Primary Care Interface+ Secondary Care

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NHS Blackburn with Darwen
NHS East Lancashire
East Lancashire Hospitals NHS Trust

A MONTHLY MEDICINES AND PRESCRIBING BULLETIN FOR HEALTHCARE PROFESSIONALS IN EAST LANCASHIRE FOCUSING ON NEW THERAPIES.

Warfarin and oral miconazole: a major interaction overlooked in practice

Miconazole oral gel is frequently prescribed for the treatment of oral candidal infection. Clinically significant increases in INR can occur when miconazole oral gel is given to patients taking warfarin because miconazole can be absorbed through the oral mucosa or from the bowel after the gel has been swallowed.

Although there are no controlled studies, there are at least 15 published case reports of an interaction between miconazole oral gel and warfarin resulting in raised INRs, with bleeding in many cases. It would seem prudent to avoid miconazole oral gel in patients taking coumarin anticoagulants but if concurrent use is considered essential, patients should be closely monitored, with more frequent INR checks. Dose reduction should be considered, if appropriate. Patients should be advised to report signs of bruising or bleeding to their anticoagulant clinic or GP.

Options for alternative treatments are limited. Nystatin can also be used for candidal infections. It is not expected to affect warfarin metabolism. However, data from a recently published retrospective case study, spanning eight years, reported raised INRs and bleeding, or both, in four out of eight patients given nystatin. This is the only report of a possible interaction and, given its nature, an interaction is by no means established. At present, there are insufficient data to recommend that nystatin be avoided in patients taking coumarins but, until more is known, it would seem prudent to bear the possibility of an interaction in mind.

The risk of an interaction with other non-systemic routes (i.e. intravaginal or cutaneous) of miconazole use is low. Nevertheless, there have been isolated cases of interactions with warfarin and some degree of caution is probably prudent.

Key points

- Systemic miconazole is a strong inhibitor of CYP2C9, one of the main enzymes involved in warfarin metabolism. It can, therefore, potentiate the anticoagulant effect of warfarin.
- The interaction between miconazole oral gel and warfarin can cause such a severe increase in INR that it can result in hospital admission.

Reference: The Pharmaceutical Journal (vol 288) 28 April 2012.

The CHADS$_2$ score

The CHADS$_2$ score is a clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation (AF), a common and serious heart arrhythmia associated with thromboembolic stroke.

It is used to determine whether or not treatment is required with anticoagulation therapy or antiplatelet therapy,[1] since AF can cause stasis of blood in the upper heart chambers, leading to the formation of a mural thrombus that can dislodge into the blood flow, reach the brain, cut off supply to the brain, and cause a stroke. A high CHADS$_2$ score corresponds to a greater risk of stroke, while a low CHADS$_2$ score corresponds to a lower risk of stroke. The CHADS$_2$ score is simple and has been validated by many studies.[2]

The CHADS$_2$ scoring table is shown below[3]: adding together the points that correspond to the conditions that are present results in the CHADS$_2$ score, that is used to estimate stroke risk.

	Condition	Points
C	Congestive heart failure	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A	Age ≥75 years	1
D	Diabetes mellitus	1
S_2	Prior Stroke or TIA	2

In August 2011 NICE published Quality and outcomes framework (QOF) indicator guidance regarding Indicator area: atrial fibrillation. This instructs indicator AF03: "the percentage of patients with atrial fibrillation who are currently treated with anti-coagulation drug therapy or an anti-platelet therapy" to be replaced by NM25: "In those patients with Atrial Fibrillation in whom there is a record of a CHADS$_2$ score of ≥1, the percentage of patients who are receiving anticoagulants".

NICE technology appraisals on AF recently published refer to assessing a patient's risk using CHADS$_2$ score. These technology appraisals are:

- **TA249** - Dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation - National Institute for Health and Clinical Excellence
- **TA256** - Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation - National Institute for Health and Clinical Excellence

References:

1. Gage BF, van Walraven C, Pearce L, *et al.* (2004). "Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin". Circulation **110** (16): 2287–92.
2. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ (2001). "Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation". *JAMA* **285** (22): 2864–70.
3. "Risk of Stroke with AF". VA Palo Alto Medical Center and at Stanford University: the Sportsmedicine Program and the Cardiomyopathy Clinic. www.cardiology.org/tools/risk_of_stroke_AF.html

MMB Guidance

Please see the **Medicines Management Board** website for prescribing information on the following; **www.elmmb.nhs.uk**

RED LIST

Alemtuzumab (MabCampath®) – off-licence use in Multiple Sclerosis (locally agreed policy)

AMBER LIST

Liothyronine tablets – chronic thyroid deficiency post total thyroidectomy for thyroid cancer until patient receives radioactive iodine ablation

GREEN LIST

Podophyllin Toxin (Warticon®) – genital warts

BLACK LIST

Cabazitaxel (Jevtana®) – prostate cancer (NICE TAG255)
Dapoxetine (Priligy®) – on demand treatment of premature ejaculation
Rotigotine patches (Neupro®) – restless legs syndrome
Azilsartan (Edarbi®) – essential hypertension

TRAFFIC LIGHT DEFINITIONS

See website for more information on these recommendations.

RED – Secondary care only (+/- recommendations)

AMBER – Secondary care initiates/recommends, then passes to primary care (+/- recommendations)

GREEN – Primary or Secondary care (+/- recommendations)

BLACK – Non-Formulary. Not recommended for prescribing in primary or secondary care

Contents:

Anaphylaxis NICE CG134; 2011

This guideline covers the assessment to confirm an anaphylactic episode and appropriate referral after emergency treatment for a suspected anaphylactic episode.

Symptoms of anaphylaxis

- **Airway:** pharyngeal or laryngeal oedema
- **Breathing:** bronchospasm with tachypnoea
- **Circulation:** hypotension and/or tachycardia

In most cases there are associated skin and mucosal changes.

Care Pathway – see full guideline

Investigation

After emergency treatment for a suspected anaphylactic reaction:

- **Adults and young people (≥16 years)**; take blood samples for mast cell tryptase testing,
- **Children (<16 years)**; consider taking blood samples for mast cell tryptase testing if the cause is likely to be venom-related, drug-related or idiopathic.
- Take a blood sample:
  - as soon as possible after emergency treatment has started, **AND**
  - again ideally within 1 to 2 hours (but no later than 4 hours) from the onset of symptoms.

Inform the person and/or parent/carer that a blood sample may be required at follow-up with the specialist allergy service.

Assessment

Document the:

- acute clinical features of the suspected anaphylactic reaction,
- time of onset of the reaction,
- circumstances immediately before the onset of symptoms to help identify the possible trigger.

Observation

- **Adults and young people (≥16 years)**; observe for 6 to 12 hours from the onset of symptoms.
- In people with reactions that are controlled promptly and easily, a shorter observation period may be considered if they receive appropriate post-reaction care prior to discharge.
- **Children (<16 years)**; admit to hospital under the care of a paediatric medical team.

Referral

Refer to a specialist allergy service (age-appropriate where possible) with healthcare professionals who have the skills and competencies to accurately investigate, diagnose, monitor and provide on-going management of, and patient education about, anaphylaxis.

Hospital trusts providing emergency treatment for suspected anaphylaxis should have separate referral pathways for adults (and young people) and children.

Management

Give an adrenaline injector as an interim measure before the specialist allergy appointment. ELHE formulary lists two products: Epipen® and Jext®. These two products have different expiries and for those patients who are likely to be less frequent users, the Jext would be more appropriate with 24 month expiry.

Definition of terms	
Anaphylaxis	a severe, life-threatening, generalised or systemic hypersensitivity reaction
Biphasic anaphylaxis	after complete recovery of anaphylaxis, a recurrence of symptoms within 72 hours with no further exposure to the allergen
Idiopathic anaphylaxis	a form of anaphylaxis where no identifiable trigger can be found
Suspected anaphylaxis	the diagnosis prior to assessment by a specialist allergist for people who present with symptoms of anaphylaxis

Counselling

Before discharge, a healthcare professional with the appropriate skills and competencies should offer people or, their parent and/or carer, information about:

- the signs and symptoms of an anaphylactic reaction,
- the risk of a biphasic reaction,
- what to do if an anaphylactic reaction occurs; use the adrenaline injector and call emergency services,
- how to use the adrenaline injector and demonstrate correct use of the device,
- how to avoid the suspected trigger (if known),
- the need for referral to a specialist allergy service and the referral process,
- patient support groups.

NICE has written a booklet for patients and the public explaining its guidance on anaphylaxis.

Visit the NICE pathway: Anaphylaxis

Pharmalgen for the treatment of bee and wasp venom allergy

NICE TA246; 2012

Pharmalgen* is recommended as an option for the treatment of IgE-mediated bee and wasp venom allergy in people who have had:

- a severe systemic reaction to bee or wasp venom, OR
- a moderate systemic reaction to bee or wasp venom and who have one or more of the following:
  - a raised baseline serum tryptase,
  - a high risk of future stings,
  - anxiety about future stings.
- Initiate and monitor in a specialist centre experienced in venom immunotherapy.

NICE has written a booklet for patients and the public explaining the guidance on Pharmalgen.

*See Summary of Product Characteristics for full prescribing information

Acknowledgement: NICE Bites Issue Number 39

Clozapine and gastrointestinal obstruction - communication from Chief Pharmaceutical Officer for Wales

Recognised fatal adverse effects of clozapine include agranulocytosis, myocarditis and cardiomyopathy. Clozapine induced gastrointestinal hypomotility is probably less well recognised but can progress to severe and fatal bowel obstruction.

The recent death of an individual from clozapine-induced constipation, exacerbated by co-administration of the anticholinergic agent pirenzapine, has triggered a request from the coroner to take appropriate action and avoid similar adverse events recurring. The letter from the CPO for Wales aims to bring this serious adverse event to the attention of appropriate healthcare workers.

Gastrointestinal obstruction caused by clozapine was reported in the UK 15 years ago and a warning added to the product information. In 1999 the Committee on Safety of Medicines published a short article on clozapine and gastrointestinal obstruction having received 20 spontaneous reports of clozapine-induced gastrointestinal hypomotility. A more recent review of 102 life threatening cases of clozapine-induced gastrointestinal hypomotility calculated the prevalence of this adverse effect to be 3 per 1000 patients exposed to clozapine.

Risk factors included recent initiation of clozapine, high clozapine dose or serum level, concomitant anticholinergic use (e.g. tricyclic antidepressants, anti-parkinsonian agents and other antipsychotics) or intercurrent illness. Clozapine can have an adverse effect on the entire gastrointestinal tract, from oesophagus to rectum, and may cause bowel obstruction, ischemia, perforation, and aspiration of faeculent matter. The underlying mechanism is likely to be clozapine's strong anticholinergic and antiserotonergic properties.

Although constipation may occur in up to 60% of patients treated with clozapine it is usually benign. The consequences of clozapine-induced hypomotility being unrecognised or undertreated and progressing to severe, even fatal, bowel obstruction are, however, probably under appreciated. Health professionals have been issued with the following advice:

- Counsel patients about the risk of constipation with clozapine
- Patient education on healthy bowel habits and lifestyle may help, but for individuals without a structured routine and those not optimally controlled, monitoring for this adverse effect is essential.
- A patient prescribed clozapine, with or without a history of constipation, who presents with abdominal pain, should be a cause for immediate concern and further investigation.

Reference: All Wales Medicines Strategy GROUP (AWMSG) 05/04/2012

Comments & feedback

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