bijwerkingen centrumlareb

Flucloxacillin and hypokalemia

Introduction

Flucloxacillin (Floxapen®) is a narrow spectrum isoxazolyl penicillin. This β-lactam antibiotic has bactericidal activity against many strains of gram-positive organisms, including streptococci and β-lactamase producing staphylococci. Flucloxacillin inhibits crosslinking of peptidoglycans in the cell wall, resulting in lysis and cell death. It is mainly used to treat *respiratory infections (e.g. pharyngitis, tonsillitis, sinusitis, pneumonia, pulmonary abscess) and infections of skin and soft tissue (e.g. impetigo, abscesses)* [1,2]. Flucloxacillin is registered in the Netherlands since 1971 as Floxapen® [1] and is registered in generic forms as well.

Hypokalemia is generally defined as a serum potassium level of less than 3.5 mmol/L. Moderate hypokalemia is defined as a serum level of 2.5-3.0 mmol/L, and severe hypokalemia as a level of less than 2.5 mmol/L. Hypokalemia is a potentially life-threatening imbalance that may be iatrogenically induced. The symptoms of hypokalemia are nonspecific and are predominantly related to muscular or cardiac function. Severe hypokalemia may manifest as bradycardia with cardiovascular collapse. Hypokalemia may result from inadequate potassium intake, increased potassium excretion, or a shift of potassium from the extracellular to the intracellular space. Drugs that have been described to cause hypokalemia include the following: diuretics (carbonic anhydrase inhibitors, loop diuretics, thiazide diuretics):, methylxanthines (theophylline, aminophylline, caffeine), verapamil (with overdose), quetiapine (particularly in overdose), high-dose penicillins, bicarbonate, antifungal agents (amphotericin B, azoles, echinocandins), gentamicin and cisplatin [3].

Reports

Between June 9, 2008 and February 19, 2020 the Netherlands Pharmacovigilance Centre Lareb received 10 reports of hypokalemia (MedDRA PT Hypokalaemia) associated with the use of flucloxacillin. Of these reports, three describe a High Anion Gap Metabolic Acidosis (HAGMA) with hypokalemia due to an interaction between flucloxacillin and paracetamol [4]. These reports were not taken into account because they describe a clinical entity which is broader than hypokalemia itself.

Table 1. Reports of hypokalaemia associated with flucloxacillin

Case, ID, sex, age, primary source	Drug, Dosage	Indication	Concomitant medication	Reported ADRs	Latency after start	Action taken	Outcome
A NL-LRB-87638, male, 70 years and older, Physician ---------- Pharmacist	Flucloxacilline 500Mg oral 4000 milligram per day	Infected osteosynthesis material olecranon	Esomeprazole, Ferrofumarate, Folic acid, Paracetamol, Tramadol	Hypokalaemia, Nephritis interstitial, Hepatic function abnormal		Drug Withdrawn	Unknown, Unknown, Unknown
B NL-LRB-126739, male, 50-60 Years, Pharmacist	Flucloxacilline 1000Mg IV 12 gram per day ---------- Hydrochlorothiazide 12,5Mg	Abscess ---------- Hypertension	Dexamethasone, Oxycodone, Diclofenac, Nifedipine Triamterene	Hypokalaemia	1 day	Dose Not Changed, Dose Not Changed	Recovered
C NL-LRB-214661, female, 70 Years and older, Physician	Flucloxacilline 2000Mg IV 8 gram per day	Bacteraemia	Alendronic acid, Calciumcarbonate/Colecalceferole, potassiumchloride, Macrogol with electrolytes, Temazepam, Timolol/Latanoprost	Hypokalaemia	10 Days	Dose Not Changed	Recovering
D NL-PFIZER INC-	Flucloxacilline 1000Mg IV 2 gram per day	Spondylo-discitis		Hypokalaemia		Drug Withdrawn	Recovered

2017051985, female, 60-70 Years, Other health professional Duplicate report = NL-LRB-78062							
E NL-LRB-00274437, female, 70 years and older, Physician	Flucloxacilline 500Mg oral 500 mg per 6 hours	Erysipelas	Furosemide, Colecalciferol Tablet 800Ie, Perindopril/ Indapamide Tablet	Hypokalaemia		Drug Withdrawn	Recovered
F NL-LRB-00311955, female, 60-70 Years, Physician	Flucloxacilline 48Mg/Ml IV	Staphylococcus aureus bacteraemia	Oxazepam, Ketoconazole, Ciclopirox, Macrogol with electrolytes,Vaselinec etomacrogol Creme, Nadroparin, Beclometason/ Formoterole, Citalopram Mirtazapine, Paracetamol	Hypokalaemia	3 Days	Drug Withdrawn	Recovering
G NL-LRB-00374275, female, 70 years and older, Physician	Flucloxacilline IV Unknown dosage used for 12 days	Staphylococcal bacteraemia	Pantoprazol Chloortalidone, Enoxaparine, Prednisolone, Naproxen	Hypokalaemia		Dose Not Changed	Recovered

It should be noted that in case G paracetamol was also used concomitantly and a metabolic acidosis was described as the outcome of further testing in the narrative of the reports, but not reported as an ADR.
The patients in case B an H use paracetamol as concomitant medication without a HAGMA being reported.

Additional information from the reports:
Case A: the patient was hospitalized for 7 days in March 2009. The patient suffered from a near collapse. Arrhythmia related to hypokalaemia was in the differential diagnosis The potassium level was 1.8 mmol/l, the patient also suffered from an interstitial nephritis and abnormal hepatic function, according to the reporter also likely due to flucloxacillin use. The patient was treated with potassium for 3 days. The patient had a moderate nutritional status due to a malignancy.
The discharge letter for this patient describes that the plasma creatinine concentration content had increased considerably since the beginning of March 2009. After discontinuation of the flucloxacillin, plasma creatinine decreased ; and was in the normal range during an outpatient visit on 23 April 2009. A
fter the start of flucloxacillin in February, before hospitalization, the plasma potassium concentration was 3.0 mmol/l. On a visit to the outpatient clinic on April 23, 2009, the potassium concentration, in the absence of potassium supplementation, was 4.2 mmol/l.

Case B: The reporter mentions that it seems logical that hypokalemia is caused by diuretics. However, according to the reporter this could not adequately explain hypokalemia in this case. In addition, triamterene is used as a potassium sparing diuretic. The reporter thinks that flucloxacillin seems to be the most likely cause. It should also be noted that the patient uses diclofenac concomitantly; The SmPC for oral diclofenac mentions thatsSimultaneous treatment with potassium-sparing diuretics can lead to increased levels of potassium in the serum.

Case C has potassium chloride as concomitant medication mentioned. It is not clear if this is concomitant medication or treatment. In the report it is stated that the patient was treated with potassium. Flucloxacillin was continued, the patient was recovering 19 days later.

Case D is a Literature report from Van Hoorn E et al [5]. A 60-70 year-old woman (height 165 cm and weight 45 kg) was treated with flucloxacillin (2 g six times daily) for spondylodiscitis during two admissions. During both admissions, hypokalaemia developed after flucloxacillin was started (after 3 and 2 days, respectively) and resolved after it was stopped. Hypokalaemia was caused by renal potassium loss. Other causes of renal potassium loss were absent, including diuretics, hypomagnesaemia,

ketonuria, bicarbonaturia, renal tubular acidosis (no acid-base disorder) and, finally, hyperaldosteronism (low-normal renin and aldosterone levels). Moreover, dietary potassium intake was normal and no causes of a shift of potassium into the cell (e.g. alkalosis or insulin) or its loss from the gastrointestinal tract (e.g. diarrhoea or laxatives) were present.
Surprisingly, the findings in this case contradicted the above. First, serum renin and aldosterone levels were low-normal and urinary chloride levels were high, both arguing against volume depletion. However, aldosterone levels may have been higher early on and should also be interpreted in the context of hypokalaemia, which reduces aldosterone secretion. Secondly, treatment with intravenous fluids (2 L of 0.9% NaCl) and a 15 day trial of spironolactone (25 mg once daily) failed to prevent hypokalaemia, nor did it reduce kaliuresis. Triamterene (50 mg once daily), which was tried for 2 days, was also unable to decrease the renal potassium loss. According to the authors, this case illustrates the class-effect of penicillins to cause hypokalaemia and its development in the absence of volume depletion, hyperaldosteronism and low distal chloride delivery. It also illustrates that low body mass index patients receiving high-dose penicillin therapy are at risk for developing severe hypokalaemia. The ineffectiveness of probenecid, volume repletion and potassium sparing diuretics (reported here) suggest an obligatory renal potassium loss that may exceed roughly 100 mmol/L. Thus, the mainstay of treatment remains aggressive potassium supplementation, for which special measures (potassium infusion pump, central venous catheter, intra-arterial line for monitoring) may be required.

Case E: Both flucloxacilline and furosemide were started on 02-03-2018. 7-3-2018 SEH assessment because of possible fracture after fall, as a secondary finding hypokalaemia was detected. Severe hypokalaemia of 1.7 mmol/l. Unknown how long this has been existing. Last known potassium evaluation on 9-9-2017: 4.5 mmol /l. There was a fast recovery, within 1 day. There appears to have been no more than 1 day of water-thin diarrhea (on the day of admission). There was no nausea or vomiting. There was no other electrolyte disorder in the patient.
The reporters mention: ‘The reason why we suspect hypokalaemia as the cause of flucloxacillin is based on clinical experience, namely that with such a short use of a normal dose of furosemide we have never seen such a deep hypokalaemia.’
It should be noted that the patient uses also uses perindopril as concomitant medication, which has the potential to increase the potassium level in the blood.

Case F: During previous use, the patient suffered from a mild hypokalaemia. The latency for this occurrence was 2-3 days after start of flucloxacillin 12 gram IV. The current reaction was deemed lifethreatening due to ECG abnormalities. Additional testing showed a metabolic acidosis with respiratory compensation, urine potassium was 38 mmol/L.

Case G: Patient was admitted on 13-01-2020 in connection with a Staphylococcus Aureus bacteremia, for which flucloxacillin 6 grams / 24h iv was started. On the day of admission the potassium of this patient was 4.1. Flucloxacillin was increased to 12 grams / 24h on 15-01-2020. The potassium was re-determined on 17-01-2020 and was then 3.1. Then potassium supplementation was started. The potassium was re-determined on 20-01-2020 and was then 3.7.

Other sources of information

SmPC
In the official product information for flucloxacillin, hypokalaemia is not mentioned as an adverse drug reaction [1].

Literature
Van der Heijden et al. [6] describe a retrospective cohort from a hospital in the Netherlands. In total, 77 patients receiving flucloxacillin (62% male, mean age 70.5 years, range 32–96 years) and 84 patients receiving ceftriaxone (46% male, mean age 70.8 years, range 28–96 years) were included; both groups had similar potassium levels at baseline (mean 3.9 mmol/l, range 3.3–4.7 mmol/l). In this cohort, treatment with high-dosed intravenous flucloxacillin was associated with a 3 times higher risk of hypokalaemia than treatment with ceftriaxone. Hypokalaemia occurred in 42% of patients treated with flucloxacillin dosed ≥6 g/day, compared to 14% in ceftriaxone-treated patients. This latter incidence is comparable to the general in-hospital occurrence of hypokalaemia according to previous studies. Moreover, moderate to severe hypokalaemia—which can cause a spectrum of symptoms ranging from muscle weakness to cardiac arrhythmias and death—developed strikingly more often during flucloxacillin than ceftriaxone therapy, occurring in over 23% compared to 10% of patients. In all cases, hypokalaemia occurred within 5 days after start of antibiotic therapy.
In addition to this study, multiple case reports describe the relation between flucloxacillin and hypokalemia [5, 7].
Also, hypokalemia is described as a class effect of related penicillinase-resistant penicillins [8-10].

Databases
Due to the fact that reports considering HAGMA caused by an interaction between flucloxacillin and paracetamol cannot be excluded in the disproportionality analysis, calculating reporting odds ratios is of limited value for this association.

Prescription data

Table 3. Number of users of flucloxacillin [11]

Drug	2014	2015	2016	2017	2018
Flucloxacillin	290,260	287,690	306,540	308,000	322,810

Mechanism
Van der Heijden et al. [6] state in their publication that hypokalaemia is suggested to develop because penicillins act as non-reabsorbable anions, causing a transmembrane potential gradient in the cortical collecting duct that is negative on the luminal side, thus enhancing potassium secretion. This action as a non-reabsorbable anion is a class-effect of penicillins.

Discussion and conclusion

Lareb received 7 reports of hypokalemia associated with the use of flucloxacillin. The consequences of this potential adverse drug reaction can be severe. In the cases older age, multi-morbidity and bacteremia could play a role. Hypokalemia is considered a multifactorial condition, with several factors acknowledged to be of influence in the general in-hospital populations, in particular kidney function and the use of kaliuretic diuretics [12,13]. In the Lareb cases the use of diuretics is a possible confounder in some cases, however two reporters have stated that they saw the flucloxacillin as a more likely cause of developing the hypokalemia in their patient. In case A the interstitial nephritis could also have been a factor in the development of hypokalemia. Van Daele et al. describe a case of severe hypokalemia in a patient with a distal renal tubular acidosis due to tubular interstitial nephritis as a symptoms of Sjogren's disease [14].
Not in all patients flucloxacillin was withdrawn, some continued treatment while receiving postassium suppletion. This association was also found in a retrospective cohort study from the Netherlands, published in 2019 [6]. In addition, case-reports, a possible mechanism and the description of a class-effect for penicillins in the literature add to the likelihood of this association. Therefore, attention for this potential adverse reaction is warranted, especially when combining flucloxacilline with hypokalemia-inducing diuretics or when other risk factors for the development of hypokalemia are present (e.g. malnutrition, renal tubule disfunction).

References

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This signal has been raised on April 1, 2020. 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