Clinical Experience with Ceftolozane/Tazobactam at a London Teaching Hospital

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Introduction

Ceftolozane/Tazobactam (Zerbaxa™), a novel cephalosporin combined with a well-known beta-lactamate inhibitor, is a novel antinfectious agent licensed in 2015 for the treatment of complicated intra-abdominal infections and urinary tract infections. Ceftolozane alone demonstrates activity against common gram-negative pathogens, and the addition of tazobactam provides stability against several beta-lactamases, including extended spectrum beta-lactamase producers. This combination has activity against carbapenem-resistant, non-carbapenemase producing pathogens and therefore offers a therapeutic option against a variety of multi-resistant Gram-negative pathogens, including Pseudomonas aeruginosa.

Aims

To describe the clinical and microbiological aspects of the application of this novel agent at a large London teaching hospital.

Materials & Methods

The clinical records of all patients treated with ceftolozane/tazobactam were studied retrospectively. Data were collected using a specific proforma. Statistical analyses were performed using Microsoft Excel™.

Results

Six patients over two years (November 2015 – November 2017) have been treated with ceftolozane/tazobactam. Patients were predominantly male (n=5, 83%) and their median age was 36. The indications in all cases were healthcare associated infections – 4/6 (67%) treatments were for pneumonia; the remainder 2 (33%) were for cholangitis. All isolates were multiresistant P. aeruginosa isolated from blood cultures (17%), sputum (33%) and urine (33%) and drain fluid (17%) with only 1 isolate being a carbapenemase producing organism (discovered later by PCR). Median duration of treatment was 12 days. One patient suffered an undesirable effect leading to discontinuation of the medication. Five (83%) patients experienced resolution of symptoms, but 4 (67%) remained culture positive post treatment.

Discussion

Treatment of P. aeruginosa infection is complicated by its ability to develop antimicrobial resistance (via a variety of mechanisms) including: pore deletion; upregulation of efflux pumps and decreased AmpC production; and more recently, tetracycline resistance. Tetracycline use after resistance to beta-lactamus and quinolones has developed including ampicillin/sulbactam and colistin which both confer a risk of nephrotoxicity. In our study, all isolates were highly resistant strains. The UK reference laboratory examined the susceptibility of 1099 P. aeruginosa isolates to ceftolozane/tazobactam and found 99.8% of isolates were susceptible. In vitro studies also demonstrate ceftolozane/tazobactam mean inhibitory concentration for P. aeruginosa four to eightfold lower than those for carbapenams. High level resistance to ceftolozane/tazobactam is noted in metallo-beta-lactamases or VEB type extended spectrum beta-lactamases. 96.8-100% of these isolates were found resistant by the UK reference laboratory. This is potentially due to a tazobactam acting as a poor permeant or good efflux substrate for P. aeruginosa. In our study, one patient had a carbapenemase producing Pseudomonas. He responded clinically to treatment, but it was noted repeated isolates continued to grow a resistant P. aeruginosa Ceftolozane/Tazobactam is currently not licensed for the treatment of chest infections. The higher dosage regimen chosen for our patients with pneumonia was based on data from Monte Carlo simulations – a trial is underway to further evidence this.

Conclusions

- Ceftolozane/Tazobactam has an important role to play in the management of multi-drug resistant Gram negative hospital associated infections.
- Careful and select use is important. Hypersensitivity reactions, treatment failure and the development of resistance are all very real risks.
- A valuable addition to the antibiotic arsenal.