IRISH MEDICINES BOARD
DRUG SAFETY NEWSLETTER

2nd Edition

This newsletter is the second of what is intended to be an occasional publication to communicate updates on issues of interest and concern to health care professionals. We would like to thank all who contacted us to confirm that the first issue was useful. We would appreciate constructive comments and indeed, suggestions relating to issues which could be covered in future newsletters.

Correspondence should be marked for the attention of:
Dr M Teeling/Ms N Arthur, ADR Section.

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ACE INHIBITORS

The risk of hypoglycaemia due to interaction of ACE inhibitors and antidiabetic drugs suspected on the basis of previously published literature was further established in a recently published pharmacoepidemiological (record - linkage) study.

In order to increase awareness of this interaction, the Board reminds prescribers that concomitant use of ACE inhibitors and antidiabetic medicines (insulin, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with the risk of hypoglycaemia. This phenomenon may be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Please report any suspected cases of this interaction to the Irish Medicines Board.

CALCIUM CHANNEL BLOCKERS
(Calcium Antagonists)

Calcium Channel blockers are well-established drugs used in the treatment of ischaemic heart disease and hypertension. Recent studies published in the medical literature suggests there is evidence of increased risk of cardiovascular events and mortality in patients with unstable angina and following myocardial infection, given high doses of short acting Nifedipine.

Following review and evaluation of the data at national level and by the EU CPMP (Committee for Proprietary Medicinal Products) the Board recommends the following:-

1. Regarding ischaemic heart disease, its use should be restricted to the prophylaxis of stable angina. Use is contraindicated in patients with unstable angina.

2. Prescribers are reminded that treatment of hypertension with short-acting nifedipine may induce an abrupt fall in blood pressure as well as tachycardia, which could lead to a detrimental outcome.

Further studies are on-going to evaluate the benefit/risk associated with all other calcium channel blockers.
The Board will issue further information/advice as appropriate.

Currently authorised short-acting nifedipine products:-

Adalat, Coracten, Nitensar Pinifed, Systepin, Vasofed, Generic Nifedipine

VITAMIN A - PRODUCTS

Towards the end of 1995 the "New England Journal of Medicine" published a study report on teratogenic effects associated with high Vitamin A intake. The study concluded that high dietary intake of Vitamin A appears to be teratogenic.

Among the babies born to woman who took more than 10,000 IU of Vitamin A per day in the form of supplements the study estimated that about 1 infant in 57 had a malformation attributable to the supplement (N Engl J Med 1995; 333; 1369 - 73).

Following publication of this paper the Board is contacting companies holding authorizations for Vitamin A containing products in order to update the Product Authorisation documents.

While vitamin supplements are frequently taken by patients without medical advice, health care professionals are requested to remind patients who are pregnant or likely to become pregnant of the potential risks associated with high doses of Vitamin A (from both dietary and supplementary sources).

ORAL CONTRACEPTIVES

In October 1995 wide public coverage was given to the results of epidemiological studies, suggesting an increased risk of thromboembolism with the use of oral contraceptives containing desogestrel or

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gestodene compared to the use of "older" contraceptive agents. The data from these studies were ultimately published in the medical literature in December 95 and January 96. The Board has been keeping this matter under review. Furthermore a recent meeting of the CPMP (on which the Board is represented) reviewed the present situation. The Committee repeated its original opinion that the results of the presently available studies indicate that the risk for venous thromboembolism is higher in users of gestodene and desogestrel-containing oral contraceptives than in users of levonorgestrel containing contraceptives. However, the impact of biases and confounders on the difference still cannot be fully evaluated. This will require further studies and further analysis of the existing studies and the CPMP has requested these data.

The Irish Medicines Board is in agreement with this position. Therefore our recommendations have not changed from our previous letter. They are as follows:

1. You are reminded that there are well defined risk attached to the use of all oral contraceptive agents and patients receiving them should be kept under regular surveillance. The results of the present studies are not such as to require that any of these products should be withdrawn at this time.

2. Patients should be advised not to discontinue their medication, until they discuss their circumstances with you.

3. Patients who are prescribed desogestrel and gestodene-containing agents should be informed of the results of these studies prior to starting or renewing therapy. It should be stated that there is an apparent twofold increased risk of venous thromboembolism with use of gestodene and desogestrel containing products compared to levonorgestrel containing products. The increased risk is small and in absolute terms amounts to approximately 2 extra cases per 10,000 women years of use. The risk of venous thromboembolic events with all combine oral contraceptives is still substantially less than the risk of such events in pregnancy. There is still inadequate information on the relative risk of use of norgestimate-containing products.

4. Treated patients judged to be at particular risk for venous thromboembolic events should be reviewed in the light of this information. Known risk factors include obesity, varicose veins and a positive family history. Use of oral contraceptives continues to be contraindicated in patient with a history of existent venous thromboembolic disorders.

In addition you are reminded of the following:

5. Discontinuation of all oral contraceptive agents should be seriously considered in situations that are associated with an increased risk of venous thromboembolic events such as immobilisation, major trauma and surgery.

6. Due to the vague symptomatology of many venous thromboembolic events discontinuation of all oral contraceptives should be considered in cases of suspected thrombosis in patients on oral contraceptives while diagnostic interventions are being pursued. In this case alternative contraceptive strategies should be discussed with the patient.

The Board, in association with the CPMP, will continue to keep the matter under review and will issue further information or advice as necessary.

Currently authorised Desogestrel-containing oral contraceptives:

Mercilon, Marviol

Currently authorised Gestodene-containing oral contraceptives:

Femodene, Minulet, Triodene, Tri-Minulet.

ORGANOPHOSPHATE SHEEP DIPS

Organophosphate sheep dips have been available in Ireland since the early 1970's and are widely used.

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These products act primarily by inhibiting the enzyme acetylcolinesterase which plays a major role in the transmission of nerve impulses. Such compounds can be toxic to the user and must be handled with respect. The Board reminds prescribers to advise users to follow the instructions for the correct handling of organophosphate sheep dips (carried on the labels of all such products authorised by the Board).
Furthermore you should be aware of the possibility of side effects due to possible contamination by organophosphate sheep dips.

The Board has circulated a background document on organophosphate sheep dips to the relevant medical authorities for information. A copy of this report is available on request from the Board.

MEFLOQUINE
(Lariam)

Mefloquine is an anti-malarial agent used in the treatment and prevention of malaria due to p. falciparum, in those areas in which resistance to earlier conventional anti-malarial therapy exists.

In the light of recent media attention on mefloquine, which referred to its safety profile, with particular emphasis on the incidence of neuropsychiatric effects, the Board would like to remind you of the following when prescribing mefloquine for your patients.

Contraindications

Mefloquine should not be used in the following situations:

1. Prophylactic use in patients with renal insufficiency or severe impairment of liver function.

2. Prophylactic use in patients with a history of or existing psychoses or epilepsy.

3. Use in patients with a known hypersensitivity to Mefloquine or related compounds (e.g. quinine).

4. Concomitant use with halofantrine.

Precautions

Patients should be informed that if they develop one of the following symptoms, they should seek immediate medical advice.

Symptoms

Psychological changes such as depression, confusion, anxiety, hallucination, psychotic or paranoid reactions, sleep disorders including abnormal dreaming, forgetfulness, abnormal thinking.

MINOCYCLINE
(Minocin)

Articles have been recently published in the literature referring to the development of hepatic and SLE-type reactions associated with longterm use of Minocycline in the treatment of acne. Although acne itself can induce arthritis and has been reported in association with autoimmunine disease, the possibility of a drug-related reaction cannot be excluded. Therefore the Board recommends the following:

1. Treatment of acne with minocycline should be limited where possible to a maximum duration of six months.

2. Treatment should only be continued beyond six months if there is a satisfactory response and if liver function and ANF are monitored.

3. Minocycline is contraindicated in patients with a history of or existin hepatic dysfunction.

4. In common with other tetracyclines, increases in liver function tests and rarely hepatitis and acute liver failure have been reported. This may or may not be associated with autoantibodies.

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