Case Report

Successful treatment of vancomycin-resistant *Enterococcus faecium* ventriculitis with combined intravenous and intraventricular chloramphenicol in a newborn

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Vancomycin-resistant *Enterococcus faecium* (VRE) infection is a rare event in paediatric patients and often occurs under immunosuppression or after surgical intervention. We report what we believe to be the first paediatric case of ventriculitis due to VRE (in a 2-month-old infant) to be successfully treated with combined intravenous (i.v.) and intraventricular chloramphenicol after failure of i.v. linezolid and intraventricular gentamicin.

Introduction

Vancomycin-resistant *Enterococcus faecium* (VRE) infection of the central nervous system (CNS) occurs quite rarely and there are no guidelines recommending an appropriate treatment. Intravenous (i.v.) linezolid has been used for successful therapy of VRE ventriculitis in two paediatric cases (Graham *et al.*, 2002; da Silva *et al.*, 2007). However, several adult cases are known where linezolid failed to eradicate VRE due to prior or long-term use of the substance (Pai *et al.*, 2002). After appropriate dosage, i.v. chloramphenicol proved to be safe and effective, even in paediatric patients (Baysallar *et al.*, 2006; Pérez Mato *et al.*, 1999). It has been shown to effectively penetrate the cerebrospinal fluid (CSF) with concentrations corresponding to approximately 70–90 % of simultaneous serum concentrations (Friedman *et al.*, 1979). Successful combined i.v. and intraventricular application of chloramphenicol in VRE meningitis has to date been published in only one case in an adult (Scapellato *et al.*, 2005).

Case report

A mature, immunocompetent, female newborn suffered from a congenital sacrococcygeal teratoma with extensive

spinal dissemination and a Dandy–Walker cyst resulting in a flaccid paralysis of her lower trunk and extremities (Fig. 1a, b). She received three broad resections of the spinal and lumbar parts of the teratoma between her second and fifth week of life, each with perioperative antibiotic treatment. An increasing hydrocephalus internus required placement of a Rickham reservoir at day 21 of life with three times daily (t.i.d.) punctures. Awaiting further surgical interventions, placement of a ventriculoperitoneal shunt was initially postponed.

At day 35 of life, she suffered from a radiologically proven pneumonia. Microbiological examination of a broncho-alveolar lavage sample at this time detected *Serratia marcescens* and physiological respiratory tract flora. I.v. antibiotic therapy with ampicillin, tobramycin and cefotaxime was initiated, followed by vancomycin due to ongoing signs of infection.

On day 53 of life, she developed a fever, an increase in C-reactive protein (253 mg l⁻¹) and interleukin-6 (732 ng l⁻¹) as well as changes in her mental status. For the first time, VRE was isolated from stool, blood and CSF samples, the latter showing a pleocytosis up to 400 cells µl⁻¹ at a maximum. The enterococcus tested susceptible to linezolid. The Rickham reservoir was removed and changed to bilateral external ventricular drainages. In addition, i.v. antibiotics were switched to linezolid [total of 110 mg=20 mg

Abbreviations: b.i.d., twice a day; CNS, central nervous system; CSF, cerebrospinal fluid; i.v., intravenous; s.i.d., once a day; t.i.d., three times a day; VRE, vancomycin-resistant *Enterococcus faecium*.

Fig. 1. T2-weighted MRI scan, postnatal. (a) Arachnoid cyst in the posterior cranial fossa with displacement of the medulla oblongata and cerebellum (*). Thoracic and cervical areas of the sacrococcygeal teratoma are also shown (arrow). (b) Lumbar areas of the teratoma showing an extensive spread of cystic and solid areas within the spinal canal (arrow) and pelvic base (*).

linezolid kg^{-1} per day, twice a day (b.i.d.)], after 10 days supplemented by intraventricular gentamicin [1 mg = 0.18 mg gentamicin kg^{-1} per day, once a day (s.i.d.)] and maintained for another 10 days (Fig. 2). Her clinical situation improved slowly and blood cultures proved to be sterile after 7 days of treatment. However, CSF samples, obtained twice a week, revealed persistence of VRE and again increasing cell counts at day 73 (Fig. 2). Repeated *in vitro* testing showed that the VRE was susceptible to linezolid (MIC 2 mg l^{-1}).

Extended antibiotic testing by Epsilometer test (Etest; bioMérieux) showed susceptibility to chloramphenicol (MIC 4 mg l^{-1}). Thus, after a total of 12 days, intraventricular gentamicin was changed to i.v. chloramphenicol at day 79 of life (start 230 mg = 42 mg chloramphenicol kg^{-1} per day increased to 420 mg = 76 mg chloramphenicol kg^{-1} per day, b.i.d., at a maximum). The intended serum trough level of 5–10 $\mu\text{g ml}^{-1}$ (combined free chloramphenicol/chloramphenicol succinate) was determined by HPLC. Despite a gradual increase of i.v. dosages, actual serum trough levels varied widely between 0.5 and 9.2 $\mu\text{g ml}^{-1}$. Within the next 28 days, this combination of antibiotics stabilized CSF cell counts at a total of 16–70 cells μl^{-1} . Nevertheless, CSF samples remained positive for VRE. Therefore, we stopped i.v. linezolid and added intraventricular chloramphenicol via the external drain at day 107 of life. The effective intraventricular dosage was gradually adjusted to 7 mg = 1.3 mg kg^{-1} per day (s.i.d.) according to CSF trough levels and dissolved in 2 ml saline. The external drainage system was temporarily occluded for 1 h after each application and we daily alternated application site between both drainages. CSF chloramphenicol/

chloramphenicol succinate levels were determined every third day via the drainage system. Samples were obtained immediately before the following intraventricular application hence 12 h after the last i.v. dose, each time dropping the first 2 ml of the sample in order to avoid contamination by the drainage system. Like serum levels, CSF trough levels varied between 2.5 and 7.2 $\mu\text{g ml}^{-1}$. Five days after the start of intraventricular chloramphenicol, CSF proved to be sterile for VRE for the first time in 7 weeks. This result persisted in three subsequent samples within 1 week.

Intraventricular and i.v. application were both terminated 1 week after the first negative microbiological examination of CSF, i.e. after a total of 12 days. Full blood count was checked routinely twice a week and we did not identify any haematological or neurological side-effects during i.v. or combined chloramphenicol treatment. After receiving three negative microbiological results for CSF specimens, a ventriculoperitoneal shunt system was successfully placed and has remained sterile to date. Testing of the long-term neurological outcome after 18 months (except for her motor deficits) showed results expected for her age.

Discussion

During the last decade, VRE has played an increasing role as a multiresistant pathogen worldwide. Within the US, there has been a rise in the overall incidence of infection by enterococci, now the third most frequent cause of nosocomial infection, and multidrug resistance has been found in up to 60% of *Enterococcus faecium* strains (Wisplinghoff *et al.*, 2004). In comparison, resistance statistics in our own

Fig. 2. CSF data and antibiotic regime. The start of i.v. chloramphenicol (CMP) is indicated by an arrow. Addition of intraventricular (i.ventr.) chloramphenicol is indicated by *. Combined i.v. linezolid/intraventricular gentamicin and i.v. chloramphenicol treatment was given over 7 weeks (week of life 7–13). The CSF culture result proved positive for VRE over 7 weeks until day 5 of combined i.v. and intraventricular chloramphenicol treatment.

institution (tertiary hospital) document a <20 % rate for VRE within the last decade.

An underlying CNS pathology and succeeding neurosurgical interventions including placement of invasive devices, prior use of antimicrobials and long-term hospitalization at an intensive-care unit contribute as risk factors for the development of otherwise rare VRE CNS infections in children.

Distinct therapy for VRE CNS infections has yet to be established. Several case reports show good response for i.v. linezolid in VRE meningitis in all ages, indicating sufficient penetration into the CSF (Zeana *et al.*, 2001; Graham *et al.*, 2002; da Silva *et al.*, 2007). In contrast, failure of linezolid therapy despite ongoing susceptibility in the antibiogram was reported by Webster *et al.* (2009) in one case in an adult. Current literature reports a 1.8 % rate of resistance among overall VRE isolates, due to prior or long-term (>21 days) use of the substance (Pai *et al.*, 2002).

In our patient, VRE persisted in the CSF despite decreasing cell counts, which led us to additional application of

intraventricular gentamicin in order to increase therapeutic effectiveness (Arnell *et al.*, 2007). However, after 3 weeks of i.v. plus intraventricular treatment, antibiotic testing was extended proving susceptibility to chloramphenicol too.

Chloramphenicol, first derived in 1947, has a bacteriostatic profile with effective trough levels of 5–10 µg ml⁻¹ and noticeable individual variations of its pharmacokinetics especially in infants and children (Friedman *et al.*, 1979). There are several paediatric case reports showing positive results in the i.v. chloramphenicol treatment of VRE CNS infections (Pérez Mato *et al.*, 1999; Baysallar *et al.*, 2006). The CSF concentration of chloramphenicol reaches approximately two-thirds of the simultaneous serum concentration with a wide range of 45–99 % (Friedman *et al.*, 1979). In our patient, we found clearance rates increasing from 6 to 67 ml kg⁻¹ min⁻¹ during the first 4 weeks of i.v. treatment accompanied by variations of serum trough levels during gradual adjustment of i.v. dosages. Both findings indicate a rather unstable steady-state and variations might reflect maturation of renal and liver function over the age range, delayed hydrolysis into the active drug and differences in administration or drug interaction (Friedman *et al.*, 1979).

In the late 1950s and 1960s, chloramphenicol was discredited based on its haematological toxicity including idiopathic bone-marrow aplasia and the occurrence of grey baby syndrome. However, in 1983, a study on 64 neonates by Mulhall *et al.* (1983) found serious toxicities only with serum chloramphenicol trough levels >25 µg ml⁻¹ due to either overprescription or overdosage.

Due to the broad variability of serum levels and failure to obtain negative CSF cultures by i.v. chloramphenicol treatment, our aim was to assure sufficient CSF levels to finally eliminate the VRE without risking any toxicities. Successful intraventricular application of chloramphenicol without considerable adverse effects has been reported in three different cases of adult VRE and in multiresistant *Staphylococcus aureus* meningitis (Anderson & Ellis, 1951; Scapellato *et al.*, 2005). Prior use of both oral and i.v. chloramphenicol had failed to eliminate the pathogen in the CSF in all cases. In 1978, Salmon reported a case series of seven infants under 1 year of age with ventriculitis caused by *Escherichia coli*, *Salmonella* or group B *Streptococcus* successfully treated by the combined use of oral and intraventricular chloramphenicol. Single daily intraventricular and oral doses of 50 mg each resulted in CSF trough levels between 18 and 134 µg ml⁻¹ with only one child suffering from a reversible decreasing reticulocyte count (Salmon, 1978).

To our knowledge, intraventricular dosages have so far varied between 25 and 50 mg s.i.d.–t.i.d. (Salmon, 1978) in infants and 0.75 mg (Anderson & Ellis, 1951)–25 mg s.i.d. (Scapellato *et al.*, 2005) in adults. We opted for a cautious approach of an additional intraventricular dose of 5 mg per day (0.9 mg kg⁻¹ per day, s.i.d.) increasing up to 7 mg per day (1.3 mg kg⁻¹ per day, s.i.d.) under close

surveillance of CSF trough levels and clinical observation of the patient's neurological status. We found a prompt and lasting microbiological response and did not observe any haematological or neurological side-effects with i.v. and intraventricular trough levels adjusted to $<10 \mu\text{g ml}^{-1}$. With an MIC of $4.0\text{--}6.0 \text{ mg l}^{-1}$ for sensitive organisms (McLaurin, 1973), higher – and therefore potentially toxic – trough levels in the serum and CSF should be avoided, especially in paediatric patients with a broad variability of trough levels.

We continued combined i.v. and intraventricular chloramphenicol treatment for 7 days after the first negative CSF culture, a total of 40 days of i.v. chloramphenicol treatment, including 12 days of combined treatment with an overall cumulative dose of 2.3 g kg^{-1} . In the literature, intraventricular treatment with chloramphenicol in two adults was terminated after 19 days and 6 days, respectively, after an increase in reversible neurological side-effects such as depression and tremor after more than 1 week of intraventricular treatment (Anderson & Ellis, 1951) was noted. Nahata (1989) reported on a statistical trend towards an increase in haematological adverse effects for paediatric patients receiving i.v. chloramphenicol with mean cumulative doses ranging from 1.2 to 1.8 g kg^{-1} compared to those receiving $0.9\text{--}1.1 \text{ g kg}^{-1}$. Keeping in mind its potential toxicity with higher cumulative doses and the lack of information on possible long-term neurological effects after intraventricular instillation, we therefore stopped treatment as early as possible after 1 week comprising three negative CSF culture results.

Since first-line antibiotics failed, a closely monitored combination of i.v. and intraventricular chloramphenicol proved to be a feasible and well-tolerated treatment alternative in infant VRE ventriculitis with a prompt and lasting clearance of the pathogen. In view of increasing numbers of multidrug-resistant infections, especially in infants and children with long-term hospital stays, old antibiotics might be rehabilitated in the treatment of otherwise uncontrollable infections. Since we base our experiences on only one single case report, further clinical investigations will be necessary in the future to obtain reliable intraventricular dosage recommendations targeting specific pathogens.

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