August 2013

Prescribing...

Hot Therapeutic Topics

- The MHRA has advised that **diclofenac** now be considered to have a cardiovascular risk similar to that of the selective COX-2 inhibitors.
- The EMEA has launched a review on the safety of combining drugs that act on the **renin-angiotensin system**.
- Oral **ketoconazole** for all patients with fungal infections and **codeine** for children under 12 years are no longer recommended.

1. New contra-indications for diclofenac

A meta-analysis of adverse events of NSAIDs has resulted in new contraindications for diclofenac, which is now considered to have a cardiovascular risk similar to that of the selective COX-2 inhibitors (coxibs).The review, published in the Lancet, undertook a meta-analysis of 280 trials of NSAIDs versus placebo (125,000 participants) and 474 trials of one NSAID versus another (230,000 participants).

It found that coxibs and diclofenac increased major vascular events by about one-third, mainly due to an increase in major coronary events (coxibs rate ratio [RR] 1·76, 95% CI 1.31 to 2.37; diclofenac RR 1.70, 95% CI 1.19 to 2.41). The authors calculated that compared with placebo, of 1,000 patients allocated to a coxib or diclofenac for a year, three more had major vascular events, one of which was fatal.

High-dose ibuprofen (2,400mg/day) significantly increased major coronary events but not vascular death (RR for major coronary events 2.22, 95% CI 1.10 to 4.48). Naproxen did not significantly increase major vascular events or vascular death.

All NSAIDs roughly doubled the risk of hospitalisation for heart failure, and all NSAID regimens significantly increased upper gastrointestinal complications.

On May 30th, the Medicines and Healthcare products Regulatory Agency (MHRA) noted that these findings were not new and reiterated its existing advice that all NSAIDs should be used at the lowest possible dose for the shortest possible time. However, the European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC) published specific recommendations for diclofenac on June 14th. Subsequently, the MHRA issued further information and details of the specific contraindications to the use of diclofenac.

Systemic formulations of diclofenac are now contraindicated in patients with established ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and congestive heart failure (New York Heart Association II-IV). For patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes, smoking) diclofenac treatment should only be initiated after careful consideration. Healthcare professionals are advised to periodically re-assess patients' need to continue with diclofenac.

Comment: Previous reviews on the use of NSAIDs in people with cardiovascular disease concluded that the cardiovascular risks associated with NSAIDs were highest for diclofenac and lowest for naproxen. The latest analysis has resulted in additional contraindications to the use of diclofenac bringing it in line with contraindications to the use of coxibs. Clinicians should review the use of systemic formulations of diclofenac in patients with established ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and congestive heart failure, as well as in those patients with significant risk factors for cardiovascular events.

2. Combining drugs acting on the renin-angiotensin system

The European Medicines Agency (EMA) has launched a review to investigate the risks of combining certain drugs that block separate stages of the renin-angiotensin system (RAS) in the treatment of hypertension and congestive heart failure. Three groups of drugs are involved:

- ACE inhibitors
- Angiotensin-II receptor antagonists (AIIRA)
- Renin inhibitor (aliskiren) ...not prescribable on States prescriptions

The review was launched in response to concerns that combining RAS-acting drugs could increase the risk of hyperkalaemia, low blood pressure and kidney failure, compared with using one RAS-acting drug on its own. Questions have also been raised about whether using two or three RAS-acting drugs is any more beneficial than using one drug in terms of reducing overall mortality.

A previous EMA review concluded that combining aliskiren with an ACE inhibitor or AIIRA could increase the risk of adverse effects involving the cardiovascular system or the kidneys. The Committee for Medicinal Products for Human Use (CHMP) concluded that such combinations are contraindicated in patients with diabetes or with moderate or severe kidney impairment, as they are at greatest risk of harm, and are not recommended in all other patients.

The EMA review follows a recent meta-analysis (33 clinical studies involving 68,405 patients) that investigated the use of dual blockade of the RAS in terms of long-term benefits (all cause mortality, cardiovascular mortality and admissions to hospital for heart failure) and harms (hyperkalaemia, hypotension, renal failure and withdrawal as a result of adverse events).The results suggested that although dual blockade was not associated with any significant benefit in terms of all-cause mortality, there was a relative risk reduction of 18% in admissions to hospital for heart failure compared with monotherapy. However, there was a significant increase in the risk of adverse events (e.g. 55% increase in the risk of hyperkalaemia, 66% increase in the risk of hypotension and 41% increase in the risk of renal failure).

Comment: Given the findings of the meta-analysis, it is important that healthcare professionals closely monitor patients who are taking more than one drug that acts on the RAS. Until the results of the EMA review are known, prescribers should take a cautious approach to the use of such combinations.

3. Oral ketoconazole for fungal infections

Doctors should no longer prescribe oral ketoconazole for fungal infections, and should review patients' treatment options because of a risk of liver injury. The European Medicines Agency's Committee on Medicinal Products for Human Use (CHMP) has advised that although liver injury such as hepatitis is a known side effect of antifungal medicines, the incidence and the seriousness are higher with oral ketoconazole than with other antifungals.

Reported cases of hepatotoxicity include hepatitis, cirrhosis, and liver failure with fatal outcomes or requiring liver transplantation. Onset of hepatotoxicity generally occurred 1–6 months after starting treatment (but has also been reported earlier than 1 month), and occurred at the recommended daily dose of 200 mg.

Efficacy studies on oral ketoconazole are limited. There are also inadequate data to support the efficacy of ketoconazole when other treatments have failed or are not tolerated, or when resistance has been detected.

The CHMP has recommended that the licences for oral ketoconazole should be suspended throughout the EU; this recommendation will now be considered by the European Commission.

Comment : Doctors are advised to stop prescribing oral ketoconazole for fungal infections. People already on it need to be reviewed with a view to stopping or to choosing an appropriate alternative. Pharmacists are advised to refer patients with a prescription for oral ketoconazole back to the prescribing doctor. Topical ketoconazole such as creams, ointments and shampoos have very low systemic absorbtion and may continue to be used as currently approved. Some people with Cushing's disease take ketoconazole off label. Arrangements being made in the UK are likely to ensure that any local patients will continue to have access to it if required.

4. Codeine in children

Some patients may be at an increased risk of rare but serious adverse reactions as a result of the way the body handles codeine and younger children may be particularly susceptible. Therefore codeine should only be used to relieve acute moderate pain in children older than 12 years and only if it cannot be relieved by other painkillers. A significant risk of serious and life-threatening adverse reactions has been identified in children with obstructive sleep apnoea who received codeine after tonsillectomy or adenoidectomy (or both). Codeine is now contraindicated in all children younger than 18 year undergoing these procedures for obstructive sleep apnoea.

Written by: Geraldine O'Riordan, Prescribing Advisor, Social Security Department, Le Truchot
St Peter Port GY1 3WH Tel: 01481-732460
Reference : NICE , Drugs and Therapeutics Bulletin DTB *2013;51:69-74 doi:10.1136/dtb.2013.6.0187*