Rates of Adverse Events Associated with Community-Based Parenteral Anti-Infective Therapy

Susan J. Rehm, MD, and David L. Longworth, MD

Objective: To determine rates of adverse events among patients receiving selected parenteral antimicrobial agents outside the hospital setting.

Design: Retrospective descriptive study using database and medical records review.

Setting: A variety of outpatient settings including an outpatient clinic, subacute care unit, nursing homes, and the home setting.

Participants: Patients receiving vancomycin, cefazolin, ganciclovir, ticarcillin-clavulanate, or gentamicin through a community-based parenteral anti-infective therapy program.

Outcome measures: Specific clinical events (diarrhea, rash, fever) and laboratory abnormalities occurring during therapy.

Results: Rash was the most frequently reported clinical event, and elevated creatinine the most common laboratory abnormality. Gentamicin had the highest antibiotic-specific rates for both clinical events (dizziness) and laboratory abnormalities (elevated serum creatinine level). The highest rates of rash and diarrhea were observed with cefazolin. Ganciclovir was associated with the highest rates of leukopenia and anemia.

Conclusions: Antibiotic-related clinical events and laboratory abnormalities in individuals receiving parenteral antibiotics outside the hospital setting are infrequent but important because of the ramifications they have on patient comfort and antimicrobial dosing. In the community setting, specific monitoring mechanisms must be established to detect and treat antibiotic-related events.

In the past 20 years, community-based parenteral anti-infective therapy (CoPAT) has been offered to patients who require a prolonged course of treatment [1–4]. Individuals with osteomyelitis, infected joint prosthesis, deep abscesses, and other infections usually requiring long courses of therapy can avoid lengthy hospital stays by receiving parenteral antibiotics in another setting [1–5]. As support systems have expanded and experience with CoPAT has increased, both hospitals and third-party payers have embraced CoPAT to reduce health care costs. To accommodate CoPAT recipients, a full range of sites for therapy has developed, including outpatient clinics, infusion centers, subacute care facilities, nursing homes, rehabilitation centers, and the home setting.

Numerous reviews have confirmed the safety, efficacy, and cost-efficiency of CoPAT [1–7], and guidelines for the delivery of CoPAT have been published by the Infectious Diseases Society of America [8]. Few studies, however, have systematically examined the rates of CoPAT-related complications in patients receiving therapy outside the hospital setting [9,10]. In this study, we analyzed data from a computerized CoPAT registry to better define the rates of adverse clinical and laboratory events occurring during therapy.

Methods

Setting
The Cleveland Clinic Foundation (CCF) operates a 900-bed tertiary care hospital and a full spectrum of outpatient clinics in Cleveland, Ohio. In 1995, a total of 41,416 patients were admitted to the hospital, rehabilitation unit, or subacute care unit, and 993,178 visits were made in the outpatient clinics.

Patient Identification and Accrual
All candidates for CoPAT at CCF are evaluated by a physician in the department of infectious disease to determine the need for continued therapy, the suitability of the patient for therapy outside the hospital, the type and duration of antibiotic therapy, and the most appropriate venous access device. No patient may leave the hospital on CoPAT without approval of an infectious disease physician, who becomes the physician of record during the course of CoPAT and who receives all reports regarding clinical events and laboratory abnormalities from patients, their supervising nurses, and their home care agencies. Most patients are examined in the

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ADVERSE EVENTS WITH CoPAT

Table 1. Weekly Laboratory Monitoring

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>CBC and Differential</th>
<th>Serum Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ticarcillin-clavulanate*</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

CBC = complete blood count.
*Serum potassium levels are also monitored once per week.

outpatient department periodically during and after the course of therapy; the frequency of outpatient visits varies depending on the nature of the problem. During these visits, physicians verify reported clinical events and question patients about the presence of problems not previously reported.

Laboratory monitoring is standardized according to the antimicrobial agent(s) used for CoPAT (Table 1). Serum levels of vancomycin and gentamicin are measured as clinically indicated, at the discretion of the individual infectious disease physician. The results of laboratory tests are reported by phone or facsimile and are recorded in the patient’s CoPAT file. The infectious disease physician adjusts dose levels or intervals of antibiotic administration as necessary on the basis of the results of laboratory tests.

CoPAT Registry

Since 1982, the department of infectious disease has maintained a registry containing demographic, clinical, and treatment data on all patients receiving CoPAT. A course of CoPAT is defined as a series of antibiotic infusions delivered outside the hospital setting. At the conclusion of each patient’s course of therapy, infectious disease physicians are asked to complete a form documenting adverse clinical, laboratory, and vascular access–related events, as well as clinical outcome for each patient (the end-of-therapy form). Physicians are specifically asked to report antibiotic-related rash, fever, diarrhea, dizziness, deafness, anemia, leukopenia, eosinophilia, hypokalemia, renal insufficiency, and other clinical or laboratory complications related to antimicrobial therapy. Clerical personnel then enter each patient’s information into the computerized registry.

Data Analysis

Using the registry, we determined that the 5 antibiotics most frequently prescribed between 1 January 1985 and 31 December 1995 were vancomycin, cefazolin, ganciclovir, ticarcillin-clavulanate, and gentamicin. We analyzed the clinical and laboratory events for these 5 antimicrobial agents as reported on end-of-therapy forms. We also utilized the registry to study specific aspects of gentamicin prescribing practices over this 11-year period.

Definitions

The definitions of the clinical events (rash, diarrhea, fever, nausea, vomiting, dizziness) were left to the discretion of the 10 treating infectious disease physicians and were in part based on patient and home care nurse reports of these events. Confirmatory tests, such as audiograms and vestibular function testing, were performed at the discretion of the physician following the patient. Physicians were asked to record the adverse event or laboratory abnormality if it was attributable to the antibiotics being used for CoPAT. If the patient was receiving more than 1 antibiotic, the registry did not link the event or laboratory abnormality to a specific causative antibiotic. Laboratory abnormalities were defined as follows: An elevated serum creatinine level was defined as a rise of 0.5 mg/dL or more above baseline. Anemia was defined as a hemoglobin concentration of less than 11 g/dL. Leukopenia was defined as a peripheral leukocyte count of ≤ 3500 cells/µL. Eosinophilia consisted of an absolute eosinophil count of ≥ 400 cells/µL. Hypokalemia was present when the serum potassium level was ≤ 3.5 mEq/L.

Results

During the review period, 3892 courses of therapy with vancomycin, cefazolin, ganciclovir, ticarcillin-clavulanate, gentamicin, or a combination of these agents were administered to CCF patients through the CoPAT program (Table 2). End-of-therapy forms were completed and all clinical information was available in the database for 2054 courses of therapy (52.8%); 1730 patients were treated. All information in this report relates to these 2054 evaluable courses, which accounted for 44,689 days of therapy with 1 of the 5 designated antibiotics. Portions of these results have been presented in abstract form [11].

The mean duration of CoPAT therapy was 21.8 days per course. The mean age of the patients was 55 years (range, 4 to 87). Sixty-two percent of the patients were men and 88.1% were white. Half of the courses were administered to patients who lived in Cleveland or its suburbs, and 36% of courses were given to patients who lived in the region.

A wide variety of infections were treated in the CoPAT program. Twenty-five percent of the courses were administered for treatment of cellulitis, wound infections, or abscesses; 16% for osteomyelitis; 16% for cytomegalovirus disease or prophylaxis; 15% for bacteremia (primary or catheter- or device-related); 10% for septic arthritis or infected joint prosthesis; 8% for infective endocarditis; and 6% for
other infections (respiratory tract, central nervous system, urinary tract). In 4% of the courses, the reason for CoPAT was not provided in the registry.

A total of 228 clinical events and 396 laboratory abnormalities were reported during the 2054 evaluable courses of therapy. Rash was the most frequent clinical event, with a cumulative rate of 1.25 events per 1000 days of CoPAT, followed by fever (0.98/1000 days), diarrhea (0.56/1000 days), dizziness (0.42/1000 days), and deafness (0.11/1000 days). Clinical event rates for individual antibiotics are summarized in Table 3. The most common event associated with a single antibiotic was dizziness with gentamicin, which occurred at a frequency of 3.42 cases per 1000 CoPAT days. The highest rates of rash (3.04/1000 days) and fever (2.28/1000 days) were noted among patients receiving gentamicin therapy; on further analysis, these rates were found to be artifactual, because most individuals receiving gentamicin were concurrently receiving a β-lactam antimicrobial agent and/or vancomycin. When gentamicin was excluded as the cause of rash, cefazolin was the antibiotic most frequently associated with this problem (1.47 cases/1000 days). Drug fever was most often associated with vancomycin (1.40 episodes/1000 days of CoPAT), while diarrhea was most common in cefazolin recipients (1.47 cases/1000 days). Ganciclovir therapy caused few clinical problems.

The most common laboratory abnormality associated with the 5 most frequently prescribed antibiotics was an elevated serum creatinine level, which occurred at a rate of 2.80 cases per 1000 days of CoPAT. Leukopenia was the second most frequent abnormality (2.24/1000 days), followed by anemia (1.83/1000 days), eosinophilia (0.92/1000 days), and hypokalemia (0.27/1000 days).

The rates of laboratory abnormalities for individual antibiotics are summarized in Table 4. The rate of gentamicin-associated creatinine elevation was 8.72 episodes per 1000 days of CoPAT, nearly 3 times the values for vancomycin and ganciclovir (3.08 and 3.04/1000 days, respectively). Although ganciclovir was linked with the highest rate of leukopenia, at 3.55 cases per 1000 days of therapy, the rates for vancomycin (2.80/1000 days) and gentamicin (2.28/1000 days) were not much lower. Further analysis demonstrated that the gentamicin value was likely confounded by the concurrent use of β-lactam antibiotics and/or vancomycin. Likewise, the gentamicin-associated eosinophilia rate of 1.90 per 1000 days of therapy was probably artifactual due to concomitant β-lactam or vancomycin administration. The highest rate of anemia, 3.04 cases per 1000 days of CoPAT, was found among patients receiving ganciclovir; cefazolin was associated with the next highest rate (2.01/1000 days).

Because of the unexpectedly high rates of fever, rash, leukopenia, and eosinophilia in recipients of gentamicin, we reviewed additional prescribing information from the registry database. This analysis included 54 additional patients for whom the end-of-therapy form was complete except for the duration of therapy. Gentamicin was administered alone in 5% of courses (monotherapy), with 1 other antibiotic in 85% of courses (dual therapy), and with 2 other antibiotics in 10%. In more than half of the dual therapy courses, vancomycin was coadministered with gentamicin during CoPAT (Table 5). Likewise, concurrent β-lactam use was common among patients receiving dual therapy, with 16% receiving a penicillin, 19% a cephalosporin, 8% an antipseudomonal penicillin, and 3% either imipenem or aztreonam during CoPAT with gentamicin. Both vancomycin and a β-lactam antibiotic were given with gentamicin during 16 of the 22 courses of 3-drug therapy, and 4 additional patients received either vancomycin or a β-lactam with gentamicin as part of a 3-drug regimen. In total, vancomycin or a β-lactam antibiotic was coadministered with gentamicin in 203 courses (91%), and gentamicin was given alone or in combination with antibiotics other than vancomycin or β-lactams in 20 courses.

**Table 2. Courses of Therapy**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>No. of Courses</th>
<th>Total</th>
<th>Evaluable (%)</th>
<th>Mean Duration of Therapy, Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>1805</td>
<td>954 (52.8)</td>
<td>20,744</td>
<td>21.7</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>677</td>
<td>340 (50.2)</td>
<td>7469</td>
<td>22.0</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>595</td>
<td>320 (53.8)</td>
<td>7893</td>
<td>24.7</td>
</tr>
<tr>
<td>Ticarcillin-clavulanate</td>
<td>475</td>
<td>271 (57.0)</td>
<td>5948</td>
<td>21.9</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>340</td>
<td>169 (49.7)</td>
<td>2635</td>
<td>15.6</td>
</tr>
</tbody>
</table>

*End-of-therapy form and all clinical information complete in registry database.  †Applies only to evaluable courses.
A total of 43 episodes of rash, fever, leukopenia, or eosinophilia were reported during 37 of the 223 courses of gentamicin therapy (Table 5). None of these occurred in the 12 patients who received gentamicin monotherapy. Fever was the most common event, complicating 9 of the 96 courses of therapy with vancomycin and gentamicin (9.4%). This drug combination was also most frequently associated with laboratory abnormalities (leukopenia, 5%; eosinophilia, 3%). The proportion of patients who developed at least 1 of the 4 specified events during combination therapy consisting of vancomycin or a β-lactam antibiotic along with gentamicin (36/203, 17.7%) is more than 3 times higher than the proportion of patients who developed these events during therapy with gentamicin alone or in combination with antibiotics other than vancomycin or β-lactams (1/20, 5.0%). One patient in the latter group developed fever during therapy with ciprofloxacin, amphotericin B, and gentamicin.

Follow-up data regarding the impact of CoPAT-related clinical events and laboratory abnormalities on subsequent patient care are incomplete. In some cases, the antibiotic was changed or prematurely discontinued because of the development of rash. Patients who developed severe or persistent diarrhea during therapy were tested for the presence of Clostridium difficile toxin; some were treated empirically with oral metronidazole. The appearance of fever during CoPAT prompted evaluation for other potential sites of infection, recurrence of the initial infection, line sepsis, and other potential causes. Ototoxic drugs were discontinued if dizziness or deafness was reported during the course of therapy. The intervals between antimicrobial doses were often extended in response to elevated creatinine levels. No patients required dialysis. Hypokalemia prompted potassium supplementation, but the presence of leukopenia, eosinophilia, or anemia was usually monitored without specific intervention or changes in therapy. As best as we were able to determine, hospital readmissions related to adverse events during CoPAT were rare.

Discussion

This study was performed over an 11-year period at a tertiary care center and to our knowledge is the largest to report adverse clinical and laboratory event rates in a cohort of patients receiving CoPAT over an extended time period. In Kunkel’s review of 607 courses of various antibiotics administered in 10 centers over a 3-month period [9], adverse events were recorded only if they led to discontinuation of outpatient antibiotic therapy. One other study in a group of 269 patients receiving 291 courses of antibiotics over 2 years was recently published by Hoffman-Terry et al [10].

Our study is important for several reasons. First, it provides complication rates for several commonly administered antibiotics in CoPAT programs in the United States and validates the observations of Hoffman-Terry et al in a much larger cohort of patients. Second, it emphasizes the importance of periodic clinical and laboratory monitoring of patients receiving CoPAT and should be helpful in formulating algorithms for following such patients. And finally, although CoPAT may shorten hospital length of stay and reduce health care expenditures, our data serve as a reminder that this form of therapy is not without risk; health care providers who manage such patients must remain vigilant for clinical and laboratory complications associated with CoPAT.

Several findings in our study warrant special comment. Gentamicin was associated with the highest single rates of clinical and laboratory events: dizziness and an elevated serum creatinine level occurred at rates of 3.42 and 8.72 events per 1000 CoPAT days. Since vestibular function testing was not performed on a systematic basis, we cannot comment on whether all of the reports of dizziness were related to gentamicin toxicity. Fourteen percent of our patients developed elevated creatinine levels during gentamicin therapy. This finding was similar to the experience of Hoffman-Terry et al in their assessment of nephrotoxicity associated with aminoglycoside therapy [10], even though the 2 reviews differed in regard to the definition of nephrotoxicity, dosing and types of aminoglycosides, patient populations, and duration of therapy. These
rates are consistent with reported frequencies of nephrotoxicity from 2% to 10% in early studies of gentamicin use [12]. The role of concomitantly administered nephrotoxic agents in the CoPAT population cannot be quantified. The significant rate of nephrotoxicity and its potential impact underscores the need to carefully monitor serum creatinine levels during therapy. It is our practice to educate CoPAT patients about the potential side effects of aminoglycoside therapy before hospital discharge, recognizing the fact that such events may occur unexpectedly during the course of therapy.

Most of the clinical and laboratory abnormalities reported in our study with cefazolin, vancomycin, ticarcillin-clavulanate, ganciclovir, and gentamicin are well-recognized; our data simply serve to document the rates of abnormalities among CoPAT patients. Several of these complications of therapy deserve special comment, however. Vancomycin-induced leukopenia has been described in the literature [13–16]; a recent review of vancomycin stated that neutropenia is found in approximately 2% of courses, but leukopenia rates were not listed [17]. In our review, leukopenia occurred in 58 of 954 evaluable courses of CoPAT, for a rate of 2.80 episodes per 1000 CoPAT days. This compares with a rate of therapy-limiting granulocytopenia of 0.88 per 1000 patient days in Kunkel’s group [9]. In the study by Hoffman-Terry et al, leukopenia complicated 13% of courses of vancomycin therapy [10], while in our group the proportion was 6%. In our experience and that of Hoffman-Terry et al, leukopenia usually developed several weeks into therapy, was gradual in onset, and reversed with cessation of vancomycin therapy [10]. Although therapy with granulocyte colony-stimulating factor has been reported for vancomycin-induced neutropenia in a home therapy patient [15], such treatment was not used in any of our cases. CoPAT recipients of vancomycin should be monitored with at least weekly complete blood counts with differential.

Our initial data suggested high rates of fever, rash, eosinophilia, and leukopenia in patients receiving gentamicin. On further analysis, we found that most CoPAT recipients of gentamicin who developed these complications were receiving other agents more apt to cause such side effects, such as vancomycin or β-lactam antibiotics [18–21]. In the minority of CoPAT patients who received gentamicin monotherapy, none of these complications developed. We believe that these complications remain rare with aminoglycoside therapy.

Our study has several important limitations. First, over the 11-year study period, end-of-therapy forms were completed in only 2054 of 3892 recipients of the 5 study drugs (52.8%). We did not systematically analyze through chart review complication rates among patients for whom forms were not completed. It is conceivable that physicians may have been more likely to complete end-of-therapy forms for patients who suffered an adverse event compared with those who did not, in which case our data overestimate the adverse clinical and laboratory event rates. Second, some clinical events such as rash, diarrhea, and dizziness were based on patient or nurse reports and were not always confirmed by physician examination. Physicians were asked to report events only if they were attributed to antimicrobial therapy, but it is possible that other concomitant medications or underlying conditions may have contributed to the adverse event rates. And finally, the coadministration of antibiotics in some courses of therapy may have confounded interpretation of which agent was indeed responsible for the reported adverse event, as occurred with gentamicin.

Notwithstanding these limitations, our data provide benchmark rates for CoPAT-related adverse events, emphasize the need for vigilant monitoring of patients on CoPAT, and validate published algorithms for clinical and laboratory follow-up.

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References

ADVERSE EVENTS WITH CoPAT

Table 5. Selected Events in Patients Receiving Gentamicin (223 Courses)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of Patients</th>
<th>Rash</th>
<th>Fever</th>
<th>Leukopenia</th>
<th>Eosinophilia</th>
<th>No. of Patients Experiencing Event (No. of Events)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin monotherapy</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gentamicin and vancomycin</td>
<td>96</td>
<td>7</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>21 (24)</td>
</tr>
<tr>
<td>Gentamicin and a cephalosporin</td>
<td>30</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Gentamicin and a penicillin</td>
<td>36</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Gentamicin and an anti-pseudomonal penicillin</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Gentamicin and imipenem or aztreonam</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Gentamicin and other†</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gentamicin and/or vancomycin and/or a β-lactam</td>
<td>20</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Gentamicin and 2 others†</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Details of courses with more than 1 event: rash with eosinophilia (2), rash with leukopenia (1), fever with eosinophilia (2), and leukopenia with eosinophilia (1).

†Antimicrobial agents other than vancomycin or β-lactam antibiotics.


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