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Very Rare Flucloxacillin-Paracetamol Interaction
risk of Metabolic Acidosis

Quick Read

Especially in patients with serious renal impairment, malnutrition or sepsis, concomitant use of flucloxacillin and maximum doses of paracetamol may very rarely be associated with high anion gap metabolic acidosis (HAGMA).

Flucloxacillin is a semi-synthetic isoxazolilpenicillin. This antibiotic has been used in Portugal since the 1970s to treat infections mainly caused by Streptococci and Staphylococci. Through various pathways, both flucloxacillin and paracetamol can cumulatively lead to an increase in 5-oxoproline (also known as pyroglutamic acid, pidolic acid or pyroglutamate).

Following an assessment of literature,[1-7] EudraVigilance (European ADR report database) and MA holder data, the European Medicines Agency (EMA) has confirmed an association between a rare type of metabolic acidosis and concomitant use of flucloxacillin and paracetamol: **high anion gap metabolic acidosis (HAGMA)**, which results from accumulation of pyroglutamic acid (5-oxoproline). Flucloxacillin inhibits 5-oxoprolinase activity resulting in the accumulation of 5-oxoproline. Paracetamol on the other hand, when used **chronically** or in **high** doses, can cause glutathione depletion, which in turn activates γ-glutamylcisteine synthetase, producing more γ-glutamylcisteine and consequently more circulating 5-oxoproline. Clearance of the latter is descreased in renal failure, which aggravates the condition. Other risk factors may also interfere with this metabolic cycle.[1]

Though very rare, this condition is serious and potentially fatal. It is all the more relevant because paracetamol is available for self-medication as over-the-counter products.

In order to inform healthcare professionals about this risk, EMA has deemed necessary that a warning be included in the SmPC to underscore those **groups of patients who are at increased risk** of developing the condition (the PIL will be updated accordingly):

4.4. Special warnings and precautions for use

Caution is advised when flucloxacillin is administered concomitantly with paracetamol due to the increased risk of high anion gap metabolic acidosis (HAGMA). Patients at high risk for HAGMA are in particular those with severe renal impairment, sepsis or malnutrition especially if the maximum daily doses of paracetamol are used. After co-administration of flucloxacillin and paracetamol, a close monitoring is recommended in order to detect the appearance of acid–base disorders, namely HAGMA, including the search of urinary 5-oxoproline. If flucloxacillin is continued after cessation of paracetamol, it is advisable to ensure that there are no signals of HAGMA, as there is a possibility of flucloxacillin maintaining the clinical picture of HAGMA (see section 4.5).

4.5. Interaction with other medicinal products and other forms of interaction

Caution should be taken when flucloxacillin is used concomitantly with paracetamol as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors. (see section 4.4.).

4.8. Undesirable effects

[…] Post marketing experience: very rare cases of high anion gap metabolic acidosis, when flucloxacillin is used concomitantly with paracetamol, generally in the presence of risk factors (see section 4.4.)

Ana Sofia Martins

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Risk of Acute Generalized Exanthematous Pustulosis (AGEP) with Acetazolamide and with Macrolides

Quick Read

Acute generalized exanthematous pustulosis is a rare skin adverse reaction that has been associated to various drugs. The anti-glaucoma agent acetazolamide, as well as the macrolide antibiotics are now being added to the list of medicines which can cause this undesirable effect.

Acute generalized exanthematous pustulosis is characterized by non-follicular aseptic pustules covering disseminated skin oedema and erythema. Scaling occurs as the reaction resolves. It usually appears on the face, neck, armpits, groins and other skin folds, and rapidly spreads in a few days to other body areas. The skin manifestations are accompanied by fever higher than 38 degrees Celsius and neutrophilia.

Acetazolamide is a carbonic anhydrase inhibitor with weak diuretic activity. It decreases the production of aqueous humour in the eyes thereby decreasing intraocular pressure. Medicinal products containing acetazolamide are indicated as adjuvants in the treatment of open-angle glaucoma, secondary glaucoma, and closed-angle glaucoma to achieve pre-operative lowering of intraocular pressure.

The macrolides make up a group of broad-spectrum antibiotics with a macrocytic lactonic ring in their molecular structure, and which inhibit the synthesis of bacterial proteins.

During routine pharmacovigilance activities, the Swedish and the Irish medicines agencies detected a safety signal associated respectively with the use of acetazolamide and macrolides (azithromycin, clarithromycin, erythromycin, roxithromycin) and the seemingly rare occurrence of acute generalized exanthematous pustulosis (AGEP).

Following assessment by the European Medicines Agency (EMA) of EudraVigilance (European ADR report database) cases, literature data concerning both acetazomide,[1-3] and macrolides,[4-10] as well as complementary data provided by MA holders, changes to SmPCs (and their PILs) will result.

SmPC section 4.8 of all the above products will list AGEP as an undesirable effect**.**

Section 4.4. on Special warnings and precautions for use will include the following text in the case of ACETAZOLAMIDE:

> The occurrence at treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP) (see section 4.8). In case of AGEP diagnosis, acetazolamide should be discontinued and any subsequent administration of acetazolamide contraindicated.

In the case of **MACROLIDE ANTIBIOTICS, Section 4.4. on Special warnings and precautions for use** will read slightly different for each individual substance. The text for azithromycin is representative:

> […]
>
> As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions have resulted in recurrent symptoms and required a longer period of observation and treatment. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

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Márcia Silva

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