Continuous intrathecal pump infusion of baclofen with antibiotic drugs for treatment of pump-associated meningitis

Case report


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Intrathecal baclofen administered by means of an implantable pump is being increasingly used for successful treatment of spasticity. Meningitis following intrathecally administered baclofen is a rare but serious complication that is difficult to treat without removal of the pump. Because success rates with intravenously administered antibiotic drugs for the treatment of meningitis have been low, intrathecal administration of antibiotic agents is often required to eradicate the pathogen. The authors report the case of a patient in whom Staphylococcus epidermidis meningitis developed after insertion of an intrathecal baclofen pump. The patient was successfully treated by intrathecal coadministration of vancomycin and baclofen.

KEY WORDS • intrathecal drug infusion • baclofen • pump-associated meningitis

INTRODUCTION

PASTICITY is a motor disorder characterized by a velocity-dependent increase in muscle tone and uncontrolled repetitive involuntary contractions of skeletal muscles. Spasticity can lead to abnormal posture, contractures, skin breakdown, and painful spasms and is often disabling with respect to patient mobility, transfers, and activities of daily living. Baclofen is an agonist of the inhibitory neurotransmitter γ-aminobutyric acid and is the most widely prescribed oral antispasmodic agent. However, the development of tolerance to the drug and undesirable CNS side effects that occur with higher oral doses may limit its use in some patients. As a result, intrathecally administered baclofen has been used with increasing success for the control of spasms, with a lower incidence of adverse CNS effects. We estimate that, in North America alone, 50,000 intrathecal pumps are currently implanted to deliver drugs for pain or spasm control. Complication rates following intrathecal baclofen delivery are reported to be relatively low. Mechanical problems with tubing and the intrathecal pump can usually be corrected with a simple revision and without causing significant morbidity to the patient. However, complications such as a CSF leak, skin necrosis, overdose, and infection can result in significant rates of morbidity and mortality.

Abbreviations used in this paper: CNS = central nervous system; CSF = cerebrospinal fluid; SBT = serum bactericidal titer.

Meningitis following intrathecal delivery of baclofen is a rare but serious complication that has been difficult to treat without removal of the intrathecal pump. Success rates with intravenously administered antibiotic drugs for the treatment of meningitis have been low; therefore, intrathecal administration of antibiotic agents is often required to eradicate the pathogen. Due to the success of intrathecally administered baclofen in controlling spasms, the optimal treatment would be the intrathecal coadministration of appropriate antibiotic agents and baclofen. Unfortunately, there is no published information regarding intrathecal baclofen’s compatibility with various antibiotic drugs. This further complicates any attempt to treat CNS infections while maintaining the integrity of the intrathecal pump.

We describe the case of a patient in whom Staphylococcus epidermidis meningitis developed following insertion of an intrathecal baclofen pump. The patient was successfully treated by intrathecal coadministration of baclofen with vancomycin.

Case Report

History. This 19-year-old man with an undefined degenerative motor neuron disorder was admitted to the hospital following a 1-week history of increased irritability and fever. Three weeks before admission a Synchromed intrathecal pump (Medtronic, Minneapolis, MN) had been placed and was being used to deliver baclofen at a dose of 185 μg/day to control his spasticity.

Abbreviations used in this paper: CNS = central nervous system; CSF = cerebrospinal fluid; SBT = serum bactericidal titer.
Examination and Treatment. An admission CSF sample obtained via lumbar puncture grew \textit{S. epidermidis}, which was sensitive to vancomycin and resistant to cloxacillin. Other CSF parameters included an elevated protein count (964 mg/L), white blood cell count (150 $\times$ 10^3/L; 45% neutrophils, 37% lymphocytes, and 18% monocytes), and red blood cell count (93 $\times$ 10^3/L). Therefore, vancomycin was started intravenously at 500 mg every 12 hours. Specimens obtained from the baclofen-containing reservoir of the pump and from blood and urine tested negative. The patient remained febrile over the next few days but was less irritable. On the 5th day of hospitalization, he experienced increased irritability. The CSF from a repeated lumbar puncture showed an elevated protein count (1462 mg/L) and white blood cell count (890 $\times$ 10^3/L; 81% neutrophils, 10% lymphocytes, and 9% monocytes) and continued to be positive for \textit{S. epidermidis}. Serum drug concentrations obtained 30 minutes before and 3 hours after the third dose of vancomycin were 3.2 mg/L (minimum concentration 2.8 mg/L) and 8.7 mg/L (maximum concentration 15.4 mg/L), respectively. Examination of a CSF sample obtained 6 hours after initiation of intravenously administered vancomycin showed the drug to be undetectable. The intravenous vancomycin dose was subsequently increased to 1000 mg every 12 hours in an attempt to achieve a maximum concentration in serum of approximately 30 mg/L.

By the 8th day of hospitalization, the patient still had not improved significantly; he remained febrile and irritable. An additional CSF specimen obtained from the baclofen port yielded a third positive culture for \textit{S. epidermidis}. Serum vancomycin concentrations obtained 30 minutes before and 3 hours after the infusion were 5.8 mg/L (minimum concentration 5.6 mg/L) and 18.8 mg/L (maximum concentration 29.5 mg/L), respectively. A CSF specimen collected from the baclofen port 6 hours after the intravenous infusion of vancomycin yielded a concentration of 2.2 mg/L. Therefore, consent was obtained from the patient’s family to administer a vancomycin/baclofen solution intrathecally by using the pump already in place. An 18-ml solution was prepared containing 90 mg vancomycin (1.8 ml), 3330 $\mu$g baclofen (6.7 ml), and 9.5 ml normal saline. This provided a final concentration of 5 mg/ml vancomycin and 185 $\mu$g/ml baclofen. The pump was programmed to deliver 1 ml of solution daily, which provided 5 mg of vancomycin and 185 $\mu$g of baclofen every 24 hours. In addition to vancomycin, a 5-mg dose of gentamicin was also administered to the patient intrathecally.

On the 11th day of hospitalization (3 days after initiation of vancomycin/baclofen infusion), the patient became afebrile. In CSF drawn from the baclofen port, the white blood cell and protein counts were shown to have fallen significantly to 132 $\times$ 10^3/L and 220 mg/L, respectively, and the CSF culture was negative. The concentration of vancomycin in the CSF 24 hours after initiation of intrathecal therapy was found to be 45.8 mg/L. The intrathecal administration of vancomycin was discontinued and a regimen of 150 mg rifampin administered orally every 12 hours was initiated to augment the intrathecal vancomycin therapy.

Serum bactericidal titers were determined at various times during this patient’s treatment course. The first SBT was assessed when the patient was receiving intravenous vancomycin alone. The serum was obtained just before the scheduled dose of intravenous vancomycin and the SBT was 1:64. The second serum sample was obtained 24 hours after initiation of the intrathecal vancomycin and gentamicin, and the SBT was 1:16. The third serum sample, obtained 8 days after initiation of rifampin and while the patient was receiving intrathecal vancomycin, yielded an SBT of 1:16.

Over the next 2 weeks the patient remained afebrile, although his spasticity worsened slightly. On the 14th day of intrathecal vancomycin/baclofen treatment, a repeated lumbar puncture revealed no growth of organisms and a CSF concentration of 31.1 mg/L vancomycin. Because of the worsened spasticity, the baclofen dose was increased and vancomycin treatment was continued for 2 more weeks. Thus, a new vancomycin/baclofen solution was prepared to provide a daily dose of 5 mg vancomycin and 211 $\mu$g baclofen.

Posttreatment Course. At the completion of this dosage of vancomycin/baclofen solution the patient’s spasticity had improved greatly, and he continued to be afebrile and nonirritable. Furthermore, an additional CSF specimen obtained from a lumbar puncture revealed no microbial growth. At last report, 9 months after completion of therapy, the patient had no recurrence of infection and showed a good therapeutic reduction in his spasticity.

Discussion

To our knowledge this is the first reported case in the literature of intrathecal coadministration of baclofen and vancomycin to treat meningitis. A search of the literature revealed two case reports of meningitis treated successfully without removal of the intrathecal pump; however, neither featured coadministration of baclofen and vancomycin.\textsuperscript{14,16} Bennett, et al.,\textsuperscript{14} successfully treated a patient who had \textit{S. epidermidis} meningitis by administering 5 mg/day of vancomycin intrathecally through the Synchromed pump. Before administration of the vancomycin, baclofen was removed from the pump and was reintroduced after resolution of the infection. Samuel, et al.,\textsuperscript{16} successfully treated an \textit{S. aureus} infection by intrathecal administration of gentamicin through a Secor pump (Cordis Endovascular, Miami, FL). Again, the baclofen was removed from the pump and not reintroduced until after resolution of the infection.

In our case it was not possible to discontinue the baclofen infusion because of the severe spasticity experienced by the patient; therefore, maintaining the integrity of the pump while eradicating the infection was the most desirable goal. The coadministration of baclofen with vancomycin appeared to be the most logical treatment alternative; however, there was no information available on the physical or chemical compatibility of baclofen with vancomycin. As a result, in vitro tests for physical compatibility were conducted before administration of the baclofen/vancomycin mixture. Three baclofen/vancomycin solutions were prepared using a sterile compounding technique. Injections of 90, 180, and 360 $\mu$g of vancomycin (Eli Lilly & Co., Indianapolis, IN) were administered into each of three separate vials, which contained 1750 $\mu$g of baclofen (Novartis Pharmaceuticals Canada, P. J. Zed, et al.
Intrathecally administered baclofen

Dorval, Quebec, Canada). Normal saline without bacteriostatic agent was added to each of the three vials to make the total volume 6 ml. The final concentrations in each vial were 15, 30, and 60 μg/ml of vancomycin and 295 μg/ml of baclofen. The solutions were observed immediately after mixing; the line of sight was 90° to the sides of the vials. Black and white backgrounds were separately used and the samples were evaluated for color change, evidence of phase separation, haze, precipitation, or gas production. Follow-up observations were made at 1, 2, 12, and 24 hours, and then daily for the next 14 days. No evidence of physical incompatibility was identified for any sample.

Despite clinically and microbiologically confirmed improvement of infection in our patient, his spasticity worsened during the first 14 days of therapy. This may have simply been an indication that the optimal dose of baclofen had not yet been achieved, as our patient was receiving increasing triturations of baclofen on admission to the hospital. Alternatively, despite our confidence that there was no physical incompatibility between baclofen and vancomycin, there may have been a chemical incompatibility rendering a certain level of baclofen inactive. Without proper chemical compatibility testing this hypothesis cannot be confirmed.

Despite adequate serum concentrations of vancomycin, the CSF concentrations of this drug achieved with intravenous administration were approximately the minimum inhibitory concentration of the drug (1 mg/L) for S. epidermidis. This confirms previous reports of the poor CNS penetration of systemically administered vancomycin. However, intrathecal administration of vancomycin yielded CSF concentrations 40 times above the minimum inhibitory concentration for the organism. The SBTs determined while the patient was receiving vancomycin alone compared with combination therapy with gentamicin or rifampin showed no added benefit with combination therapy. The total duration of vancomycin therapy in this patient was 30 days, which may have been longer than required. However, because of the need to increase the baclofen dose after 14 days of therapy we believed that a longer treatment period with vancomycin was justified for our patient.

Conclusions

We believe that the intrathecal coadministration of baclofen and vancomycin can be safely used to treat CNS infections involving susceptible pathogens. This should provide optimal therapy to eradicate the infection while maintaining treatment for spasm control.

References


Manuscript received May 11, 1999. Accepted in final form October 5, 1999. Address reprint requests to: Fawziah Marra, Pharm.D., Clinical Services Unit, Pharmaceutical Sciences, Vancouver Hospital and Health Science Centre, 855 West 12th Avenue, Vancouver, British Columbia V5Z 1M9 Canada. email: fawziah@unixg.ubc.ca.