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Scientific letter

Ceftobiprole, a new option for multidrug resistant microorganisms in the outpatient antimicrobial therapy setting

Ceftobiprole, una nueva opción de tratamiento para microorganismos multirresistentes en el ámbito del tratamiento antimicrobiano domiciliario

Ceftobiprole is a broad spectrum fifth-generation cephalosporin. Ceftobiprole is approved in several European countries for the treatment of community-acquired pneumonia and hospital-acquired pneumonia, excluding ventilator-associated pneumonia. Respiratory infections in patients with bronchiectasis have special characteristics because they are frequently caused by *Haemophilus influenzae*, *Pseudomonas aeruginosa*, respiratory viruses, and less frequently, *Moraxella catarrhalis*, *Staphylococcus aureus*, and Enterobacteriaceae.[1] The high number of exacerbations leads to high antibiotic pressure. Ceftobiprole is stable for up to 24 h at 25 °C and protected from light, which allows for potential administration in OPAT.[2,3] There is limited experience and research data of its use at home. The specific characteristics of our OPAT programme have been described previously.[4]

We present the case of a 32-year-old male patient diagnosed with cystic fibrosis at the age of 5 (homozygous for the CFTR gene with the delta-F508 mutation) and colonized with multidrug-resistant (MDR) *Pseudomonas aeruginosa*, and methicillin-susceptible *Staphylococcus aureus* (MSSA) since 1995. A bipulmonary transplant was performed in October 2019 (8 months previously) with multiple subsequent complications. Mucoid phenotype *Pseudomonas aeruginosa* resistant to quinolones, piperacillin-tazobactam, aminoglycosides, ceftazidime, cefepime, and carbapenems was isolated in a sputum culture three months before. Susceptibility to ceftazidime/avibactam, ceftobiprole, and ceftolozane/tazobactam are not test routinely in our hospital. The patient was admitted at the beginning of June 2020 with fever and respiratory symptoms. Procalcitonin and C-reactive protein were compatible with a bacterial aetiology. Nevertheless, a cytomegalovirus serology and viral load were requested to rule out possible reactivation. Blood and sputum cultures were taken, without making identification. Urinary antigens for *Legionella* and *Streptococcus pneumoniae* were negative. Empirical treatment was started with piperacillin-tazobactam 4 g every 8 h, with no improvement after three days. A CT scan showed alveolar infiltrates compatible with an infectious cause. Taking into account the resistance pattern of *Pseudomonas aeruginosa*, we decided to start empirical treatment with ceftobiprole 500 mg over 2 h, every 8 h. Within 48 h, the patient became afebrile, the respiratory parameters improved, and acute phase reactants normalized. Since the patient was clinically stable, it was proposed that he continue antibiotic therapy at home in our OPAT programme. Ceftobiprole was prepared daily, diluted in 0.9% saline solution at a concentration of 3 mg/mL, then refrigerated. The antibiotic solution was administered by electronic pump over 2 h every 8 h. Three days after being discharged, the patient became asymptomatic, and ceftobiprole was stopped after 7 days of therapy. He showed no adverse events and no changes in the control analysis carried out at home. We examined him in the pneumology clinic one month later, with no clinical incidents. After 3 months of follow-up by telephone, he has shown no new episodes of infection.

To our knowledge this is the first case report providing a clinical and safety evaluation of ceftobiprole in OPAT. The stability of the drug using an elastomeric pump has not been tested.

A history of colonization or infection with resistant gram-negative bacilli in the previous 12 months, previous hospitalization with exposure to broad-spectrum antibiotics, and cystic fibrosis, among others, have been reported in the literature to increase the risk of resistant gram-negative bacilli. A recently published consensus statement based on a Delphi survey of expert opinion recommends the use of empirical therapy against resistant gram-negative bacilli, including *Pseudomonas aeruginosa*, in patients with any of these risk factors.[1] Ceftobiprole could be a good option in this scenario due to its broad spectrum of activity. There are no recommendations in cases without improvement using an initial antipseudomonal beta-lactam in the absence of an aetiological diagnosis. In such cases, the strategy should be based on previous clinical experience and local epidemiological data. One study reported the activity of ceftobiprole against a large set of clinical isolates obtained from hospitalized patients in the United States in 2016 that caused serious infections, including pneumonia, in which 72.7% of 1,017 isolates of *Pseudomonas aeruginosa* were susceptible to ceftobiprole.[5] In an unpublished observational study including respiratory, skin, genitourinary tract, body fluid, and gastrointestinal clinical isolates from Europe isolated in 2018, the rate of susceptibility to ceftobiprole in 376 *Pseudomonas aeruginosa* isolates ranged from 59% to 76.3%.[6] In the presented case, ceftazidime/avibactam and ceftolozane/tazobactam would have been good empirical treatment options against *Pseudomonas aeruginosa*. The decision to use ceftobiprole was taken in the absence of precise data on susceptibility data to *Pseudomonas aeruginosa* in our setting, considering its high activity against MSSA and MRSA, and the possibility to be used in OPAT.

More data are needed to demonstrate the safety and efficacy of ceftobiprole and specific use in the outpatient setting.

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Conflicts of interest

LELC has served as scientific advisor for Novartis, speaker for MSD, Pfizer, Angelini, ViiV, Gilead and Correvio, and has served as trainer for MSD and ViiV. The rest of authors have no conflicts of interests to declare.

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Piomiositis del músculo obturador interno: no todo es artritis séptica

Obturator internus pyomyositis: not everything is septic arthritis

Sr. Editor:

La piomiositis es una infección bacteriana del músculo estriado, que suele evolucionar a absceso muscular. Afecta principalmente a grandes músculos de las extremidades inferiores[1,2], siendo excepcional la localización en el músculo obturador interno (MOI), poco documentada y todo un reto diagnóstico. Presentamos el caso de un adolescente de 15 años, que acude al servicio de Urgencias por un cuadro de una semana de evolución de fiebre, dolor en región glútea derecha y cojera. No refiere traumatismo, ejercicio físico intenso reciente, ni ningún proceso infeccioso previo. En la exploración se observa una posición antiálgica con la cadera derecha en flexión, rotación externa y abducción. En la analítica sanguínea destacan 70,6% de neutrófilos sin leucocitosis (7,6·10$\hat{9}$/L) y PCR de 8,9 mg/dl. Se realizan radiografías de pelvis y caderas sin hallazgos relevantes y ecografía de cadera que objetiva derrame articular. Se ingresa al paciente con sospecha clínica de artritis séptica.

Se realiza artrocentesis resultando el gram y el cultivo negativos. Los hemocultivos son positivos para *Staphylococcus aureus* sensible a meticilina (SAMS), iniciando tratamiento con cloxacilina intravenosa. Se completa estudio con ecografía abdominal, que descarta apendicitis; en RMN de cadera se aprecia edema de partes blandas peritrocantéreas sin signos de artritis séptica. Repetida una RMN de control a los 5 días, se objetiva un absceso de 6 × 1,5 × 5,5 cm en el MOI con probable osteomielitis pélvica asociada (fig. 1). Se realiza drenaje de la colección guiado por ecografía, obteniendo 12 cm^3 de líquido purulento y aislamiento en el cultivo de un SAMS (idéntica sensibilidad que hemocultivos). A su vez, se amplía cobertura antibiótica con vancomicina y clindamicina, previa retirada de cloxacilina.

La evolución clínica y analítica fue favorable, pero sin resolución completa en sucesivas RMN de control, por lo que se decidió prolongar tratamiento parenteral durante 6 semanas, las 4 primeras en régimen de hospitalización, y al alta, con dalbavancina semanal 2 semanas más, asociada a clindamicina oral.

La piomiositis primaria es una entidad infrecuente, que se observa fundamentalmente en climas tropicales, aunque en las últimas décadas ha incrementado notablemente en nuestro medio, asociado sobre todo a situaciones de inmusupresión[2–4].

La patogenia no es del todo conocida, pero clásicamente se ha asociado con traumatismos locales (15-50%) o ejercicio físico extenuante[1–5]. Suele originarse por diseminación hematógena, siendo las bacterias grampositivas responsables de prácticamente todos los casos, y el *Staphylococcus aureus* el microorganismo más frecuente[2,4].

La piomiositis del músculo obturador interno (PMOI) es una entidad extremadamente rara de la que hay descritos escasos casos en la literatura, sin embargo, su incidencia está aumentando en los últimos años[3,5]. Es más frecuente en edad pediátrica[1,5], y suele manifestarse con fiebre, dolor en cadera o muslo, cojera y posición antiálgica con cadera en flexión, rotación externa y abducción[1,5]. En la mitad de los casos se complica con infección de músculos adyacentes u osteomielitis pélvica[1,5], como ocurrió en nuestro caso.

El diagnóstico suele ser tardío por la inespecificidad clínica y analítica[3], confundiéndose con otras patologías osteoarticulares o intraabdominales, especialmente la coxartritis séptica[1,3,6]. La ecografía es útil como aproximación diagnóstica pero el *gold standard* es la RMN, que presenta una gran sensibilidad y especificidad,