IRISH MEDICINES BOARD

DRUG SAFETY NEWSLETTER

9th Edition

Selective Serotonin Re-uptake Inhibitors (SSRIs)

(fluoxetine - Prozac, paroxetine - Seroxat, citalopram - Cipramil, fluvoxamine - Faverin, sertraline-Lustral)

A recent paper* published in the British Medical Journal reported on an association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding. This was a population based case-control study undertaken in general practices included in the UK General Practice Research Database (GPRD).

This study concluded that SSRIs increase the risk of upper gastrointestinal bleeding however, the absolute effect is moderate and about equivalent to low dose ibuprofen. Concurrent use of non-steroidal anti-inflammatory drugs or aspirin with SSRIs greatly increases the risk of upper gastrointestinal bleeding.

Arising from this publication, the IMB, in conjunction with our national experts and European colleagues has evaluated the available data regarding the occurrence of all haemorrhagic disorders associated with use of SSRIs and are currently working with the product authorisation holders to update the prescribing information, as appropriate. All relevant updated changes will be notified.

Prescribers are reminded to exercise caution when using SSRI's in patients with a history of previous bleeding abnormalities and those receiving concomitant treatment with anticoagulants, drugs which effect platelet function (eg NSAIDs, acetylsalicyclic acid and ticlopidine) or other drugs that may increase risk of bleeding.

Any suspected adverse reactions should be notified to the IMB in the usual way.

British Medical Journal,* 1999; **319 : 1106-1109

Grepafloxacin (Raxar) withdrawal from marketplace

Grepafloxacin is a fluoroquinolone antibiotic indicated for the treatment of infections caused by strains of susceptible bacteria following diseases, community acquired pneumonia; acute bacterial exacerbations of chronic bronchitis; uncomplicated gonorrhoea (urethritis and cervicitis); urethritis and cervicitis caused by Chlamydia Pneumoniae. It was approved by the IMB and came on the market in Ireland in March 1998.

The company, GlaxoWellcome undertook a worldwide voluntary withdrawal of this product following a review by the company of the safety of grepafloxacin. This review concluded that due to an effect of grepafloxacin on cardiac repolarisation, manifested as QT interval prolongation, some patients may be at risk from a rare but serious ventricular arrhythmia known as Torsades de Pointes when treated with the product. To date, no such reports have been received by the IMB.

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Correspondence/Comments should be marked for the attention of:
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Doxycycline and oesophageal injury

(Brand names: Doryx, Vibramycin & Doxycycline Caps)

The IMB, in conjunction with our European colleagues, has reviewed the available data regarding the occurrence of oesophageal disorders associated with doxycycline hydrochloride.

While such effects are known to occur with all doxycycline preparations, the available data suggest an increased risk of such injuries particularly with **doxycycline hydrochloride** formulations. The mechanism for such injuries appears to be the direct result of prolonged contact of high concentrations of an irritant medication.

The current product information for doxycycline hydrochloride products recommends that adequate amounts of fluids should be taken with these preparations to reduce the risk of oesophageal damage and the patient should be advised to remain in an upright position for at least 30 minutes after ingestion.

The IMB is currently working with the product authorisation holders to ensure inclusion of comprehensive information and advice on this issue on the product information for doxycycline hydrochloride formulations, including patient information leaflets.

Practitioners are requested to remind patients to carefully adhere to the dosing recommendations as outlined above and to report any suspected adverse reactions to the IMB in the usual way.

Halogenated anaesthetic agents

(halothane, isoflurane, enflurane, sevoflurane)

The IMB has become aware of a recently published report* concerning the occurrence of cardiac arrhythmias in children who were treated with halothane during outpatient general anaesthesia for dental procedures.

This study in children aged 3-15 years, identified arrhythmias in 48% of those anaesthetised with halothane, compared with 8% receiving incremental sevoflurane and 16% receiving 8% sevoflurane. Halothane - associated arrhythmias were mainly ventricular and six children in the halothane group had ventricular tachycardia. The methods of sevoflurane administration did not differ significantly for the frequency of arrhythmias. Sevoflurane association arrhythmias were mainly single supraventricular ectopic beats.

To date, the IMB has not received any reports of suspected cardiac adverse reactions associated with use of halothane in adults or children in Ireland.

Following a review of the relevant literature on halogenated anaesthetics and in consultation with our expert advisers, the IMB is liaising with the relevant product authorisation holders to amend the current product information to include a recommendation that use of halogenated anaesthetics for dental procedures be continued in hospitals only.

The Lancet;* 1999; **354 : 1864-1866

Isotretinoin (Roaccutane)

As part of its remit for monitoring the safety and efficacy of all medicines available on the Irish market, the IMB occasionally requests that Post-marketing Surveillance Programmes (PMS) are carried out by pharmaceutical companies in respect of specific medicines. Such programmes are useful in providing information on the incidence and frequency of occurrence of suspected adverse drug reactions associated with use of the medicines concerned. This information is helpful in ensuring that the prescribing information accurately reflects the data available to the IMB in respect of these medicines.

Roaccutane (isotretinoin) is authorised for use in the treatment of cystic and conglobate forms of acne vulgaris or in those forms of severe acne which has failed to respond or rapidly relapse following adequate courses of accepted therapy. Roaccutane is recommended for use under the supervision of dermatology specialists having the facility to monitor its usage.

A PMS programme was initiated by Roche Pharmaceuticals at the end of August 1999, at the request of the IMB. The intention of this surveillance

programme is to monitor all patient usage of Roaccutane in order to review and evaluate the safety of its use in Ireland. The IMB has already written to Irish dermatology specialists informing them of the start of the surveillance programme and requesting their co-operation in order that sufficient data may be generated. The requirement to collect these data has been included as a condition for this authorisation and is currently referred to on the product information for Roaccutane.

The IMB understands that this surveillance programme cannot be carried out successfully without the co-operation of dermatology specialists and greatly appreciates their contribution to date. For any further information regarding the PMS programme, please contact Dr. M.Teeling/Ms. N. Arthur at the IMB or the company (Roche Pharmaceuticals Ltd.). Dermatologists and others monitoring patients currently taking Roaccutane are requested to co-operate with the company in the undertaking of this surveillance programme.

Erythromycin and pyloric stenosis

Recent reports* have been published in the United States of a possible association between the use of erythromycin in neonates and an increased risk of development of hypertrophic pyloric stenosis. *

Although no data exist to confirm a safe and effective alternative to erythromycin prophylaxis of neonates exposed to pertussis, these findings indicate a need for further examination of these recommendations. The high case-fatality ratio of pertussis in neonates demonstrates the need to prevent pertussis in this age group. However, public health physicians should continue to use caution in defining risk groups to minimise unnecessary prophylaxis. Physicians who prescribe erythromycin to newborns should inform parents about the possible risks for IHPS and counsel them about signs of developing IHPS.

The IMB is working with the companies concerned to further evaluate these findings.

Any suspected cases of pyloric stenosis following use of oral erythromycin in neonates should be reported to the Irish Medicines Board.

**The Lancet 1999;* 354: 2101-2105

Herbal Medicines (St. John's wort/Hypericum perforatum)

Following a recommendation from the Irish Medicines Board (IMB), the herbal medicine St. John's wort (Hypericum perforatum) has recently been made subject to prescription control. The background to the IMB recommendation is as follows:

1) St. John's wort has been promoted for the treatment of depression and symptoms suggestive of depressive illness. The mechanism of action of the postulated antidepressant effects is unclear. Depression can be a serious medical condition, therefore, self-diagnosis and self-treatment is considered inappropriate and raises safety concerns.

2) St John's wort has been reported to induce the metabolism of common prescription medications[1,2] such as antidepressants, the oral contraceptive pill, warfarin, theophylline, digoxin, indinavir[2], cyclosporin[2], anaesthetic agents[2] and may also interfere with the action of non-prescription medications. The net effect of induction of metabolism is a reduction in the plasma concentrations and reduced clinical efficacy. In addition, concomitant use of St. John's wort and serotonin reuptake inhibitors has resulted in symptoms characteristic of central serotonergic syndrome.

3) St. John's wort has been claimed to be without side-effects. However, it is known to cause photosensitivity, gastro-intestinal disturbances, fatigue and nervousness.

4) St. John's wort is a medicine and not a food supplement as has been suggested in media reports. Under existing Irish legislation the IMB is responsible for the regulation of all medicinal products.

The IMB considers that regulation is necessary to ensure the safe and appropriate use of this herbal medicine. At present, there is no licensed formulation of St. John's wort available on the Irish market, therefore, no recommendations can be made with respect to quality, safety or efficacy.

Herbal remedies and complementary medicines are widely used despite a lack of information about their pharmacology, pharmacokinetics and drug interactions. Prescribers and pharmacists are advised to question their patients about the use of herbal medicines such as St. John's wort. Because of the potential for serious interactions outlined should not be taken with any other medication.

1. *Lancet 1999;* **354**: 1362, 2014-2016.
2. *Lancet 2000;* **355**: 134-138, 547-549.

Update on Adverse Drug Reaction (ADR reporting)

During 1999 the IMB received a total of 1,018 nationally occurring ADR reports. All cases were reviewed and evaluated prior to inclusion on the IMB's ADR database, with feedback information provided to reporters, as appropriate. The following table shows the breakdown of reports by source:

G Ps	**48.4%**
Pharmaceutical Companies	**29%**
Hospital Doctors	**13.3%**
Pharmacists	**6.5%**
Nurses	**2.6%**
Dentists	**0.2%**

The IMB's ADR database includes anonymised case reports and is regularly reviewed to identify and evaluate adverse drug effects. This information is used to monitor drug safety on an ongoing basis and when considered appropriate to revise prescribing information accordingly.

The IMB's ADR database currently includes approximately 25,000 adverse reaction reports provided by health care professionals and pharmaceutical companies in Ireland since 1968. This information is helpful not only to the IMB in its evaluation of the safety profile of medicinal products, but is also useful in dealing with enquiries from healthcare professionals.

Spontaneous reporting of suspected adverse reactions is an inexpensive and effective method for the lifetime surveillance of medicines following their introduction to the marketplace. While an individual's experience may be limited to one or two cases, when collated with additional reports from other sources, such cases may contribute considerably to the assessment of a possible safety hazard.

Healthcare professionals are reminded that it is not necessary to determine a causal relationship between a drug and subsequent event prior to reporting of suspected adverse drug reactions.

You are particularly reminded to report:

- All suspected adverse reactions to new medicinal products (i.e. those available on the market for less than two years).
- Serious suspected reactions to established medicines. A serious reaction is defined as one which is fatal, life threatening, results in persistent or significant disability/incapacity, results in or prolongs hospitalisation. This definition also includes congenital abnormalities or birth defects and serious adverse clinical consequences.
- Any suspected increase in the frequency of minor reactions.
- Any suspected teratogenic effects.
- Any suspected reactions associated with the use of vaccines.

The IMB is always keen to help, encourage and establish ADR monitoring and reporting practices. Any centres wishing to develop their reporting system should contact the Pharmacovigilance Unit of the IMB.

Data Sheet and Summary of Product Characteristics Compendium 1999 - 2000

The IMB has been informed by the Irish Pharmaceutical Health Care Association (IPHA), that the 1999 - 2000 compendium of product information has been circulated to hospital consultants, general practitioners and community and hospital pharmacists. This edition is also being made available in CD ROM format. Further information or copies of the compendium may be obtained, on request from IPHA, Franklin House, 140 Pembroke Road, Dublin 4.
Tel: (01)-6603350, e-mail: info@ipha.ie.