IRISH MEDICINES BOARD

DRUG SAFETY NEWSLETTER

10th Edition

Sabril (Vigabatrin)

The European Scientific Committee for Proprietary Medicinal Products (CPMP) recently undertook a review of the occurrence of visual field defects (VFDs) associated with the use of vigabatrin and recommended restrictions on its use, together with a need for visual field screening and monitoring of patients. Following this review the marketing authorisation holder (Aventis Pharma) circulated a "Dear Doctor" letter regarding implementation of these regulatory changes to update the product information for vigabatrin.

In keeping with the European Commission Decision and in order to further evaluate the incidence and risk of vigabatrin - associated visual field defects, Aventis Pharma has agreed to collect data on patients currently or recently treated with vigabatrin among EU member states. A specific protocol known as SCOPE (sabril collection of ophthalmolgic patient experience) has been developed, which is intended solely for collection of data on the ophthalmic experience of patients treated with vigabatrin. Monitoring of patients under the SCOPE protocol is due to start in Ireland shortly and the company are currently liasing with relevant specialists regarding identification and follow-up of patients.

In order to ensure that the most complete and comprehensive data is available to evaluate this important safety issue, the IMB encourages physicians to participate in this monitoring programme and to report any suspected adverse reactions in the usual way.

Antipsychotic Medicines and Sudden Death

Over the years the IMB has received a number of suspected adverse reaction reports, notifying cases of sudden death associated with cardiac arrhythmias in patients treated with antipsychotic medicines. A number of these cases have occurred in relatively young patients without any underlying, previously recognised cardiac pathology.

A recent study suggests that lengthening of the QTc interval on ECG is dose-related in patients treated with antipsychotic medications.[1] QTc prolongation is an established predictor of malignant cardiac arrhythmias in patients with heart disease and congenital QTc prolongation syndromes. However, the relationship between antipsychotic medication, arrhythmia and sudden death remains unclear.[2]

Information on the occurrence of side effects such as sudden or unexplained death, fatal cardiac arrest or cardiac arrhythmias is included in the product information for all relevant products. Prescribers are reminded to monitor patients, particularly those receiving multiple medications, and to report any suspected cases to the IMB.

1. *Lancet 2000;* **355:** 1048-1052
2. *Antipsychotic drugs, In: Side Effects of Drugs Annual 21.;* **1998:** 42-65

Heparins

Therapeutic doses of both unfractionated and low molecular weight heparins can inhibit the secretion of aldosterone.[1] This causes an increase in plasma potassium which may be clinically significant.[2] Certain types of patients appear to be more susceptible to the suppression of aldosterone secretion such as those with diabetes mellitus, chronic renal failure, pre-existing acidosis, raised plasma potassium or those taking potassium-sparing drugs. The risk appears to increase with the duration of treatment, but is usually reversible. Plasma potassium should be measured in patients at risk before starting heparin and

Drug Safety - August 2000 - Issue No. 10

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monitored regularly thereafter, particularly if heparin is to be continued for more than seven days.

In addition, prescribers are reminded that heparin has been associated with thrombocytopenia, sometimes known as heparin induced thrombocytopenia (HIT). Type I HIT is a mild, clinically insignificant, transient, non-immune based thrombocytopenia which occurs frequently within four days of exposure to anti-coagulant doses of heparin. Type II (Immune HIT) is a limb and life threatening condition. It may be less likely to complicate therapy with low molecular weight heparin than unfractionated heparin, however, no conclusions have been reached regarding this.[3]

In order to avoid the development of such reactions, platelet counts should be ideally monitored during any heparin use (unfractionated or low molecular weight heparin, prophylactic or therapeutic), from days five to fourteen, or days two to fourteen in patients previously exposed to heparin during the past year. Such close monitoring may be difficult in patients treated in the community but a high index of suspicion for the diagnosis should be maintained. Thrombosis may precede thrombocytopenia. Laboratory confirmation of the development of heparin induced antibody is desirable, but not always easy. Prescribers are reminded that heparin must be immediately withdrawn if immune HIT is suspected.

1. *Am. J.Med. 1995;* **98:** 575-586
2. *Eur.J.Clin.Pharmacol. 1989;* **37:** 415-418
3. *Prescriber's Journal. 2000:* **40:** (1) 60-63

Warfarin

Since 1996, the IMB has received several anecdotal reports from prescribers indicating that some patients have experienced large alterations in their INRs and poor anti-coagulant control. These cases were initially reported when Warfant replaced the previously available brand of warfarin and occurred in patients who were reported to have been stable prior to the changeover. Since the changeover, isolated reports have continued to be reported with Warfant.

While limited information in relation to these reports has been received to date, the IMB has attempted to follow-up data in respect of any identifiable batches, none of which has suggested any reason for the discrepancies observed.

In conjunction with the investigations into the individual reports, a literature review has also been carried out to ascertain if similar INR instability has been reported elsewhere. This review has highlighted a potential effect of test methods on the PT/INR results.

Reports from these studies show that coagulometers can give different readings from those obtained using the reference manual method and that there may be within-coagulometer variation. It was noted that for some instruments, the differences can be clinically significant and that such findings may not be well known.[1,2] As such, the IMB considers it appropriate to bring this to your attention.

Details of the studies are referenced below. If any prescribers/hospitals would like copies of these publications, they should contact the Pharmacovigilance Unit of the IMB.

1. *Am.J. Health-S.Pharm. 1999;* **56:** 1619-1623
2. *J. Clin.Pathol. 1990;* **43:** 679-684

COX-2 Selective Inhibitors

Two new non-steroidal anti-inflammatory drugs (NSAIDs), Vioxx (rofecoxib) and Celebrex (celecoxib) have recently been authorised for marketing in EU Member States, including Ireland. These NSAIDs are reported to exhibit selective inhibition of cyclo-oxygenase-2 (COX-2). Data from clinical trials suggest that they are as efficacious as standard NSAIDs, but in clinical trials they have been reported to induce a lower incidence of gastroduodenal ulceration due to selective inhibition of (COX-2).

In view of the novel activity of these NSAIDs and data from initial post-marketing surveillance which suggests that they are being used in older and high risk patients, the IMB requests healthcare professionals to report any suspected adverse reactions associated with their use, in the usual way.

Ziagen (abacavir)

In July 1999, abacavir was authorised throughout the European Union as an anti-retroviral agent for use in combination with other anti-retroviral therapy for the treatment of HIV infected adults.

Since marketing, hypersensitivity reactions have continued to be the major issue of concern with use of this product. These have occurred in about 4% of patients exposed to Ziagen in clinical trials.

Hypersensitivity reactions with rapid onset, including life-threatening reactions have occurred after re-starting Ziagen in patients who had only one of the key symptoms of hypersensitivity (skin rash, fever, gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise) prior to stopping Ziagen. More importantly on very rare occasions hypersensitivity reactions have been reported in patients who have re-started therapy and who

had no preceding symptoms of a hypersensitivity reaction. If a decision is made to re-start Ziagen, this must be done in a setting where medical assistance is readily available.

Hypersensitivity reactions to Ziagen are characterised by the appearance of symptoms indicating multi-organ system involvement and may occur at any time during therapy. Symptoms usually appear within the first six weeks of initiation of treatment with Ziagen. Patients should be monitored closely, especially during the first two months of treatment with Ziagen, with consultation every two weeks.

The IMB wishes to draw attention to the following updated information on the management of hypersensitivity reactions to Ziagen:

To avoid delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, Ziagen must be discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (e.g. respiratory diseases, flu-like illness, gastroenteritis, or reactions to other medications). **If reintroduction is judged necessary it must be done in a hospital setting.**

- Prescribers must ensure that patients are fully informed regarding hypersensitivity reactions. Each patient should be reminded to read the package leaflet and the alert card included in the pack.
- Some patients with hypersensitivity reactions were initially thought to have respiratory disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases.
- Ziagen® MUST NEVER be restarted in patients who have stopped therapy due to hypersensitivity reaction.
- Restarting Ziagen® must be avoided in patients in whom a hypersensitivity reaction cannot be excluded.
- Patients experiencing ONE OR MORE symptoms of the following:

1) fever
2) shortness of breath, sore throat or cough
3) skin rash (redness and/or itching).
4) nausea or vomiting or diarrhoea or abdominal pain.
5) severe tiredness or achiness or generally ill feeling.

SHOULD CALL THEIR DOCTOR IMMEDIATELY for advice on whether they should stop taking Ziagen®.

This updated prescribing information has been circulated to all physicians.

Coal Tar Preparations

Products containing coal tar have been used in dermatological practice for many years. Some refined coal-tars contain polycyclic aromatic hydrocarbons (PAHs) which are known to be carcinogenic in animal studies. However, epidemiological studies in patients treated with coal tar are inconclusive. The IMB's Expert Sub-Committee of the Advisory Committee on Human Medicines has recently reviewed this issue and the important role of coal tar products in dermatology was acknowledged. It was considered that the risk/benefit analysis of these products merits their continued clinical use.

The IMB is currently including the following warning statements in the product information for coal tar preparations at the time of renewal of the licences for these products.

Section 4.8 - Undesirable Effects

Although carcinogenicity of coal tar has been demonstrated in animal studies, no studies demonstrating an increased risk of skin cancer with normal therapeutic use in humans have been reported. There is no unequivocal evidence to link the use of topically applied coal tar products with skin cancer (See also section 5.3).

Section 5.3 - Preclinical Safety Data

Tar preparations have been in wide use for many years. Although coal tar preparations containing polycyclic aromatic hydrocarbons (PAHs) have been demonstrated to be carcinogenic in the skin of experimental animals, present evidence based upon epidemiology studies in humans and follow-up trials, reveals no evidence of increased risk of skin or internal cancer, particularly when the product is used as directed.

PIL/Labelling

Unless otherwise directed by your doctor or pharmacist, only use once or twice weekly. Because of a theoretical risk of skin damage if used for long periods, if the condition persists, you should seek advice from your doctor or pharmacist before continuing treatment.

CFC Free Inhalers

Following international evaluation of the impact of chlorofluorocarbons (CFCs) on the ozone layer, the

European Community has developed a strategy for the phaseout of CFCs in metered dose inhalers (MDIs), without jeopardising essential supplies. The transition from CFC inhalers to CFC-free replacement products has already started in Europe and should be completed by the year 2003.

Recently approved reformulated inhalers use hydrofluorolkanes (HFAs), instead of CFCs as the propellant. On changing to the new propellants, patients may notice a slight taste difference and a different sensation as the spray contacts the oropharynx. It is helpful to draw their attention to this in advance so that the change comes as an expected one. In most cases, no dosage adjustment is necessary when patients are switched to CFC-free MDIs. However, with some approved products a change of dose is advised and this may also be the case for others not yet authorised. Prescribers are encouraged to familiarise themselves with the relevant information before using the new products.

Testing of HFA- MDIs in clinical trials has not identified any new safety issues that were not previously recognised with equivalent CFC-containing products. However, in order to confirm the safety of the new CFC-free products pharmaceutical companies are encouraged by the European Commission to perform post authorisation surveillance studies to effectively monitor their introduction to the marketplace. Healthcare professionals are encouraged to participate in studies undertaken to evaluate the safety of these products in routine clinical practice, to monitor patients using them and to report any suspected adverse reactions in the usual way.

For further information regarding the European Commission Strategy, please contact the Pharmacovigilance Unit of the IMB.

Thiomersal

Thiomersal is an organo-mercurial compound with an anti-microbial action related to the release of ethylmercury. It has been used for many years in medicinal products, including vaccines and eye/nasal preparations where it is mainly used as a preservative in the finished product. Thiomersal may also be used in the manufacturing process in biopharmaceuticals. Its removal thus could affect solubility, antigenicity and stability. Cumulative exposure to mercury from a range of sources (food, medicinal products etc), could lead to a concern because of its potential for accumulation in various organs.

With a view to limiting exposure to mercury and organo-mercurial compounds, the European Medicines Evaluation Agency's (EMEA) scientific Committee for Proprietary Medicinal Products (CPMP), recently undertook an evaluation of the benefit-risk of medicinal products containing thiomersal and a number of recommendations were issued as follows:

1. In relation to vaccines, the European Review concluded that although there is no evidence of harm caused by the level of exposure to thiomersal in vaccines, where feasible it would be prudent to encourage in infants and toddlers the use of vaccines without thiomersal or other mercurial containing preservatives, as a precautionary measure. It has requested vaccine manufacturers to submit their plans to eliminate organo-mercurials used as preservatives in their final products.

A stepwise approach in the removal of such preservatives has been considered acceptable (as previously stated by the EMEA - July 1999). A similar approach has been recommended by the Centre for Disease Control and Prevention (CDC) in the USA.

2. In relation to immunoglobulins and eye/nasal preparations containing thiomersal no regulatory action was deemed necessary at this time. However, it was recommended that the presence of thiomersal (and other preservatives) in the composition of other medicinal products should be stated on the label.

3. Because of the potential of thiomersal to stimulate sensitisation, it was agreed that appropriate warning statements should be included in all product information to advise prescribers about this potential and to alert the public to inform healthcare professionals about any history of allergy and any possible hypersensitivity effects following vaccination.

All relevant pharmaceutical companies have been contacted by the IMB with regard to implementation of appropriate warning statements.

Any suspected adverse reactions should be notified to the Irish Medicines Board in the usual way.

Adverse Reaction Reporting

Adverse Reaction report forms are available on request from the IMB, telephone 353-1-6764971 or fax. 353-1-6767836. A version of the Adverse Reaction report form may also be downloaded from the Irish Medicines Board web site at http://www.imb.ie These forms may be forwarded by free post to the IMB at:-

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Pharmacovigilance Unit,
Irish Medicines Board,
Block A,
Earlsfort Terrace,
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