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Treatment of external ventricular drain-associated ventriculitis caused by *Enterococcus faecalis* with intraventricular daptomycin

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Sir,

External ventricular drains (EVDs) are essential monitoring devices in neurosurgery, and direct portals for the removal of cerebrospinal fluid (CSF), including the temporary control of raised intracranial pressure, and for the instillation of therapeutic agents. Their benefits must be balanced against the complications associated with their use, the most important of which is infection (ventriculitis). Most patients with EVD-associated ventriculitis can be cured by instilling antibiotics directly into the ventricles.[1] We describe here a patient with such an infection treated by administering daptomycin using this route.

A 62-year-old man was admitted to this hospital with a subarachnoid haemorrhage and underwent coil occlusion of an anterior communicating artery aneurysm. Four days later, he became confused and was noted to have raised intracranial pressure; a lumbar drain was inserted. He subsequently became pyrexial and culture of CSF obtained via the lumbar drain yielded *Klebsiella pneumoniae*. An EVD was inserted and the ventriculitis was successfully treated with a 14 day course of intravenous ceftazidime and intraventricular gentamicin. The intention was to remove the EVD on day 30. However, Gram's stain examination of a sample of CSF showed Gram-positive cocci, and *Enterococcus faecalis*, which was susceptible to ampicillin and vancomycin, but exhibited high-level resistance to gentamicin (MIC $>$ 200 mg/L), was isolated. Vancomycin (10 mg) was instilled into the ventricles, but, after 8 days of therapy, *E. faecalis* was still recovered from the CSF. The MIC of daptomycin for this strain was 2.0 mg/L, as determined by an Etest on Mueller–Hinton agar, and this drug was administered intravenously at a dosage of 1 g (12 mg/kg) once daily. In addition, the EVD was removed and an Ommaya reservoir was implanted. Following a further 4 days of therapy with intraventricular vancomycin, *E. faecalis* was again recovered from the CSF. It was therefore decided to instil daptomycin into the ventricles at a dosage of 10 mg every third day; consent was obtained from the patient. Trough and peak daptomycin CSF concentrations (determined just before and 30 min after a dose, respectively, by high-performance liquid chromatography at the Department of Medical Microbiology, Southmead Hospital, Bristol, UK) were 23 and 483 mg/L, respectively. The dosage of daptomycin was reduced to 5 mg every third day, and trough and peak daptomycin CSF concentrations at the lower dosage were 9.9 and 139 mg/L, respectively. The CSF became sterile within 3 days of commencing intraventricular daptomycin and remained so throughout the 2 week treatment period. The patient remained well and he was eventually discharged from hospital. However, he was re-admitted 28 days later with symptoms and signs of meningitis. Culture of a sample of CSF yielded *E. faecalis* with the same antibiogram as the original isolate and treatment with intraventricular daptomycin at a dosage of 5 mg every third day was restarted. In addition, the Ommaya reservoir was replaced with an EVD. Daptomycin was administered for 4 weeks during which time he experienced transient pyrexias after each instillation of daptomycin; this side effect was resolved when the treatment was discontinued. The CSF became sterile, the EVD was removed and he was discharged from hospital 39 days after he had been re-admitted. Clinical and bacteriological cures were sustained after follow-up for more than 1 year.

EVD-associated ventriculitis is one of the most common infections in neurosurgical practice. Until recently, only three antibiotics have been available in formulations suitable for intraventricular use: vancomycin, gentamicin and colomycin. Enterococci are increasingly being recognized as causes of ventriculitis in neurosurgical patients, and some strains exhibit resistance to vancomycin or high-level resistance to the aminoglycosides, thereby limiting treatment options. Linezolid has been used successfully as systemic therapy in such cases.[2,3] However, this antibiotic is not bactericidal and prolonged courses increase the risks of adverse effects. Daptomycin is the first of a new class of antibiotics, the cyclic lipopeptides. It has been shown to be rapidly bactericidal against enterococci, including vancomycin-resistant strains.[4] Daptomycin penetrates poorly into the CSF compartment when given by the systemic route. In a rabbit model of meningitis caused by *Streptococcus pneumoniae*, only 5% of the corresponding serum concentration was achieved in the CSF, and the drug failed to sterilize the CSF after 4 days, despite the administration of a high dosage.[5] On the other hand, a study involving a rabbit model of *Staphylococcus aureus* ventriculitis demonstrated that intraventricular daptomycin achieved greater bactericidal activity, more rapid killing kinetics and a longer half-life in the ventricles than intraventricular vancomycin.[6] Many years' experience of managing patients with EVD-associated ventriculitis by instilling antibiotics into the ventricles encouraged us to treat the patient described in this report with intraventricular daptomycin. This present experience suggests that intraventricular daptomycin is an effective therapy of patients with EVD-associated ventriculitis caused by enterococci; it may be equally appropriate as treatment

for patients with ventriculitis caused by other Gram-positive bacteria and those with CSF shunt infections. However, additional clinical data are needed to confirm its clinical efficacy and safety in this setting.

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J. E. and D. P. have nothing to declare. E. B. has served on Novartis advisory boards and received speaker's fees from Novartis.

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Minor emtricitabine intolerance in treatment-stable patients switched from tenofovir/lamivudine to a fixed-dose combination of tenofovir/emtricitabine (Truvada®)

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Sir,

Emtricitabine[1] has characteristics similar to lamivudine with respect to activity, safety and resistance profile, and according to the current treatment guidelines, the two drugs are interchangeable.[2] As the fixed-dose combination of emtricitabine and tenofovir was approved (Truvada®) (TVD), tenofovir and lamivudine have been replaced in many patients by TVD for convenience.

We report the safety of simplification from tenofovir/lamivudine to TVD in virologically suppressed HIV-infected patients on highly active antiretroviral therapy between November 2005 and May 2006 in 10 Spanish hospitals. This study was designed and conducted according to the principles of the declaration of Helsinki. It was approved by the Ethics Committee of the Hospital Virgen de la Victoria. Of the 295 patients who underwent the change from tenofovir/lamivudine to TVD, 6 (2%) suspended emtricitabine due to adverse effects. In all six cases, lamivudine was reintroduced with no problems and viral suppression was maintained. The reasons for suspension were neurological symptoms in five patients and hyperpigmentation of the palms of the hands in one patient. The symptoms in the five patients with CNS toxicity, which appeared during the first 3 days after the switch, were insomnia, irritability and confusion. One of the five patients with CNS symptoms also experienced nausea and vomiting (Table 1). All other patients tolerated the new combination well.

Although lamivudine and emtricitabine may theoretically be comparable, small differences exist, including a varying pattern of adverse effects resulting in some patients being unable to tolerate emtricitabine. An earlier study found that 8% of the patients who changed from lamivudine to emtricitabine had to stop it during the first month due to adverse effects, mostly neurological.[3] In another study, the change from lamivudine to emtricitabine was associated with a 3% rate of discontinuation due to adverse effects, again as a result of neurological symptoms.[4] Whatever the case, the percentage of patients who have to suspend emtricitabine due to adverse effects, mainly neurological symptoms, is small and most patients can switch from lamivudine to emtricitabine for convenience with no problems.

Table 1. Reasons for switching back from emtricitabine to lamivudine in the 6 patients with 'emtricitabine intolerance' of the 295 who undertook the change

Cases	Reason for switch
Patient 1	felt 'unwell' (confused)
Patient 2	fatigue, felt 'strange' (confused)
Patient 3	fatigue, muscle aches, sweats, insomnia, irritability
Patient 4	fatigue, felt 'strange' (confused), insomnia
Patient 5	insomnia, irritability, nausea and vomiting
Patient 6	hyperpigmentation of the palms of the hands