IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

21st EDITION

Propofol Infusion Syndrome (Diprivan/Propofol/Propofol-Lipuro)

Propofol is a short-acting intravenous anaesthetic agent authorised for:

- Induction and maintenance of general anaesthesia in adults and children;
- Sedation of ventilated adult patients in the intensive care unit;
- Conscious sedation for surgical and diagnostic procedures in adults.

Previous IMB newsletter articles (April & September 2001) highlighted the findings of a randomised, controlled clinical trial in paediatric ICU patients, which identified an increase in the number of deaths in patients treated with standard selective agents. Following evaluation of available data at national and European level, the use of propofol was contraindicated for use as ICU sedation in patients of 16 years of age or younger. As further reports of the so-called 'propofol infusion syndrome' continue to be reported both in the literature and spontaneously, the IMB wishes to remind healthcare professionals of the issue.

Sedation of ventilated patients in the ICU (Intensive Care Unit):

Propofol should be administered by continuous infusion; the rate to be determined by the desired depth of sedation. In most patients sufficient sedation can be obtained with a dosage of 0.3 - 4 mg/kg/h of propofol. Very rare cases of metabolic acidosis, rhabdomyolysis, hyperkalaemia and/or rapidly progressive cardiac failure (in some cases with fatal outcome) have been reported in adults who were treated for more than 58 hours with dosages in excess of 5 mg/kg/h. This exceeds the maximum dosage of 4 mg/kg/h currently advised for sedation in the intensive care unit. The patients affected were mainly (but not only) seriously head-injured patients with raised intracranial pressure. The cardiac failure in such cases was usually unresponsive to inotropic supportive treatment.

Anaesthetists and intensivists are reminded:

- Not to exceed the dosage of 4 mg/kg/h, if possible.
- To remain alert to the possible undesirable effects.
- To consider decreasing the propofol dosage or switching to an alternative sedative at the first sign of symptoms (Patients with raised intracranial pressure should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications).

Use in children:

a. General anaesthesia:

Propofol is not advised for general anaesthesia in children younger than 1 month of age.

b. Sedation:

Propofol is contraindicated for ICU sedation in patients of 16 years of age or younger. Although no causal relationship has been established, serious undesirable effects with (background) sedation in patients younger than 16 years of age (including cases with fatal outcome) have been reported during unlicensed use. In particular, these effects concerned metabolic acidosis, hyperlipidemia, rhabdomyolysis and/or cardiac failure. These effects were most frequently seen in children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the intensive care unit.

Finally we would take this opportunity to remind healthcare professionals that any suspected cases of propofol infusion syndrome should be notified to the IMB in the usual manner.

BCG Vaccine SSI – Retrospective Review of Serious Local Adverse Reactions

Further to previous IMB articles on BCG vaccine in MIMS Ireland (April 2003, September 2004 and February 2005) and in the June 2003 issue of the IMB Drug Safety Newsletter, this article outlines the conclusions of a retrospective review of suspected adverse reactions associated with BCG vaccine reported in Ireland from 2002 to 2004 and the possible reasons for an observed increase in the rate of reporting during the period.

BCG Vaccine SSI [Danish 1331 strain] was first authorised in Ireland in 2001 and became the only available BCG vaccine in 2002 following withdrawal of the previously used Evans BCG vaccine [Copenhagen 1077 strain] from the Irish market due to concerns regarding possible sub-potency of some batches of vaccine.

From 1992-2002 a total of 41 ADR reports were spontaneously notified to the IMB in association with BCG vaccine. Following introduction of BCG Vaccine SSI in 2002 a significant increase in the number of suspected adverse reaction reports notified to the IMB was observed. A detailed review of cases classified as "serious", within the agreed regulatory definition of the term, was initiated. This review included distribution of a questionnaire to the original reporters of adverse reactions in association with BCG over the two-year period from August 202 to July 2004. IMB staff together with paediatric experts reviewed and evaluated both the original reports and the completed questionnaires. A total of 121 adverse reactions were reported during the study period; 59 cases of regional lymphadenopathy, 58 cases of local reactions exceeding 10 mm in diameter and 4 cases of generalised rash. Interestingly, administration of an incorrect dose or administration by an incorrect route were reported factors in 10 of the adverse reaction reports.

Evaluation of the data suggested that the observed increase in notification o f adverse reactions during the two-year period between 2002 and 2004 may have been due to a number of factors. These included a heightened awareness surrounding the use of the newly available BCG Vaccine SSI following the publicity associated with the withdrawal of the previously used product, a change in vaccine potency and reactogenicity [the Danish 1331 strain is known to be a more potent than the Copenhagen 1077 strain] and administration errors due to incorrect dose or route of administration.

Overall there was a significant increase in the notification of suspected adverse reactions following introduction of the Danish 1331 BCG strain in Ireland, however, the reporting rate remained within the frequency of adverse reactions expected for BCG and was consistent with what has been observed in other countries following introduction of the Danish 1331 strain.

Since the end of the study period there has been a downward trend in adverse reaction reporting associated with BCG Vaccine SSI. This decrease was partly expected following a number of initiatives taken by the IMB to highlight issues regarding the use and safety of the product, to encourage adverse reaction reporting and to highlight that the BCG Vaccine SSI should be administered intradermally in accordance with the approved product information.

The IMB would like to sincerely thank those healthcare professionals who contributed to this review by submission of reports and provision of follow up information, including completed questionnaires. As always, the essential contribution of busy healthcare professionals to the continued surveillance of the safety of medicines through the spontaneous reporting system is greatly appreciated.

References:
1. IMB Articles in MIMS Ireland, April 2003, September 2004, February 2005.
2. IMB Drug Safety Newsletter 2003; 17:4.
3. 'BCG Vaccine and Experience with associated Adverse Reactions reported in Ireland', National TB Advisory Committee.

Review of the Safety of Antidepressants in Children & Adolescents

SSRIs/SNRIs

Evaluation of data at national and European level regarding concerns related to the potential for psychiatric disorders (including self-harm, suicidal ideation and hostility) in adult patients treated with selective serotonin re-uptake inhibitors (SSRIs) and serotonin norepinephrine re-uptake inhibitors (SNRIs), has been the subject of previous IMB newsletter articles and several monthly items in MIMS Ireland. Following these reviews, a formal Referral procedure was initiated at European level to undertake an evaluation of the clinical data available in support of the following SSRIs/SNRIs, particularly in relation to their use in the paediatric populations: fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram, atomoxetine, duloxetine, venlafaxine, mianserine, milnacipran, reboxetine and mirtazapine.

This review was completed in August 2005 and concluded that there is a signal of suicidal behaviour, including suicide attempts, suicidal ideation and/or related behaviour like self-harm, hostility and mood lability in children and adolescents treated with SSRIs and SNRIs. The following recommendations to update the SPCs for the above products in accordance with the outcome of the review were issued and are being implemented by the IMB:

Use in children and adolescents under 18 years of age

[Invented name] should not be used in the treatment of children and adolescents under the age of 18 years <except for patients with [approved indication]>. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking[1].

The package leaflets for products containing these substances will be updated accordingly to highlight the possibility of increased risk of adverse reactions and to encourage patients to report any such reactions to their doctor.

Tricyclic Antidepressants [TCAs]

The issue of the use of tricyclic antidepressants in children and adolescents under the age of 18 was also considered in late 2005. That review concluded that the product information for TCAs should be updated to include the following information:

[Invented name] should not be used in the treatment of children and adolescents under the age of 18 years. Studies in depression in this age group did not show a beneficial effect for tricyclic antidepressants. Studies with other classes of antidepressants (specify classes) have shown a risk of suicidality, self-harm and hostility related to these compounds. This risk cannot be excluded with [invented name]. In addition, [invented name] is associated with a risk of cardiovascular adverse events in all age groups. Furthermore, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available (see also section 4.8 Undesirable effects and section 4.9 Overdose).

The IMB has requested all relevant MAHs to amend their product information to include this information.

The IMB will continue to monitor the quality, safety and efficacy of all antidepressant medicines and initiate any further regulatory action deemed necessary. Any suspected adverse reactions observed with use of these products, including any adverse reactions associated with use in children and adolescents, should be notified to the IMB in the usual way.

Reference:
1. Commission Decision of 19-VIII-2005 concerning the placing on to the market, under Article 31 of Directive 2001/83/EC of the European Parliament and the Council, of the medicinal products for human use which contain the active substances Atomoxetine, Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Mianserine, Milnacipran Mirtazapine, Paroxetine, Reboxetine, Sertraline and Venlafaxine [EMEA/H/A-31/651].

Intravenous Antibiotics and Anaphylaxis

Following a number of reports of anaphylaxis, including one that resulted in a fatality, after intravenous administration of co-amoxiclav in patients who had previously tolerated oral co-amoxiclav, the IMB wishes to highlight this issue to healthcare professionals.

As part of their history taking, healthcare professionals should consider the possibility of cross-sensitivity with other medicines. Other factors such as dose and route of administration should also be taken into consideration. In the event of anaphylaxis, emergency treatment, including appropriate medication, should be readily available

Reporting Adverse Drug Reactions [ADRs] - Reminder

Healthcare professionals are reminded that any suspected ADRs should be notified to the IMB Pharmacovigilance Unit. A version of the ADR report form is available to download from the IMB's website (www.imb.ie). Downloaded forms may be completed and sent by freepost to the IMB. Envelopes should be marked "Freepost", Pharmacovigilance Unit, Irish Medicines Board, The Earlsfort Centre, Earlsfort Terrace, Dublin 2.

Alternatively, completed forms may be submitted by fax (01- 6762517). Post-paid report cards are also available from the Pharmacovigilance Unit at the IMB (01-6764971).

Correspondence/Comments should be marked for the attention of:
The Pharmacovigilance Unit, Irish Medicines Board, Earlsfort Centre, Earlsfort Terrace, Dublin 2.

Tel: 676 4971-7 Fax: 676 2517