Ministry of Health
Pharmacy and Poisons Board

SAFETY UPDATES AND RECOMMENDATIONS FOR HEALTH CARE PROFESSIONALS

The Pharmacy and Poisons Board (the Board) is mandated under the Pharmacy and Poisons Act (Cap 244) to disseminate information on medical products to health professionals and to the public in order to promote their rational use. The Board therefore wishes to remind the health professionals on the safety updates and prescribing information for the following products; Diclofenac, Ceftriaxone and Calcium interaction and use of Opioids with other central nervous system depressants.

1. Diclofenac

Diclofenac is a widely used medicine for relieving pain and inflammation, particularly in painful conditions such as arthritis. It belongs to a group of medicines called 'non-steroidal anti-inflammatory drugs' (NSAIDs). The safety of NSAIDs has been closely monitored by regulatory authorities in the European Union. Reviews of these medicines carried out in 2005, 2006 and 2012 have confirmed that NSAIDs as a class are associated with a small increased risk of arterial thromboembolic events (blood clots in the arteries) especially in patients with underlying heart or circulatory conditions or with certain cardiovascular risk factors, which in some cases has led to heart attack or stroke, particularly if used at high dose and for long periods.

A class warning of this risk is in place and the product information for all NSAIDs recommends that these medicines be used at the ***lowest effective dose*** for the ***shortest period*** of time necessary to control symptoms. As the risk is known to be somewhat higher with the subgroup of NSAIDs known as selective COX-2 inhibitors, increased measures to minimize risk are recommended in their product information.

- Clinical-trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150 mg daily) and in long-term treatment.
- Use of diclofenac is contraindicated in patients with established congestive heart failure (New York Heart Association class II-IV), ischemic heart disease, peripheral arterial disease or cerebrovascular disease.
- Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.
- As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.
- In the light of the above, all patients receiving regular diclofenac therapy should be reviewed at the next scheduled appointment.

2. Ceftriaxone and Calcium

a. Contraindications

Section 4.3 of the summary of product characteristics (SPC) states that Ceftriaxone is contraindicated if a patient requires (or are expected to require) intravenous calcium treatment, or calcium-containing infusions due to the risk of precipitation of a ceftriaxone-calcium salt.

b. Interaction with calcium containing products

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term neonates aged less than 1 month have been described. At least one of them had received ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than neonates, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. *In vitro* studies demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups.

In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing intravenous solutions, even via different infusion lines or at different infusion sites.

However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing total parenteral nutrition (TPN) solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation.

If the use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion and the infusion lines flushed between solutions

c. Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases, fatal adverse reactions have been reported in pre-term and full-term neonates (aged < 28 days) who had been treated with intravenous ceftriaxone and calcium. Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults.

Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g. ≥ 80 mg/kg/day or total doses exceeding 10 grams) and who have other risk factors (e.g. dehydration, confinement to bed). This event may be asymptomatic or symptomatic, and may lead to ureteric obstruction and postrenal acute renal failure, but is usually reversible upon discontinuation of ceftriaxone.

Precipitation of ceftriaxone calcium salt in the gallbladder has been observed, primarily in patients treated with doses higher than the recommended standard dose. In children, prospective studies have shown a variable incidence of precipitation with intravenous application - above 30 % in some studies.

d. Incompatibilities

Based on literature reports, section 6.2 of SPC states that ceftriaxone is not compatible with amsacrine, vancomycin, fluconazole and aminoglycosides.

Solutions containing ceftriaxone should not be mixed with or added to other agents except those mentioned above. In particular diluents containing

calcium, (e.g. Ringer's solution, Hartmann's solution) should not be used to reconstitute ceftriaxone vials or bottles or to further dilute a reconstituted vial or bottle for intravenous administration because a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions including total parenteral nutrition.

If treatment with a combination of another antibiotic with ceftriaxone is intended, administration should not occur in the same syringe or in the same infusion solution.

3. Opioids with other CNS depressants

Morphine should be used with caution in patients who are concurrently receiving other central nervous system depressants including sedatives gabapentin and alcohol. The interaction results in respiratory depression, hypotension, profound sedation or coma.

This may occur even when morphine is administered at its therapeutic dose. (Morphine Summary of Product Characteristics).

The Board would like to thank the health care providers for the continued efforts to ensure safety of the patients and encourage them to provide feedback by contacting PPB through 0795 743 040 or sending an email to pv@pharmacyboardkenya.org or report any suspected adverse events or quality defects on medical products and health technologies at http://pv.pharmacyboardkenya.org.

CHIEF EXECUTIVE OFFICER
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