Higher Occurrence of Hepatotoxicity and Rash in Patients Treated with Oxacillin, Compared with Those Treated with Nafcillin and Other Commonly Used Antimicrobials

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This study compared adverse drug reactions (ADRs) to oxacillin with those to nafcillin and other antibiotics. We reviewed the medical records of 222 children receiving outpatient parenteral antimicrobial therapy (OPAT) from February 1995 through June 1999. The diagnosis, antibiotics used, ADRs, action taken, and patient demographics were recorded. The most common ADRs were neutropenia (9.8%), rash (8.5%), and hepatotoxicity (3.8%). ADRs occurred more frequently in the oxacillin group (58.5%) than in the nafcillin group (29.3%; \( P < .004 \)), the clindamycin group (12.5%; \( P < .001 \)) and the “other” antibiotics group (14.4%; \( P < .001 \)). Hepatotoxicity and rash occurred more frequently in the oxacillin group (22% and 31.7%, respectively) than in the nafcillin group (0% \( [P < .001] \) and 10.3% \( [P = .008] \)), the clindamycin group (1.4% \( [P < .001] \) and 8.3% \( [P = .001] \)), and the other antibiotics group (1.4% \( [P < .001] \) and 1.4% \( [P < .001] \)). On the basis of this retrospective analysis, oxacillin use in children was associated with a higher incidence of hepatotoxicity and rash, compared with the use of nafcillin and other intravenous antimicrobials.

The choice of a drug for outpatient parenteral antimicrobial therapy (OPAT) should be based on the drug’s efficacy as well as its safety profile [1]. Penicillinase-resistant penicillins (PRPs), such as oxacillin and nafcillin, are considered first-line treatment for osteoarticular infections [2, 3] which are frequently diagnosed in patients receiving OPAT. Oxacillin and nafcillin have similar antimicrobial coverage and are often used interchangeably in clinical settings [4–7]. We noticed that, when our institution replaced nafcillin with oxacillin in the formulary, an unexpected high number of adverse drug reactions (ADRs), including hepatotoxicity, occurred; this finding warranted that the antimicrobial be changed or discontinued.

A higher number of ADRs has been reported among home care patients receiving nafcillin or oxacillin, compared with patients receiving other antibiotics [8]. However, a comparison of oxacillin with nafcillin and other antimicrobials has not been reported previously. The objective of this study was to compare the incidence of ADRs to oxacillin with that of ADRs to nafcillin and to other intravenous antibiotics commonly used in children in the home care setting.

PATIENTS AND METHODS

We performed a retrospective review of the medical records of pediatric patients who received OPAT from February 1995 through June 1999 and were followed...
by the Division of Pediatric Infectious Diseases of the University of Florida Health Science Center at Jacksonville. Patients had regular follow-up outpatient visits, and all patients were monitored with weekly laboratory testing, including analysis of complete blood count with differential, erythrocyte sedimentation rate and C-reactive protein. Results of liver function studies were initially monitored only for patients who developed symptoms. At the time of identification of a high number of abnormal results among oxacillin-treated patients, liver functions were monitored for the rest of the patients who received oxacillin in the study period, regardless of whether they had symptoms.

Data on the age, sex, diagnosis, other underlying conditions, antimicrobial agent (or agents) used, duration of use, dosage, and type of vascular access were recorded on a standardized data collection sheet. In our setting, because OPAT was delivered predominantly by the same pharmacy and home care agency, the same drug preparations and modes of delivery were used. All probable ADRs were recommended, regardless of whether they were reported by the patient, caretaker, or home nurse or were discovered on laboratory testing. The day of onset of the ADRs as well as the subsequent action taken, if any, were also recorded.

An “ADR” was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug. An ADR was considered to be probably related to the drug if it occurred after administration of the drug, stopped after discontinuation of the drug, and could not be explained by other factors. “Neutropenia” was defined by an absolute neutrophil count of <1000 cells/mm³. “Hepatotoxicity” was defined by the elevation of both the alanine aminotransferase level and the aspartate aminotransferase level to more than twice the upper range for age, whether it was associated with symptoms (e.g., nausea, vomiting, or abdominal pain) or not (silent hepatic injury). Reported rashes were confirmed by a health care professional (nurse or physician).

The patients were classified into 4 major groups on the basis of the antibiotic used: “oxacillin,” “nafcillin,” “clindamycin,” and “other.” The “other” antibiotics recorded included cefotaxime, ceftriaxone, cefazolin, cefazidime, vancomycin, ampicillin-sulbactam, piperacillin-tazobactam, imipenem-cilastatin, trimethoprim-sulfamethoxazole, aztreonam, gentamicin, amikacin, metronidazole, cefepime, ciprofloxacin, and other less commonly used antibiotics.

**STATISTICAL ANALYSIS**

χ² tests, t tests, and analysis of variance with post hoc comparisons were used to analyze differences between antibiotic groups. The significance level was P < .05.

**RESULTS**

Data were recorded for 222 patients who received 317 courses of OPAT. The mean patient age was 7.5 years (range, 2 days to 19 years). The mean age of patients with ADRs was 7.5 years, which was not statistically different from a mean of 7.7 years for those without ADRs (P = .78). The mean age of patients in each antibiotic group showed no statistically significant difference by 1-way analysis. A total of 129 (58.1%) of all 222 patients were male. By use of the χ² test, no statistically significant difference was found between the different antibiotic groups with regard to sex distribution (P = .907). The most frequent diagnosis overall was osteomyelitis (185 courses [58.5%]). It accounted for 30 (73%) and 42 (72%) of all diagnoses in the oxacillin and nafcillin groups, respectively. Other diagnoses included septic arthritis (42 [13.2%]), abscess (24 [7.5%]), empyema (21 [6.5%]), and other miscellaneous infections. OPAT was delivered most commonly through central venous catheters (161 [51%]), followed by peripherally inserted central catheters (121 [38%]). The type of vascular access and the mode of delivery were not statistically different between the oxacillin and nafcillin groups (P = .70). We have previously described elsewhere catheter-associated complications of OPAT in our patients [9].

ADRs occurred in association with 69 (21.8%) of all 317 recorded courses of antibiotics. These ADRs included neutropenia (in 31 patients), rash (27), hepatotoxicity (12), and other (diabetes, 2; serum sickness, 1; pruritus, 1; dyspnea, 1; and

### Table 1. Occurrence of adverse drug reactions (ADRs) among patients in antimicrobial treatment groups.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Hepatitis No. (%)</th>
<th>Rash No. (%)</th>
<th>Neutropenia No. (%)</th>
<th>Overall ADRs No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxacillin (n = 41)</td>
<td>9 (22)</td>
<td>13 (21.7)</td>
<td>5 (12.2)</td>
<td>24 (58.5)</td>
</tr>
<tr>
<td>Nafcillin (n = 58)</td>
<td>0</td>
<td>&lt;.001</td>
<td>9 (17.2)</td>
<td>.490</td>
</tr>
<tr>
<td>Clindamycin (n = 72)</td>
<td>1 (1.4)</td>
<td>&lt;.001</td>
<td>2 (2.8)</td>
<td>.046</td>
</tr>
<tr>
<td>Other (n = 146)</td>
<td>2 (1.4)</td>
<td>&lt;.001</td>
<td>14 (9.6)</td>
<td>.626</td>
</tr>
</tbody>
</table>
increased serum creatinine, 1). Some patients had ≥1 ADR. No cases of phlebitis were found, probably because of the predominant use of central lines. Results of the analysis of ADRs, by antibiotic group, are shown in table 1. The percentage of ADRs overall was higher in the oxacillin group (24 patients [58.5%]), compared with the nafcillin group (16 [27.5%]), the clindamycin group (9 [12.5%]) and the “other” antibiotics group (21 [14.4%]). These differences were statistically significant (P values were .004, <.001, and <.001 for nafcillin, clindamycin, and others respectively, when compared with oxacillin).

Neutropenia was the most frequently occurring ADR, occurring in association with 30 antibiotic courses (9.5%). Rash was the next most frequently occurring ADR, in 27 courses of antibiotics (8.5%). There was no statistically significant difference between oxacillin and nafcillin with regard to incidence of neutropenia (12.2% vs. 17.2%; P = .49). However, neutropenia occurred significantly less frequently in the clindamycin group (2 ADRs [2.8%]; P = .046). On the other hand, oxacillin was associated with a significantly higher incidence of rash, compared with nafcillin, clindamycin, and other antibiotics (table 1).

Liver functions were tested, for various reasons, in 48 patients (18 patients receiving oxacillin, 7 receiving nafcillin, 13 receiving clindamycin and 10 receiving “other” antibiotics). For all 317 antimicrobial courses recorded, 12 cases (3.8%) of hepatotoxicity were found. Nine of these patients with hepatotoxicity received oxacillin. The difference in the percentage of hepatotoxicity between the oxacillin group and the other groups was striking, with a P value of <.001 (table 1). Four patients (44%) with oxacillin-related hepatotoxicity had nausea, vomiting, fatigue, and/or abdominal pain. Two patients presented with skin rash, whereas hepatotoxicity was detected by laboratory testing for an additional 3 patients without overt clinical manifestations. Further details of hepatotoxicity cases are outlined in table 2. Liver function studies were performed for 18 patients who received oxacillin (44%). The characteristics of the patients with oxacillin-related hepatotoxicity, compared with those of patients receiving oxacillin therapy who did not have hepatotoxicity, are shown in table 3. The age, diagnosis, and the dose average and range were similar between the 2 groups. However, although there was an equal distribution, by sex, among patients without hepatotoxicity, 7 patients (77%) with oxacillin-related hepatotoxicity were male. None of the patients had an underlying medical condition that would predispose them to develop hepatotoxicity, nor did they have any other factors to explain the findings. For all patients with hepatotoxicity, the symptoms resolved and normalization of the liver transaminase levels occurred promptly after discontinuation of oxacillin. Therefore, we considered the hepatotoxicity to be probably related to oxacillin. The average time to resolution of hepatotoxicity (defined by a return of the liver transaminase levels to less than twice the upper range of normal levels) was 14.2 days after the discontinuation of oxacillin. The patients’ liver functions were followed at weekly intervals until resolution of hepatotoxicity.

The mean duration of intravenous antibiotic treatment was 32.5 days, whereas the onset of ADRs occurred at a mean of 22.8 days for all intravenous antibiotic courses recorded. In the oxacillin group, the mean time of onset was 17.7 days for hepatotoxicity, 19.5 days for rash, and 24.4 days for neutropenia. There was no statistically significant difference dem-
Table 3. Characteristics of patients with oxacillin-related hepatotoxicity, compared with those without hepatotoxicity.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with hepatotoxicity (n = 9)</th>
<th>Patients without hepatotoxicity (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (range)</td>
<td>8.9 (0.8–16)</td>
<td>6.29 (0.8–16)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Osteomyelitis, %</td>
<td>88.9</td>
<td>74</td>
</tr>
<tr>
<td>Onset of hepatitis, mean day (range)</td>
<td>17.7 (6–43)</td>
<td>—</td>
</tr>
<tr>
<td>Duration of oxacillin therapy, mean days (range)</td>
<td>—</td>
<td>18.8 (1–36)</td>
</tr>
<tr>
<td>Dosage, mg/kg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>176</td>
<td>188</td>
</tr>
<tr>
<td>Range</td>
<td>130–200</td>
<td>130–215</td>
</tr>
</tbody>
</table>

Oxacillin-related hepatotoxicity has been reported in the adult medical literature to a limited extent [10–16]. However, reports in the pediatric literature are lacking, and the pediatric infectious diseases textbooks do not emphasize hepatotoxicity as a potential complication of oxacillin therapy [17, 18].

Most of the antibiotic-induced hepatic injuries are considered idiosyncratic reactions [19]. Immune-related drug reactions are one of the most common sources of idiosyncratic toxicity [20]. The chronological relationships between drug administration and both onset and resolution of liver injury are the most important considerations in the diagnosis of drug-induced hepatitis. The criteria for diagnosis include the relationship to onset, the course of the reaction after discontinuation of the drug (“dechallenge”), and the response to readministration of the drug (“rechallenge”). The presence of extrahepatic features, such as skin rash, eosinophilia, and other organ involvement, implicate an immune-mediated (hypersensitivity) reaction. However, these manifestations occur only in a minority of cases [19]. When this kind of reaction is suspected, withdrawal of the drug, followed by resolution of the liver function abnormalities, may eliminate the need for extensive and invasive diagnostic procedures. It also raises ethical issues against rechallenge.

The limitations of this study include those inherent to its retrospective nature: the drug treatments were not randomized and the degree of monitoring of hepatic function was not homogenous among all the patients. It is possible that some cases of asymptomatic elevation of transaminase levels in patients receiving other antibiotics may have gone undetected, which would make the difference among antibiotic groups less prominent. Nevertheless, several factors make us believe that the phenomenon of higher incidence of oxacillin-induced hepatotoxicity and rash is real. The initial patients with hepatotoxicity were symptomatic, which was the reason behind the increased monitoring of liver function. The elevation of transaminase levels (especially of the more liver-specific alanine aminotransferase...
level) was remarkable, with levels increasing to >10 times the upper range of normal in most cases. The temporal association between the administration of oxacillin and the onset and resolution of the reactions is suggestive of a cause-effect relationship.

CONCLUSION

On the basis of this retrospective review, the use of intravenous oxacillin in children was associated with a significantly higher incidence of hepatotoxicity and rash, when compared with the use of nafcillin and other intravenous antibiotics commonly used in the home setting. These results suggest that, whenever possible, it would be prudent to avoid the use of oxacillin in the treatment of childhood infections that require OPAT. In the event that oxacillin is used, patients should be warned to report nonspecific features that may represent the prodrome of a drug-induced reaction—particularly unexplained nausea, vomiting, right upper-quadrant abdominal pain, lethargy, or fever—and liver function studies should be monitored periodically. This is especially true when the duration of treatment is anticipated to exceed 2 weeks.

References