediate' group, and 2.6 (CI 1.4-4.8) for the 'high' group of antidepressants.

In a cohort study, a greater risk of GI bleeding was associated with increasing inhibition of serotonin reuptake (9). This study is supported by a case control study which found a 3-fold increase in risk of gastrointestinal bleeding in primary care patients using antidepressants with a high degree of serotonin inhibition (fluoxetine, paroxetine, sertraline, clomipramine) (10). The risk was increased in patients concurrently on NSAID's; relative risk (RR) 15.6 (CI 6.6-36.6). Another recent study showed an increased risk in upper gastrointestinal bleeding in patient's using SSRI's, a moderate increase in those using non-SSRI antidepressants, and no increase in those using antidepressants with no effect on serotonin uptake inhibition (11).

In summary;

- Consideration of the degree of serotonin reuptake inhibition of antidepressants in patients with a high of GI bleeding may be important.
- Antidepressants commonly used in New Zealand with intermediate or high inhibition of serotonin reuptake, include the SSRI's (fluoxetine, paroxetine and citalopram) and the tertiary tricyclics (clomipramine and amitriptyline).
- The concomitant use of NSAID's and SSRI's should probably be avoided in patients with risk factors for upper GI bleeding.
- Risk factors for GI bleeding include: female, previous history of GI bleeding, Helicobacter Pylori infection and the elderly.

Is there an increased risk of GI bleeding with calcium channel blockers?

Calcium channel blockers have been shown to inhibit platelet function in experimental studies. They are also known to have a vasodilatory effect that may interfere with the normal vasoconstrictive response to bleeding. Early studies with nimodipine were terminated prematurely due to an increased risk of fatal haemorrhagic events. Other studies have not demonstrated any increased risk when adjusted for markers of co-morbidity (12). The RR of hospitalisation due to upper or lower GI tract bleeding has been estimated at 2.6 (CI 1.33-3.17) with calcium channel blockers when compared to beta blockers (beta blockers used as the reference with a RR of 1) (13).

- In summary the evidence to date for GI bleeding associated with calcium channel blockers suggests that the risk may approximate that of low dose aspirin, but data is conflicting and further randomised controlled trials are required.

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