Outpatient Parenteral Antimicrobial Therapy for Central Nervous System Infections

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Patients with central nervous system (CNS) infections are increasingly treated with intravenous antimicrobials outside the hospital, but the safety and problems associated with this therapy have not been well defined. To examine this issue, we reviewed 68 cases in which outpatient intravenous antimicrobial therapy (OPAT) was received through our physician office–based infusion clinic. All infections were cured, and no deaths occurred during therapy. Seizures occurred in 2 patients but without significant injury and apparently were unrelated to antimicrobial therapy. Eleven patients (16%) were hospitalized after starting OPAT, 5 for procedures and 6 for medical reasons. The antimicrobial used was changed in 13 cases (19%) because of an adverse effect or clinical failure. OPAT can be safe and effective for patients with CNS infections, but patients must be carefully selected and monitored closely.

Infections of the CNS, such as meningitis, brain abscess, encephalitis, and spinal fluid shunt infections, are generally acknowledged to be among the most serious, difficult, and potentially debilitating. Intravenous antibiotic therapy is generally required in order to ensure rapid and optimal penetration of the infected brain and spinal fluid. Because of the seriousness of CNS infections, the intensive antimicrobial therapy necessary, and the potential for complications, patients with these infections are almost always hospitalized.

See editorial response by Poretz on pages 1400–1.

The most difficult and unpredictable phase of therapy usually is during the first few days of hospitalization. Patients who survive this early phase and begin to recover neurological function are unlikely to encounter new problems or complications, provided they receive a prolonged course of iv antimicrobial therapy to eradicate the infection and prevent relapse. Thus, it has been the standard of practice in many communities to keep patients in the hospital for iv antimicrobial therapy for 2 weeks in cases of meningitis and for 4–8 weeks in cases of brain abscess [1–5]. Patients in the later phase of treatment are often not acutely ill and may benefit medically and emotionally from being at home.

Recently, there has been increasing interest in providing care to patients outside the hospital when their infections necessitate administration of iv antimicrobials. Each year, >250,000 Americans receive outpatient parenteral antimicrobial therapy (OPAT) [6], made possible by the development and growth of available home care services, long-acting antimicrobials, and improved technology in vascular access, as well as infusion devices [7, 8]. According to several published series, 1%–12% of patients who receive OPAT are being treated for meningitis or brain abscess [8–10].

The use of OPAT is likely to increase because, with the pressures presented by managed care, physicians must take advantage of the significant cost savings of outpatient therapy in comparison with hospitalization. A number of studies have suggested daily savings of several hundred (United States) dollars [9, 11–15]. Given the average hospital charges of $1000/day, OPAT offers a significant opportunity for savings [16, 17]. In 1 study of Medicare patients, hospital savings were >$6000/patient for those discharged to a physician-based OPAT program [10].

Additional benefits associated with home and outpatient care include improved quality of life and a high level of patient satisfaction [10, 18–20]. OPAT is also gaining interest because of growing concern about nosocomial infections and the proliferation of antibiotic-resistant organisms in hospitals [18, 21, 22]. The advantages of outpatient therapy are particularly striking in pediatrics, with benefits for both children and their families.

Several studies of children who received OPAT for CNS infections have been reported. In 1987, Powell and Mawhorter described 26 such patients who did well [13]. In 1988, Bradley et al. reported treating 54 carefully selected children with bacterial meningitis, all of whom did very well during an average of 4.6 days (range, 1–8 days) of OPAT [23].

Complications included diarrhea in 7 (13%) of the patients, and 1 case was due to Clostridium difficile. Seventeen percent of these children had fevers at home, similar to the reported percentage with fever among those treated in the hospital. No
Table 1. Data concerning patients receiving outpatient parenteral antimicrobial therapy (OPAT) for CNS infections.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Meningitis</th>
<th>Brain abscess</th>
<th>Encephalitis</th>
<th>Other*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>29</td>
<td>19</td>
<td>5</td>
<td>15</td>
<td>68</td>
</tr>
<tr>
<td>Age in years, mean (range)</td>
<td>34.2 (1-70)</td>
<td>43.5 (15-81)</td>
<td>30.0 (8-60)</td>
<td>41.5 (4-71)</td>
<td>37.3 (1-81)</td>
</tr>
<tr>
<td>Duration of OPAT, days</td>
<td>232</td>
<td>744</td>
<td>31</td>
<td>279</td>
<td>1286</td>
</tr>
<tr>
<td>Mean (range)</td>
<td>8 (3-21)</td>
<td>39.2 (8-89)</td>
<td>6.2 (3-9)</td>
<td>18.6 (2-47)</td>
<td>18 (2-89)</td>
</tr>
<tr>
<td>Site of OPAT, no. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>19</td>
<td>15</td>
<td>5</td>
<td>9</td>
<td>48 (71%)</td>
</tr>
<tr>
<td>Office</td>
<td>9</td>
<td>3</td>
<td>0</td>
<td>5</td>
<td>17 (25%)</td>
</tr>
<tr>
<td>Skilled nursing facility</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Duration of hospitalization, days</td>
<td>168</td>
<td>242</td>
<td>38</td>
<td>179</td>
<td>627</td>
</tr>
<tr>
<td>Mean (range)</td>
<td>5.8 (2-14)</td>
<td>12.2 (4-53)</td>
<td>7.6 (6-9)</td>
<td>11.9 (2-33)</td>
<td>9.5 (2-53)</td>
</tr>
</tbody>
</table>

* Includes shunt infections (6), epidural abscess (5), neurosyphilis (1), intraspinal C-7 abscess (1), subdural abscess (1), and infected hematoma (1).

child was rehospitalized. Congeni et al. used OPAT for 57 children, aged 7 weeks to 12 years; they had minimal problems, although 11 (20%) had diarrhea [24].

Despite these successful outcomes, concerns about the potential problems associated with OPAT for CNS infections are reasonable, as are questions about the complications of OPAT itself and unforeseen factors that may not have been adequately studied. The home environment will never be as well controlled as that of the hospital. Outpatient infection control and outcome-monitoring programs, though beginning to emerge, have thus far been minimal [25, 26]. Certainly the most obvious difference between the 2 settings in regard to safety is the lack of medical staff or emergency equipment readily available to patients in their homes.

A better understanding of the potential consequences of OPAT for serious CNS infections is needed, particularly in light of growing economic pressure for early hospital discharge. Appropriate patient selection is crucial to the prevention of complications related to OPAT [14, 15, 27–29]. There may also be aspects of outpatient therapy specific to the treatment of CNS infections that need to be identified and understood.

Waler et al. [21] and Bradley et al. [23] have proposed guidelines for using OPAT programs for children with meningitis. Many of these criteria may also apply to adults.

Because of the limited information available about OPAT for CNS infections in adults, as well as concerns about the safety of OPAT in general, we undertook a retrospective study of patients with CNS infections treated through our clinic.

Methods

Infections Limited is a private clinic that provides infectious disease consultations and physician-directed services for a population of ~500,000 people in Tacoma, Washington, and the surrounding area. More than 4000 patients have received OPAT since the program’s inception in 1981. Patients are generally seen by an infectious disease physician and an iv therapy nurse once or twice weekly while receiving OPAT, and laboratory studies usually are done twice weekly [30]. The outpatient unit employs registered iv therapy nurses and licensed pharmacists. The OPAT program includes only patients who are seen and followed by the clinic physicians. Patient care is consistent with the guidelines of the Infectious Diseases Society of America (IDSA) on community-based iv antimicrobial therapy [31], and the clinic is accredited as an ambulatory infusion center by the Joint Commission on Accreditation of Healthcare Organizations.

Data on patients treated for CNS infections during the period of 1986 through 1997 were gathered from billing records and an internal case-reporting system for OPAT [32]. Diagnostic categories were reviewed for all patients with bacterial meningitis, brain abscess, encephalitis, and CNS shunt infections. Patients with AIDS-associated cryptococcal meningitis were excluded because of the complexity of their disease, the complications associated with amphotericin B, and the option of oral therapy. Charts were reviewed by a registered nurse to verify the accuracy and completeness of the information obtained. The data gathered from patients’ charts were also verified by the treating physicians, who documented outcomes and problems for their own patients.

Results

Review of records revealed 68 patients with CNS infections who received OPAT during the period of 1986 through 1997. Infections included 29 cases of meningitis, 19 of brain abscess, 5 of encephalitis, and 15 of other infections (table 1). The “other” category consisted of 6 shunt infections, 5 epidural abscesses, and single cases of neurosyphilis, intraspinal C-7 abscess, subdural abscess, and infected hematoma. The mean age was 37 years, ranging from 12 months to 81 years. There were more males (41) than females (27).

The total number of days of OPAT was 1286, and the duration of courses was 2–89 days (mean, 18 days; median, 17 days). The 89-day course of therapy was that of a patient with a Nocardia asteroides brain abscess. OPAT was initiated for 5 patients (7%) who were not hospitalized, whereas 63 were hospitalized initially for an average of 9.5 days (range, 2–53 days) of iv therapy before discharge. Of the 11 patients (16%) who were hospitalized after OPAT was started, 5 returned to OPAT for an additional 118 days.
Table 2. Pathogens isolated from patients who received outpatient parenteral antimicrobial therapy (OPAT) for CNS infections.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Meningitis</th>
<th>Brain abscess</th>
<th>Encephalitis</th>
<th>Other†</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><em>Viridans streptococcus</em></td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Haemophilus influenza</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>8</td>
<td>0</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>None (culture negative)</td>
<td>11</td>
<td>7</td>
<td>2</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>29</strong></td>
<td><strong>19</strong></td>
<td><strong>5</strong></td>
<td><strong>15</strong></td>
<td><strong>68</strong></td>
</tr>
</tbody>
</table>

NOTE. Data are no. of patients.
† Includes shunt infections (6), epidural abscess (5), neurosyphilis (1), intraspinal C-7 abscess (1), subdural abscess (1), and infected hematoma (1).

For 17 patients (25%), the antimicrobial was given daily in the office. Forty-eight patients (71%) or their caregivers administered the medicine at home. Three patients received OPAT at a skilled nursing facility: 1 because of iv drug abuse, 1 because of extensive nursing care needs, and another because of advanced HIV disease.

Table 2 lists the organisms identified by type of infection. An obvious pathogen was recovered from 42 patients (62%). The most frequently identified bacterial organism was *Streptococcus pneumoniae*, recovered from 8 patients who had meningitis. *Staphylococcus aureus* was recovered from 7 patients: 3 with meningitis following surgery, 3 with epidural abscesses, and 1 with a brain abscess. Herpes simplex was recovered from 3 patients. An additional 4 cases were treated empirically for herpes infections. Although no pathogen was recovered from 11 patients with meningitis, the clinical situation indicated the need for iv antimicrobial therapy. Many had received antibiotics before cultures were performed.

The antimicrobials prescribed are shown in table 3. The primary antimicrobial used, ceftriaxone, was administered to 37 patients (54%), of whom 18 had meningitis and 11 had brain abscess. The second most frequently used antimicrobial, penicillin, was given to 15 patients (22%), including 7 with brain abscess and 4 with meningitis. Ayclovir was used for encephalitis in 5 patients and meningitis in 2. Ceftriaxone was given once daily, whereas penicillin was always given by continuous infusion via a battery-driven ambulatory infusion pump. Ayclovir was usually given by intermittent infusion and was self-administered every 8 h by means of gravity or a syringe pump system.

The outcomes and adverse effects among the study patients are shown in table 4. All infections were cured, although some patients were hospitalized before OPAT was complete. Seizures occurred in 2 patients, 1 with a brain abscess and 1 with meningitis; neither had a history of epilepsy. One patient had a seizure on day 2 of OPAT and started receiving phenytoin (diphenylhydantoin, or Dilantin; Parke-Davis, Morris Plains, NJ). After she had a second seizure on day 69, phenobarbital was added to the regimen, and she had no further episodes.

The second patient had a single seizure, on day 12 of OPAT, at which time treatment with phenytoin was initiated. In neither case was significant injury associated with the seizure, and in both cases a family member was present during the event. Although 12 (63%) of the 19 patients with brain abscess had significant neurological deficits as a result of the infection, all but 1 were able to complete the course of antimicrobial therapy at home with the assistance of a family member or care-giver. The patient whose neurological deficits were too severe to permit home care completed his course of therapy at a skilled nursing facility. Neither seizures nor neurological deficits appeared to be associated with OPAT or the antimicrobials used.

No deaths occurred during OPAT. There were no problems with compliance. No secondary infections occurred, although several patients had concurrent infections at the beginning of therapy, including wound infections (3), sinusitis (3), mastoiditis (2), and septic arthritis of the knee (1), all of which resolved with the therapy.

Of 11 patients (16%) hospitalized after the initiation of OPAT, 5 were admitted for surgical procedures, including revision of shunt (2 patients), repitition of aspiration of brain abscess (1), resection of infected tissue (1), and repair of a dural leak (1). None of these procedures were performed on an emergency basis. Six patients were admitted for medical reasons, including deep venous thrombophlebitis of the leg (1 patient), seizure (1), nausea with headache (1), increasing headache (1), seizure with vomiting and right-sided weakness (1), and renal failure (1). The renal failure could have been due to the cephalosporin, penicillin, or 1 of the anticonvulsant drugs given. The patient received no vancomycin or aminoglycoside.

In no case was there any indication that appropriate care was not given or was delayed because of the outpatient setting. Five of the hospitalized patients were discharged again to continue OPAT and completed their course of iv therapy as outpatients.

The antimicrobial used was changed in 12 instances for 9...
patients. In 9 cases there was an adverse reaction, including rash (4 patients), nausea and vomiting (1), decrease in hearing (1), anxiety (1), renal failure (1), and a seizure with vomiting and right-sided weakness (1). The last 2 complications led to hospitalization. For 3 patients, the antimicrobial was changed because of clinical failure, involving a slow clinical response in 1 case and, in the other 2, brain abscesses that appeared larger on CT scan.

Two patients (2.9%) were switched to oral antimicrobials earlier than planned. One switched from iv to oral acyclovir because of venous access problems. The other, in whom central venous access had been lost, experienced severe tingling with the administration of chloramphenicol into a peripheral vein. He had completed a 63-day course of parenteral treatment for a brain abscess and was switched to oral ciprofloxacin. Both patients responded well to the oral therapy.

A variety of other, less serious and expected problems occurred in 19 patients (27.9%). These included difficulty with vascular access. Central venous catheters had to be removed from 2 patients. In 2 cases, an infusion device malfunctioned, but no dosings were missed. There were also problems with sterile phlebitis, line maintenance, and the “red man” syndrome with vancomycin, but they did not interrupt therapy. Diarrhea and mucocutaneous candidiasis also occurred but responded easily to standard interventions and did not compromise care. In 1 instance the patient forgot to refrigerate the antibiotic, but it was replaced and no dosings were missed.

Discussion

There were no reports of deaths or life-threatening emergencies in this study population, although they may occur during OPAT [33]. However, seizures did occur in 2 patients, which is an incidence no higher than expected for brain abscesses and meningitis [34]. In both instances, family members were present and there were no associated serious injuries. Seizures did not seem to be related to the antimicrobial used, although caution must be exercised, since high concentrations of some of the antimicrobials used for CNS infections—such as penicillin, acyclovir, and metronidazole—cause seizures. Seizures occur in 20%—30% of patients with meningitis, usually at the time of diagnosis or within the first few days of hospitalization [5, 35], and are a late complication in up to 90% of patients with brain abscesses [36].

Patients with CNS infections, especially brain abscesses and meningitis, should be carefully observed for seizures, and prophylactic medication should be strongly considered for them. Patient-selection criteria for OPAT should include the availability of family and caregivers who can be with a patient if a seizure occurs. Patients at risk for seizures should also be counseled to avoid activities that may place them or others in danger, such as operating a motor vehicle.

Sixteen percent of patients were hospitalized after starting OPAT. The reasons varied considerably and did not appear to be related to events that would not have occurred if they had stayed in the hospital. However, this circumstance does emphasize the need for close medical follow-up and a system for rapid communication with patients and caregivers when problems arise.

In this study there was no indication of an adverse outcome because of a delay in hospital admission. Some of the rehospitalizations might have been avoided by delaying discharges, but the criteria for this, other than effective seizure prophylaxis, are not clear.

There were adverse reactions to antimicrobials during OPAT, but at a rate no higher than expected with iv therapy in the hospital and associated with no more severe reactions than expected with iv antimicrobial use [37]. The number of cases was too small to enable us to draw conclusions about the tolerance and safety of the antimicrobials used, but prior studies have indicated ceftriaxone to be well tolerated in OPAT [38]. The other antibiotics also seemed safe for use in patients with CNS infections, given the monitoring and follow-up provided. This generally included twice-weekly visits to the physician office for patients whose conditions were stable or improving [31, 39]. More frequent monitoring and doctor visits were required when the patient’s condition was unstable. A recent article by Hoffman-Terry et al. has emphasized the importance of close follow-up and regular laboratory test monitoring with OPAT [40].

Quality-of-life issues are also an important consideration. Patients may be more responsive and less depressed at home [41]. Prior studies have indicated a high level of patient satisfaction with outpatient therapy and a strong preference for OPAT over hospitalization if another course of iv therapy were to be needed [15, 42].

Cost savings has been a major driving factor in the growth of OPAT. The 68 patients studied accounted for 1286 days of therapy. Although all the financial-impact studies have indicated a cost savings with OPAT compared with hospitalization, the exact amount is unclear and varies greatly among communities and organizations and over time [10, 43]. The cost of
adverse effects from the antibiotics and rehospitalization for therapeutic failures should also be considered. On the basis of an estimated cost savings of $300 per day, OPAT saved >$385,000 for the insurance companies and payers. This is money that can be well used in other aspects of health care.

The cost savings have provided a tremendous incentive for OPAT growth, but there is a limit to the extent to which those benefits can be realized before they affect the quality of patient care. Payors are most knowledgeable about costs and are anxious to reduce them. Economic benefits are much easier to measure than quality of care. The physician is ultimately responsible for the quality of care, which should be as good as in the hospital. Otherwise, it is difficult to justify sending a hospitalized patient home. This means that patients should be carefully selected for OPAT and that some patients should not be discharged, despite the economic pressures to do so.

The criteria that have been suggested for screening children with meningitis for early hospital discharge [21, 23] need to be considered for adults. Table 5 shows criteria that may be used to screen children for OPAT, as well as additional factors that should be considered for adults. These may be useful in evaluating patients as well as dealing with discharge planners and case managers. Guidelines for OPAT have recently been developed and published by the IDSA [31]. They outline the components of patient selection to be considered and provide general guidelines for antimicrobial use and follow-up of patients.

Another consideration in the decision to send a patient with a CNS infection home for OPAT is the quality of the program that will be providing the care. Outpatient resources vary among communities. The IDSA guidelines also address this issue and list criteria that an infusion provider should be able to meet and information that they should share with the prescribing physician. Unfortunately, outpatient and home infusion providers have been under increasing pressure from managed care to reduce costs, and as a result, this may compromise the quality of care they provide.

Despite the problems that may occur with OPAT providers, the physician remains ultimately responsible and legally accountable for the quality of care provided to the patient and thus the quality of the infusion company as well. A good working relationship between the neurologists and infectious disease physicians has been helpful in ensuring the quality of patient care in our community.

Our results are consistent with those of prior studies of children and demonstrate the reasonable safety of treating patients with CNS infections with iv antimicrobials on an outpatient basis, for at least a portion of the course of therapy. OPAT for children with meningitis has been studied well, although the numbers are small. For adults, there are additional considerations when they have seizures and/or significant loss of mental function. Given the benefits to patients, the reduced cost, and the safety of OPAT when patients are selected and followed carefully, this form of therapy should always be considered for patients with CNS infections.

This review demonstrates that iv antimicrobial therapy for CNS infections can be safely and effectively provided outside the hospital. There are cautions, however, especially with regard to seizures. OPAT should be started only after a careful patient-selection process and with plans for close medical follow-up for the variety of medical and surgical problems that may occur during therapy.

Acknowledgments

We thank Barbara Nolet, James DeMaio, Lawrence Schwartz, and Philip Craven for their assistance and review of the study.

Table 5. Factors to consider in evaluating a patient with a CNS infection for outpatient parenteral antimicrobial therapy (OPAT).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Requirements and considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Establish pathogen if possible; patient afebrile with clinically stable or improving condition</td>
</tr>
<tr>
<td>Antimicrobial</td>
<td>First dose given under medical supervision and without reaction; selection of antimicrobial and dosing to avoid seizure</td>
</tr>
<tr>
<td>Other disease(s)</td>
<td>Stable, improving, or not significant; need for nursing care</td>
</tr>
<tr>
<td>Vascular access</td>
<td>Reliable intravenous line and infusion device, if needed</td>
</tr>
<tr>
<td>Neurological state</td>
<td>Risk of seizures; need for medications; neurological dysfunction</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Plan for physician visits, nurse visits, laboratory monitoring, and emergencies</td>
</tr>
<tr>
<td>Patient’s abilities</td>
<td>Cooperative and willing to participate in OPAT; able to mentally and physically comply with OPAT program; no active drug or alcohol abuse</td>
</tr>
<tr>
<td>Family support</td>
<td>Able to assist in care, infusions, transportation, and emergencies; domestic problems</td>
</tr>
<tr>
<td>Home environment</td>
<td>Safe environment; telephone, utilities, food, refrigerator</td>
</tr>
</tbody>
</table>

References

4. Adams RD, Victor M, Ropper AH. Infections of the nervous system (bacterial, fungal, spirochetal, parasitic and sarcoid). In: Adams RD, Victor...


