and linezolid 600 mg twice daily. At that time the patient was also receiving venlafaxine 150 mg nocte for depression.

Twenty days after commencing the oral antibiotic regimen the patient was noted to be confused and disorientated, with disturbance of his sleep–wake cycle, and was intermittently aggressive. A computed tomography scan of the brain did not reveal any significant abnormality, serum biochemistry was normal, full blood examination (FBE) showed normal white cell count and there was no clinical evidence of sepsis. His vital signs were within the normal range and clinical examination did not reveal a specific reason for his altered mental status. Four days later the patient became drowsy and was transferred from the rehabilitation centre to an acute hospital. There he was found to have a reduced level of consciousness and fever of 37.6°C. He had widespread increased tone, generalized myoclonic jerks and down-going plantar reflexes. FBE and electrolytes did not show any significant abnormality and creatinine kinase was within the normal range. A drug reaction was suspected; linezolid and venlafaxine were stopped. Within 2 days the patient had recovered to his usual level of mental functioning. The most likely diagnosis was serotonin syndrome due to the interaction between linezolid and venlafaxine.

Serotonin syndrome is caused by excessive central nervous system and peripheral serotonergic activity, predominantly 5HT-1a (5-hydroxytryptamine). This is usually due to drug interactions between agents that promote release of serotonin, or inhibit the reuptake or metabolism of serotonin in the presynaptic space. Onset may be acute or delayed after instigation of offending agents. The syndrome manifests as altered mental status, including agitation, confusion and coma, neuromuscular hyperactivity (restlessness, myoclonus, hyperreflexia, tremors), and autonomic dysfunction. It may be clinically confused with neuroleptic malignant syndrome (NMS), although resolution is generally faster, creatinine kinase levels are only minimally raised in proportion to the degree of rigidity and the ‘lead-pipe’ rigidity seen in NMS is absent.

The diagnosis is based on clinical signs and symptoms and an appropriate drug history. Treatment is symptomatic, although the use of serotonin-receptor antagonists may speed resolution. Cyproheptadine is a drug with 5HT-1a and 5HT-2 receptor blocking activity, and may be used.

Linezolid is the first member of the synthetic oxazolidinone family of antimicrobials to be used in clinical practice. This group of drugs was originally developed as monoamine-oxidase inhibitors for the treatment of depression, but was subsequently noted to have antimicrobial properties against Gram-positive organisms and was further developed for this purpose. As an antimicrobial, linezolid inhibits bacterial ribosomal protein synthesis, preventing formation of the 70S initiation complex. This unique process precludes cross-resistance to other agents.

Linezolid is active against major Gram-positive pathogens, Neisseria spp., Nocardia spp. and possibly Mycobacteria spp. It has 100% bioavailability, does not require dosage adjustment for renal or hepatic disease and comes in oral and intravenous forms. Other than reversible marrow suppression, the drug has a very favourable side-effect profile and is tolerable to patients. These factors all make linezolid a very attractive option for the treatment of complicated Gram-positive infections on an outpatient basis.

A Phase III study of linezolid included 52 patients receiving concomitant linezolid and an SSRI with no reports of serotonin syndrome. Given the limited treatment experience with these agents in combination, physicians were alerted to be aware of the potential for interaction.

Serotonin syndrome has been reported in a patient receiving low-dose venlafaxine (a serotonin noradrenergic reuptake inhibitor) alone; however, it is most commonly caused by drug interactions. The syndrome has been now been described as being the result of interaction between linezolid and citalopram, linezolid and paroxetine.

Linezolid is a useful antimicrobial that has a role in treating difficult Gram-positive infections. There is an increasing body of reports of clinically important interactions between linezolid and serotonergic antidepressant drugs. Physicians need to be continually aware of the potential for significant interactions, particularly in these groups of patients with complex infections, in whom depression is common.

Acknowledgements

We would like to acknowledge the assistance of the ward pharmacist Poh Sin Kok.

References

Sir,

Post-neurosurgical meningitis is a serious complication. When this disease is caused by a multidrug-resistant pathogen, the management of such a case is challenging. Multidrug-resistant Acinetobacter baumannii has become one of the more common nosocomial pathogens in hospitals. Infections caused by this bacterium are more common in patients with severe underlying diseases, and after multiple courses of antibiotic treatment.1 When the infection involves the meninges, the choice of an antibiotic is further limited by the blood–brain barrier. Intrathecal treatment is often the last resort in such cases.2 Polymyxins have not been used frequently, and in cases of multiple resistance, might be one of the only options. This class of antibiotic has been given intrathecally only to very few patients.3,4 We present a case of Acinetobacter meningitis, cured by intrathecal polymyxin E.

A 49-year-old woman had a history of recurrent craniotomies (in another hospital) due to a recurrent meningioma in the base of her skull. She was blind in both eyes and anosmic, since the first operation in 1989. Her history included serious complications such as CSF leak and recurrent meningitis. She first presented to our neurosurgical department in 1999 with recurrence of the tumour in the lower frontal lobes and invasion of the sphenoidal, ethmoidal and right maxillary sinuses. In the first operation in our department, which was carried out via subcranial approach, the tumour was totally removed with reconstruction of the large bone defect at the base of the skull using an artificial dural patch. On the fourth day after surgery, her temperature was 38°C and she was lethargic. Piperacillin–tazobactam was started as empirical treatment. On the 11th day, her temperature was 40.2°C with CSF rhinorrhea, evidenced by high glucose levels in the fluid. Meropenem and vancomycin were substituted for the piperacillin–tazobactam combination. This multi-resistant isolate was further limited by the blood–brain barrier. Intra- 

Table 1. Representative culture and laboratory results

<table>
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<tr>
<td>Cells (CSF)</td>
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<tr>
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<tr>
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<td>Enterobacter</td>
<td>Acinetobacter</td>
<td>MRSA</td>
<td>Acinetobacter</td>
<td>Acinetobacter</td>
<td>Candida</td>
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<td>base of skull</td>
<td>base of skull</td>
<td>base of skull</td>
<td>culture</td>
<td>CF (from the shunt)</td>
</tr>
</tbody>
</table>

MRSA, methicillin-resistant Staphylococcus aureus; CSF, cerebrospinal fluid.
*Post-operative day (first surgery).
possibly due to prolonged treatment with multiple antibiotics. Sulbactam is bacteriostatic for this bacterium. Experience with this drug is limited to one case report. We elected to treat the patient with intrathecal polymyxin E, in spite of the numerous central nervous system side effects that have been reported, and the limited experience with this treatment modality. Rapid improvement of the patient’s mental status and the disappearance of fever and other inflammatory symptoms proved that this rare application of polymyxin is effective in Gram-negative meningitis.

References

Journal of Antimicrobial Chemotherapy DOI: 10.1093/jac/dkh306
Advance Access publication 9 June 2004

Treatment of meningeal coccidioidomycosis with caspofungin
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Keywords: echinocandins, meningitis, Coccidioides

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Sir,
Current mainstays of therapy for disseminated coccidioidomycosis are fluconazole and itraconazole, with amphotericin B chiefly reserved for refractory cases. Lifelong azole therapy is suggested for those with meningitis. Despite the use of these agents, many patients still relapse with disease progression often leading to death. Many of the new and investigational antifungal agents have been evaluated for activity against Coccidioides immitis in vitro and in limited animal studies. Those agents identified to have potential for use in coccidioidomycosis include voriconazole, caspofungin and posaconazole. We present a case report describing the presumed failure of caspofungin to treat a person with disseminated coccidioidomycosis complicated by chronic fungal meningitis.

A 23-year-old African-American male developed disseminated coccidioidomycosis with chronic meningitis after an environmental exposure while working as a truck driver in Arizona in the Spring of 2002. Initially, he was seen at an outside facility after developing mental status changes. Following his initial diagnosis, he was treated with amphotericin B and then a lipid-based formulation of amphotericin B, the change prompted by renal dysfunction. He was discharged on oral fluconazole. He was first seen in our system after a referral from the Emergency Department for re-evaluation and follow-up. At that time, he was not taking his fluconazole either as ordered or at all. His dose of fluconazole was increased to 800 mg daily as an outpatient, but after several episodes of mental status changes and reports of medical non-adherence, he was admitted to our institution for further evaluation and therapy. At the time of this admission in August 2002, he was found to have multiple subcutaneous and retroperitoneal abscesses, painful lower extremity bone lesions, as well as continued meningitis with mild-moderate hydrocephalus. CSF parameters showed pleocytosis, abnormal protein concentration, and a coccidioidal complement fixation (CF) antibody titre of 1:4 in the CSF (Table 1). Serum CF titre at that time was 1:256. All coccidioidal CF antibody testing was carried out at the University of California at Davis Coccidioidomycosis Serology Laboratory of Dr D. Pappagianis. His bone lesions, subcutaneous and retroperitoneal abscesses were treated surgically and fluconazole therapy continued. He responded initially to this therapy, with CSF WBC improving to 9 cells/mm³ (96% mononuclear cells) in February of 2003. Unfortunately, his medical non-adherence continued and episodes of delusional psychosis led to attempts to deliver his therapy by direct observation. In July 2003, his CSF parameters had worsened and CSF CF antibody titres were noted to be 1:8. As a result of continued questions of medical non-adherence, and his CSF parameters, his therapy was changed to directly-observed oral voriconazole at 400 mg, and later 600 mg/day. The patient continued to clinically deteriorate on outpatient therapy, with increased delusional thinking, leading to repeat hospitalization in September 2003 for re-evaluation of therapy. At admission, he was treated with intravenous liposomal amphotericin B and a ventriculoperitoneal CSF shunt was placed. At the time of shunt placement, a lumbar intrathecal catheter and reservoir were also placed for potential future use. On liposomal amphotericin B, he again developed acute renal insufficiency, leading to withdrawal of that agent and initiation of a trial of caspofungin. He was given a loading dose of 70 mg intravenously, and 50 mg/day thereafter of caspofungin. During 22 days of echinocandin therapy, our patient developed right ankle pain, but otherwise did not appear to worsen or improve clinically. Bone scan carried out on the 19th day of this therapy found increased uptake about his ankle, a site previously involved. A similar