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Occurrence of Clindamycin-Resistant Anaerobic Bacteria Isolated from Cultures Taken Following Clindamycin Therapy

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MICs of clindamycin were determined by the agar dilution method against anaerobic organisms isolated from endometrial cultures in women with pelvic soft tissue infections. Cultures were obtained from 100 women both before and after clindamycin therapy, from 107 women before therapy with clindamycin or another antimicrobial agent or after treatment with an antimicrobial agent other than clindamycin, and from 9 women 1 to 9 weeks after they were discharged from the hospital following clindamycin therapy. Only 5 (0.7%) of 685 isolates tested from women who had not received clindamycin therapy were resistant to clindamycin. From the 100 cultures taken immediately after clindamycin therapy, 57 anaerobic bacteria were isolated from 28 cultures. Of the 40 anaerobic organisms for which MICs of clindamycin were determined, 25 (62.5%) were resistant to clindamycin (MIC ≥ 8 μg/ml). The most common organisms isolated after therapy were the anaerobic gram-positive cocci (of which 32 isolates were discovered); of 28 coccal isolates tested, 64% were clindamycin resistant. Four of seven (57%) of the *Bacteroides* isolates tested, one unidentified gram-positive nonsporing rod, one unidentified gram-negative coccus, and one *Mobiluncus* sp. were also clindamycin resistant. Of 18 anaerobic isolates from the nine cultures taken 1 to 9 weeks after hospital discharge, 55% were resistant to clindamycin. The clinical significance of these findings is unknown since all patients recovered without incident and remained well. However, the data suggest that physicians need to be aware that patients with recent exposure to clindamycin may have clindamycin-resistant anaerobic organisms in a current infection. This may prevent the infection from responding to clindamycin treatment.

Clindamycin is one of the most common antimicrobial agents used in the treatment of anaerobic infections and continues to be highly effective in most situations (4, 12). In obstetric and gynecologic practice, clindamycin plus an aminoglycoside is a frequent treatment regimen for pelvic soft tissue infections and in studies of safety and efficacy of new antimicrobials is often used as the standard treatment with which newer treatment regimens are compared (2, 7, 22). In the studies we have done, we have noticed that whereas the clinical outcomes from the clindamycin regimen have been acceptable, a number of clindamycin-resistant anaerobic bacteria, especially anaerobic gram-positive cocci, were isolated from posttreatment cultures. Whereas some investigators have noted the occurrence of clindamycin-resistant anaerobic bacteria in in vitro studies (3, 9, 14, 18, 21), they have not specified the relationship of this occurrence to clindamycin treatment. Others who have presented results of studies in which clindamycin was used to treat obstetric or gynecologic infections have not reported results of posttreatment cultures or the susceptibilities of organisms from these cultures (2, 6, 23). The purpose of the present study was to review pre- and posttreatment culture results, organism susceptibility to clindamycin, and outcomes of treatment for patients who were enrolled in prospective antibiotic treatment trials for female upper genital tract infection and who were treated with clindamycin.

MATERIALS AND METHODS

Data were compiled from five studies conducted between 1980 and 1985 in which clindamycin plus an aminoglycoside or aztreonam was offered as treatment for pelvic soft tissue infections. Data were also compiled on women who received alternative treatment (cefoperazone, moxalactam, cefoxitin-doxycycline, or SCH 34343) in the studies that were comparative trials. Patients enrolled in these studies had signed written informed consents approved by the university's human research committee.

For those who received clindamycin, treatment consisted of 600 mg of the antibiotic given intravenously every 6 h plus the aminoglycoside or aztreonam given as indicated in the study protocol. For those who received alternate therapy, the antimicrobials were given as indicated in the study protocol.

Most patients were being treated for acute salpingitis or postpartum endomyometritis. Saline washings or brushings of the endometrial cavity were obtained from patients at the time they were admitted into the studies and at the time they were discharged from the hospital after treatment. In addition, seven patients had endometrial cultures taken from 1 to 9 weeks after their discharge. At the time pretreatment cultures were taken most women had received no antimicrobial therapy for at least 2 months. Some women had received penicillins, cephalosporins, or tetracycline. One woman had received erythromycin, and two others had received clindamycin plus tobramycin.

Endometrial washings were done by slowly injecting saline into the endometrial cavity and reaspirating the saline through a long cannula. Endometrial brushings were obtained with a double catheter brush device in a method described by Knuppel et al. (11). Since both of these methods were transcervical, there was some possibility of contamination of the endometrial specimen with lower genital tract flora.

Specimens were inoculated into a variety of media for isolation of aerobic and anaerobic organisms (22). Anaerobic

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TABLE 1. Susceptibilities and resistances to clindamycin of anaerobic bacteria isolated from endometrial cultures after clindamycin treatment

Organism	No. of isolates susceptible to clindamycin (MIC ≤ 4 μg/ml)	No. of isolates resistant to clindamycin (MIC ≥ 8 μg/ml)[a]
P. asaccharolyticus	2	4
P. magnus	1	9
P. prevotii	3	0
P. tetradius	1	2
Unidentified anaerobic gram-positive cocci	2	3
Peptostreptococcus anaerobius	1	0
B. fragilis	2	0
Bacteroides ovatus	1	0
B. vulgatus	0	1
B. capillosus	0	1
Bacteroides species	0	2
Unidentified anaerobic gram-positive nonsporing rod	1	1
Mobiluncus sp.	0	1
Veillonella parvula	1	0
Unidentified anaerobic gram-negative cocci	0	1

[a] All resistant organisms had clindamycin MICs of >64 μg/ml except two *P. magnus* isolates with MICs of 8 μg/ml and a *Mobiluncus* sp. with an MIC of 32 μg/ml.

organisms were identified through the use of prereduced anaerobically sterilized media and gas-liquid chromatography (8). MICs of antibiotics were determined by the agar dilution method with either Wilkins-Chalgren agar or supplemented Brucella agar as a base (15, 20). Control organisms were run with each set of organisms tested. Organisms were considered resistant to clindamycin if MICs were ≥8 μg/ml (1, 24).

RESULTS

Pretreatment and posttreatment cultures were done on most patients and received extensive workup in the research laboratory. Culture results and MIC data were available from both pretreatment and posttreatment cultures from 100 of 121 patients who received either clindamycin-tobramycin, clindamycin-gentamicin, or clindamycin-aztreonam treatment according to study protocol. Length of treatment at the time that posttreatment cultures were taken ranged from 2 to 11 days, with a mean of 5 days. In addition, data on MICs of clindamycin were available for organisms from 109 pretreatment or posttreatment cultures of patients who had been treated with antibiotics other than clindamycin; MIC data were also available for pretreatment cultures of those who were treated with clindamycin but who had no posttreatment culture.

From pretreatment cultures done on the 100 clindamycin-treated patients, both aerobic and anaerobic organisms were isolated from 80 cultures, aerobic organisms only were isolated from 14 cultures, anaerobic organisms only were isolated from 1 culture, and 5 cultures showed no growth. MICs of clindamycin were determined for 284 anaerobic organisms, and all were susceptible to clindamycin (MICs ≤4 μg/ml).

Of 100 postclindamycin treatment cultures, 27 showed no growth, 45 showed growth of only aerobic organisms, 25 showed growth of both aerobic and anaerobic organisms, and from 3 cultures only anaerobic organisms were isolated.

A total of 57 anaerobic bacterial organisms were isolated from the 28 posttreatment cultures that yielded anaerobic growth. These included 32 gram-positive cocci, 17 *Bacteroides* sp. (including 4 from the *Bacteroides fragilis* group), 4 gram-positive nonsporing rods, 1 *Mobiluncus* sp., 1 *Veillonella* sp., 1 unidentified gram-negative coccus, and 1 unidentified gram negative rod. Information on the MICs of clindamycin was available for 40 of these organisms (Table 1).

Of the anaerobic bacteria isolated following clindamycin therapy, the gram-positive cocci accounted for 56%. Of the 28 isolates for which MICs of clindamycin were determined, 18 (64%) were clindamycin resistant, with MICs ranging from 8 μg/ml to >128 μg/ml. Seven of the resistant organisms (two *Peptostreptococcus asaccharolyticus* isolates, three *Peptostreptococcus magnus* isolates, one unidentified gram-positive coccus, and one *Peptostreptococcus tetradius* isolate) were also taken from pretreatment cultures. Clindamycin MICs against these pretreatment isolates ranged from ≤0.03 to 1.0 μg/ml.

Of the 25 posttreatment isolates that were not gram-positive cocci, MICs of clindamycin were determined against 12. Most of those not tested were *Bacteroides* isolates that did not grow well enough on either Wilkins-Chalgren or supplemented Brucella agars to determine MICs. Four of seven (57%) of the *Bacteroides* isolates tested, including one *B. fragilis* group isolate, were resistant to clindamycin (Table 1). Six of these seven *Bacteroides* isolates occurred in cultures from which clindamycin-resistant cocci were also isolated. Three of the resistant isolates (two unidentified *Bacteroides* isolates and one *Bacteroides capillosus* isolate) were also found in pretreatment cultures; clindamycin MICs were ≤0.25 μg/ml for these isolates from pretreatment cultures.

In addition, three other posttreatment isolates were resistant to clindamycin: an unidentified gram-positive nonsporing rod, an unidentified gram-negative coccus and a *Mobiluncus* sp. (Table 1).

Information on organisms isolated and MICs of clindamycin against these organisms was also available from seven endometrial cultures taken approximately 1 to 9 weeks after patients were discharged from the hospital. Cultures from two patients, one of whom had a clindamycin-resistant *P. magnus* strain in her discharge culture, showed no growth. From the other five cultures 20 anaerobic bacteria were isolated, and clindamycin MICs were determined for 13 of these (Table 2). The clindamycin-susceptible organisms except for *P. tetradius* were isolated from a single culture taken

TABLE 2. Susceptibilities and resistances to clindamycin of anaerobic bacteria isolated from endometrial cultures 1 to 9 weeks after clindamycin treatment

Organism	No. of isolates susceptible to clindamycin (MIC ≤ 4 μg/ml)	No. of isolates resistant to clindamycin (MIC ≥ 8 μg/ml)[a]
P. asaccharolyticus	1	4
P. magnus	0	3
P. prevotii	0	1
P. tetradius	1	0
Unidentified anaerobic gram-positive cocci	2	1
B. fragilis	1	0
B. melaninogenicus	1	0
Bacteroides sp.	2	1

[a] All resistant organisms had clindamycin MICs of >64 μg/ml.

9 weeks posttreatment. The *P. tetradius* was isolated from a culture taken 8 weeks posttreatment; an isolate of *P. asaccharolyticus* with a clindamycin MIC of >128 μg/ml was also taken from this culture. The other resistant isolates were from cultures taken 1 to 3 weeks after hospital discharge. None of the patients who had clindamycin-resistant anaerobic bacteria in the cultures taken 1 to 9 weeks postdischarge had clindamycin-resistant anaerobic bacteria in the cultures taken at discharge. None of the patients experienced complications following discharge. All were discharged home on clindamycin.

The length of clindamycin treatment at the time posttreatment cultures were taken ranged from 2 to 11 days. Clindamycin-resistant anaerobic bacteria occurred in cultures taken from 2 to 7 days after treatment was begun.

MICs of clindamycin were determined for 405 anaerobic organisms, including 198 anaerobic gram-positive cocci and 159 *Bacteroides* isolates from 109 pre- and posttreatment cultures of patients who subsequently received treatment other than clindamycin and from pretreatment cultures of patients who subsequently received clindamycin but did not have a posttreatment culture done. A total of 396 organisms from 103 cultures were susceptible to clindamycin. Cultures from six patients showed one or more organisms each (for a total of nine organisms) for which the MIC of clindamycin was ≥8 μg/ml. Cultures from two patients had one organism each (one *Bacteroides thetaiotaomicron* strain and one unspeciated *Bacteroides* strain) with a clindamycin MIC of 8 μg/ml. From another culture an unidentified anaerobic gram-positive nonsporing rod with a clindamycin MIC of >128 μg/ml was isolated along with several other anaerobic organisms with clindamycin MICs of ≤2 μg/ml. From a fourth patient a *Bacteroides bivius* strain and a *P. asaccharolyticus* strain, both with MICs of >64 μg/ml, were isolated. Nothing in the medical histories of these four patients indicated that they had previously received clindamycin or erythromycin. From two other patients, four organisms (two *P. magnus* isolates, a *P. asaccharolyticus* isolate, and an unidentified *Bacteroides* sp.) with clindamycin MICs of >64 μg/ml were cultured (Table 2). These two patients had each received clindamycin treatment within 2 months before the cultures were taken. All patients recovered without incident. Three were treated with clindamycin-tobramycin, one with moxalactam, one with cefoxitin-doxycycline, and one with SCH 34343, a new beta-lactam antibiotic under investigation.

DISCUSSION

The occurrence of resistance of anaerobic bacteria to clindamycin is not new, but most reports have been confined to studies of *Bacteroides*, mainly the *B. fragilis* group. Furthermore, the conditions under which the clindamycin-resistant anaerobes occurred in relation to clindamycin therapy have usually not been noted. Yee et al. (25) have shown that *B. fragilis* resistance to clindamycin appeared to be related to previous clindamycin or erythromycin treatment. We did not see any clindamycin-resistant *B. fragilis* group organisms among isolates from our obstetric and gynecologic population except for a *Bacteroides vulgatus* strain isolated after clindamycin treatment. The *B. fragilis* group organisms are less frequently isolated from female upper genital tract infections than are anaerobic gram-positive cocci and other *Bacteroides* species (6, 22, 23). Because clindamycin is frequently used to treat these infections, it is necessary to consider susceptibilities to clindamycin of anaerobic gram-positive cocci and *Bacteroides* species other than the *B. fragilis* group.

Resistance of anaerobic gram-positive cocci to clindamycin has been reported from 0 to 17% (3, 9, 14, 18, 19, 21). In reports in which peptococci and peptostreptococci were differentiated, resistance was noted among the peptococci rather than the peptostreptococci. Our findings are consistent with these data, since *P. magnus*, *P. asaccharolyticus*, and *P. prevotii* were previously classified as *Peptococcus* species (5).

The occurrence of clindamycin resistance in *Bacteroides* species other than the *B. fragilis* group appears to be infrequent (1, 3, 10, 19, 21). We saw no clindamycin resistance in *B. disiens* and the *B. melaninogenicus* group, and we found only one resistant isolate of *B. bivius*, the most frequent *Bacteroides* isolates in pelvic soft-tissue infections (6, 22). Except for the *B. bivius* isolate, the clindamycin-resistant *Bacteroides* organisms that we did see were limited to those isolated after clindamycin therapy. We have no data to relate clindamycin resistance to previous erythromycin therapy, as to our knowledge only one of our patients received erythromycin prior to any of the cultures. A single anaerobic isolate from the culture after erythromycin treatment was susceptible to clindamycin.

The clinical significance of the appearance of clindamycin-resistant organisms in cultures taken after clindamycin therapy is unknown. All our patients recovered without incident and remained well, including those who harbored clindamycin-resistant organisms several weeks after treatment. Furthermore, two patients who were readmitted to the hospital for pelvic inflammatory disease approximately 1 month after clindamycin treatment were found to have clindamycin-resistant organisms in endometrial cultures taken at the time they were readmitted. However, since the susceptibilities were not known at the time, one of these patients was treated again with clindamycin and recovered without incident. No anaerobic bacteria were isolated from cultures taken after this patient's second course of clindamycin therapy. The other patient recovered on moxalactam therapy. Other investigators, however, have found that the presence of clindamycin-resistant *B. fragilis* group organisms accounted for the increased severity and duration of infections in patients being treated with clindamycin (25). In the cases in which these resistant *Bacteroides* organisms were clearly the pathogens, patients did not recover until alternative therapy was instituted.

One possible reason why our patients did not suffer adversely from clindamycin-resistant organisms is that these organisms were cervical or vaginal contaminants in the endometrial cultures. It has been shown in several instances that occurrence of resistant organisms at infection sites after therapy may be of doubtful clinical significance, especially when cultures from these sites may be contaminated with endogenous flora. Yee et al. (25) found that when clindamycin-resistant *Bacteroides* organisms at infection sites after clindamycin or erythromycin therapy or prophylaxis played a doubtful role in the infection, the patients recovered despite inappropriate therapy for resistant organisms. Ohm and Galask (16, 17) found cephalosporin-resistant organisms in vaginal apex cultures following hysterectomy in which cephalosporin prophylaxis was used. However, either these organisms were not associated with the infections, or when cephalosporins were used to treat the infections, the patients recovered without incident. Louria and Kaminski (13) found sputum colonization with resistant organisms after penicillin, streptomycin, or tetracycline treatment; but again, in most cases patients were asymptomatic, and most organisms disappeared after treatment had been discontinued for sev-

eral weeks. Therefore, when resistant organisms are cultured from sites that may be contaminated by endogenous flora, the condition of the patient and the quality of the specimen must be taken into account before therapy is instituted or changed.

However, since lower genital tract organisms can be implicated in upper genital tract infections, the presence of clindamycin-resistant organisms in the lower genital tract should also be of concern. Physicians need to be aware that patients who have had recent prior treatment with clindamycin may be colonized or infected with clindamycin-resistant anaerobic bacteria and that clinical failure to respond to the standard regimen of clindamycin plus an aminoglycoside may be caused by such resistant organisms rather than enterococci or *Enterobacteriaceae*. Our findings also suggest that susceptibility testing of anaerobic bacteria recovered from patients with recent exposure to clindamycin may be useful.

LITERATURE CITED

1. **Acar, J. F., F. W. Goldstein, M. D. Kitzis, and M. T. Eyquem.** 1981. Resistance pattern of anaerobic bacteria isolated in a general hospital during a two-year period. J. Antimicrob. Chemother. **8**(Suppl. D):9–16.
2. **Blanco, J. D., R. S. Gibbs, P. Duff, Y. S. Casteneda, and P. J. St. Clair.** 1983. Randomized comparison of ceftazidime versus clindamycin-tobramycin in the treatment of obstetrical and gynecological infections. Antimicrob. Agents Chemother. **24**:500–504.
3. **Brown, W. J., and P. E. Waatti.** 1980. Susceptibility testing of clinically isolated anaerobic bacteria by an agar dilution technique. Antimicrob. Agents Chemother. **17**:629–635.
4. **Dhawan, V. K., and H. Thadepalli.** 1982. Clindamycin: a review of fifteen years of experience. Rev. Infect. Dis. **4**:1133–1153.
5. **Ezaki, T., N. Yamamoto, K. Ninomiya, S. Suzuki, and E. Yabuuchi.** 1983. Transfer of *Peptococcus indolicus*, *Peptococcus asaccharolyticus*, *Peptococcus prevotii*, and *Peptococcus magnus* to the genus *Peptostreptococcus* and proposal of *Peptostreptococcus tetradius* sp. nov. Int. J. Syst. Bacteriol. **33**:683–698.
6. **Gall, S. A., A. P. Kohan, O. M. Ayers, C. E. Hughes, W. A. Addison, and G. B. Hill.** 1981. Intravenous metronidazole or clindamycin with tobramycin for therapy of pelvic infections. Obstet. Gynecol. **57**:51–58.
7. **Gibbs, R. S., J. D. Blanco, Y. S. Casteneda, and P. J. St. Clair.** 1982. A double-blind randomized comparison of clindamycin-gentamicin versus cefamandole for treatment of post-cesarean section endomyometritis. Am. J. Obstet. Gynecol. **144**:261–267.
8. **Holdeman, L. V., E. P. Cato, and W. E. C. Moore (ed.).** 1977. Anaerobe laboratory manual, 4th ed. Virginia Polytechnic Institute and State University, Blacksburg.
9. **Kaye, D., W. Kobasa, and K. Kaye.** 1980. Susceptibilities of anaerobic bacteria to cefoperazone and other antibiotics. Antimicrob. Agents Chemother. **17**:957–960.
10. **Kirby, B. D., W. L. George, V. L. Sutter, D. M. Citron, and S. M. Finegold.** 1980. Gram-negative anaerobic bacilli: their role in infection and patterns of susceptibility to antimicrobial agents. I. Little-known *Bacteroides* species. Rev. Infect. Dis. **2**:914–951.
11. **Knuppel, R. A., J. C. Scerbo, J. Dzink, G. W. Mitchell, C. L. Cetrulo, and J. Bartlett.** 1981. Quantitative transcervical uterine cultures with a new device. Obstet. Gynecol. **57**:243–248.
12. **LeFrock, J. L., A. Molavi, and R. A. Prince.** 1982. Clindamycin. Med. Clin. North Am. **66**:103–120.
13. **Louria, D. B., and T. Kaminski.** 1962. The effects of four antimicrobial drug regimens on sputum superinfection in hospitalized patients. Am. Rev. Respir. Dis. **85**:649–665.
14. **Martin, W. J., M. Gardner, and J. A. Washington II.** 1972. In vitro antimicrobial susceptibility of anaerobic bacteria isolated from clinical specimens. Antimicrob. Agents Chemother. **1**:148–158.
15. **National Committee for Clinical Laboratory Standards.** 1985. Reference agar dilution procedure for antimicrobial susceptibility testing of anaerobic bacteria. National Committee for Clinical Laboratory Standards, Villanova, Pa.
16. **Ohm, M. J., and R. P. Galask.** 1975. The effect of antibiotic prophylaxis on patients undergoing vaginal operations. II. Alterations of microbial flora. Am. J. Obstet. Gynecol. **123**:597–604.
17. **Ohm, M. J., and R. P. Galask.** 1976. The effect of antibiotic prophylaxis on patients undergoing total abdominal hysterectomy. I. Effect on morbidity. Am. J. Obstet. Gynecol. **125**:442–447.
18. **Rolfe, R. D., and S. M. Finegold.** 1981. Comparative in vitro activity of new beta-lactam antibiotics against anaerobic bacteria. Antimicrob. Agents Chemother. **20**:600–609.
19. **Sorrell, T. C., J. R. Marshall, and A. W. Chow.** 1981. Antimicrobial therapy of postpartum endomyometritis. I. Comparative susceptibility of mezlocillin and other antibiotics to genital anaerobic bacteria. Am. J. Obstet. Gynecol. **141**:242–245.
20. **Sutter, V. L., D. M. Citron, and S. M. Finegold.** 1980. Wadsworth anaerobic bacteriology manual, 3rd ed. C. V. Mosby Co., St. Louis.
21. **Sutter, V. L., and S. M. Finegold.** 1976. Susceptibility of anaerobic bacteria to 23 antimicrobial agents. Antimicrob. Agents Chemother. **10**:736–752.
22. **Sweet, R. L., M. J. Ohm-Smith, D. V. Landers, and M. O. Robbie.** 1985. Moxalactam versus clindamycin plus tobramycin in the treatment of obstetric and gynecologic infections. Am. J. Obstet. Gynecol. **152**:808–817.
23. **Swenson, R. M., T. C. Michaelson, M. J. Daly, and E. H. Spaulding.** 1974. Clindamycin in infections of the female genital tract. Obstet. Gynecol. **44**:699–702.
24. **Tally, F. B., A. Sosa, N. V. Jacobus, and M. H. Malamy.** 1981. Clindamycin resistance in *Bacteroides fragilis*. J. Antimicrob. Chemother. **8**(Suppl. D):43–48.
25. **Yee, M. H., D. Guiney, P. Hasegawa, and C. E. Davis.** 1982. The clinical significance of clindamycin-resistant *Bacteroides fragilis*. J. Am. Med. Assoc. **248**:1860–1863.