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

Introduction

In September 2015 Lareb informed the Medicines Evaluation Board (MEB) about a signal concerning high anion gap metabolic acidosis (HAGMA) associated with the use of paracetamol in interaction with flucloxacillin (1). This Signal described 10 reports of metabolic acidosis associated with the concomitant use of paracetamol and flucloxacillin. In April 2016 metabolic acidosis following administration of flucloxacillin in association with paracetamol was discussed in the PRAC, after evaluation of the reports in the EudraVigilance database and the literature concerning this topic. Because of the small number of cases and confounding factors, a causal relationship between flucloxacillin or other penicillins and metabolic acidosis was not considered sufficiently robust to warrant further action at this stage. Therefore it was concluded that the MAHs of flucloxacillin- and other penicillin-containing products should continue to monitor metabolic acidosis as part of routine safety surveillance (2).
At request of the MEB, this current signal provides an update of the reports received by Lareb of metabolic acidosis after administration of flucloxacillin and paracetamol.

Reports

From 18 May 2008 up till 28 September 2016 the Netherlands Pharmacovigilance Centre Lareb received 13 reports concerning metabolic acidosis associated with the concomitant use of paracetamol and flucloxacillin. Ten reports were previously described in the Signal from 2015 (1). From 31 March 2015 up to 28 September 2016, the Netherlands Pharmacovigilance Centre Lareb received 3 additional reports concerning metabolic acidosis associated with the concomitant use of paracetamol and flucloxacillin.

A summary of all the 13 received cases from 18 May 2008 up till 28 September 2016 is described here:
Lareb received 13 reports of metabolic acidosis associated with the concomitant use of paracetamol and flucloxacillin. Six reports concerned literature reports sent by marketing authorization holders, one a solicited report sent by the marketing authorization holder and six reports were sent by healthcare workers (including students). All reports concerned females. The ages varied between 38 and 87 years, mean 70,1 years, median 72 years. In all patients the HAGMA was diagnosed after several weeks of concomitant use of the drugs, in two reports the latencies were not reported. All patients had an infection. One patient (B) had a sepsis which may have been a predisposing risk factor in causing the HAGMA. In most reports (8/13) the role of 5-oxyproline as the culprit acid residue that causes the HAGMA was confirmed by urine tests.

Table 1: An overview of the 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**
A (3)	F	71 years and older	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
B (4)	F	71 years and older	3 weeks after start of flucloxacillin therapy during therapy with paracetamol	Not reported	Female, older age	Yes

			(doses unknown, unknown duration)			
C (5)	F	71 years and older	20 days after start of flucloxacillin (cumulative dose of 168g) and during therapy with paracetamol (cumulative dose 56g)	Not reported	Female, older age	Yes
D (6)	F	61-70	2 months after starting paracetamol during therapy with flucloxacillin (unknown duration)	Not reported	Female	Yes
E (7)	F	71 years and older	Flucloxacillin 12g per day, paracetamol 4g per day, unknown duration	Morphine	Female, older age	Yes
F (8)	F	51-60	9 days after start of flucloxacillin (12 g per day) during therapy with paracetamol	Not reported	Female, no other risk factors	No
G (Lareb report 117863)	F	71 years and older	(unknown dose, unknown duration) 3 weeks after starting flucloxacillin during therapy with paracetamol (duration 4 weeks)	Naproxen Metfomin Omeprazol Risedronic acid Amlodipine Perindopril	Female, older age	No
H (Lareb report 122515)	F	71 years and older	34 days after start of the paracetamol during therapy with flucloxacillin (unknown duration)	Not reported	Female, older age	Yes
I (Lareb report 183271)	F	61-70	5 weeks after start of paracetamol, 4 weeks after start of flucloxacillin and 3 weeks after start of the dosage increase of	Oxycodone Simvastatin Metoclopramide Ibuprofen Dalteparin Olanzapine Macrogol	Female, older age	Yes

			flucloxacillin from 6 dd 1000mg intravenously to 6 dd 2000mg intravenously			
J (Lareb report 194620)	F	71 years and older	13 days after simultaneous start of paracetamol and flucloxacillin 6 dd 2000mg	Pantoprazol	Female, older age, renal function disorder, malnourishment	No
K (Lareb report 201177)	F	71 years and older	Not reported	Not reported	Female, older age, renal function disorder	No
L (Lareb report 202396)	F	31-40 years	Not reported	Carbamazepine Calcium carbonate Carbasalate calcium Ginkgo biloba extract Sildenafil Nifedipine Tramadol Meloxicam Methotrexate Folic acid Prednisone	Female, pre-existing low weight, malnutrition, bosertan other suspect drug	No
M (Lareb report 205635)	F	71 years and older	5 weeks after simultaneous start of paracetamol and flucloxacillin 6 dd 2000mg	Insulin aspart Insulin glargine Esomeprazole Loperamide Metoclopramide Nadroparin Rifampicin Potassium chloride Heparin Vancomycin Omeprazole	Female, older age, moderate renal function	Yes

The cases received after the previous Signal (cases K, L and M) are described in more detail here:

Case K (201177) (received 13-7-2015)
This spontaneous report from a specialist doctor concerns a female aged 71 years and older, with tachypnoea probably based on metabolic acidosis and drug interaction (due to combination of renal function disorder, paracetamol and flucloxacillin) and renal function disorder (differential diagnostically based on dehydration and tubulointerstitial nephritis due to flucloxacillin) following administration of flucloxacillin for prothesis related infection and paracetamol for pain with unknown latency. An oxiprolin value was not reported. The drugs paracetamol and flucloxacillin were withdrawn. The patient is recovering. At the moment of reporting the patient also experienced coughing and had high urea and investigations were still running. Concomitant medication was not reported.
Three days before start of the reaction, the patient had removal of an infected hip prothesis with post-surgery non ST-segment elevation myocardial infarction. The patient has no known past drug therapy.

Case L (202396) (received 21-07-2015 through the MAH)
This serious (Hospitalisation, Death) solicited study report from the Tracleer (bosentan) post-marketing surveillance program (DUO Registry) from an unknown reporter concerns a female aged 31-40 years with scleroderma associated digital ulcer who died of metabolic acidosis following administration of bosentan, flucloxacillin and paracetamol with an unknown latency. Other reported reactions were digital ulcer, disease progression, pneumonia, general physical health deterioration, drug intoxication, respiratory insufficiency, necrosis and toe amputation. During hospitalization because of multiple digital ulcers, the patient developed Kussmaul breathing and was diagnosed with metabolic acidosis (5-oxoprolin intoxication with paracetamol and flucloxacillin), in the settings of pre-existing low weight and malnutrition. Paracetamol and flucloxacillin were withdrawn. Bicarbonate infusion was started. The patient subsequently developed respiratory insufficiency and became hemodynamic unstable. The patient died of metabolic acidosis. Concomitant medication included carbamazepine, calcium carbonate, carbasalate calcium, ginkgo biloba extract, sildenafil, nifedipine, tramadol, meloxicam, methotrexate, folic acid, and prednisone.
The patient had a medical history of gastrointestinal disorder, ANA present, Raynaud's phenomenon, pneumonia, low weight and malnutrition.

Case M (205635) (received 9-10-2015)
This serious (Lifethreatening) spontaneous report from a hospital pharmacist concerns a female aged 61-70 years, with metabolic acidosis and drug interaction following administration of paracetamol for pain and flucloxacillin for infection with a latency of 5 weeks after start. The 5-oxoproline value was strongly elevated. Laboratory values were: pyroglutamic acid (oxiproline) was 52842 micromol/l, creatinine 21137 mmol/mmol. The drug paracetamol was withdrawn. The drug flucloxacillin was withdrawn and switch to another unspecified antibiotic drug. The patient blood gases were corrected with infusion of electrolytes. The reporter mentioned that another circumstance that might have caused or aggravated the reaction was a moderate renal function. The patient recovered two weeks later. Concomitant medications were insulin aspart, insulin glargine, esomeprazole, loperamide, metoclopramide, nadroparin, rifampicin, potassium chloride, heparin, vancomycin, omeprazole.
The medical history indicates that the patient had multiple myeloma and paraparesis due to a complicated spinal fusion.

Other sources of information

SmPC

Metabolic acidosis or HAGMA is not mentioned as the possible result of an adverse drug interaction between paracetamol and flucloxacillin in the Dutch SmPCs of these drugs (9;10).

Literature

As reported in the previous Signal (1), 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 (11).
Liss *et al.* reviewed the published cases of HAGMA in settings of paracetamol exposures; in several of the cases flucloxacillin was concomitantly used. Liss *et al.* recommended to exclude more common causes for HAGMA as well and advised to measure glutathione synthetase activity, because of the hypothesis of possible previously unrecognized inborn genetic errors in glutathione metabolism might play as role in the occurrence of HAGMA (12).

In addition to the literature described in the previous Signal, a case was published concerning a 55-year old woman who developed symptomatic overproduction of 5-oxoproline during flucloxacillin treatment for severe sepsis while receiving paracetamol to control fever (13), and a case concerning a 82-year old woman with septic shock caused by methicillin-sensitive Staphylococcus aureus-induced arthritis, who developed HAGMA with elevated urinary pyroglutamate after administration of flucloxacillin, rifampicin and acetaminophen (14).

Discussion and conclusion

This Update Signal describes 15 cases of metabolic acidosis associated with the concomitant use of paracetamol and flucloxacillin: in addition to the 10 cases described in the previous Signal (1), Lareb received 3 reports and 2 additional cases were described in the literature.

Although in all the cases possible additional risk factors for acidosis were described, a causal relationship HAGMA and the concomitant use of paracetamol and flucloxacillin, is strongly suspected.

Reference List

(1) Lareb Signal "High anion gap metabolic acidosis (HAGMA) following an adverse drug interaction between paracetamol and flucloxacillin". http://www lareb nl/Signalen/KWB_2015_3_fluclox_par aspx 2015 September 22 [cited 2016 Sep 28];
(2) Minutes of the PRAC meeting on 11-14 April 2016. http://www ema europa eu/docs/en_GB/document_library/Minutes/2016/06/WC500207977 pdf 2016 May 10 [cited 2016 Sep 28];
(3) Kortmann W, van Agtmael MA, van Diessen J, Kanen BJ, Jacobs C, Nanayakkara PW. 5-Oxoproline as a cause of high anion gap metabolic acidosis: an uncommon cause with common risk factors. Neth J Med 2008 Sep;66(8):354-7.
(4) Veldhuijzen N, Kamphuis S, van den Bergh F, Spronk P, Braber A. Madam, why are you so sour? Cause, diagnosis and complication of 5-oxoprolinemia. Eur J Anaesthesiol 2012 Aug;29(8):398-400.
(5) de Vette LC, Bax NM, te Velde LF. Severe high anion gap acidosis due to therapeutic drugs. NVIC Nederlandse Intensivistendagen 2012 Case reports. http://resources interactie org/2012/nvic/intensivistendagen/programma pd 2012 February [cited 2016 Oct 26];Available from: URL: http://resources.interactie.org/2012/nvic/intensivistendagen/programma.pdf
(6) Brusee P, Simons K, Moviat M. Fatal increased anion gap acidosis after long term treatment with acetaminophen. Nederlandse Internistendagen 2013 Abstracts 2013.
(7) Rolleman EJ, Hoorn EJ, Didden P, Zietse R. Guilty as charged: unmeasured urinary anions in a case of pyroglutamic acidosis. Neth J Med 2008;66(8):251-3.
(8) Bergh FAJTM, Klooster R, ten Bos R, Straathof-Galema L. 5-oxoprolinurie: een verworven stofwisselingsstoornis door behandeling met flucloxacilline en paracetamol. Ned Tijdschr Kolin Chem Labgeneeskunde 2008;33(1):39-42.
(9) Dutch SmPC Floxapen ® poeder voor oplossing voor injectie 250 mg, 500 mg en 1 g. http://db cbg-meb nl/IB-teksten/h05990 pdf 2015 July 30 [cited 2016 Sep 28];
(10) Dutch SmPC Sanalgin® tabletten. http://db cbg-meb nl/IB-teksten/h01400 pdf 2014 April 23 [cited 2016 Sep 28];
(11) Peter JV, Rogers N, Murty S, Gerace R, Mackay R, Peake SL. An unusual cause of severe metabolic acidosis. Med J Aust 2006;185(4):223-5.
(12) Liss DB, Paden MS, Schwarz ES, Mullins ME. Liss DB, Paden MS, Schwarz ES, Mullins ME. What is the clinical significance of 5-oxoproline (pyroglutamic acid) in high anion gap metabolic acidosis following paracetamol (acetaminophen) exposure? Clin Toxicol.(Phila) 2013;51(9):817-27. Clin Toxicol (Phila) 2013;51(9):817-27.
(13) Luyasu S, Wamelink MM, Galanti L, Dive A. Pyroglutamic acid-induced metabolic acidosis: a case report. Acta Clin Belg 2014 Jun;69(3):221-3.
(14) Lanoy C, Bouckaert Y. Metabolic acidosis and 5-oxoprolinuria induced by flucloxacillin and acetaminophen: a case report. J Med Case Rep 2016 Jun 23;10(1):184.

This signal has been raised on January 2017. 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.cbg-meb.nl