IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

41ST EDITION

Paracetamol – Available evidence does not support a causal relationship with asthma in children after exposure in pregnancy or use in early infancy

Paracetamol was first introduced into clinical practice in the 1950s, and has become one of the most widely used analgesic-antipyretics. Due to its safety profile, when used within therapeutic doses, it is considered the analgesic of choice in pregnancy and in children. In the paediatric population in particular, paracetamol has displaced the use of aspirin after the association with Reye syndrome was established.

A possible association between paracetamol and childhood asthma was initially postulated based on the observation that the displacement of paediatric aspirin use in favour of paracetamol had coincided with an increased prevalence of asthma in Western countries.[1] In 2008 the Pharmacovigilance Working Party (PhVWP) of the European Medicines Agency (EMA) considered the available data and concluded that a causal association between paracetamol and asthma after exposure in utero or in early infancy could not be established.

Since then a number of new epidemiological studies investigating this possibility have been published and a further review was undertaken to evaluate the results of these studies[2-10] (see the PhVWP monthly report at the link below for further information).
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/02/WC500102322.pdf

To date, most of the studies conducted to investigate the possible causal association between paracetamol and asthma after exposure in pregnancy or early infancy were cross-sectional surveys which had limitations in their design.[11-18]

More recent studies[2-10] including birth cohort studies, have reported conflicting results. Evaluation of these studies has highlighted the difficulties surrounding the issue due to possible confounding by indication, as paracetamol is commonly used to treat symptoms of febrile illness/respiratory infections, which may be associated with an increased risk of asthma.

The most recent PhVWP review of these studies has therefore concluded that a causal association between paracetamol exposure in utero and in early infancy and asthma has not been established from the studies available to date.[2-10]

The PhVWP noted the lack of therapeutic alternatives to paracetamol for use during pregnancy and in children. Considering the uncertainties surrounding the current evidence, no regulatory action is considered necessary. Any newly emerging data will be carefully reviewed. As with other medicines, paracetamol should only be used during pregnancy or in children if clearly necessary.

Key message

- **The available evidence does not support a causal relationship between paracetamol and asthma in children after exposure in pregnancy or use in early infancy.**
- **As with other medicines, paracetamol should only be used during pregnancy or in children if clearly necessary.**

A list of references is available from the Irish Medicines Board on request.

In this edition

Provigil (modafinil) – EU wide restriction of use and updated recommendations to support safer use

Modafinil is a wakefulness-promoting agent that acts on the central nervous system, first authorised in Ireland in 1998. It was initially indicated for the symptomatic relief of excessive sleepiness associated with narcolepsy (with or without cataplexy), obstructive sleep apnoea/hypopnoea, moderate to severe chronic shift work disorder and idiopathic hypersomnia. A European review of the benefits and risks of modafinil was recently completed by the Committee for Human Medicinal Products (CHMP) of the EMA. The committee concluded that the use of modafinil should be restricted to treat only excessive sleepiness associated with narcolepsy, and that it should no longer be used for the treatment of excessive sleepiness associated with obstructive sleep apnoea, chronic shift work sleep disorder or idiopathic hypersomnia.

The review took account of the available information on the efficacy of modafinil in these indications and all safety concerns, including psychiatric and serious skin reactions and the potential for cardiovascular adverse effects. The benefit-risk balance of modafinil was considered to be positive only in patients with narcolepsy. Therefore, all other indications will be withdrawn from the marketing authorisations of modafinil containing medicines. Information about the restricted use of modafinil as a result of this review was communicated to healthcare professionals by the manufacturing authorisation holder in February 2011 (available on www.imb.ie).

Based on this evaluation of the currently available data the CHMP also made further recommendations to support safer use of modafinil:

Modafinil should not be used in the following groups:
- Patients with uncontrolled hypertension
- Children up to 18 years old
- Women who are pregnant or breastfeeding

All patients should be monitored before and during treatment:
- A baseline electrocardiogram should be done before treatment initiation. Patients with abnormal findings should be further evaluated by specialists before modafinil treatment can be initiated.
- Cardiovascular function—especially blood pressure and heart rate—should be monitored regularly. Modafinil should be discontinued in patients who develop arrhythmia or moderate to severe hypertension, and should not be restarted until the condition has been adequately evaluated and treated.

Modafinil should be discontinued and not restarted should cases of serious skin or hypersensitivity reactions or psychiatric disorders such as suicidal ideation occur. Caution is advised in patients with a history of psychosis, depression, or mania and also in those with a history of abuse of alcohol, drugs, or illicit substances. These patients should be monitored closely and advised to report any suspected adverse behaviours or thoughts. Patients should be assessed immediately and treatment stopped if appropriate. Further information on the risks and benefits of modafinil and details of dosing recommendations are available in the Summary of Product Characteristics (SmPC) on www.imb.ie.

Advice to Healthcare Professionals:
- Prescribers should be aware of the safety profile of modafinil-containing medicines and patients monitored appropriately.
- Modafinil should be withdrawn in patients who experience skin reactions or psychiatric symptoms.
- Patients should have their treatment reviewed at the next routine appointment.
- Suspected adverse reactions to modafinil should be reported to the IMB via the usual routes.

Key Message:
- **Modafinil is only indicated in adults with excessive sleepiness in patients with narcolepsy, with or without cataplexy.**
- **Modafinil should no longer be used to treat:**
  - **Obstructive sleep apnoea/hypopnoea syndrome**
  - **Moderate to severe chronic shift work sleep disorder**
  - **Excessive sleepiness associated with chronic pathological conditions**
- **Modafinil should be withdrawn in patients who experience skin reactions or psychiatric symptoms.**
- **Prescribers should be aware of the updated information on cautions for use; criteria for stopping treatment; and monitoring requirements during treatment.**

Tygacil (tigecycline) – recommendations for use

Tigecycline is a glycylcycline antibacterial structurally related to the tetracyclines which is authorised through a European assessment procedure since 2006 for the treatment of complicated skin and soft tissue infections and complicated intra-abdominal infections. It should only be used in situations where it is known or suspected that other drugs are not suitable.

Data from clinical studies has identified a numerically higher mortality rate among patients treated with tigecycline for both approved and unapproved indications, compared to those receiving comparator anti-infective drugs. The studies involved treatment of complicated skin and soft tissue infections, complicated intra-abdominal infections, diabetic foot infections, nosocomial pneumonia and resistant pathogens. In all studies (phase 3 and phase 4 complicated skin and soft tissue infections and complicated intra-abdominal infections), death occurred in 2.3 % (52/2216) of patients receiving tigecycline and 1.5% (33/2206) of patients receiving comparator drugs. The cause of these findings remains unknown, but poorer efficacy and safety than the study comparators cannot be ruled out.

Poorer outcomes have been identified in patients who develop super-infections, in particular nosocomial pneumonia, and therefore patients should be closely monitored for the development of super-infection. If medically indicated, these patients should be switched to alternative antibiotic treatment that has been demonstrated to be efficacious in the treatment of the specific type of infection(s) present.

Key Message:

- **An analysis of pooled results from clinical trial comparator drugs in a range of infections has shown numerically higher mortality in patients receiving tigecycline. Therefore, prescribers are advised to use tigecycline only when other antibiotics are unsuitable.**

Efient (prasugrel) – reports of hypersensitivity reactions

Prasugrel is a thienopyridine derivative, authorised centrally in the EU in 2009. When co-administered with aspirin, prasugrel is indicated in the prevention of atherothrombotic events in patients with acute coronary syndrome who are undergoing percutaneous coronary intervention.

Reports of serious hypersensitivity reactions in patients receiving prasugrel have been received and review of these indicated that prasugrel can induce the occurrence of hypersensitivity reactions including angioedema. In addition there seems to be a possibility for cross-reaction between clopidogrel (which belongs to the same class) and prasugrel.

In the majority of the reports prasugrel was used without previous administration of other thienopyridines. In two cases the patients were switched from prasugrel to clopidogrel, with no allergic reaction appearing after initiation of clopidogrel. In other reports the patient was switched from clopidogrel to prasugrel and the allergic reaction reappeared. The underlying pathophysiological mechanism for the hypersensitivity reactions is unknown. Cases reported had a variable time to onset, ranging from immediate over a few hours to 5-10 days. The product information for Efient has been updated with a warning in relation to possible hypersensitivity reactions and a Direct Healthcare Professional Communication was distributed by the manufacturing authorisation holder in April 2011 (available on **www.imb.ie**).

Advice to healthcare professionals:

- Prescribers should be aware of the potential risk of hypersensitivity reactions including angioedema in patients receiving prasugrel.
- Prescribers should be aware that hypersensitivity reactions have also been reported in patients with a previous known history of hypersensitivity reactions to thienopyridines.
- Patients should be advised to tell the physician immediately if they experience symptoms suggestive of hypersensitivity.

Key Message:

- **Hypersensitivity reactions including angioedema have been reported in patients receiving prasugrel including in patients with a history of hypersensitivity reaction to clopidogrel.**
- **Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.**

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Revlimid (lenalidomide) – risk of venous and arterial thromboembolic events

Revlimid (lenalidomide) is an immunomodulating agent structurally related to thalidomide which was first licensed via a European assessment procedure in 2007 subject to a number of risk minimisation measures to ensure safe use of the product. It is authorised for use in combination with dexamethasone for the treatment of multiple myeloma in patients who have received at least one prior therapy.

Multiple myeloma is an independent risk factor for thromboembolic complications. Evidence from clinical trials and case reports of adverse drug reactions suggests that lenalidomide may further increase the elevated risk of both venous and arterial thromboembolic reactions, including deep vein thrombosis, pulmonary embolism, myocardial infarction and cerebrovascular accident, in patients with myeloma. In reports of arterial and venous thromboembolic events received by the manufacturing authorisation holder, the use of thromboprophylaxis was not documented in most patients with a medically confirmed thromboembolic event, despite risk factors other than myeloma being identified.

Advice for healthcare professionals:

- Patients receiving lenalidomide should be closely monitored for evidence of arterial and venous thromboembolic events.
- Modifiable risk factors for thromboembolic events should be managed wherever possible (e.g. smoking, hypertension, and hyperlipidaemia).
- Prophylactic anti-thrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors (including prior thrombosis). The decision to take anti-thrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.
- Other agents that may increase the risk of thrombosis (e.g. oestrogen or erythropoietic agents) should be used with caution in multiple myeloma patients receiving lenalidomide.
- If a patient experiences any thromboembolic event, treatment with lenalidomide should be discontinued and anticoagulation therapy started. Once the patient has been stabilised on anticoagulation treatment and any complications of the thromboembolic event have been managed, lenalidomide may be restarted at the original dose, based on a benefit risk assessment. Anticoagulation should then be continued throughout the course of lenalidomide treatment.
- Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling.

Key Message:

- **In patients with multiple myeloma, the combination of lenalidomide and dexamethasone is associated with an increased risk of venous and arterial thromboembolism (predominantly deep vein thrombosis, pulmonary embolism, myocardial infarction and cerebrovascular accident).**
- **Risk factors for thromboembolic events should be considered and managed wherever possible. Appropriate thrombotic prophylaxis medication should be considered during lenalidomide treatment, particularly in patients with multiple thrombotic risks factors, after careful assessment of the balance of risks and benefits in individual patients.**
- **Direct Healthcare Professional Communication has been issued by the manufacturing authorisation holder. Further information on the risks and benefits of lenalidomide can be found in the SmPC available on www.imb.ie or in the European Public Assessment report (EPAR) for lenalidomide at the link: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000717/human_med_001034.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125**

Direct Healthcare Professional Communications published on the IMB website since the last drug Safety Newsletter:

Product	Safety Issue
Keppra (levetiracetam)	Calibration changes in dosing syringe and new presentations
Revlimid (lenalidomide)	Risk of venous and arterial thromboembolic events
Oruvail and Orugesic (ketoprofen)	Photosensitivity and supply information
Provigil (modafinil)	Restriction of indications
Lucentis (ranibizumab)	Blocked needles in some administration packs
Zerit (stavudine)	Restriction of indications
Efient (prasugrel)	Hypersensitivity reactions including angioedema
Tygacil (tigecycline)	For use only when other antibiotics unsuitable
Thyrogen (thyrotropin alfa)	Update on prescribing information