CASE REPORT

The successful treatment of a multidrug-resistant *Achromobacter xylosoxidans* corneal ulcer with topical meropenem

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SUMMARY

Microbial keratitis is a common corneal condition, with many known risk factors. We present a case of an 88-year-old female patient with a multidrug-resistant *Achromobacter xylosoxidans* corneal ulcer in a previously failed second penetrating keratoplasty, successfully managed with topical meropenem drops administered hourly around the clock, for five days preceding and then hourly day only, for five days following a repeat third penetrating keratoplasty. Topical meropenem 50 mg/mL was prepared by mixing a 500 mg vial of meropenem with 10 mL of sterile water with pharmacy advice that administration should be within an hour. To the best of our knowledge, this is the first report of the use of topical meropenem in the management of *A. xylosoxidans* keratitis. This case highlights the importance of the mean inhibitory concentrations for antibiotics when considering sensitivities. Topical meropenem may be a useful treatment option for multidrug-resistant bacterial corneal ulcers that are resistant to conventional therapy.

BACKGROUND

Microbial keratitis is a common corneal condition, with many known risk factors. It most commonly affects contact lens wearers but also occurs in patients with other ocular surface conditions. These include keratoconjunctivitis sicca, neurotrophic keratopathy, surface disease and extended exposure to courses of topical steroids, such as following corneal graft procedures. We present a case of a patient with a multidrug-resistant *Achromobacter xylosoxidans* corneal ulcer in a previously failed second penetrating keratoplasty. This was successfully managed with hourly topical meropenem drops administered for five days preceding and five days following a repeat third penetrating keratoplasty. We discuss the optimal method to prepare this treatment, which to the best of our knowledge, has not previously been reported for use topically in *A. xylosoxidans* keratitis. This may be a useful treatment option for multidrug-resistant bacterial corneal ulcers that are resistant to conventional therapy.

CASE PRESENTATION

An 88-year-old female patient presented to the corneal clinic at our tertiary referral unit with a right non-healing recurrent epithelial defect. She had a medical history of hypertension, hypothyroidism,

hypercholesterolaemia and non-inflammatory arthritis. Her regular medications included aspirin, bisoprolol, levothyroxine, ramipril and simvastatin. She had a past ocular history of Fuchs endothelial corneal dystrophy and had developed corneal decompensation which was managed with bilateral penetrating keratoplasties, performed 25 years earlier. Right cataract surgery was performed two years previously. Postoperative vision failed to improve from 6/60 (pinhole 6/36) due to corneal decompensation postcataract surgery. A redo right penetrating keratoplasty was performed ten months after the cataract surgery. This was followed by a graft rejection episode six months later. This was managed with topical hourly dexamethasone but the right eye developed a recurrent epithelial defect which was treated with a lower lid ectropion repair, lateral tarsorrhaphy and subsequent amniotic membrane graft.

Four months after this, the patient was admitted with an episode of presumed bacterial keratitis. The corrected distance visual acuity (CDVA) on the right was perception of light only. There was an epithelial defect measuring 5.2 mm (vertical) by 2.0 mm (horizontal), with a 1.4 mm round infiltrate and 0.6 mm hypopyon. A corneal scrape was performed and hourly day and night topical cefuroxime 5.0% and gentamicin 1.5% were administered. The corneal scrape cultured *A. xylosoxidans*, identified by Microflex MALDI Biotyper mass spectrometer (Bruker-Daltonics, Fremont, California, USA). Initial sensitivity testing of the isolated demonstrated sensitivity to gentamicin and ceftazidime, but resistance to ciprofloxacin. Herpes simplex viral PCR testing was negative. There was gradual improvement on this treatment. Twelve days after presentation, the epithelial defect had fully resolved, leaving a dense scar. Topical prednisolone 0.5% was added and given four times per day and tapered to twice daily over the next two months.

Two months later, the patient represented with a right corneal abscess measuring 3.5 mm by 5 mm. A repeat corneal sample grew *A. xylosoxidans* and repeat viral PCR was negative. Hourly topical cefuroxime 5.0% and gentamicin 1.5% were restarted. The zone sizes of the isolate by disk diffusion were: ceftazidime (28 mm); ciprofloxacin (13 mm); gentamicin (18 mm); meropenem (40 mm); piperacillin/tazobactam (37 mm); co-trimoxazole (26 mm); ertapenem (36 mm); minimum inhibitory

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concentrations (MIC) for ceftazidime, ciprofloxacin, gentamicin, tobramycin, amikacin and meropenem were determined by E-test. They were: ceftazidime (2 µg/mL); ciprofloxacin (2 mg/L); gentamicin (16 mg/L); tobramycin (8 mg/L); amikacin (32 mg/L); and meropenem (0.12 mg/L). Although there had been an initial clinical improvement with gentamicin, the subsequent deterioration was thought to be due to the micro-organism having a high gentamicin MIC. CDVA remained at perception of light only in the right eye due to extensive corneal scarring with graft failure and a persistent epithelial defect.

TREATMENT

A tectonic penetrating keratoplasty was planned for visual and therapeutic indications. Topical meropenem 50 mg/mL was prepared by mixing a 500 mg vial of meropenem with 10 mL of sterile water with pharmacy advice that administration should be within an hour. Meropenem drops were given hourly for five days around the clock immediately prior to the penetrating keratoplasty, and then hourly during daytime only for a further five days postoperatively. The aim of meropenem use was to reduce the likelihood of further infection with *A. xylosoxidans* following the redo therapeutic penetrating keratoplasty. The abscess was considered to be less dense with the meropenem use preoperatively, however given the graft had failed a redo therapeutic penetrating keratoplasty was required. Histology of the corneal button revealed irregular epithelium, half absent Bowman's layer, stromal oedema, an intact Descemet membrane and absent endothelium. Culture of the corneal button confirmed the presence of *A. xylosoxidans* with sensitivity to meropenem. Five days following the tectonic penetrating keratoplasty, and a further five days of hourly meropenem, the patient was discharged on topical dexamethasone 0.1% second hourly.

OUTCOME AND FOLLOW-UP

At last follow-up, four months after the final penetrating keratoplasty, uncorrected visual acuity was 6/60, with pinhole improvement to 6/24. The corneal graft was clear with no sign of disease recurrence.

DISCUSSION

To the best of our knowledge, this is the first report of the use of topical meropenem in the management of *A. xylosoxidans* keratitis. *A. xylosoxidans* (formally known as *Alcaligenes xylosoxidans*) is a gram-negative bacillus first described in 1971.¹ It is an opportunistic pathogen that most commonly affects immunocompromised individuals, and has been described as causing pneumonia, urinary tract infections, sepsis and meningitis.² It has been found in swimming pools, clinical hospital fluids (such as distilled water and disinfectant solutions) and humidifiers.³ The organism is usually sensitive to broad-spectrum penicillins, ceftazidime, imipenem, trimethoprim and quinolones.^{2,4} However, drug resistance has been reported, specifically with cephalosporins and first generation aminoglycosides.⁵ Drug resistance can be intrinsic or acquired. Intrinsic drug resistance in *A. xylosoxidans* is thought to be due to both resistance-nodulation-cell division (RND)-type multidrug efflux pumps and a chromosomally encoded narrow-spectrum class D β-lactamase.⁶ Acquired drug resistance in *A. xylosoxidans* is the result of genes carried on mobile genetic elements, such as integrons.⁶ It is proposed that the multiple efflux pump systems in *A. xylosoxidans*, particularly the RND pumps, play the most significant role for the intrinsic drug resistance seen with this organism.⁶

A recent review has examined 24 cases in the literature of *A. xylosoxidans* keratitis.⁷ Risk factors include contact lens wear,⁵ history of previous corneal surgery (Laser-assisted *in situ* keratomileusis (LASIK)^{8,9}; keratoplasty⁴) and a compromised ocular surface.⁵ A proposed mechanism for contact lens keratitis is based on hypoxia leading to elevated levels of lactic acid and relative glycogen deficiency that result in corneal epithelial injury, with loss of barrier function, which may permit the motile *A. xylosoxidans* bacterium to penetrate the cornea.⁸ Various treatment regimens have been reported for *Achromobacter* keratitis, but the organism was typically sensitive to quinolones and ceftazidime.⁷ Our patient had several risk factors for keratitis including a previously rejected corneal graft, use of topical steroids and a compromised ocular surface. Despite original susceptibility to gentamicin and cefuroxime, there was only a limited clinical response to this treatment. Considering this, topical meropenem was proposed following microbiological evaluation as an alternative treatment. This was administered in combination with a tectonic penetrating keratoplasty due to the extensive involvement of the already failed previous graft.

Meropenem is a carbapenem β-lactam antibiotic with broad-spectrum activity against both gram-positive and gram-negative bacteria. It has approved use by the Food and Drug Administration (FDA) for the treatment of skin and gastrointestinal infections, as well as for bacterial meningitis.¹⁰ Its intravitreal use in the treatment of endophthalmitis resistant to other antibiotic agents has also been reported.¹¹ There has been a report of its topical use in successfully treating cases of pseudomonal keratitis.¹² The meropenem drops were prepared using a similar protocol to that previously described by using a 500 mg vial containing powdered meropenem (Ronem, Venus Remedies) reconstituted with 10 mL of distilled water, to give a final concentration of 50 mg/mL.^{12,13} These drops were applied hourly. The preparation once made was considered stable for use within an hour. The dilution was performed second hourly to allow a dose to be given immediately and then one hour following. The challenges and cost of frequent preparation are a barrier to the application of meropenem in routine cases of bacterial keratitis. However, as highlighted by our case and previous reports,¹² it can be a safe alternative to standard topical antimicrobial agents and may be considered for non-responding multidrug-resistant cases of bacterial keratitis as guided by the microbiological culture and sensitivity.

Our case highlights the importance of the antibiotic MIC when considering sensitivity. There are no nationally/internationally agreed breakpoints for this organism, but breakpoints from a comparable organism (in this case *Pseudomonas aeruginosa*) can be used but interpreted with caution. By the criteria set by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for *Pseudomonas* spp,¹⁴ treatment with ceftazidime, piperacillin/tazobactam or a carbapenem could have been considered effective, but the ciprofloxacin and aminoglycoside MICs were sufficiently high to consider the organism resistant. There are no comparable zone size criteria for co-trimoxazole for *Pseudomonas* spp, but it has been proposed that zone sizes of <27 mm and ≥28 mm for *A. xylosoxidans* should be considered resistant and sensitive, respectively.¹⁵ Based on the MIC and zone sites in this case, resistance to three classes of antibiotic was detected (ciprofloxacin, gentamicin and co-trimoxazole, zone sites of 13 mm, 18 mm and 26 mm, respectively) the organism was therefore considered multidrug resistant.¹⁶

It is also important to recognise that the epidemiological cut-off MIC (ECOFF) values applied by clinical laboratories are based on the pharmacokinetic and pharmacodynamics properties

of the antibiotic at the site of infection (usually systemic). There is very little pharmacokinetic/pharmacodynamic data available for topical antimicrobials, which may be significantly different to systemically administered drugs, and there is a lack of consensus on the optimal usage of topical agents. On the other hand, the application of current ECOFF values to identify non-wild type susceptibility profiles could be useful to highlight potential resistance mechanisms, which may predict a higher probability of clinical failure.

This case presents a method for preparation and topical administration of meropenem perioperatively with penetrating keratoplasty in a case of multidrug-resistant *A. xylosoxidans* keratitis. We have demonstrated that topical meropenem is safe and effective, although the formulation and administration are laborious. With the increase of antibiotic drug resistance, topical meropenem may be considered as part of the armamentarium for the management of multidrug-resistant organisms causing bacterial keratitis.

Learning points

- All corneal ulcers should be referred to an ophthalmologist for further management. A corneal scrape should then be considered (by the ophthalmologist), to ascertain the organism responsible and this will help to determine the antibiotic sensitivities.
- It is important to consider the antibiotic minimal inhibitory concentration when considering antibiotic sensitivities.
- With the increase of antibiotic drug resistance, topical meropenem may be considered as part of the armamentarium for the management of multidrug-resistant organisms causing bacterial keratitis.

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