IRISH MEDICINES BOARD

DRUG SAFETY NEWSLETTER

12th Edition

MMR Vaccine

The safety of MMR vaccine was previously reviewed in an earlier issue of the IMB's Drug Safety Newsletter.[1]

This vaccine recently received much attention again following the article by Wakefield et al. published in the *Adverse Drugs Reactions and Toxicological Reviews* in January 2001.[2] The IMB has reviewed this paper and concludes that it does not present any new data - it merely reviews a number of published studies. The article is highly selective and papers that do not support the author's views are not mentioned. It is important to note that no other research group has been able to confirm the laboratory findings that led to the original hypothesis raised by Dr. Wakefield. In addition, repeated studies have not identified an association between MMR vaccine and inflammatory bowel disease or autism.

The Irish Medicines Board (IMB), the National Immunisation Advisory Committee, our European colleagues and many international groups have repeatedly reviewed the safety of the MMR vaccine. All have concluded on each review that there is no evidence to support any association between administration of MMR vaccine and the subsequent development either of inflammatory bowel disease or autism. The World Health Organisation and the Centre for Disease Control in the United States has also reached this conclusion.

To date, more than 500 million doses of MMR vaccine have been used worldwide. The combined MMR vaccines were extensively studied and tested in Scandinavia and the USA before they were introduced in Ireland. The vaccines have now been successfully used in over 30 European countries as well as the USA, Canada, Australia and New Zealand.

The evidence does not support the suggestion that single component vaccines should be administered separately. The IMB considers that the current policy of giving MMR in two doses is safer than giving the three component vaccines sequentially with six injections. With the mono-component vaccines given sequentially, children would be at risk of infection for longer periods; they would be exposed to the risk of local adverse reactions on each occasion and it is likely that there would be a significant dropout rate for the successive vaccinations.

The safety of all medicines, including this vaccine is monitored continuously by the IMB. Various data sources are used, including reports of suspected adverse reactions received from Ireland and worldwide, regular safety updates from the companies, the worldwide medical literature, data from epidemiological studies and information from independent researchers, as well as from other regulatory authorities around the world. The IMB remains of the view that vaccination with MMR is a safe and effective means of protecting children from serious and occasionally fatal illness.

The IMB will continue to assess any new information available regarding the safety of this vaccine, to take any regulatory action deemed appropriate and to notify Healthcare professionals accordingly.

References:

1. *IMB Drug Safety Newsletter 1998; 8: 2*
2. *Adverse Drug Reactions & Toxicological Reviews 2000; 19 (4): 265-283*

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Thioridazine(Melleril/Melzine/Thiozine)

Further to a publication by Reilly et al[1]., which identified an increased risk of QT prolongation with thioridazine, the IMB and its national experts recently undertook urgent regulatory action, to implement variations to restrict use and increase existing warning statements regarding the risk of cardiotoxicity of thioridazine.

Thioridazine has been authorised for more than twenty years in Ireland and has in the past, been prescribed for anxiety and tension disorders, including those associated with agitation, behavioral disorder, senile confusion and severe mental/behavior problems in children. Following review, the IMB has recommended that thioridazine should not be used for the treatment of these conditions and should not be prescribed for children.

Use of thioridazine is now restricted to second line treatment in adult schizophrenia only, under the supervision of a consultant psychiatrist.

A history of clinically significant cardiac disorders including arrhythmias, conduction disorders or a history of QTc prolongation are contraindications for use.

It is important to note that medical conditions or other drugs taken concurrently which may lead to electrolyte imbalance may increase the risk of serious cardiac arrhythmias.

In addition, the IMB recommends that patients have ECG screening and electrolyte measurements performed before receiving thioridazine and periodically during treatment. Detailed information on the revised recommendations was notified to doctors and pharmacists in mid-December.

Healthcare professionals are requested to report any relevant, suspected adverse drug reactions (ADRs) to the IMB.

Reference:

1. The Lancet 2000; 355: 1048-1-52

Droperidol (Droleptan)

The Irish Medicines Board has recently been informed that the Marketing Authorisation Holder for the above product (Janssen-Cilag) intends to discontinue its availability.

In Ireland, oral formulations of droperidol injection are not authorised. Because of concerns about serious cardiac arrhythmias, the injectable formulation has been restricted to use in anaesthesia as an anti-emetic, in the technique of neuroleptanalgesia and to a specific use in psychiatry (in hospitals only, except in emergency situations) to rapidly calm the manic, agitated patient. The company has assured the IMB that alternative preparations are available for use in these indications.

Janssen-Cilag Limited has decided to voluntarily discontinue availability of droperidol worldwide, following an extensive benefit/risk assessment. This raised concerns about the potential effect of oral preparations of droperidol, when used chronically, on the QTc interval. This has led to the conclusion that droperidol should be discontinued, to prevent use in chronic conditions. As a result, the company do not consider it feasible to continue manufacturing the injectable formulation, which will also be discontinued.

Any questions arising with regard to the discontinuation of Droleptan should be addressed to the Medical Information Department of Janssen-Cilag on 1800 709 122.

Bupropion (Zyban)

Recent media attention has highlighted reports of suspected adverse drug reactions (ADRs) including reports of fatalities which occurred in patients during treatment, in the UK.

Information from the Medicines Control Agency (MCA), UK, indicated that the contribution of bupropion in the reports of fatalities, is unproven. Furthermore, it was noted that in relation to reports of seizures, approximately half of the patients had either a past history of seizure(s) and/or risk factors for the development of seizure(s). It appears therefore, that in some of the cases, the product appears to have inappropriately used.

The Irish Medicines Board (IMB) reiterates its advice that this medicine should be prescribed only in accordance with the recommendations for use included in the product information.[1]

Bupropion was approved by the IMB in June 2000 and it is estimated that to date, approximately 23,000 patients have been treated in Ireland. During this period, the IMB has received 65 reports of suspected adverse reactions associated with its use of these, the majority were in keeping with the type expected for the product and most patients recovered completely. The IMB has received 3 reports of seizure associated with use of bupropion, for which further information is awaited. One report of a fatality which occurred during bupropion treatment has been notified however a post mortem report suggests that

there was a well defined, pre-existing cause of death and that the outcone was unrelated to treatment with bupropion.

Prescribers are reminded to report any suspected adverse reactions with this new medicinal product to the IMB.

Reference:
IMB Drug Safety Newsletter 2000; 11: 3

Propofol (Diprivan/Propofol/Fresenius Propofol)

Propofol is an intravenous anaesthetic agent licensed for both induction and maintenance of general anaesthesia, sedation of ventilated adult patients in intensive care and sedation of adults for diagnostic and surgical procedures, alone or in combination with regional anaesthesia. It is authorised for use only in hospitals or fully equipped day care units, by anaesthetists only, with constant monitoring of patients vital signs.

A recent publication in the Lancet [1] reported on five adult patients with head injuries, all sedated with propofol, who inexplicably had fatal cardiac arrests in a neurosurgical intensive care unit, and the subsequent retrospective study carried out to investigate the possible relationship further. The events took place after the introduction of a sedation formulation containing an increased concentration of Propofol (2% versus 1%). The retrospective study showed that 7 of 67 head injured adults sedated with propofol for more than 48 hours developed an apparent propofol infusion syndrome. The signs and symptoms included various cardiac dysrhythmias, metabolic acidosis, hyperkalaemia, rhabdomyolysis and/or acute cardiac failure. The cases were characterised by a continuously increasing need for inotropic and vasopressor support that became evident 24-48 hours after the start of the propofol infusion. All had received propofol at rates higher than 5mg/kg/hr for more than 35 hours. The study found a dose-dependent association between long-term high dose propofol infusion and cardiac failure but was unable to establish a causal relationship from the available data.

Prescribers are reminded that the maximum licensed dose of propofol for use in sedation of adult patients is 4mg/kg/hr. Although licensed for a maximum duration of use of seven days for sedation, in view of the above findings, extension of sedation beyond 48 hours should only be undertaken with caution. Patients should at all times be closely monitored for the development of undesirable effects and measures taken to decrease the dose or change to alternative forms of sedation should symptoms or signs develop.

Following discussion of this issue with our EU colleagues, the current view is that the benefit/risk balance for propofol remains positive, when used in accordance with the current prescribing recommendations. However, further data are needed to confirm any association between the development of these suspected adverse reactions and propofol, the frequency of occurrence, the underlying mechanism and whether risk factors for specific patients may be identified. The Marketing Authorisation Holders have been approached regarding proposals for further studies to address these issues.

Prescribers are requested to report any suspected ADRs to the IMB.

Reference:
The Lancet 2001;357:117-1

Stavudine (Zerit) and Didanosine (Videx)

Stavudine and didanosine are nucleoside reverse transcriptase inhibitors (NRTIs) indicated for use in combination with other antiretroviral agents for the treatment of HIV infection. Both products were authorised through European procedures of assessment, prior to approval by the Irish Medicines Board.

Recently, the IMB was made aware of seven cases of lactic acidosis in pregnant women treated with a combination of stavudine and didanosine, which occurred in other countries. Three of these cases were fatal. Of the three women who died, one also had pathologically confirmed hepatic steatosis and two had pancreatitis. Two of these maternal deaths occurred in a multinational randomised clinical trial. One patient was taking the triple combination therapy of didanosine / stavudine / nelfinavir, whilst the other was treated with a triple combination of didanosine/stavudine plus an investigational protease inhibitor. The third death and the four additional non-fatal cases of lactic acidosis were identified through worldwide post-marketing surveillance. One baby survived from the three pregnancies with a fatal outcome, the other two died prior to the mother's death, at between 32 and 36 weeks gestation.

Lactic acidosis is a known side effect of NRTIs. Consequently, the product information of all NRTIs used in the treatment of HIV infection (stavudine, lamivudine, abacavir, zidovudine, didanosine and zalcitabine) warn of the risk of lactic acidosis, which may be fatal. Prescribers are also informed of the need for caution when prescribing to any patient (particularly obese women), with

a history of hepatomegaly, hepatitis or other known risk factors for liver disease.

Following review of the available data at European level, it is considered that at present there is insufficient information to decide whether pregnancy is an additional risk for lactic acidosis. It is also uncertain whether any increased risk of lactic acidosis is specific to stavudine and didanosine, or whether it might be increased with all combinations of nucleoside analogues. It should be noted that except for the use of zidovudine in the preventation of materno-foetal transmission of HIV, the use of nucleoside analogues during pregnancy is not recommended, unless the potential clinical benefits clearly outweigh the potential risks.

Additional information has been requested from the relevant pharmaceutical companies and this issue will be further evaluated at European level for the whole class of NRTIs and further information provided when this evaluation has been completed.

Topical Chloramphenicol (Actinac, Chloromycetin, Chloroptic, Minims Chloramphenicol & Chloramphenicol)

Chloramphenicol is available as both 0.5% drops and 1% ointment. It has a broad spectrum of activity, is inexpensive and has a low incidence of adverse events. However, use of topical chloramphenicol has been associated with bone marrow toxicity and cases of major adverse haematological events (bone marrow depression, aplastic anaemia) have been rarely reported.

Following publication of a review article in the BMJ [1], *"Use of chloramphenicol as topical eye medication: time to cry halt?"* urging physicians to restrict their use of ocular chloramphenicol, this issue was reviewed with our Experts.

In order to facilitate this safety review, the holders of currently licensed antibiotic eye drops were asked to provide updated safety information and an extensive literature search was undertaken.

It was noted that the documented spectrum of activity of chloramphenicol, in the treatment of superficial eye infections includes *Escherichia coli, Haemophilus influenzae, Staphylococcus aureus, Streptococcus haemolyticus, Morax-Axenfeld, Klebsiella/Enterobacter species* among others.

Following review of the available data it was the conclusion of our Experts that the risk/benefit profile of chloramphenicol remains unchanged. However, in keeping with the current recommendations and warnings for use, prescribers are reminded that topical chloramphenicol should be reserved for use only in infections for which it is indicated and only where a family history of drug-related haemopoietic toxicity has been excluded. In addition, prescribers are requested to report any suspected cases to the IMB, in the usual way.

Reference:
1. BMJ 1995; 310: 1217-8.

Clinical Trials

As part of our on-going review of the clinical trial application process we have identified a number of academic investigator led applications which failed to get approval first time round, due to an inadequate amount of information submitted for review.

Depending on the category of trial, we provide general guidelines regarding the amount of information required to support an application.

These guidelines should be adapted to the particular type and phase of clinical trial proposed. However for all submissions, we require a protocol outlining the design, conduct and analysis of the proposed clinical trial. In order to facilitate review of clinical trial applications from academic centres we have devised a clinical trial protocol template covering the core areas that are assessed during the review process. The objective of this document is to provide guidance to the investigators on an approach to clinical trial design and analysis and to ensure the safety of participants in that clinical trial.

These guidelines are not to be interpreted as mandatory requirements by the IMB for approval of a clinical trial application. They constitute an acceptable approach to meeting regulatory requirements. This template is available on our web-site at http://www.imb.ie or on request from the Clinical Trials Unit.