



# Therapeutics Today

October 2009  
Number 10

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## **Update on oral contraceptives and venous thromboembolism**

More than 100 million women use oral contraceptive pills worldwide. An association between the use of combined oral contraceptives (COCs) and an increased risk of venous thrombosis (VT) has been reported since the 1960s and, while rare, is one of the most serious side effects of COCs. Lowering the oestrogen dose of the COC from the original level in the first COCs (100µg) has been associated with a decreased risk of VT. In addition, COCs contain different types of progestogens, (including levonorgestrel, norethisterone, desogestrel, gestodene, norgestimate and drospirenone); several studies have suggested an increased risk of VT with use of some of these progestogens compared with others. We report on 2 recent observational studies, which assessed the risk of VT with use of different COCs.

A case control study from the Netherlands included 1,524 women (aged 18-50 years) with first episode of VT and 1,760 controls (*BMJ 2009; 339: b2921*). Exclusion criteria included women who were post-menopausal, pregnant, 4 weeks post-partum and use of hormonal contraception other than COC. Overall results showed that current COC use was associated with a 5-fold increased risk of VT, compared with non-users. The risk was highest during the first 3 months of use. The level of increased risk of VT depended on the type of progestogen used: 3.6-fold increase for levonorgestrel-containing COCs; 5.6-fold increased risk for those containing gestodene; 6.3-fold increase for drospirenone and 7.3-fold increase for desogestrel. The study also found that the risk of VT was positively associated with oestrogen dose; using the most commonly used oestrogen dose (30µg) as reference, COCs containing 20µg were associated with a decreased risk of VT and those containing 50µg with an increased risk.

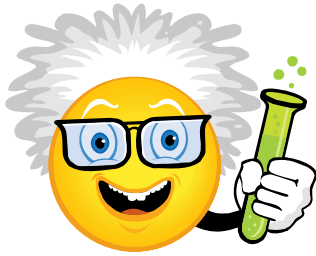
A cohort study from Denmark (*BMJ 2009; 339: b2890*) assessed the risk of VT in current users (aged 15-49 years) of different types of hormonal contraception. Results also showed that the risk of VT in current users of COCs decreases with decreasing oestrogen dose and duration of use and that COCs, with the same dose of oestrogen, containing desogestrel, gestodene, or drospirenone were associated with a higher risk of VT than those containing levonorgestrel. This study found no increased risk of VT with use of progestogen only pills and hormone releasing intrauterine devices.

An accompanying editorial (*BMJ 2009; 339: 521-2*) noted that, despite the limitations inherent in observational research, these studies showed remarkably similar results, which supports the validity of their findings. The author states that the results provide reliable estimates of the risk of VT associated with the newer progestogen drospirenone. Although the absolute risk of having VT is low (5:100,000 person years, increasing to 15-25:100,000 person years with COC use) he recommends that patients with a personal or family history of VT should not take COCs.



## **Proton Pump Inhibitor (PPI) Prescribing Initiative.**

The Barry report entitled "Economies in Drug Usage in the Irish Healthcare Setting" outlined potential savings on prescribing costs without compromising patient care. The NMIC's recent bulletin on generic prescribing (available at [www.nmic.ie](http://www.nmic.ie)) discussed the background to generic medicines and noted that generic prescribing was cost-effective and safe for the patient. In August of this year, the Primary, Community and Continuing Care (PCCC) unit of the HSE issued guidance on quality prescribing of proton pump inhibitors (PPIs) to GPs. The advice is designed to aid clinical decision making for the prescriber. The guidance is accompanied by a useful colour chart, containing details of the approved indications and costs of the currently authorised PPIs in Ireland and a user-friendly patient information leaflet that prescribers can use when discussing possible changes in PPI prescribing with their patients. Further information on this initiative is available from the PCCC unit, HSE, Dr Steevens Hospital, Steeven's Lane Dublin 8 or from Dr Joe Clarke, GP Advisor, HSE at [joe.clarke@hse.ie](mailto:joe.clarke@hse.ie)



**What is a cytokine?** The importance of cytokines in the development of disease and as potential treatments of disease is becoming increasingly recognised. A recent article outlined the main types of cytokines and their functions (*DTB 2009; 47: 89-91*). Cytokines are a group of >100 small proteins, produced by various cell types throughout the body. They act via cell surface receptors to alter cell behaviour. They usually have a short duration of effect and generally, but not always, exert their action close to their site of production. **Cytokine groups** include interferons,

interleukins, tumour necrosis factor (TNF) cytokines and haematopoietins (colony stimulating factors). **Cytokine actions** in the body include pro- and anti-inflammatory effects (depending on the cytokine), involvement in specific immunity (via effects on the T and B lymphocytes), effects on haematological stem cells and involvement in the movement of immune cells around the body (so-called chemotactic cytokines). It is worth noting that many cytokines exert their effect via more than one of these mechanisms. **Cytokines in disease:** Cytokines have been implicated in the pathogenesis of a wide range of diseases including rheumatoid arthritis (RhA), multiple sclerosis (MS), asthma and COPD, myocardial infarction, stroke and heart failure, inflammatory bowel disease and psoriasis. In most cases no specific cytokine has been implicated but there are some well-elucidated cases (e.g. Still's disease and abnormal activity of interleukin-1 beta). In addition, TNF has been found to be a crucial factor in the pathogenesis of RhA, via activation of pro-inflammatory cytokines and release of enzymes that lead to destruction of cartilage and subchondral bone. **Cytokines as medicines - Interferons:** Interferon alpha has anti-viral activity and is used to treat chronic hepatitis B and C. Interferon beta acts as an immunomodulator in the management of MS. Interferon gamma is thought to have an immunostimulatory function and has been used in the management of serious infection. **Interleukins** and interferons have also been used in the management of certain cancers (immunomodulatory function). **Colony-stimulating factors** are commonly used to reduce the duration of chemotherapy-induced neutropenia. **Medicines that modulate cytokines - TNF antagonists** (infliximab, etanercept, adalimumab) are used to treat RhA, psoriatic arthritis, ankylosing spondylitis and psoriasis. Adalimumab and infliximab are also used in inflammatory bowel disease. **Interleukin antagonists** (IL-1 and IL-6 antagonists) are used in the management of moderate to severe RhA.



**"Bisphosphory Jaw"** The European Medicines Agency (EMA) recently reviewed the risk of osteonecrosis of the jaw (ONJ) associated with bisphosphonates. Data from all sources including case reports, published literature, medical experts and patient representatives were included in the review. ONJ associated with bisphosphonate use was defined as an area of exposed or dead bone in the jaw lasting >8 weeks, in a patient exposed to a

bisphosphonate who had not had received radiation therapy to the jaw. Although several theories have been proposed, the mechanism of effect is as yet undefined. The most important risk factors appear to be the potency, dose and route of administration of the bisphosphonate. Other risk factors for development of ONJ should also be considered including: genetic factors, smoking, concomitant treatments or diseases. **The review reported that the risk of ONJ was low in those taking oral bisphosphonates and those being treated for non-cancer indications (e.g. osteoporosis) compared to cancer patients receiving IV bisphosphonates.** The EMA recommendations include the following:

- The risk/benefit of each patient should be considered before starting a bisphosphonate,
- Patients with poor oral hygiene / cancer should have a dental review before treatment,
- Good oral hygiene with regular dental review should be maintained during treatment.

The EMA concluded that further data are needed to determine the precise measures that could minimise risk of ONJ. Further information on the review, together with recommendations for patients, dentists and prescribers is available in a useful Q & A document at: [www.emea.europa.eu](http://www.emea.europa.eu).

[Editor's note: These results are reassuring in terms of relative risk. However, the EMA was unable to give guidance on whether or not to stop oral bisphosphonates before dental treatment. The NMIC will provide any future updates on this ongoing safety review.]

*Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. References are available on request. This newsletter is produced by the National Medicines Information Centre, St. James's Hospital (SJH) Dublin 8 and Dept of Therapeutics Trinity College, Trinity Centre, SJH. Tel: Direct Line (01) 473 0589 or 1850 727 727 Fax: (01) 473 0596 Email: [nmic@stjames.ie](mailto:nmic@stjames.ie)*