

## 1.1. High anion gap metabolic acidosis (HAGMA) following an adverse drug interaction between paracetamol and flucloxacillin

### Introduction

Paracetamol is a widely used analgesic which is available in a variety of products, including over the counter products. It is indicated for the relieve of *fever and pain associated with colds and flu, fever and pain after vaccination, headache, rheumatic pain, menstrual cramps and toothache*. Paracetamol is on the market since 1893 [1].

Flucloxacillin is a narrow spectrum isoxazolylpenicilline of the  $\beta$ -lactam group of antibiotics.

It has a bactericidal effect on many Gram-positive organisms and is primarily indicated for treatment of *infections caused by penicillinase forming staphylococcus, as in upper respiratory infections such as pharyngitis, tonsillitis, sinusitis, lower respiratory tract infections such as pneumonia, bronchopneumonia, pulmonary abscess and infections of the skin and soft tissue, such as impetigo, and abscesses*. Flucloxacillin has been granted marketing authorization in the Netherlands since January 1971 [2,3].

Metabolic acidosis is characterized by a low blood pH and low blood carbonate [ $\text{HCO}_3^-$ ]. There are two possible causes for this low blood pH: accumulation of acids or loss of bicarbonate. To be able to find the cause of the metabolic acidosis one can calculate the anion gap. A distinction is made between an acidosis with a high anion gap or an acidosis with a normal anion gap. The anion gap is the difference between the concentration of the cation [ $\text{Na}^+$ ] and the anions [ $\text{Cl}^-$ ] and [ $\text{HCO}_3^-$ ] which is constant and represents the concentration in the blood of the not measured anions ( $\text{HPO}_4^{2-}$ , lactate and so on) and the not measured cations ( $\text{K}^+$ ,  $\text{Ca}^{2+}$  and so on). A high anion gap indicates an overproduction or decreased excretion of acid residues. The concomitant use of paracetamol and flucloxacillin is associated with high anion gap metabolic acidosis (HAGMA) and is characterized by an elevation of 5-oxoproline levels in serum and urine often found after excluding other factors, such as lactic acidosis, ketoacidosis, renal failure or exposure to salicylates or toxic alcohols [4].

Although there are several case-reports in the literature [5-10] this interaction is not included in the summary of product characteristics of flucloxacillin and paracetamol [2,11-15] and is not monitored in pharmacy drug interaction monitoring systems.

### Reports

On March 31<sup>st</sup> 2015, the database of the Netherlands Pharmacovigilance Centre Lareb contained 10 reports of metabolic acidosis associated with the concomitant use of paracetamol and flucloxacillin. Six reports concern literature reports sent by marketing authorization holders [5-10]. These reports are summarized in Table 1. Four reports (A-D) are sent by health care professionals (in training). These reports are described in more detail below. The first report from a health care professional was received in February 2011.

#### Case A (117863)

This report from a physician with own pharmacy describes a female of 71 years and older, with metabolic acidosis (according to the reporter most probably due to an excess of 5-oxoproline, pyroglutamic acidemia) due to a possible drug interaction following administration of flucloxacillin 1000mg for empyema (with unknown dose) and paracetamol 3 dd 1000mg for pain with a latency of 4 weeks after start of the paracetamol and 3 weeks after start of the flucloxacillin. The drugs flucloxacillin and paracetamol were withdrawn. The patient was treated with sodium bicarbonate and potassium; she recovered. Concomitant medications were naproxen 2 dd 250mg, metformin 2 dd 850mg, omeprazole (unknown dose), risedronic acid 35mg per week, amlodipine 1 dd 5mg, and perindopril 1 dd 4mg.

#### Case B (122515)

This report from a physician describes a female aged 71 years and older, with metabolic acidosis (excess of 5-oxoproline, pyroglutamic acidemia) due to drug interaction following administration of flucloxacillin and paracetamol with a latency of 34 days after start of the paracetamol. The drug paracetamol was withdrawn. The action taken for flucloxacillin is unknown. The patient was treated with acetylcysteine. The patient had a sepsis; she eventually died. Concomitant medication was not

reported, the patient had no known medical history and had no known past drug therapy. 5-Oxoproline is confirmed in the urine.

Case C (183271)

This report from a medical specialist describes a female aged 61-70 years, with high anion gap metabolic acidosis (HAGMA) caused by endogenous acid production following administration of paracetamol 4 dd 1000mg for pain and flucloxacillin for staphylococcal infection. The HAGMA was diagnosed 5 weeks after start of paracetamol, 4 weeks after start of the flucloxacillin and 3 weeks after start of the dosage increase of flucloxacillin from 6 dd 1000mg intravenously to 6 dd 2000mg intravenously. The drugs paracetamol and flucloxacillin were withdrawn. The patient was not responsive and had a Kussmaul breathing; she was treated with bicarbonate and recovered after 2 days. Concomitant medications were oxycodone 2 dd 10mg slow release and 4 dd 5mg, simvastatin 1 dd 40mg, metoclopramide 3 dd 10mg, ibuprofen 2 dd 600mg, dalteparin 1 dd 25,000IE, olanzapine 1 dd 5mg, and macrogol 2 dd powder for drink. Presence of 5-oxoproline in the urine was confirmed.

Case D (194620)

This report from a medical specialist describes a female aged 71 years and older years with metabolic acidosis following a drug interaction after administration of flucloxacillin 6 dd 2000mg for arthritis and paracetamol 4 dd 1000mg for pain with a latency of 13 days after start. Flucloxacillin and paracetamol started on the same day, both drugs were withdrawn. The patient was hospitalized with hyperventilation, was admitted for 14 days and treated with bicarbonate. She recovered. Concomitant medication was pantoprazole. The patient had renal function disorders and was mal-nourished.

Table 1: An overview of literature reports sent to the Netherlands Pharmacovigilance Centre Lareb of metabolic acidosis following concomitant use of paracetamol and flucloxacillin.

Literature reports	Gender	Age (years)	Time to onset	Co-medication	Risk factors	5-oxoproline confirmed in urine or blood
1 [5]	F	79	3 weeks after start of flucloxacillin (12g per day) during therapy with paracetamol (3g per day) for 2 months	Gentamycin	Female, older age, renal function disorder	Yes
2 [6]	F	72	3 weeks after start of flucloxacillin therapy during therapy with paracetamol (doses unknown, unknown duration)	Not reported	Female, older age	Yes
3 [7]	F	87	20 days after start of flucloxacillin (cumulative dose of 168g) and during therapy with paracetamol (cumulative dose 56g)	Not reported	Female, older age	Yes
4 [8]	F	65	2 months after starting paracetamol during therapy with flucloxacillin (unknown duration)	Not reported	Female	Yes
5 [9]	F	72	Flucloxacillin 12g per day, paracetamol 4g per day, unknown duration	Morphine	Female, older age	Yes
6 [10]	F	52	9 days after start of flucloxacillin (12 g per	Not reported	Female, no other	No

day) during therapy with paracetamol (unknown dose, unknown duration)	risk factors
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## Other sources of information

### SmPC

High anion gap metabolic acidosis is not mentioned as the possible result of an adverse drug interaction between paracetamol and flucloxacillin in the Dutch SmPCs of these drugs [13,14]. It is mentioned as a possible overdoses reaction in some of the Dutch SmPCs of paracetamol [12,15]. In the Dutch SmPCs of flucloxacillin injections and capsules it is not mentioned [2,3].

### Literature

Several case-reports and review articles of HAGMA following concomitant use of paracetamol and flucloxacillin are published.

Peter *et. al.* describe a 50-year-old man that was transferred to the intensive care unit with HAGMA. Investigations suggested a diagnosis of pyroglutamic (5-oxoproline) academia. Factors contributing to the acidosis were drugs (paracetamol and flucloxacillin), sepsis and renal failure. The acidosis resolved with supportive therapy and withdrawal of the drugs [16].

Bergh *et.al.* describe a 52-year-old female patient with bacterial arthritis receiving high dose flucloxacillin (12 gram per day). Paracetamol was used as an analgesic. After 10 days she developed a metabolic acidosis with respiratory compensation. Laboratory investigation revealed a high anion gap of 20 mmol/l [10].

Liss *et. al.* reviewed the published cases of HAGMA in settings of paracetamol exposures; in several of the cases flucloxacillin was concomitantly used [17].

There are a few case-reports of patients using either paracetamol or flucloxacillin which resulted in HAGMA [4,18].

Several publications mention female sex, malnutrition, and infectious disease as possible risk factors for HAGMA [18,19]. Women are more likely to acquire 5-oxoproline acidosis, possibly due to gender differences in the enzyme activities of the  $\gamma$ -glutamyl cycle [20]. Other conditions that seem to predispose for this disorder are pregnancy, vegetarian diet, sepsis, chronic renal insufficiency, and/or hepatic dysfunction, especially liver disease that results from chronic alcohol use [19,21].

### Databases

The Lareb cases include the 4 reported cases (A, B, C, D), 1 case report of paracetamol and metabolic acidosis without flucloxacillin, 6 literature reports of the adverse drug interaction between paracetamol and flucloxacillin and two literature reports of HAGMA associated with paracetamol in the absence of flucloxacillin [4-10,22].

The WHO received 22 reports of metabolic acidosis in which both paracetamol and flucloxacillin were reported as suspected, interacting or concomitant. The WHO received 16 reports of metabolic acidosis in which both paracetamol and flucloxacillin were reported as suspected or interacting.

To calculate the disproportionality for adverse drug interactions in Vigibase™, a disproportionality measure, omega ( $\Omega$ ), is used. It describes the relative reporting rate of two drugs and one adverse reaction (drug-drug-adverse drug reaction, DDA) in relation to the background reporting. If the  $\Omega$  is greater than zero the DDA is reported more often than expected [23,24].

For the reports where paracetamol and flucloxacillin are reported as suspected, interacting or concomitant drugs the omega is 2.59. For the reports where paracetamol and flucloxacillin are reported as suspected or interacting drugs the omega is 3.95.

Prescription data

A large part of paracetamol is dispensed as an over the counter medicine and not included in the database of health insurances. Therefore data on paracetamol prescriptions is not included.

Table 2. Number of patients using flucloxacillin in the Netherlands between 2009 and 2013 [25]. Over the counter dispenses are not included.

	2009	2010	2011	2012	2013
Flucloxacillin	255,180	262,170	267,120	270,270	280,180

Mechanism

5-Oxoproline is a product of disordered glutathione metabolism in the  $\gamma$ -glutamyl cycle: glutathione deficiency removes the feedback inhibition resulting in the formation of  $\gamma$ -glutamylcysteine and elevated concentrations of  $\gamma$ -glutamylcysteine leading to the formation of 5-oxoproline, which is degraded by 5-oxoprolinase. Both paracetamol and flucloxacillin interact with the  $\gamma$ -glutamyl cycle. Paracetamol is metabolized by CYP enzymes to N-acetyl-parabenzoquinone imine (NAPQI) which depletes glutathione and flucloxacillin inhibits 5-oxoprolinase and so serves as an additional factor for 5-oxoproline accumulation, see Figure 1. The accumulation of 5-oxoproline, an acid residue, may lead to HAGMA [17,26]. Although this effect on the  $\gamma$ -glutamyl cycle may not be limited to paracetamol and flucloxacillin, we did not receive any reports or find any publications of other drugs that lead to an increase of 5-oxoproline and subsequently HAGMA.

Flucloxacillin

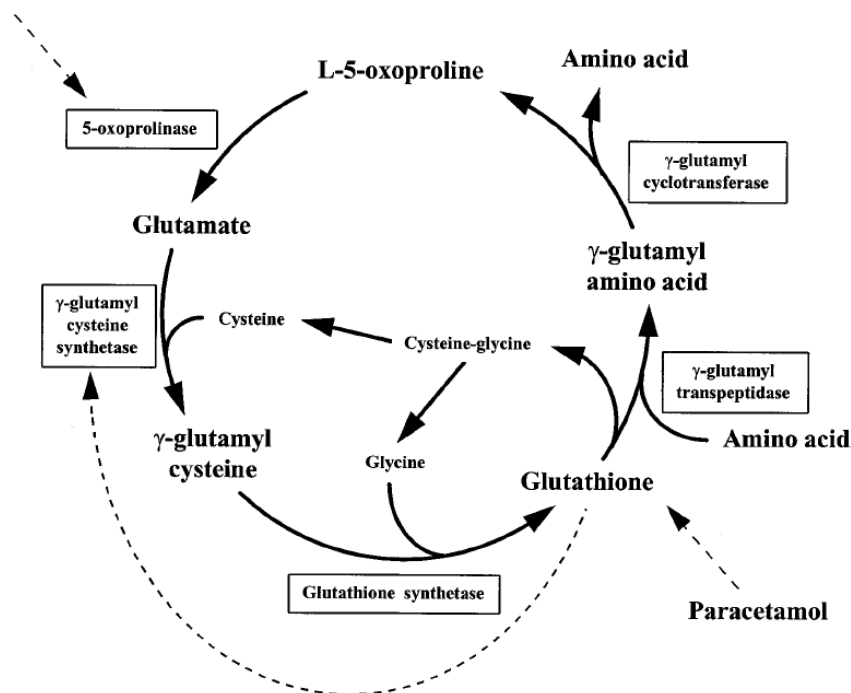


Figure 1. The  $\gamma$ -glutamyl cycle, illustrating proposed mechanism of 5-oxoproline excretion as a result of concomitant use of flucloxacillin and paracetamol.

## Discussion and conclusion

Lareb received 10 reports of metabolic acidosis associated with the concomitant use of paracetamol and flucloxacillin. Six reports concern literature reports sent by marketing authorization holders, four reports are sent by healthcare workers (including students). In all patients the HAGMA was diagnosed after several weeks of concomitant use of the drugs. All reports concern (older) females and all had an infection (patient B had a sepsis); the infection may have contributed to the development of the HAGMA. In most reports (7/10) the role of 5-oxoproline as the culprit acid residue that causes the HAGMA was confirmed by urine tests. In the WHO-database the adverse drug interaction is reported more often than expected. All this points to an adverse drug interaction between paracetamol and flucloxacillin which should be mentioned in the SmPCs of both drugs.

- High anion gap metabolic acidosis should be mentioned in the SmPCs of both paracetamol and flucloxacillin in section 4.4 or/and 4.5

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*This signal has been raised on July 2015. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB [www.cbq-meb.nl](http://www.cbq-meb.nl)*