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An occasional bulletin from the Yellow Card Centre West Midlands

If in doubt, fill one out

The Yellow Card Centre West Midlands exists to promote the reporting of adverse drug reactions and raise general awareness of iatrogenic disease.

Bleeding and Dabigatran (▼)

Dabigatran is an anticoagulant (a reversible thrombin inhibitor), which unlike warfarin does not require frequent INR measurements or dietary restrictions. However, in the event of a trauma, such as a road traffic accident, warfarin anti-coagulation can be reversed rapidly using several agents (such as vitamin K) and the degree of coagulation is easily measured.

Concerns about the lack of an antidote to dabigatran, and a readily available measure of coagulation have been raised following cases of trauma which have led to cases of fatal haemorrhage in the US (*N Engl J Med* 2011;**365**:2039-2040).

Additionally, cases of fatal haemorrhage have been reported in Japan. These have occurred in elderly patients with renal impairment and other risk factors for bleeding (such as concomitant medication).

The MHRA have issued the following advice (*Drug Safety Update* 2011;**5(5)**:A2):

- ☐ Do not start dabigatran in any patient with severe renal impairment (Creatinine clearance <30mL/min)
- ☐ Assess renal function in all patients before starting dabigatran, when a decline in renal function is suspected, at least annually in the over 75 year-old, and annually in patients with renal impairment.
- ☐ Check for signs of bleeding or anaemia and stop treatment if severe bleeding occurs.

Bleeding is a serious adverse reaction. Reports of bleeding associated with any medication should be reported to The Yellow Card scheme at http://www.mhra.gov.uk/yellowcard

PPIs and *clostridium difficile*

FDA Drug Safety Announcement, 8th Feb 2012 http://www.fda.gov/Drugs/DrugSafety/ucm290510.htm

Pump pump inhibitors (PPIs) such as omeprazole and pantoprazole, are widely prescribed drugs used in the treatment of gastro-oesophageal reflux disease, gastrointestinal ulcers, and oesophageal ulceration. They are also prescribed as a preventative treatment for non-steroidal anti-inflammatory drugs (NSAIDs).

The U.S. Food and Drug Administration has recently warned of an increased risk of Clostridium difficile-associated diarrhea (CDAD) associated with the use of PPIs. Cases reported to the FDA were generally elderly, had chronic or concomitant underlying condition, or were taking broad spectrum antibiotics.

Additionally, a FDA review of observational studies showed a majority of studies indicated an increased risk of CDAD associated with PPI use. The risk was 1.4 to 2.75 times higher in those taking PPIs compared to those not.

The FDA have advised that:

- ☐ A diagnosis of of CDAD should be considered in PPI users with unresolved diarrhea
- ☐ Patients taking PPIs should seek immediate advice if they experience watery stools that does not go away, abdominal pain, or fever.
- ☐ The lowest dose of PPI and shortest duration of treatment should be used appropriate to the condition.

We welcome reports of suspected *Clostridium difficile* associated with PPIs via the Yellow Card scheme.

Do your patients yawn?

If you find patients often yawn in your presence, don't take it personally. It might be an ADR.

A recent review of drug induced yawning highlighted a number of drugs that may be associated with increases in yawning.

Patatanian and Williams (*Ann Pharmacother* 2011;**45**:1297-301) found some evidence of drug-induced yawning associated with the administration of antidepressants (paroxetine, fluoxetine, duloxetine), induction agents (thiopental, propofol), and after the withdrawal of fentanyl and midazolam. There are limitations of the data; studies were small and case reports were a major source of information.

While yawning may not be of major clinical significance, it can be irritating for patients, and socially difficult in some work situations.

Treatment consists of withdrawal and substitution of an alternative drug. Dose reduction may also reduce yawning.

Drugs under intensive surveillance

Drugs indicated by a black triangle within the BNF are subject to intensive surveillance. Any reaction, no matter how trivial, should be reported. The following are recent additions to the intensive surveillance scheme.

Apixban (Eliquis®)	Venous Thrombolic Event Prevention
Fampridine (Fampyra®)	Multiple sclerosis

Grapefruit, a reminder

American Journal of Emergency Medicine (2012) **30**, 248.e5–248.e

Not all drug interactions are with other drugs. Some are with food. One example is grapefruit, which is a potent inhibitor of cytochrome P450 enzymes. A case report highlights the importance of awareness of this potential for drug-food interactions.

An 83-year-old female patient with a prior history of acute myocardial infarction and paroxysmal atrial fibrillation was admitted to an emergency department with syncope and atrial fibrillation. Chemical conversion was attempted, which resulted in bradycardia, extra systoles, and eventually torsades des pointes. On examination of the patient's bedside table, grapefruit juice was found. The patient admitted to regularly drinking more than one litre a day.

One glass of grapefruit juice (250ml) can have an appreciable effect on cytochrome P450 enzyme activity. The authors speculate that the regular grapefruit consumption had led to complete inhibition of hepatic CYP3A4 and CYP1A, triggering the proarrythmic actions of amiodarone.

A list of significant drug interactions with grapefruit juice is available in the British National Formulary. We are interested in any drug-food interactions, which can be reported at http://www.mhra.gov.uk/yellowcard

Need a speaker?

If you require a speaker for a lunchtime meeting or your CPD programme, why not contact our unit?

Our centre can provide training on adverse drug reactions, drug safety and pharmacovigilance. We will visit any location in the West Midlands region.

Call 0121 507 5672 or email help@yccwm.org.uk now to arrange a booking.

Yellow Card Centre West Midlands

We encourage Yellow Card reports for all suspected adverse drug reactions to new (▼) drugs, vaccines and unlicenced herbal remedies, all suspected reactions in children, and serious or unusual reactions to well-established drugs. You do not have to be certain a drug caused a reaction to report it.

Please send report to MHRA, CHM, Freepost, London, SW1W 9SZ or use www.mhra.gov.uk/yellowcard

Comments about this bulletin can be sent to Prof R.E. Ferner at r.e.ferner@bham.ac.uk