14 June 2013
EMA/350259/2013

PRAC recommends restricting the use of codeine when used for pain relief in children

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended a series of measures to address safety concerns with codeine-containing medicines when used for the management of pain in children. This follows the PRAC's review of reports of children who developed serious adverse effects or died after taking codeine for pain relief. Most of the cases occurred after surgical removal of the tonsils or adenoids for obstructive sleep apnoea (frequent interruption of breathing during sleep).

Codeine is an opioid that is authorised as painkiller in adults and children. It is converted into morphine in the patient's body. The children who had suffered severe side effects had evidence of being 'ultra-rapid metabolisers' of codeine. In these patients, codeine is converted into morphine in the body at a faster rate than normal, resulting in high levels of morphine in the blood that can cause toxic effects such as respiratory depression.

The PRAC recommended the following risk minimisation measures to ensure that only children for whom benefits are greater than the risks are given the medicine for pain relief:

- Codeine-containing medicines should only be used to treat acute (short lived) moderate pain in children above 12 years of age, and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen, because of the risk of respiratory depression associated with codeine use.
- Codeine should not be used at all in children (aged below 18 years) who undergo surgery for the removal of the tonsils or adenoids to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory problems.
- The prescribing information should carry a warning that children with conditions associated with breathing problems should not use codeine.

The PRAC further recommended that, as the risk of side effects with codeine may also apply to adults, codeine should not be used in people of any age who are known to be ultra-rapid metabolisers nor in breastfeeding mothers, because codeine can pass to the baby through breast milk. The prescribing information for codeine should also include general information for healthcare professionals, patients and carers on the risk of morphine side effects with codeine, and how to recognise their symptoms.

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Having assessed all the available data, the PRAC noted that the pharmacokinetic profile of codeine (how the body handles the medicine) has been studied in adults but very limited information is available in children, and the reported cases of respiratory depression with codeine indicate that children below 12 years of age may be at increased risk of morphine side effects. In addition, the limited data on the effectiveness of codeine as a pain relief in children suggest that the effect of codeine on pain is not significantly better than non-opioid painkillers such as paracetamol or ibuprofen.

The PRAC recommendation will now be considered by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) at its meeting on 24-26 June 2013. Patients who have any questions should speak to their doctor or pharmacist.

More about the medicine

Codeine is a widely used opioid medicine for pain relief. It is also used in the treatment of coughs, although this use in not covered by the current review. In the European Union (EU), codeine-containing medicines have been approved via national procedures, and are available either on prescription or over the counter in the different Member States. Codeine is marketed as a single-ingredient medicine or in combination with other substances such as aspirin or paracetamol.

The effect of codeine on pain is due to its conversion into morphine. Codeine is converted into morphine in the body by an enzyme called CYP2D6. It is well known that some patients who are 'CYP2D6 ultra-rapid metabolisers' convert codeine to morphine at a faster than normal rate. This results in high levels of morphine in the blood, which can lead to toxic effects such as breathing difficulties.

More about the procedure

The review was initiated on 3 October 2012, at the request of the United Kingdom medicines agency under Article 31 of Directive 2001/83/EC. After discussions, on 31 October 2012 the scope of the review was extended from post-surgery pain relief in children to pain relief in children.

During the review, the PRAC assessed all available data on the benefits and risks of codeine when used for pain relief, including pharmacokinetic data, clinical studies, post-marketing data in Europe and other published literature. The Agency also invited stakeholders, including healthcare professionals, patients' organisations and the general public, to submit data relevant to the procedure.

As the review only covers nationally authorised medicines, the PRAC recommendation will now be forwarded to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which will adopt a final position. The CMDh is a medicines regulatory body representing the EU Member States.

If the CMDh position is agreed by consensus, the agreement will be directly implemented by the Member States where the medicines are authorised. Should the CMDh position be adopted by majority vote, the CMDh position will be sent to the European Commission, for the adoption of an EU-wide legally binding decision.

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