Dear Dave

Dave and other members of the bpac[nz] team answer your clinical questions

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SSRIs and bleeding disorders

SSRIs can cause bleeding disorders

The selective serotonin re-uptake inhibitors (SSRIs) (e.g. fluoxetine, paroxetine, citalopram) have been associated with a variety of bleeding disorders and these started to be reported soon after their introduction. Reported reactions have ranged from mild spontaneous bleeding such as bruising and epistaxis to serious conditions including GI haemorrhage, genitourinary bleeding, intracranial haemorrhage and increased bleeding during surgery.

Proposed mechanisms include decreased platelet serotonin leading to impaired haemostatic function and prolonged bleeding time, and an increased pre-disposition to bleeding in the presence of coagulopathy. The true incidence of such bleeding disorders is unknown as the data are based on spontaneous reports and observational studies. They appear to be quite rare but vigilance and an appreciation of contributory risk factors are important in order to prevent potentially serious events.

SSRIs are associated with increased risk of Upper GI bleeding (UGIB)

The evidence is again conflicting due to the variable objectives and quality of observational studies. There has been wide variance in the significance of the increased risk of UGIB associated with SSRIs reported in the literature. A study based on the UK GP research database suggested a risk similar to that of low dose ibuprofen (de Abajo, 1999) whereas a retrospective cohort study found no evidence of increased risk (Dunn, 2000). A recent case control study (Tata, 2005) found that both SSRIs and NSAIDs were associated with a two fold increase in the risk of UGIB (OR 2.38; 2.08 – 2.72 for SSRIs and 2.15; 2.02 – 2.28 for NSAIDs). The latter results are similar to the findings of earlier studies which also found that SSRIs were associated with a similar or just marginally lower risk of UGIB compared with NSAIDs (Mort, 2006).

Whilst at this stage we can't be sure of the magnitude of the increased risk, the available evidence suggests that SSRI use is associated with an increased risk of UGIB especially in high risk patients such as NSAID/aspirin users, those taking anticoagulants, the elderly and people with a history of GI bleeding (Yuan, 2006; Dall 2006; Weinrieb, 2005).

Increased risk with SSRIs and NSAIDS taken together

Several studies have investigated the risk of UGIB associated with combined use of NSAIDs with SSRIs. Yet again the size of the effect is the subject of much debate, but most studies and reviews have concluded that the risk of UGIB is increased with concurrent use of NSAIDs, including low dose aspirin. (Mort, 2006; Weinrieb, 2005, Dall, 2006). Two studies have in fact reported a multiplicative effect from concomitant NSAID and SSRI use (de Abajo, 1999, Dalton, 2003). For example, in the later study the authors found the risk ratios for SSRIs and NSAIDs were 3.6 and 4.5 respectively but the combination gave a risk ratio of 12.2 (Dalton, 2003: Table 1).

Studies did not include or were not designed to measure any differential effect of Cyclooxygenase-2 inhibitors (Coxibs) so there is no evidence they are safer than NSAIDs in this context.

Table 1. Risks of UGIB associated with SSRIs, NSAIDs alone and in combination (Dalton, 2003)

	Risk Ratio (95% CI)
SSRI only	3.6 (2.7 – 4.7)
NSAID only	4.5 (3.9 – 4.2)
SSRI and low dose aspirin	5.2 (3.2 – 8.0)
SSRI and NSAID	12.2 (7.1 – 19.5)

SSRIs plus low dose aspirin may also pose an increased risk

Although the confidence intervals overlap with SSRI alone and NSAID alone there is an indication (Table 1) that low dose aspirin increases the risk of UGIB when added to an SSRI. Other studies have shown a similar effect (de Abajo, 1999).

What about other antidepressants?

The evidence to date suggests that Tricyclic Antidpressants (TCAs) are not associated with a significant risk of bleeding but they have not been studied to the same extent as the SSRIs. Due to its potent serotonergic properties it has been suggested that clomipramine may be associated with a similar risk to SSRIs. There are some reports of bleeding associated with venlafaxine and it is not known if this drug is safer than SSRIs with respect to bleeding risk.

Caution also advised with SSRIs and warfarin

Bleeding risk may be increased from this combination by two mechanisms.
Firstly, as SSRIs can cause bleeding alone, the anticoagulant (warfarin) may increase the severity of any bleeding disorder due to the SSRI. As SSRIs probably cause bleeding by a direct affect on platelets, signs of increased bleeding may be noticed without a change in the INR.

Secondly, SSRIs have been reported to increase the INR in patients taking warfarin; probably due to inhibition or warfarin metabolism in the liver. Patients should be advised to be extra vigilant for signs of bleeding and have their INR monitored closely after starting this combination (Stockley, 2005).

The risk of a serious bleed in patients on an SSRI, NSAID and warfarin has not been evaluated but the increased risk is likely to be at least additive. Avoid this combination unless absolutely essential.

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Practical Advice

The combination of an SSRI and an NSAID is not contraindicated but awareness and management of the possible increased bleeding risk are important to prevent adverse drug events.

All patients started on an SSRI should be advised to report signs of bleeding such as easier bruising, nose bleeds or gum bleeding. This is particularly important, if the patient is at increased risk of a serious bleeding disorder, including UGIB. If an alternative cause of increased bleeding cannot be identified, consider stopping the SSRI and switching to a non-SSRI antidepressant, such as a TCA.

Patients on an SSRI plus an NSAID (including low dose aspirin) appear to be at increased risk of UGIB, and close monitoring is essential. If possible, avoid the combination in patients at increased baseline risk of UGIB including the elderly and those with a previous history of bleeding disorders. Consider the use of paracetamol instead of an NSAID and gastro protection in high risk patients who need to be on the combination.

The New Zealand Context

From encrypted NHI and Pharmhouse data we identified about 11,000 patients over 50 who were dispensed an SSRI and an NSAID in the period July to December 2005. We can't tell if all patients took both drugs at the same time and we also can't account for over-the-counter use of NSAIDs.

References

Dall M, Hallas J. Is the use of selective reuptake inhibitors associated with an increased risk of bleeding ? Ugeskr Laeger 2006;168(23):2232-6.

Dalton SO, Johansen C, Melemkjaer L, Norgard B, Sorensen HT, Olsen JH. Ue if selective reuptake inhibitors and risk of upper gastrointestinal tract bleeding. Arc Intern Med 2003;163:59-64.

de Abajo FJ, Rodriguez LAG, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding; population based case-control study. BMJ 1999;319:1106-9.

Dunn NR, Pearce GL, Shakir SA. Association between SSRIs and upper gastrointestinal bleeding. SSRIs are no more likely than other drugs to cause such bleeding. BMJ 2000;320:1405-1406.

Mort JR, Aparasu RR, Baer RK. Interaction between selective serotonin reuptake inhibitors and nonsteroidal antiinflammaory drugs: Review of the literature. Pharmacotherapy 2006;26(9):1307-1313.

Stockley's Drug Interactions, 7th Ed., 2005. Pharmaceutical Press (UK).

Tata LJ, Fortun PJ, Hubbard RB, Smeeth L, Hawkey CJ, Smith CJ, Whitaker HJ, Farrington CP, Card TR, West J. Does concurrent prescription of selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs substantially increase the risk of upper gastrointestinal bleeding? Aliment Pharmacol Ther. 2005 Aug 1;22(3):175-81.

Weinrieb RM, Auriacombe M ,Lynch KG, Lewis JD. Selective serotonin re-uptake inhibitors and the risk of bleeding. Expert Opin Drug Saf 2005;2:337-44.

Yuan Y, Tsoi K, Hunt RH. Selective serotonin reuptake inhibitors and risk of upper GI bleeding: Confusion or Confounding? Am J Med 2006;119:719-727.

Who is Dave?

Pharmaceutical Programme Manager Dave Woods is a graduate of Manchester University (B.Sc. [Hons]) and the University of Otago (MPharm). Dave has extensive experience in hospital pharmacy, drug information, rational use of drugs and quality assurance. He has published on a range of subjects and holds editorial positions for several international journals.

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