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ACKNOWLEDGMENTS

Conflict of Interest: No author listed on this manuscript has declared any conflict of interest.

Author Contributions: Bose-Brill, Pressler-Vyrda, Taylor: study concept and design. Belanger, Kobe, Ballenger, Kretovics: participant recruitment, data collection and preparation. Bose-Brill, Belanger, Kobe, Pressler-Vyrda: data analysis. Bose-Brill, Belanger, Kretovics, Ballenger, Pressler-Vyrda, Taylor: data interpretation. Bose-Brill, Belanger, Kretovics, Pressler-Vyrda: manuscript preparation.

Sponsor's Role: There was no sponsor for this study.

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ADVANCED AGE AND FEMALE SEX AS RISK FACTORS FOR HIGH ANION GAP METABOLIC ACIDOSIS AFTER A DRUG INTERACTION BETWEEN PARACETAMOL AND FLUCLOXACILLIN: A CASE SERIES

To the Editor: High anion gap metabolic acidosis (HAGMA) is a rare but possible outcome of an adverse drug interaction (ADI) between paracetamol and flucloxacillin.[1] Although many risk factors are mentioned in literature, it is not clear in which population HAGMA occurs and who is at high risk and should be closely monitored. Paracetamol is a widely used analgesic and antipyretic drug that is available in a variety of products, including over-the-counter products. Flucloxacillin is a narrow-spectrum isoxazolyl penicillin of the β-lactam group of antibiotics and has a bactericidal effect on many Gram-positive organisms. It is primarily indicated for the treatment of infections caused by penicillinase-forming *Staphylococcus*. The concomitant use of paracetamol and flucloxacillin has been associated with HAGMA, which is characterized by high serum and urine 5-oxoproline levels.[2]

The aim of this study was to retrospectively and systematically review all cases of HAGMA after the use of paracetamol and flucloxacillin reported to the Netherlands Pharmacovigilance Centre Lareb (NPCL) to determine who is at high risk for this ADI.

METHODS

The NPCL maintains the spontaneous adverse drug reaction (ADR) database of the Netherlands. ADRs are coded according to the Medical Dictionary for Regulatory Activities,[3] and drugs are classified according to the World Health Organization Anatomical Therapeutic Chemical classification system. All reports of HAGMA after the use of paracetamol and flucloxacillin in the NPCL database up to December 31, 2015, were included in this study and systematically assessed.

RESULTS

The NPCL received 12 reports of cases of metabolic acidosis in individuals concomitantly using paracetamol and flucloxacillin. All were women and had an average age of 73.8 (range 52–85); 11 were aged 65 and older. The average reported time between the beginning of the latest started drug or increase of dose of one of the two drugs and metabolic acidosis was 25.1 days (range 9–60 days); mean reported time was 21 days. In two cases, latency time was not reported. Seven reports had already been published at congresses or in Dutch journals. The 12 cases are summarized in Table 1.

Table 1. Overview of Cases (Including Literature Reports) Reported to the Netherlands Pharmacovigilance Centre Lareb of Metabolic Acidosis After Concomitant Use of Paracetamol and Flucloxacillin

Case	Sex	Age	Time to Onset	Co-Medication	Indication for Flucloxacillin	Treatment	Risk Factors, Relevant Medical History	5-Oxoproline Confirmed
1	Female	67	5 weeks after start of paracetamol (4 g/d) and 3 weeks after start of dosage increase of flucloxacillin from 6 to 12 g/d	Oxycodone, simvastatin, metoclopramide, ibuprofen, dalteparin, olanzapine, macrogol	Phlegmon (hand) with *S. aureus* on blood culture	Sodium bicarbonate supplementation, paracetamol and flucloxacillin withdrawn		Yes
2	Female	78	4 weeks after start of paracetamol (3 g/d) and 3 weeks after start of flucloxacillin (unknown dose)	Naproxen, metformin, omeprazole, risedronic acid, amlodipine, perindopril	Pleural empyema (*S. aureus*)	Sodium bicarbonate and potassium supplementation, paracetamol and flucloxacillin withdrawn	Medical history: rheumatoid arthritis	No
3	Female	72	34 days after start of paracetamol (unknown dose) and flucloxacillin (unknown latency and unknown dose)	Not reported	Not reported	Acetylcysteine, paracetamol withdrawn	Sepsis, eventually died	Yes
4	Female	85	13 days after start of paracetamol (4 g/d) and flucloxacillin (12 g/d)	Pantoprazole	Arthritis left knee	Sodium bicarbonate supplementation; paracetamol and flucloxacillin withdrawn	Risk factors: arthritis, malnourished, renal function disorders	No
5	Female	84	Flucloxacillin: 1,000 mg 6 times per day, paracetamol 1,000 mg oral 4 times per day (unknown latency)	Not reported	Prosthesis-related infection			No
6	Female	79	3 weeks after start of flucloxacillin (12 g/d) during therapy with paracetamol (3 g/d) for 2 months	Gentamycin (past drug therapy)	Spondylodiscitis due to *S. aureus*	Sodium bicarbonate 8.4%, acetylcysteine (600 mg/8 hours) paracetamol and flucloxacillin withdrawn	Risk factors: renal failure (Cockcroft-Gault CrCl 28 mL/min, probably due to diabetes mellitus, urinary tract infection and previous use of gentamycin) Eventually died	Yes
7	Female	72	3 weeks after start of flucloxacillin intravenous therapy (unknown dose) during therapy with paracetamol (unknown dose, unknown duration)	Carbasalate calcium, paracetamol, metformin	Traumatic cruris fracture complicated by a *S. aureus* wound infection	Sodium bicarbonate, paracetamol then flucloxacillin withdrawn	Urinary 5-oxoproline concentration normalized after withdrawal	Yes
8	Female	87	20 days after start of flucloxacillin (6 g/d) and during therapy with paracetamol (4 g/d, unknown duration)	Metformin	Culture-confirmed *S. aureus* septic arthritis of left shoulder complicated by positive blood cultures for *S. aureus*	Sodium bicarbonate, acetylcysteine, paracetamol and flucloxacillin withdrawn		Yes

(continued)

Table 1 *(continued)*

Case	Sex	Age	Time to Onset	Co-Medication	Indication for Flucloxacillin	Treatment	Risk Factors, Relevant Medical History	5-Oxoproline Confirmed
9	Female	65	2 months after starting paracetamol (cumulative dose 56 g) during therapy with flucloxacillin (cumulative dose 164 g)	Not reported	*S. aureus* on blood culture	Sodium bicarbonate 8.4%, correction of potassium, paracetamol and flucloxacillin withdrawn	Medical history: rheumatoid arthritis Eventually died	Yes
10	Female	72	10 days after flucloxacillin 12 g/d and paracetamol 4 g/d (unknown duration)	Artificial feeding	Osteoarthritis	Sodium bicarbonate 8.4% and acetylcysteine 600 mg/8 hours); paracetamol and flucloxacillin withdrawn	Risk factors: malnourishment, renal function disorders (Cockcroft-Gault CrCl 20 mL/min), liver insufficiency	Yes
11	Female	52	9 days after start of flucloxacillin (12 g/d) during therapy with paracetamol (unknown dose, unknown duration)	Not reported	*S. aureus* positive arthritis right knee	Sodium bicarbonate 8.4%, potassium citrate, paracetamol withdrawn 4 days after high anion gap metabolic acidosis, flucloxacillin withdrawn	Medical history: small cell lung cancer	No
12	Female	72	Flucloxacillin (12 g/d) and paracetamol (4 g/d) (unknown duration)	Morphine, nonsteroidal anti-inflammatory drugs, bronchodilators	Positive blood and abscess cultures of *S. aureus*	Sodium bicarbonate 8.4%, paracetamol withdrawn, flucloxacillin withdrawn		Yes

S. aureus = *Staphylococcus aureus*; Cr Cl = creatinine clearance.

DISCUSSION

Several publications mention female sex and infectious disease (the indication for flucloxacillin) as possible risk factors for HAGMA.[4,5] Women are more likely to acquire 5-oxoproline acidosis, possibly because of sex differences in the enzyme activities of the γ-glutamyl cycle. Sex differences in glutathione transferase activity and lower glutathione stores in women than in men also make women more susceptible to pyroglutamic acidemia.[6] Sepsis and longer-lasting infections increase the degree of oxidative stress, redox imbalance, and cell injury, which causes depletion of glutathione in addition to that caused by N-acetyl-p-benzoquinone imine.[7–9] One woman had reported sepsis, and four had positive blood cultures for *Staphylococcus aureus*. Except for the infection for which flucloxacillin was administrated, information on this risk factor was lacking in these cases. Aging introduces additional risk factors; decline in renal function may contribute to 5-oxoproline accumulation because it is excreted in the urine.[4]

Other conditions that seem to predispose to HAGMA are hepatic dysfunction, especially liver disease that results from chronic alcohol use, vegetarian diet, and malnourishment,[4] the last two probably because of low protein intake, the source of glycine and cysteine.[10]

High anion gap metabolic acidosis was diagnosed during concomitant use of paracetamol and flucloxacillin after an average period of approximately 3 weeks, which indicates a role for accumulation or exhaustion of scavenging mechanisms. In one woman (#7), paracetamol but not flucloxacillin was stopped and led to improvement in but not to recovery from HAGMA. The role of acetylcysteine is unknown.[11] Withdrawal of both drugs and treatment with sodium bicarbonate seems to be the mainstream treatment.

CONCLUSION

Cases reported to the NPCL show that elderly women may be at risk of HAGMA after the concomitant use of paracetamol and flucloxacillin for approximately 3 weeks. These characteristics offer a chance for specific drug monitoring. Extra alertness in this population is recommended.

Because many drugs interfere in the gamma-glutamyl cycle, whether or not by depleting glutathione, HAGMA as a possible outcome of ADI after the use of other drugs should be enquired.

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ACKNOWLEDGMENTS

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions: Jessurun: concept and design, acquisition of subjects and data, analysis and interpretation of data, preparation of manuscript. van Marum, Hermens: analysis and interpretation of data, preparation of manuscript. van Puijenbroek: concept and design, analysis and interpretation of data, preparation of manuscript.

Sponsor's Role: Not applicable.

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PROGRESSION OF VOICE BREAKS IN A NONPATHOLOGICAL VOICE AS AN INDICATOR OF AERODIGESTIVE HEALTH

To the Editor: During normal aging, structural and functional changes in the aerodigestive tract can affect swallowing and breathing. Such changes are often evidenced in perceived voice production, which indicates a weakened or otherwise aging laryngeal system. These voice production changes, often starting in the fifth decade, can result in slower speech and elongated words;[1] tremor, instability, and aspiration;[2] reduced loudness;[3] speaking pitch changes;[4] and dysphonia.[5] Such voice changes affect quality of life[6] and may portend health problems with swallowing function and breathing regulation.

One aspect of the aging voice that has received little attention is voice instability. The current study examined changes in the voices of two men, using archived recordings, to track the progression of their voice breaks and instabilities with age. These instabilities may be an indicator of greater aerodigestive age changes.

Both men were associated with a private (religious) university where they delivered frequent public addresses over a span of many decades. In addition to the unique longitudinal breadth of the speeches (40–50 years), several characteristics make the set of recordings unique: a speaking style similar to reading aloud or lecture-style speech rather than a performance speech, with a focus on intelligibility rather than a specific voice quality; a consistent acoustical environment in one of two

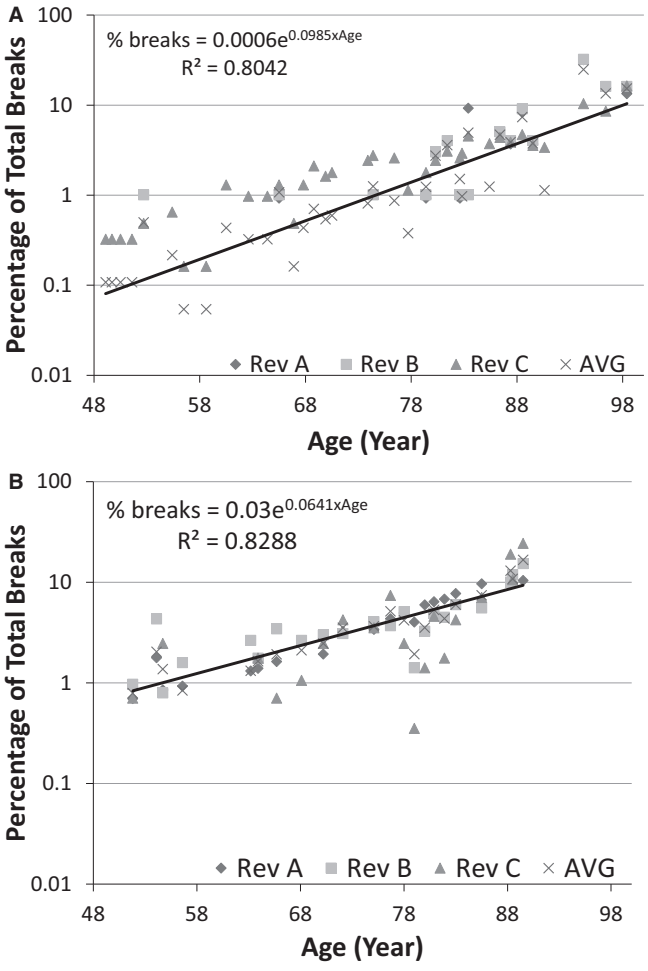

Figure 1. Normalized number of instabilities (percentage of total) chronologically for (**A**) Speaker 1 and (**B**) Speaker 2 as determined according to three judges. The solid line is the exponential fit (azimuth is logarithmic) to the average percentage of breaks for the three judges.