Comparison of Ceforanide and Cephalothin Prophylaxis for Vaginal Hysterectomies

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We compared the safety and efficacy of a six-dose regimen of ceforanide for the prevention of infection after elective vaginal hysterectomy. A total of 150 patients were randomly assigned to either regimen. The overall incidence of documented pelvic infection was 5.3% and did not differ significantly between the prophylaxis groups when stratified by type of surgery. No serious adverse reactions were encountered in either group, but phlebitis was significantly more common in patients receiving cephalothin. We conclude that a two-dose regimen of ceforanide given intramuscularly is as effective as, and possibly better tolerated than, a six-dose regimen of cephalothin.

Postoperative pelvic infections in patients who have had a vaginal hysterectomy are notoriously difficult to diagnose. Using different criteria, numerous investigators (2, 4) have reported the incidence of such infections to be 30 to 40% in patients not receiving prophylactic antibiotics. Febrile morbidity, variously defined, has been noted in 30 to 50% of such patients. Both clinically diagnosed infection and febrile morbidity have been reduced by perioperative antibiotic prophylaxis. Although this has been established by appropriately conducted studies (2) and is now widely accepted, the optimal choice of antibiotic and timing of administration remain fruitful areas for inquiry.

Cephalosporins have been widely used for prophylaxis in vaginal hysterectomies, and they have been effective and well tolerated (1, 2, 4, 7, 8, 10). Ceforanide is a new antibiotic in this class which has an antibacterial spectrum similar to that of cephalothin, with enhanced activity against many cephalothin-resistant strains of Escherichia coli and Enterobacter spp. (3). Its major distinguishing characteristics are a prolonged serum half-life, approximately 3 h (9), and its relative lack of irritation when given intramuscularly (i.m.).

These characteristics could prove useful in resolving two potential problems which commonly accompany the use of antibiotics for prophylaxis in patients undergoing surgery. The drugs used for prophylaxis are generally administered when the patient is called to the operating room or several hours before the procedure. The antibiotic dose is not usually repeated during the operation, even though most drugs in the cephalosporin class would be at very low levels at the time the operative site is at greatest risk of infection. Additionally, antibiotics prescribed for prophylaxis are often continued long beyond the perioperative period (11). When these drugs are given intravenously, they increase the risk of phlebitis. Thus, a perioperative antibiotic regimen capable of producing high tissue levels during an operation and one which would not increase the risk of postoperative phlebitis would seem desirable. Because a two-dose, i.m. administration schedule for ceforanide seemed to meet these requirements, we chose to compare it with a multidose intravenous administration schedule for cephalothin in a randomized controlled study in patients having vaginal hysterectomy.

MATERIALS AND METHODS

Patients scheduled for elective vaginal hysterectomy, who were not allergic to penicillin or cephalosporins and who voluntarily agreed to participate, were enrolled in the study. The patients were divided into two groups: (i) those scheduled for hysterectomy only and (ii) those scheduled for hysterectomy and anterior or posterior repair or both. Within each group, the patients were randomly assigned to receive one of the antibiotic regimens. Ceforanide (500 mg) was given i.m. when the patient was called for surgery and repeated 12 h later. Cephalothin (1 g) was given intravenously when the patient was called for surgery, repeated during the operation, and repeated every 6 h for 24 h. Thus, patients received either two doses of ceforanide or six doses of cephalothin.

All patients had pre- and postprophylaxis complete blood counts, liver and renal function tests, and urinalyses. Daily urine cultures were performed on catheter specimens from patients with indwelling bladder catheters. When appropriate, aerobic and anaerobic cultures of blood, sputum, vaginal secretions, pus, or
midstream urine were done. Radiographic, ultrasound, and radioisotope studies were obtained as clinical circumstances dictated.

Specimens of uterine tissue and plasma obtained at the time of the operation were analyzed for ceforanide concentration by the cup-plate method (6).

The records of all patients were reviewed daily, and patients with fever, defined as an oral temperature of greater than 38°C, were seen by or discussed with one of the authors.

Additional antibiotics were any antibacterial compounds administered after the last dose scheduled by the protocol. The use of such antibiotics was the prerogative of the attending gynecological surgeon.

A postoperative surgical infection was defined by the presence of inflammation and purulence in the vagina, vaginal cuff, or pelvis. A surgically or radiographically demonstrable abscess also constituted a postoperative surgical infection.

Bacteria isolated from postoperative infections were tested for susceptibility to cephalothin and ceforanide by the disk diffusion and broth dilution methods.

A telephone call to the patient's physician was made 4 to 6 weeks after discharge to discover any late postsurgical infections.

The protocol for this study was approved by the Human Experimentation Committee of the LDS Hospital.

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**RESULTS**

A total of 150 patients were studied. Sixty had a vaginal hysterectomy only, and 90 had hysterectomy with repair (Table 1).

In the hysterectomy-only group, 28 patients received ceforanide and 32 received cephalothin. The average age in each drug group was 36 years. Fever and the consequent use of additional antibiotics were more common in patients receiving cephalothin, but the differences were not statistically significant ($P = 0.14$ and 0.57, respectively).

Urinary tract infections occurred during hospitalization in two patients in each group. Two additional urinary tract infections occurred in ceforanide-treated patients postdischarge. None of the patients in the ceforanide group had a postoperative wound or pelvic infection. Four patients (13%) in the cephalothin group had such infections. One patient had pelvic cellulitis, and three patients had vaginal cuff infections. One of these infections was recognized during hospitalization, and the remaining three became apparent after discharge. The difference between infection rates in the two groups is not of statistical significance ($P = 0.15$). The average length of hospitalization was also not different between the two groups. No clinically important abnormalities of hematological, renal, or hepatic function attributable to the prophylactic drugs were detected in either group. A single patient who had received cephalothin developed phlebitis of moderate severity.
In the hysterectomy-with-repair group, 90 patients were studied; 48 received ceforanide, and 42 received cephapirin. The mean age in both groups was 48 years. Postoperative fever was more common in women undergoing repair (57%) than in women having hysterectomy only (37%), but the difference between the ceforanide and cephapirin prophylaxis groups was not significant. Additional antibiotics were prescribed for a similar number of patients in each drug subgroup. Forty-three percent of the patients received additional antibiotics. Urinary tract infections occurred during hospitalization in three patients receiving ceforanide and in two patients receiving cephapirin. An additional four patients in each group developed urinary tract infections after discharge. Wound infections also occurred with similar frequency, involving two patients in each group. All four wound infections occurred during hospitalization. Three were cases of vaginal cuff infection, and one was a vaginal cuff abscess. One patient in the cephapirin group, with a vaginal cuff infection, had Bacteroides fragilis bacteremia. The average length of stay, 8.0 days, was identical in both groups but longer than the 5.6-day average stay for patients not having a repair performed.

No clinically significant drug-related laboratory abnormalities were detected in either subgroup. However, 8 of 42 (19%) of the patients assigned to receive cephapirin developed phlebitis, compared with none of the 48 receiving ceforanide \((P = 0.003)\). One case of phlebitis was considered moderately severe, and the others were regarded as mild.

Urine culture results were available for 13 of 19 patients with urinary tract infections. The bacteria isolated were enterococci (eight isolates), E. coli (three isolates), and one isolate each of Citrobacter, Pseudomonas, Klebsiella, Enterobacter, and Staphylococcus aureus. Three patients had mixed infections. The enterococci and Pseudomonas isolates were resistant to cephapirin and ceforanide. The one E. coli isolate available for testing was susceptible to both drugs (minimal inhibitory concentration [MIC] of ceforanide, 3 \(\mu g/ml\)). The Citrobacter and Klebsiella isolates were resistant to cephapirin by disk diffusion but sensitive to ceforanide (MICs, 0.8 and 1.5 \(\mu g/ml\), respectively). The organisms isolated from vaginal cultures from patients with postoperative surgical infections were enterococci (four isolates), E. coli (six isolates), and Bacteroides fragilis (one isolate). The three enterococci tested were resistant to both study drugs. Four E. coli isolates tested were sensitive to both agents. They required MICs of ceforanide of 0.2, 1.5, 12.5 and 12.5 \(\mu g/ml\).

**Table 2. Plasma and uterine tissue concentrations of ceforanide at the time of vaginal hysterectomy**

<table>
<thead>
<tr>
<th>No. of samples</th>
<th>Time after i.m. dose (min)</th>
<th>Plasma concn. ((\mu g/ml))</th>
<th>Uterine concn. ((\mu g/g))</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>(\leq 120)</td>
<td>24.6</td>
<td>10.5</td>
</tr>
<tr>
<td>4</td>
<td>121-180</td>
<td>27.5</td>
<td>9.9</td>
</tr>
<tr>
<td>1</td>
<td>&gt;180</td>
<td>16.0</td>
<td>7.6</td>
</tr>
</tbody>
</table>

Levels of ceforanide in plasma and in surgically removed tissue obtained at various times after the first i.m. dose of the drug are shown in Table 2. At the time of surgery, plasma and tissue levels were substantially above the MIC for most susceptible bacteria.

Additional antibiotics were frequently administered to patients because of suspected infection in the course of this study, but documented infections were quite uncommon. The antibiotics were more often prescribed for patients with fever (63%) than for those without fever (13%) \((P < 0.001)\). The drugs most often prescribed during hospitalization were the cephalosporins: cefazolin, cefalothin, cephradin, cephadine (32 patients), ampicillin (28 patients), gentamicin (16 patients), clindamycin (5 patients), tetracyclines (3 patients), nitrofurantoin (3 patients), cefoxitin (2 patients), and cefamandole (2 patients). Twenty-five percent of all patients were discharged from the hospital with instructions to begin or continue antibiotics. Of these, 32% were patients who had 1 or no days with fever during hospitalization. The drugs most commonly used were an oral cephalosporin (15 patients), ampicillin (19 patients), clindamycin (2 patients), tetracyclines (2 patients), and gentamicin (1 patient), which was administered i.m.

Patients with obvious evidence of infection while hospitalized were understandably treated with antibiotics. Of the 94 patients who received no additional antibiotics, only 1 developed a late postoperative pelvic infection (Table 3). This case occurred in 1 of 22 patients having simple hysterectomy with cephapirin prophylaxis. That rate, 5%, was not significantly different from the zero incidence of wound infections in 22 similar patients who had ceforanide for prophylaxis. Three patients who received no antibiotics had bacteriuria during hospitalization, and seven developed clinically diagnosed cystitis after discharge. The incidence did not differ in the two prophylaxis groups.

Fever for more than 2 days was neither a highly sensitive nor a specific predictor of documented infection in this study. Of eight patients with fever for 2 or more consecutive days who were not treated with antibiotics, none were ultimately shown to have an infection. Con-
versely, of eight patients with documented surgical infections, six (75%) had fever for this period of time.

The age of the patient was not a good predictor of either prolonged postoperative fever or documented infection. In the hysterectomy-only group, the average age of those with more than 1 day of fever was 39.1 years (standard deviation, 3.5), compared with 34.9 years (±7.07) in those with 1 or more days of fever. In the group undergoing repair, the corresponding ages were 47.1 years (±16.1) and 47.8 years (±12.4). The average age of patients with documented infections in each group was not significantly different from the average age of patients without infection.

DISCUSSION

Documented surgical infections were uncommon in patients treated with either drug regimen in this study, and there were no significant differences in the prophylactic efficacy of either drug. Similar findings in a study comparing penicillin and cefazolin prophylaxis have been reported (5). However, two important points should be considered in the interpretation of our results. First, the cephalothin regimen specified an intraoperative dose of that antibiotic to insure adequate levels during surgery. This may have decreased the number of postoperative infections from the number that might be expected when no such intraoperative dose is given. Second, because additional antibiotics were prescribed for a substantial number of patients in both prophylactic groups, the observed low rate of documented infections should not be regarded as the absolute rate. Some patients with fever but no documented infection may indeed have had infections which responded to their additional antibiotics. However, because additional antimicrobial agents were used with similar frequency in both prophylactic groups, this does not negate the conclusion that there was no observable difference in the efficacy of each regimen.

Neither regimen prevented all postoperative infections and, not surprisingly, when infection occurred, it was often due to drug-resistant bacteria. This phenomenon has occurred, and can be anticipated, with almost any prophylactic regimen.

No serious abnormalities in the laboratory data collected were noted in either group, but the adverse effect of phlebitis was significantly more common in the cephalothin prophylaxis group. This is, perhaps, not surprising since the alternative drug was given i.m., but it confirms the recognized potential of cephalosporins to produce venous inflammation.

The plasma and tissue levels of ceforanide

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Mean age (yr)</th>
<th>Mean length of stay (days)</th>
<th>Mean duration of fever (days)</th>
<th>No. of patients having fever for: 0 days (no fever)</th>
<th>1 day</th>
<th>2 days</th>
<th>3 days or more</th>
<th>No. of patients having wound infections</th>
<th>No. of patients having surgical wound infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hysterectomy only</td>
<td>21</td>
<td>35.5</td>
<td>5.3</td>
<td>18.66</td>
<td>3 (14)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (5)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Ceforanide</td>
<td>22</td>
<td>36.0</td>
<td>5.7</td>
<td>15.68</td>
<td>4 (18)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4 (16)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>26</td>
<td>46.7</td>
<td>7.5</td>
<td>18.69</td>
<td>5 (19)</td>
<td>2 (8)</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy with repair</td>
<td>25</td>
<td>47.4</td>
<td>7.0</td>
<td>16.64</td>
<td>8 (32)</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ceforanide</td>
<td>26</td>
<td>48.6</td>
<td>7.5</td>
<td>18.69</td>
<td>5 (19)</td>
<td>2 (8)</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cephalothin</td>
<td>25</td>
<td>47.4</td>
<td>7.0</td>
<td>16.64</td>
<td>8 (32)</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Numbers in parentheses indicate percentage of the subgroup.
confirmed the assumption that a preoperative i.m. dose does provide adequate levels during surgery. Our findings in patients having vaginal hysterectomy suggest that prophylaxis with two doses of ceforanide given i.m. 12 h apart is as effective as a multidose regimen of cephalothin and is associated with fewer clinical adverse reactions. However, one benefit of prophylaxis was not achieved with either drug regimen in this study: eliminating the use of postoperative antibiotics. A number of studies have shown that even "prophylactic" antibiotics are often continued well beyond the perioperative period (11; M. R. Britt, L. L. Goodell, R. Turner, L. F. Rikkers, and C. Halverson, Clin. Res. 28:43A, 1980). Understandably, some of the surgeons with patients enrolled in this study may have been accustomed to that practice and, hence, uncomfortable with a protocol which required prophylaxis to stop approximately 24 h postsurgery. However, most additional antibiotics were prescribed after an antibiotic-free interval when pain, fever, or both raised clinical suspicion of infection. Fever in the postoperative gynecological patient, though it is often due to a variety of noninfectious causes, may in fact indicate infection. Thus, some additional antibiotics may have been appropriately given for real but undocumented infection. It is obvious that to achieve the full benefits of perioperative prophylaxis, we must give more attention to its appropriate duration, and we must develop sensitive, specific, rapid diagnostic tests that will help identify the minority of febrile postoperative gynecological patients who indeed have infections that would benefit from antibiotic or surgical therapy or both.

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LITERATURE CITED