Hypokalaemia probably associated with ceftolozane/tazobactam treatment: Three case reports☆

Probable hipocalemia secundaria al tratamiento con ceftolozano/tazobactam: a propósito de 3 casos

Introduction

Ceftolozane/tazobactam is a cephalosporin indicated for the treatment of intra-abdominal and urinary tract infections caused by Enterobacteriaceae, non-fermenting Gram-negative bacilli (except *Stenotrophomonas maltophilia* or *Acinetobacter* spp.) and *Pseudomonas aeruginosa* (PAE). The most prevalent adverse effects (1–10%) are thrombocytosis, hypokalaemia, hypotension, insomnia, anxiety, headache, dizziness, rash, pyrexia, infusion site reactions, elevation of transaminases and gastrointestinal disorders.[1]

Results

Case 1

This was a 75-year-old woman who was admitted with septic shock secondary to obstructive cholangitis. She spent 26 days in hospital and had a percutaneous transparietal-hepatic biliary drain inserted. She was readmitted 24 h after discharge with pyrexia and increased drain output. She was started on treatment with omeprazole, phytonadione, paracetamol, pancreatic enzymes, ciprofloxacin, linezolid and fluconazole. An extremely drug-resistant (XDR) PAE sensitive to ceftolozane/tazobactam, colistin and amikacin was isolated in the patient's bile fluid culture. On day +5, the antimicrobial treatment was adjusted according to cultures: amikacin, ceftolozane/tazobactam, linezolid and fluconazole. At the start of the treatment, her serum potassium (SP) was 3.5 mEq/l.

On day +9, she developed moderate hypokalaemia (K = 2.6 mEq/l) and treatment was started with oral potassium (25 mEq/12 h). On day +10, her SP was 2 mEq/l and the supplements were increased (25 mEq/8 h orally and intravenous potassium chloride 80 mEq/day). During this period there were no changes to the patient's pharmaceutical therapy, she was tolerating diet and the biliary drain had been removed (day +4). An adverse event (AE) related to ceftolozane/tazobactam was suspected and it was changed to colistin. On day +12 her SP was 4 mEq/l.

Case 2

This was a 68-year-old man admitted for a purulent abscess in a graft on the right lower leg which required debridement and antibiotic therapy to cover the bacteria isolated in the latest cultures: ceftolozane/tazobactam (XDR PAE in rectal swab) and amikacin, vancomycin and metronidazole for *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus* and *Bacteroides fragilis* respectively. He was also on treatment with omeprazole, ondansetron, enoxaparin, paracetamol, dexketoprofen and lorazepam. His SP on admission was 3.9 mEq/l and by 12 h later, he was tolerating diet. After 32 h of treatment with ceftolozane/tazobactam, the patient was found to have mild hypokalaemia (K = 3 mEq/l) and treatment was started with oral potassium (25 mEq/12 h). He was kept on the same antibiotics for 13 days and the hypokalaemia resolved 48 h after starting the supplement.

Case 3

This was a 69-year-old woman diagnosed with bladder perforation due to radiation cystitis who required radical cystectomy. After six days, she was started on treatment with colistin and amikacin because of an XDR PAE in urine culture. On day +16, she was found to have renal deterioration (GFR-CKD-EPI 28 ml/min) and the colistin was changed to ceftolozane/tazobactam after verifying its sensitivity.

The prescribed treatment when starting on ceftolozane/tazobactam was: omeprazole, ondansetron, enoxaparin, dexpanthenol, paracetamol, metamizole and dexketoprofen. At the beginning of the treatment with ceftolozane/tazobactam,

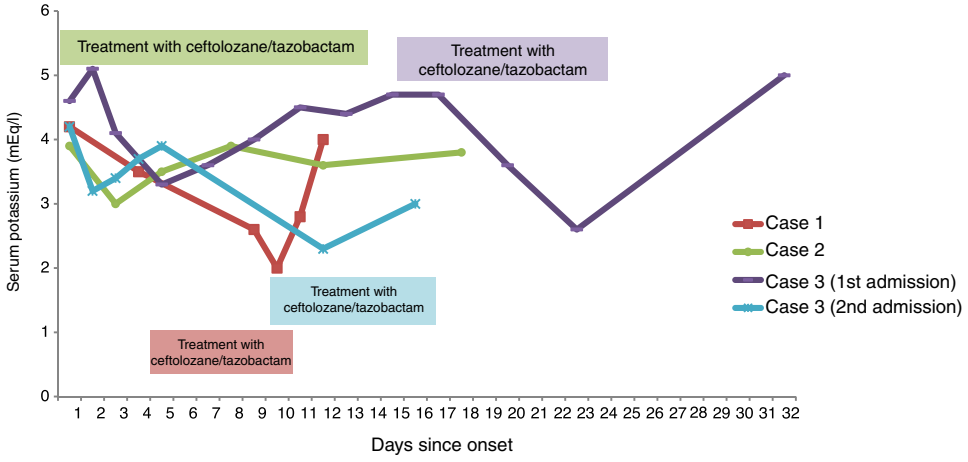

Fig. 1. Serum potassium determinations for the three cases.

DOI of original article: https://doi.org/10.1016/j.eimc.2018.06.013.

☆ Please cite this article as: Toro Blanch C, Gratacós Santanach L, Díez Vallejo C, Sacrest Güell R. Probable hipocalemia secundaria al tratamiento con ceftolozano/tazobactam: a propósito de 3 casos. Enferm Infecc Microbiol Clin. 2019;37:483–484.

the patient's SP was 4.7 mEq/l and at seven days she developed moderate hypokalaemia (K = 2.6 mEq/l). The antibiotics were discontinued after 14 days of treatment and she was discharged.

Two weeks later, she was readmitted with pyrexia and low back pain and treatment was restarted with colistin and amikacin, changing the colistin to ceftolozane/tazobactam due to nephrotoxicity on day +10. On day +12, the patient was again found to have moderate hypokalaemia (K = 2.3 mEq/l) and was started on 25 mEq/12 h of oral potassium. On day +16 the treatment was completed with her potassium level at 3 mEq/l.

In both admissions her potassium returned to normal a few days after finishing the treatment.

The changes in the potassium levels of all three cases are shown in Fig. 1.

Discussion

We have found in our clinical practice that the incidence of hypokalaemia caused by treatment with ceftolozane/tazobactam may be higher than described in clinical trials (<3%).[2,3] In our hospital, three of the 10 patients treated with ceftolozane developed hypokalaemia.

For the other drugs prescribed, hypokalaemia is only described in the summary of product characteristics for linezolid (1–10%) and fluconazole (0.01–0.1%), both prescribed in the first patient. That patient was on treatment with linezolid and fluconazole for almost four weeks without developing hypokalaemia.

Applying the Naranjo algorithm, levels of imputability for PROBABLE were obtained for the first and second cases and DEFINITE for the third. All three cases were reported to the Spanish Pharmacovigilance System.

Based on our experience, we consider it strongly advisable to monitor SP in patients treated with ceftolozane/tazobactam.

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2529-993X/

Prevalence and risk factors for fosfomycin resistance among *Escherichia coli* strains isolated from males with community febrile urinary tract infection

Prevalencia y factores de riesgo de resistencia a fosfomicina en cepas de Escherichia coli *aisladas de hombres con infección del tracto urinario febril comunitaria*

Dear Editor,

Escherichia coli is responsible for most febrile urinary tract infections (FUTI) in men the majority of which are acute prostatitis (AP).[1] Fluoroquinolones (FQ) achieve high prostatic concentrations and are considered the first choice in patients with AP.[2] *E. coli* is becoming increasingly resistant to FQ limiting its empirical use.[3] Given the lack of new antimicrobials it is necessary to reevaluate already existing agents.

Fosfomycin, a bactericidal antibiotic that targets peptidoglycan formation, is active against most *E. coli* causing FUTI, including extended-spectrum beta-lactamase producing *E. coli* (ESBL-EC) strains.[4] Fosfomycin trometamol achieves reasonable intraprostatic concentrations and has been used in the treatment of chronic prostatitis caused by multidrug-resistant bacteria.[5] We aimed to assess the prevalence, trends and risk factors associated to fosfomycin resistance (FR) in *E. coli* from males with a community FUTI.

An ambispective cross-sectional study was performed at a primary care hospital. Data were recorded retrospectively from January 2008 to October 2009 and prospectively from then to December 2015. FUTI was defined as an armpit temperature ≥38 °C together with UTI symptoms. When urinary symptoms were absent, diagnosis was accepted if no other infections were found. Variables reviewed included: age, dementia, diabetes mellitus, chronic kidney or heart failure, cirrhosis, neoplastic or lung disease, use of immunosuppressive agents, the Charlson score, any antibiotic intake in the previous 30 days, prior UTI and existence of urinary abnormalities. A healthcare-associated FUTI was considered in case of: hospitalization in the previous 90 days; residence in a long term care facility; outpatient care, therapy, or invasive urinary tract procedures, 30 days before the FUTI and presence of an indwelling urethral catheter. Urine samples were obtained from midstream urine or from urinary catheters and cultured on MacConkey agar. Positive urine cultures were defined by bacterial growth ≥10^3 CFU/mL. Identification of *E. coli* was performed by biochemical methods. Antimicrobial susceptibility was tested by agar diffusion (CLSI criteria). Intermediate and resistant strains were grouped together.

The study included 385 males with a community FUTI due to *E. coli*. Eight (2.1%) isolates were FR and 377 (97.9%) fosfomycin susceptible (FS). Resistance to FQ (p = 0.006), amoxicillin–clavulanate (p = 0.01), cefuroxime (p = 0.03), ceftriaxone (p = 0.024) and gentamicin (p = 0.015) was more frequent in FR strains. Among the 29 (7.5%) ESBL-EC, 27 (93.1%) were FS. In the univariate analysis FR was associated to older age (p = 0.048), dementia (p = 0.028) and recent FQ use (p = 0.036). The frequency of FR remained stable over the study while there was an increase in the proportion of ESBL-EC (chi square for linear trend 17.4; p < 0.001) (Fig. 1).

The overall prevalence of FR was comparable with that previously reported in Spain[6] and lower when focusing in ESBL-EC strains.[6,7] The low frequency of FR in *E. coli* despite extensive use of fosfomycin has been attributed to a decreased bacterial fitness.[8] However, Spanish studies have suggested the existence of a correlation between fosfomycin consumption and FR in *E. coli* isolates, mainly in ESBL-EC.[6,9] Resistance to fosfomycin is generally related to chromosomal mutations in the target or in the transporter genes