Cerebrospinal Fluid (CSF) Pharmacokinetics of Intraventricular Vancomycin in Patients with Staphylococcal Ventriculitis Associated with External CSF Drainage

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We studied the efficacy and pharmacokinetics of intraventricularly administered vancomycin in three patients with shunt-associated staphylococcal ventriculitis. We instilled 10 mg of the drug intraventricularly every 24 hours. Cerebrospinal fluid (CSF) levels were measured 1 hour after instillation and then every 2 hours. Peak vancomycin levels reached a mean of 292.9 μg/mL. The mean trough levels, measured immediately before readministration of vancomycin, were 7.6 μg/mL; this level has proved to be sufficient for maintaining the necessary steady-state serum concentration of vancomycin. All three patients were cured clinically and bacteriologically, and CSF parameters returned to normal within 5–13 days. No side effects were observed. Our results suggest that intraventricularly administered vancomycin is a valuable therapeutic strategy for treating shunt-associated staphylococcal ventriculitis. In addition, we provide evidence that 10 mg of vancomycin, administered intraventricularly every 24 hours, allows maintenance of therapeutic drug levels in the CSF for at least 24 hours.

Infection is a major complication and cause of failure of CSF shunting devices used to control hydrocephalus; the incidence of this complication ranges from 1% to 39% [1]. External ventricular drainage, used as a temporary tool to control acute obstructive hydrocephalus that leads to raised intracranial pressure, is similarly, if not more frequently, associated with ascending infection resulting in ventriculitis [1]. The organisms involved are predominantly gram positives, and coagulase-negative staphylococci are the most common [1, 2]. In general, staphylococcal ventriculitis associated with a permanent shunt necessitates removal of the shunt [2]. Several investigators have reported the partially successful intraventricular administration of vancomycin in varying dosage regimens [1, 3–5]. However, little is known about the drug’s pharmacokinetics, potential accumulation, and toxic levels in human CSF [3]. We describe three patients who developed staphylococcal ventriculitis that was treated successfully with intraventricular vancomycin. CSF levels were measured every 2 hours, and these measurements provided actual intraventricular pharmacokinetic data.

Patients and Methods

Two patients with tuberculous meningitis and one patient with severe traumatic brain injury required external CSF drainage because of the onset of obstructive hydrocephalus. Both patients with tuberculous meningitis had a relapse of ventriculoperitoneal shunt–associated staphylococcal ventriculitis after they received intravenous vancomycin therapy. The third patient had severe trauma-related intraventricular hemorrhage, trauma-related multiorgan failure, and external shunt–associated staphylococcal ventriculitis. As CSF cultures for all patients yielded highly resistant staphylococci, the intraventricular administration of vancomycin was considered inevitable and least dangerous. Ten milligrams of vancomycin, at a concentration of 1,000 μg/mL, was instilled via an external drain, which was then flushed with 2 mL of NaCl [6] and clamped for 1 hour. Vancomycin levels were measured immediately before (re)instillation and every 2 hours thereafter. The therapy was continued until apparent cure was achieved. Measurements were performed by using a fluorescence polarization immunoassay (TDx/TDxFLx vancomycin; Abbott, Vienna, Austria) after centrifugation (2.123 g for 7 minutes at 14 ± 5°C) [7, 8]. Finally, the means ± SDs of the corresponding levels were calculated.

Results

Methicillin-resistant Staphylococcus aureus (MRSA) was identified as the cause of drain-associated ventriculitis in all three patients; the first patient was cured by intraventricular administration of 10 mg of vancomycin after 5 days, the second was cured after 8 days, and the third was cured after 13 days. Mean CSF levels of vancomycin ±SDs measured before intraventricular administration of the drug, 1 hour after administration, and then every 2 hours are shown in figure 1. The drug did not accumulate in any of the patients, even after >1 week of intraventricular therapy. Bacteriologic cure (i.e., a sterile
CSF culture) was achieved within 1–3 days, whereas normalization of CSF parameters took 5–11 days.

Discussion

Vancomycin is highly efficacious against coagulase-negative staphylococci, the main causative agents of shunt- and drain-related ventriculitis. Vancomycin is therefore a valuable drug for treatment of implant device–associated infections. However, therapeutic CSF levels are difficult to achieve in patients with staphylococcal ventriculitis because the usually mild, acute inflammatory response of the meninges results in poor penetration of vancomycin through the blood-brain barrier. Bayston et al. [1] treated 18 of 33 patients with ventriculitis successfully with intraventricular vancomycin; these patients had had unfavorable courses when they were treated intravenously. Moreover, it has been reported that CSF levels of vancomycin never rose above 6 µg/mL after intravenous administration [3]. In contrast, when vancomycin was given intraventricularly, CSF levels were found to be as high as 100 µg/mL [4]. In addition, Arroyo and Quindlen [4] observed an accumulation of vancomycin throughout a period of 9 days, rising from 70 µg/mL after the first dose to 606 µg/mL after the ninth day. It is important to note that no side effects were seen in these patients.

Although an empirical intraventricular dose (10–20 mg) of vancomycin, given every 24 hours, is recommended, very little is known about the pharmacokinetics of the drug when it is administered via this route [9]. Arroyo and Quindlen [4] and Ressor et al. [5] have measured CSF levels once and twice daily in patients receiving intraventricular vancomycin therapy. Ressor et al. found a doubling of the elimination half-life of vancomycin after 24 hours of therapy [5]. Information about the pharmacokinetics of vancomycin and their clinical and bacteriologic implications in patients with shunt device–associated ventriculitis is insufficient and conflicting. Most of the data available so far have been collected in cases of aresorptive hydrocephalus. Even less is known in the case of obstructive hydrocephalus, where the CSF circulation is more profoundly altered. In two of our patients, severe tuberculous meningitis leading to obstructive hydrocephalus necessitated the implantation of a ventriculoperitoneal shunt. The shunt-associated ventriculitis that they developed could not be contained by intravenous antibiotic therapy. The shunting devices were removed, and within a few days, the onset of severe hydrocephalus prompted immediate external ventricular drainage.

At this time, ventricular CSF samples still showed signs of inflammation, and ventricular CSF cultures were positive for MRSA. Consequently, intraventricular administration of vancomycin was initiated. No drug accumulation was observed with peak dose levels ($C_{\text{max}}$), ranging from a minimum of 72.2 µg/mL (day 4 for patient 1) to 812.6 µg/mL (day 7 for patient 2). However, the predose levels ($C_{\text{min}}$) always decreased to <20 µg/mL, even when peak levels of >800 µg/mL had been measured. Therefore, the notion of drug accumulation reaching potentially toxic levels [4] has to be reconsidered.

Therapeutically effective mean steady-state serum concentrations of vancomycin range from 15 µg/mL to 40 µg/mL [5, 10]. For all three of our patients, both bacteriologic clearance and clinical cure were achieved with mean trough CSF levels of 7.6 µg/mL (dose, 10 mg of vancomycin every day). This level lies exactly within the level range of 5–10 µg/mL that is needed to maintain a mean steady-state serum concentration of ~15 µg/mL as recommended by Cooper and Given [3]. As we found, this concentration has already been shown to corre-
late with good clinical efficacy in the absence of excessive toxicity [3].

In conclusion, daily intraventricular administration of 10 mg of vancomycin appears to be an efficacious, safe, and cost-effective treatment for staphylococcal ventriculitis. Whether a lower intraventricular dose of vancomycin that is administered more frequently will lead to similar clinical results is conceivable but still needs to be determined.

References