

## Dabigatran to be listed in 2011

### What is dabigatran?

Dabigatran is an oral direct thrombin inhibitor anticoagulant that is now approved in New Zealand for the prevention of stroke in patients with atrial fibrillation and for short-term use to prevent thromboembolism after hip or knee replacement surgery. It therefore provides an alternative to warfarin or enoxaparin (Clexane) for these indications. Dabigatran (Pradaxa) will be listed on the Pharmaceutical Schedule, without restriction. The listing date will be confirmed in the next few months.

### What is dabigatran used for

At this stage, dabigatran looks promising as a new anticoagulant medicine. Studies show that it is as effective as warfarin for preventing stroke in patients with atrial fibrillation and as effective as enoxaparin for prophylaxis of thromboembolism after hip and knee surgery, with similar rates of bleeding.<sup>1,2,3</sup> For some patients dabigatran may be a more convenient option, especially compared to warfarin, because it does not require intensive laboratory monitoring. In addition, other advantages of dabigatran include:<sup>4,5</sup>

- A more rapid onset of action – patients are fully anti-coagulated within 36 hours
- A more rapid return to normal coagulation after discontinuation (48 hours)
- A wider therapeutic window with a more predictable effect on coagulation irrespective of age, ethnicity and weight (warfarin often has an unpredictable effect, individual variation and a narrow therapeutic window)
- A fixed daily dose is taken unlike the variable dose often required for warfarin. However, for stroke prevention patients should be aware that it is a twice daily dose.
- A lower interaction rate with other medicines and with food when compared to warfarin

However, despite these potential advantages, dabigatran should still be used cautiously because it is a new medicine

and its use in clinical practice is not well known in New Zealand. Clinical experience and data on longer term safety is lacking. For example, although dabigatran was approved for use in Canada in 2008 for the prevention of thromboembolism, it has only as recently as October 2010 been approved for stroke prevention in patients with atrial fibrillation.<sup>6</sup> Similarly, dabigatran has been approved for use in the USA for stroke prevention since October 2010.<sup>7</sup> An increased risk of a rare adverse event has not been ruled out. Although not altering the conclusions of the study, re-evaluation of the database for the RE-LY trial, has identified 81 new events that included four patients with clinical myocardial infarction (MI), 28 patients with silent MI and 69 further events of major haemorrhage.<sup>8</sup>



Further information on dabigatran will appear in a future edition of Best Practice Journal.

### References

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## New recommendations advise that the majority of broad-spectrum antibiotics do not affect the contraceptive effectiveness of the combined oral contraceptive

International recommendations now advise that the majority of broad-spectrum antibiotics do not affect the contraceptive effectiveness of the combined oral contraceptive.<sup>1,2</sup> No change in advice has as yet been announced in New Zealand.

The implication of the new recommendations is that women taking a combined oral contraceptive, who require treatment with an antibiotic for three weeks or less,\* no longer need to use additional precautions to prevent pregnancy. However, women should still be advised about the importance of correct contraceptive practice during periods of illness, e.g. if vomiting or diarrhoea occur.

This change in advice **does not** apply:

- To every antibiotic – patients taking antibiotics that induce liver enzymes, e.g. rifampicin and rifabutin, DO require additional precautions (see sidebar)
- If an antibiotic causes vomiting or diarrhoea – patients should be advised to follow the “seven day rule”

\* Gastrointestinal flora was believed to recover sufficiently after three weeks of antibiotic treatment (unless a new antibiotic was prescribed) so that additional contraceptive precautions were not required.<sup>2</sup>

### Background to the changes

It has been standard practice for many years for doctors to advise patients who are taking a combined oral contraceptive that antibiotics affect its efficacy and that they must observe the “seven day rule” when taking antibiotics. The “seven day rule” refers to advice to use other methods of contraception, e.g. condoms, or to abstain from sexual intercourse, for the duration of antibiotic treatment and the following seven days.

The theory supporting this approach was based on the potential for antibiotics to reduce the gastrointestinal flora

## Contraceptive hormone metabolism

The contraceptive hormones, ethinylloestradiol and progestogen, when taken orally are absorbed from the small intestine. Absorption may be affected indirectly by medicines that cause vomiting or severe diarrhoea and medicines that alter gastric pH or gut transit. The hormones then undergo extensive first-pass metabolism in the small bowel mucosa and liver before reaching the systemic circulation.

Ethinylloestradiol is metabolised in the mucosa of the small intestine and in the liver. As much as 60% of orally administered ethinylloestradiol undergoes first-pass metabolism and thus only 40% is bioavailable. The bioavailability of progestogens varies.

Microsomal enzymes involved in the metabolism of contraceptive hormones and other drugs are found in the liver and intestinal mucosal cells. The oestrogen component, ethinylloestradiol, of the combined oral contraceptive is metabolised in the liver and conjugated with glucuronide to form inactive conjugates. These conjugates are water soluble and can be excreted in the bile. Under normal gut flora conditions, enzymatic activity of the gastrointestinal bacteria cleave this conjugate and free up oestrogen, which can then be reabsorbed (enterohepatic recycling).<sup>2</sup>

Cytochrome P-450 is the most important family of enzymes in drug metabolism and CYP3A4 is the major subtype found in adult hepatocytes and intestinal mucosal cells. If cytochrome P-450 enzymes or glucuronidation are induced the metabolism of ethinylloestradiol is increased, resulting in reduced levels of ethinylloestradiol and progestogens, potentially reducing their clinical effect. It takes 28 days for enzyme activity to return to normal after cessation of an enzyme inducing drug.<sup>2,4</sup>

responsible for increasing the reabsorption of oestrogens from the gastrointestinal tract (see sidebar). A reduction in gastrointestinal flora, could therefore result in a reduction in circulating hormone levels required for effective contraception.<sup>3</sup> However, the validity of this theory has been debated by specialists in women's health as there is no evidence that confirms this potential interaction.<sup>1,2,3</sup>

In 2009, the World Health Organisation, changed its recommendation to state that most broad spectrum antibiotics do not affect the contraceptive effectiveness of combined oral contraceptives and that no restriction on use is required when using these medicines at the same time.<sup>1</sup> This recommendation was adopted by the Centers for Disease Control and Prevention in the United States in 2010. In January 2011, the Faculty of Sexual and Reproductive Healthcare in the United Kingdom also changed its advice in support of this recommendation and the latest edition of the British National Formulary (BNF) includes this updated advice.<sup>2,4</sup>

#### **Evidence for the change in advice**

There is a lack of evidence that antibiotic use reduces the efficacy of the combined oral contraceptive.<sup>2</sup> Studies have not shown a decrease in the levels of ethinyloestradiol or any effect on gonadotrophin concentration with antibiotic use.<sup>2</sup>

A recent case-crossover study showed no association between contraceptive failure and antibiotic use in women taking combined oral contraceptives.<sup>3</sup> Although the authors state that an increase in risk of contraceptive failure cannot be ruled out due to limitations of the study design, they conclude that antibiotics have a limited effect on the metabolism of the combined oral contraceptive.

Other studies, that indirectly support the lack of a causal relationship between antibiotic use and contraceptive failure, include evidence that:<sup>1,2</sup>

- Combined oral contraceptive efficacy is not reduced

in women who have had a colectomy and ileostomy, and therefore have no enterohepatic circulation of ethinyloestradiol.

- Reports of pregnancies in women taking antibiotics have included women taking high doses of a combined oral contraceptive, e.g. containing 30 µg or more of ethinyloestradiol. Low dose combined oral contraceptives containing 20 µg ethinyloestradiol are effective contraceptive agents so it seems unlikely that the theoretical small reduction in ethinyloestradiol concentration resulting from reduced enterohepatic circulation would be the cause of contraceptive failure in women taking higher doses.
- Reports of pregnancies have occurred in women taking erythromycin and fluconazole which actually increase levels of ethinyloestradiol.
- Study results may be confounded by other reasons for contraceptive failure, e.g. missed pills, antibiotic induced vomiting and diarrhoea.

#### **Contraceptive advice for women using enzyme inducing antibiotics**

The BNF recommends that an alternative method of contraception is always required for women using combined oral contraceptives and rifampicin or rifabutin.<sup>4</sup>

Induction of cytochrome P-450 enzymes explains the proven interaction with these antibiotics,<sup>2</sup> which are potent enzyme inducing drugs.

If rifampicin or rifabutin is required (either short or long-term) the recommended strategy is for the woman to change to an alternative method of contraception that is not affected by enzyme inducers.<sup>2,4</sup> Options include injectable or implantable progestogens, an intrauterine contraceptive device or a levonorgestrel intrauterine system. If an enzyme inducer is required short term (i.e. less than two months) a practical solution would be to

temporarily stop the combined oral contraceptive and administer a one-off depot medroxyprogesterone acetate (DMPA) injection to cover the treatment course and the following 28 days.

A less favoured approach is to increase the dose of the combined oral contraceptive to give 50 µg or more of ethinyloestradiol to account for the increased metabolism and also recommending the use of condoms as an additional precaution.<sup>5</sup> This combination may be considered as an option if the enzyme inducing medicine is for short-term use (< two months) but is not recommended if the enzyme inducer is required for a longer term. Women taking an enzyme inducing medicine must continue to take a higher dose of combined oral contraceptive and use additional precautions for the time they are taking an enzyme inducer and for four weeks after finishing the course.<sup>2,4</sup>

 For further information about other important drug interactions with combined oral contraceptives see: "Combined oral contraceptive: issues for current users" BPJ 12 (Apr 2008).

#### References:

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#### Did you see "Prescription kitchen"?

On 5 May, 2011 bpac<sup>nz</sup>, in conjunction with PHARMAC and Mobile Surgical Services, participated in a live interactive television show about nutritional supplements and special foods, broadcast on Sky TV. The show was hosted by Ian Fraser and the panellists included GPs, dietitians, paediatricians and geriatricians. The main topics of discussion were the management of cows' milk allergy in infants and the place of oral nutritional supplements in elderly people.

If you missed the show, you can download it from the bpac<sup>nz</sup> website (follow the link from the home page): [www.bpac.org.nz](http://www.bpac.org.nz)

A handbook on Special Foods in support of this programme has now been published. A CME quiz, based on material from the show, can also be completed online: [www.bpac.org.nz](http://www.bpac.org.nz)

