Research letters

Itraconazole demonstrated better antifungal activities, but posaconazole was the only clinically active antifungal agent against Alternaria species if adequate drug levels are achieved at the site of infection. Most isolates of A. infectoria and A. alternata had high MICs of voriconazole, although the environmental isolates of A. malorum (a non-human pathogenic species) had lower MICs. Isavuconazole had high MICs similar to voriconazole with complete inhibition endpoints exhibiting MIC90 values of 4 mg/L against all Alternaria isolates. Posaconazole demonstrated better in vitro activity than voriconazole and isavuconazole with an MIC90 of 1 mg/L. Posaconazole had the lowest MIC90 (0.25 mg/L) of all the azoles. The echinocandin drugs caspofungin and anidulafungin had similar MIC90 values of 4 mg/L, suggesting a potential role in therapy and prophylaxis if adequate drug levels are achieved at the site of infection. For example, posaconazole demonstrated potent activity (MIC90 0.25 mg/L) against all clinical and environmental isolates of Alternaria, but it remains to be confirmed that high enough drug levels can be reached at a remote site of infection. Isavuconazole has not been used clinically for Alternaria infections, but posaconazole was the only clinically active antifungal drug in the treatment of a severe invasive Alternaria infection in an immunocompetent patient. In the present study, the antifungal activities of posaconazole and anidulafungin were superior against clinical isolates of A. infectoria. Furthermore, we demonstrated better activity of anidulafungin compared with that of caspofungin, but it is not known whether these in vitro differences are clinically significant. In conclusion, posaconazole and anidulafungin demonstrated the highest in vitro antifungal activity against Alternaria species, including those clinical and environmental isolates that had higher MICs of voriconazole and isavuconazole; their clinical effectiveness in the treatment of Alternaria infection remains to be determined.

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Successful treatment with doripenem and tobramycin of ventriculitis due to imipenem- and meropenem-resistant Pseudomonas aeruginosa

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Sir,

*Pseudomonas* ventriculitis is an unusual infection associated with neurosurgical procedures or trauma. Treatment is usually with a combination of an intravenous (iv) anti-pseudomonal β-lactam and an aminoglycoside, administered iv and/or intrathecally (it). Ceftazidime has been the β-lactam used most frequently for pseudomonal CNS infections. Meropenem is the only carbapenem approved for CNS infections. The carbapenem class is the class of β-lactams most likely to encounter emerging antimicrobial resistance when used for treatment of *Pseudomonas aeruginosa* infections. We recently treated a patient with *P. aeruginosa* ventriculitis where the isolate developed resistance to all β-lactams except doripenem. A combination of doripenem and tobramycin (iv and it) was used with successful eradication of infection.

**Case**

An adult quadriplegic patient was transferred to our hospital for management of an infected ventriculoperitoneal (VP) shunt. VP shunting was first performed on this patient at the age of 27 months for congenital type 1 Arnold-Chiari malformation with a meningomyelocele. Three weeks prior to admission at our hospital, headache and fever developed and the patient was hospitalized at another facility. Tracheostomy site was noted to have eroded in close proximity to the VP shunt and examination of the CSF showed evidence of bacterial meningitis. Culture of CSF grew *P. aeruginosa*, susceptible to imipenem, meropenem, ceftazidime, cefepime, piperacillin/tazobactam, tobramycin and ciprofloxacin (Kirby-Bauer disc diffusion method). iv ceftazidime, meropenem and tobramycin were given and the patient was transferred to our hospital.

Computed tomography (CT) of the abdomen showed no abscess or fluid collection. Cultures of the blood and urine were negative. Chest radiograph did not reveal infiltrates. The white blood cell count was 19 100 cells/mm³. Measurements of renal and hepatic function were normal. CT of the head with iv contrast showed right parieto-occipital VP shunt and no hydrocephalus.

Meropenem (1 g iv every 8 h) and tobramycin (5 mg/kg iv daily) were continued. On the third day of hospitalization, the VP shunt was removed and an external ventricular device (EVD) was placed. Cultures of the VP shunt and wound grew *P. aeruginosa* susceptible to tobramycin, amikacin and ciprofloxacin, but resistant to cefepime, ceftazidime, imipenem, piperacillin/tazobactam and aztreonam (MicroScan, Dade Behring Inc., Sacramento, CA, USA).

Two days later, culture of CSF obtained from the EVD grew *P. aeruginosa* with susceptibilities identical to those previously reported. Additional testing of the isolate showed resistance to meropenem with an MIC of >8 mg/L and susceptibility to doripenem with an MIC of 1.5 mg/L (Etest, AB bioMerieux, Durham, NC, USA) and colistin.

Meropenem was discontinued and doripenem (1 g iv infused over 60 min every 8 h) and tobramycin (10 mg it daily) were started. iv tobramycin was continued. Ciprofloxacin was not used as the patient had a history of anaphylaxis following administration of ofloxacin.

Additional cultures of CSF obtained 3, 5, 6, 7 and 8 days after VP shunt removal grew *P. aeruginosa* with identical antimicrobial susceptibilities. Magnetic resonance imaging of the head with gadolinium contrast showed no evidence of an intracranial abscess or fluid collection.

CSF cultures obtained 9, 12, 13, 14 and 15 days after VP shunt removal did not grow any organisms. Fourteen days of doripenem and it tobramycin and 21 days of iv tobramycin were administered. The patient experienced no adverse effect attributed to the antimicrobials (e.g. myoclonus, seizure or renal dysfunction). Audiometry was not performed.

Eighteen days after removal of the VP shunt, a left VP shunt was placed and the EVD was removed. One month after placement of the new VP shunt, the patient remained stable with no evidence of recurrent ventriculitis.

Usual therapy of VP shunt infection includes removal of the infected shunt and administration of iv and/or it antibiotics. iv and/or it colistin has been used successfully in the management of CNS infections due to multiresistant Gram-negative organisms. Use of colistin in our patient was considered and would likely have been used had the patient failed to respond to doripenem and tobramycin. Ciprofloxacin has been successfully used in *Pseudomonas* ventriculitis, but our patient’s history of anaphylaxis following ofloxacin administration precluded its use.

Meropenem is the only anti-pseudomonal carbapenem approved for the management of CNS infections. The isolate in our patient was initially susceptible to anti-pseudomonal β-lactams, but became resistant after exposure to ceftazidime and meropenem. The isolate from the initial hospital was not available for genetic testing to establish a clonal relationship with the isolates from our hospital, but we suspect that the isolate developed resistance as a result of antibiotic exposure.

Doripenem is a recently approved carbapenem with improved activity against *P. aeruginosa*. Resistance appears less likely to emerge after exposure of *P. aeruginosa* to doripenem *in vitro* and possibly *in vivo*. Combining doripenem with an aminoglycoside may delay emergence of resistance.

*P. aeruginosa* isolates resistant to imipenem and meropenem may retain susceptibility to doripenem, as occurred in our patient.

Doripenem is currently approved only for intra-abdominal and urinary tract infections with the usual dose of 500 mg iv every 8 h. We chose to use a higher dose of 1 g every 8 h to approximate serum concentrations achieved with meropenem. Doripenem is recognized to have potential neurotoxicity, especially when used in patients with neurological disorders and in high doses. Based on animal models and the results of clinical trials, doripenem may be less epileptogenic than other carbapenems.

No neurotoxicity was observed in our patient.

With antimicrobial resistance limiting therapeutic options, treatment of CNS infections may increasingly leave clinicians in a therapeutic quandary. Additional future reports of clinical experiences in these situations will be helpful and may aid healthcare providers in decision making.

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Rhabdomyolysis and acute renal failure associated with the co-administration of daptomycin and an HMG-CoA reductase inhibitor

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Research letters

A patient suffered a fall injury with a resulting fracture of the femoral bone at the site of previous total hip arthroplasty. Irrigation and debridement and removal of the prosthesis were performed. Intravenous (iv) vancomycin (1 g every 24 h) and cefepime (1 g every 12 h) were given post-operatively. Copious amounts of purulence had been encountered at the arthroplasty site, but no organisms grew from intraoperative cultures. For the next 2 weeks, there was no fever, but the white blood cell (WBC) count remained elevated (18000–23000 WBC/mm3). Four days later, the daptomycin dose was changed to 7.2 mg/kg every 48 h.

Six days after stopping daptomycin, the serum creatinine concentration reached a peak of 3.4 mg/dL. Urinalysis revealed 1+ albumin and a urine Hansel stain showed eosinophils. The patient’s usual medications included simvastatin (80 mg each evening), extended-release niacin (500 mg each evening) and esomeprazole (20 mg daily) and were continued throughout her hospitalization.

Six days after stopping daptomycin, the serum creatinine returned to baseline. Seven days after stopping daptomycin, the CPK concentration had decreased to 125 IU/L.

A 4 week course of linezolid was completed, followed by oral minocycline 100 mg twice daily. The arthroplasty was successfully revised and the patient was discharged on long-term suppressive minocycline therapy, continuing to do well after 1 year with no evidence of recurrent infection.

Few cases of daptomycin-induced rhabdomyolysis have been described in the literature.2–5 In clinical trials, up to 6.7% of subjects experienced an increase in CPK concentrations.6 In Phase 3 cSSSI studies, 0.2% of patients treated with daptomycin had delayed resistance.7

In a patient with a fracture of the femoral bone at the site of a previous total hip arthroplasty, daptomycin was administered post-operatively. Despite the absence of organisms, the white blood cell count remained elevated. Four days later, the daptomycin dose was adjusted.

Six days after stopping daptomycin, serum creatinine exceeded 125 IU/L.

A 4 week course of linezolid was followed by oral minocycline 100 mg twice daily. The arthroplasty was revised, and the patient was discharged on minocycline therapy, continuing to do well after a year. No recurrent infection was observed.

Few cases of daptomycin-induced rhabdomyolysis have been reported. In clinical trials, up to 6.7% of subjects experienced an increase in CPK concentrations.6 In Phase 3 cSSSI studies, 0.2% of patients treated with daptomycin had delayed resistance.7

In conclusion, daptomycin is a lipopeptide antibiotic approved for the treatment of complicated skin and skin structure infections (cSSSIs) due to specified organisms. Although well tolerated in clinical trials and use, there have been reports of elevations in serum creatinine phosphokinase (CPK) concentrations, occasionally with accompanying rhabdomyolysis and acute renal failure. Here, we report this first case of CPK elevation with rhabdomyolysis and acute renal failure that developed during the co-administration of daptomycin and an HMG-CoA reductase inhibitor. Symptoms resolved after discontinuation of daptomycin.