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Anaerobic Wound Infections in Cancer Patients: Comparative Trial of Clindamycin, Tinidazole, and Doxycycline

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Clindamycin, tinidazole (a parent compound to metronidazole), and doxycycline were compared in vitro against 376 anaerobic bacteria isolated from clinical specimens. Bacteriostatic tests indicated that clindamycin was the most active drug, on a weight basis, against these strains except for *Clostridium* species. The three drugs were compared as therapies for anaerobic wound infections in cancer patients. In a randomized double-blind study, no statistically significant differences between clindamycin and tinidazole could be documented. Doxycycline was less active presumably because of the lack of clinical response in three out of four patients infected with doxycycline-resistant strains. No major untoward effects were observed. The bactericidal dilution of the serum was predictive of the clinical outcome.

Infection in a malignant, ischemic, traumatic, or other process that is destructive of tissue, especially when near a mucosal surface laden with normal microflora, is frequently caused by anaerobic bacteria. In recent years, special emphasis has been put on those infections caused by organisms belonging to the *Bacteroides* group of bacilli, and it has been found that surgical complications and neoplasms, especially adenocarcinoma of the colon, are two important factors associated with bacteremia due to *Bacteroides* sp. (11). Although the incidence of septicemia caused by these microorganisms in a population of patients with malignant diseases may not be very high (2% of all septicemias) (7), *Bacteroides* sp. and other anaerobic microorganisms can be isolated from many localized lesions in cancer patients and might have there an important pathogenic role. The precise importance of *Bacteroides* sp. and other anaerobic microorganisms in wound infections is often difficult to assess when a bacteremia cannot be documented. This is due to the frequent association of aerobic pathogens, especially gram-negative rods, with the anaerobic microorganisms within the wound and, also very often, to the complexity of the local infection, especially when the lesion is superimposed on a tumor. The effect of surgical drainage and debridement further complicates the investigation of the pathogenesis and treatment of this type of infection.

Antimicrobial therapy of infections caused by anaerobic microorganisms consists of penicillin as the drug of choice, except for *Bacteroides fragilis*. At the present time, several drugs have been proposed as possible active therapies in infections caused by *B. fragilis* species. These include chloramphenicol, doxycycline, clindamycin, and metronidazole, but the optimal therapy should be selected on the basis of in vitro tests for susceptibility, since the susceptibility of microorganisms to antimicrobial agents may change as time passes and from place to place. Moreover, a rational choice of treatment should be based on controlled clinical trials comparing the efficacy and toxicity of the various proposed regimens.

For this reason we compared the effectiveness of doxycycline, clindamycin, and tinidazole (a parent compound to metronidazole with more favorable pharmacokinetic characteristics [15]) against strains of anaerobic microorganisms isolated from clinical infections and as sole therapy for wound infections presumed to be caused by anaerobes in patients with cancer.

MATERIALS AND METHODS

In vitro studies. The susceptibility to various antibiotics, including doxycycline, tinidazole, and clindamycin, was determined for the following strains, all of which had been isolated from clinical specimens: 200 *B. fragilis* organisms (157 *B. fragilis* subsp. *fragilis*, 21 *B. fragilis* subsp. *thetaiotaomicron*, 9 *B. fragilis* subsp. *vulgatus*, 8 *B. fragilis*

subsp. *distasonis*, 5 *B. fragilis* subsp. *ovatus*), 72 *Clostridium* species (63 *C. perfringens*, 1 *C. oedematiens*, 2 *C. septicum*, 2 *C. paraputrificum*, 1 *C. barate*, 1 *C. bifermentans*, 1 *C. perenne*, 1 *C. sardiniensis*), 54 *Fusobacterium* species (41 *F. nucleatum*, 3 *F. naviforme*, 2 *F. russii*, 4 *F. gonidiaformans*, 3 *F. novum*, 1 *F. varium*), 20 *Bacteroides melaninogenicus*, and 31 anaerobic cocci (6 *Peptostreptococcus anaerobius*, 5 *P. intermedius*, 4 *P. micros*, 2 *P. productus*, 9 *Peptococcus asaccharolyticus*, 3 *Peptococcus prevotii*, and 2 *Peptococcus magnus*). This distribution indicates the spectrum of anaerobic microorganisms isolated in our laboratory over the past 2 years and those that were considered clinically significant pathogens.

The identification of these various microorganisms was determined according to the Virginia Polytechnic Institute *Anaerobe Laboratory Manual* (8). Anaerobic conditions for cultures were provided by the use of the GasPak system (BBL). No anaerobic cabinet was used for the plating of clinical specimens or for the manipulations required by subculturing. In most cases, however, the clinical specimens were plated within a few minutes after collection. No special precautions were taken for specimen transport.

The susceptibility of the microorganisms to antibiotics was tested by the inocula-replicating method of Steers et al. (12), using Schaedler broth (BBL) with agar plates containing twofold dilutions of the antibiotics to be tested. The culture medium used for testing the susceptibility of the strains of *B. melaninogenicus* contained, in addition, 5% sheep blood.

The inoculum consisted of an overnight culture of the microorganisms in peptone-yeast-glucose broth, prepared as indicated by the *Anaerobe Laboratory Manual* (8) (approximately 10^7 microorganisms per ml). The microorganisms were inoculated on the surface of the agar with an automatic inoculating apparatus in a volume of approximately 0.003 ml. The plates were incubated for 48 h under anaerobic conditions at 37°C and then examined for evidence of growth. The lowest concentration at which no macroscopic growth could be seen on the plates was considered to represent the minimum inhibitory concentration (MIC).

The inhibitory activity of patients' sera against the strains responsible for clinical infections was determined on 96-well plastic plates (Cook microtiter plate). Sera were diluted serially with peptone-yeast-glucose broth, and a 25-μl volume of these diluted sera was mixed with 25 μl of a suspension of the microorganism to be tested in peptone-yeast-glucose broth. This suspension consisted of an overnight culture in peptone-yeast-glucose broth. The plates were then incubated for 48 h under anaerobic conditions at 37°C and examined for evidence of growth. The highest dilution at which no macroscopic growth could be seen was considered the maximum bacteriostatic dilution. The clear wells were plated on Schaedler broth with agar and incubated under anaerobic conditions for 48 h at 37°C to determine the maximum bactericidal dilution.

Clinical studies. Three groups of 25 patients, all of whom presented an underlying malignancy, were studied, but ultimately anaerobic infection could be demonstrated in only 19 patients who received doxycycline, 18 who received tinidazole, and 19 who received clindamycin. All these patients were hospitalized at the Institut Jules Bordet, which is the clinical center for cancer therapy of Brussels University. All the patients considered here presented a similar degree of debilitation. No major differences in regard to the underlying tumor were found among the three groups. Patients were admitted into the trial if they presented a wound infection, an abscess, a tumor infection, or an infection of the tracheobronchial tree superimposed on a tracheostomy considered likely to be caused by anaerobic microorganisms.

The various antibiotics studied were obtained from the manufacturer as powders and distributed in identical capsules containing 50 mg of doxycycline D, 200 mg of tinidazole, or 200 mg of clindamycin. The regimen consisted of two capsules every 8 h for 8 consecutive days. The antibiotics, under an identical presentation, were available in boxes identifiable by numbers only and were administred to the patients in a sequence predetermined by a random choice.

Favorable clinical responses were considered to have been effected when the initial clinical signs and symptoms related to the infection disappeared during therapy or improved markedly. Bacteriological cure was not considered to be necessary for a favorable clinical response. Mild intolerance to the antibiotics, not requiring their discontinuation, and asymptomatic colonization of the site of the infection were considered to be compatible with a favorable clinical response when indicated.

Aerobic and anaerobic cultures were obtained from the site of the infection and from blood in all patients before and during therapy; in most patients these cultures were repeated after discontinuation of the antibiotics. Complete hematological examination and determination of blood urea nitrogen, creatinine, alkaline phosphatase, bilirubin, and oxalacetic-glutamic and glutamic-pyruvic transaminases were performed before, during, and after therapy.

RESULTS

Microbiological studies. Figure 1 shows the subsceptibility of 200 strains of *B. fragilis* to 10 antibiotics (penicillin, ampicillin, cephalothin, carbenicillin, erythromycin, chloramphenicol, tetracycline, doxycycline, clindamycin, and tinidazole). It can be seen that clindamycin has the best activity when expressed on a weight basis among all the antibiotics tested. The 50 and 90% MICs were 0.07 and 0.5 μg/ml, respectively; this is much lower than the concentrations that can be achieved and maintained in the blood of patients receiving regular doses of clindamycin (5). The next most active drug was tinidazole. The median MIC was 0.20 μg/ml and the 90% MIC was 3 μg/ml. These levels

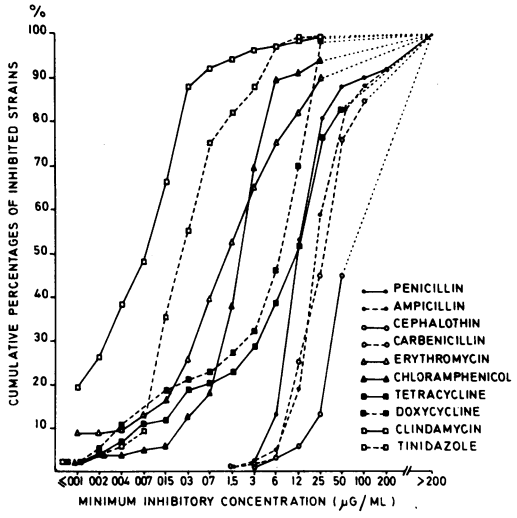

FIG. 1. *Susceptibility in vitro of 200 strains of B. fragilis to common antibiotics.*

of tinidazole are easily attainable in the serum after normal therapeutic doses (15).

Erythromycin and chloramphenicol appeared quite effective in vitro against strains of *B. fragilis* and had a median MIC of 1.5 μg/ml. Tetracycline and doxycycline were similarly effective on most strains tested, but 100% of these strains could not be inhibited by 50 μg of tetracycline per ml, whereas doxycycline, at a concentration of 25 μg/ml, inhibited all strains. The median MIC was between 6 and 12 μg/ml for both drugs, and therefore it is likely that many strains of *B. fragilis* will be resistant clinically to tetracycline or doxycycline when these are given at the usual dose. It has been shown in our hospital that infections caused by strains of aerobic bacteria with an MIC >3 μg/ml for doxycycline do not respond clinically (9). The penicillins tested here (penicillin G, ampicillin, and carbenicillin) and cephalothin were definitely less active. It should be stressed that carbenicillin at a concentration of 100 μg/ml, which is attainable under clinical conditions, inhibited 85% of the strains tested. This is in accordance with the work published by Sutter and Finegold (13).

Figures 2 and 3 show the susceptibility of strains of *B. melaninogenicus* and *Fusobacterium* to the various antibiotics studied. The median MIC for these strains was within achievable levels of all the antibiotics tested here, with the exception of erythromycin in the case of *Fusobacterium* species. The 90% MIC varied more depending on the antibiotic tested. Against *B. melaninogenicus*, clindamycin, penicillin G, ampicillin, cephalothin, and erythromycin were particularly active. With *Fusobacterium* species, doxycycline, clindamycin, and penicillin were the most active antibiotics; doxycycline and clindamycin were capable of inhibiting 100% of the strains tested at a lower concentration (6 μg/ml) than the other antibiotics tested.

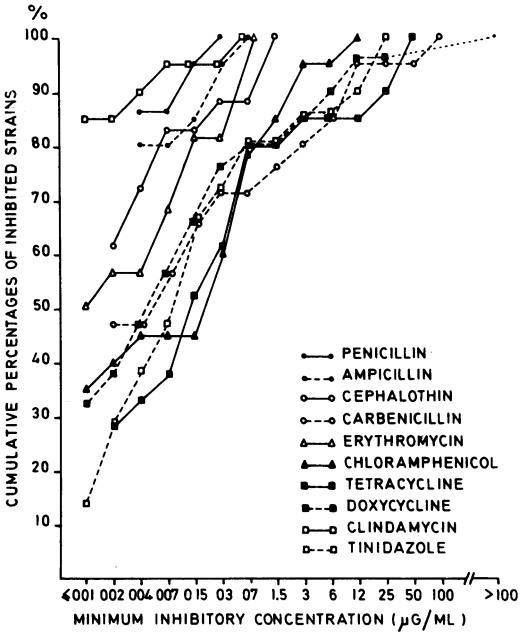

FIG. 2. *Susceptibility in vitro of 20 strains of B. melaninogenicus to common antibiotics.*

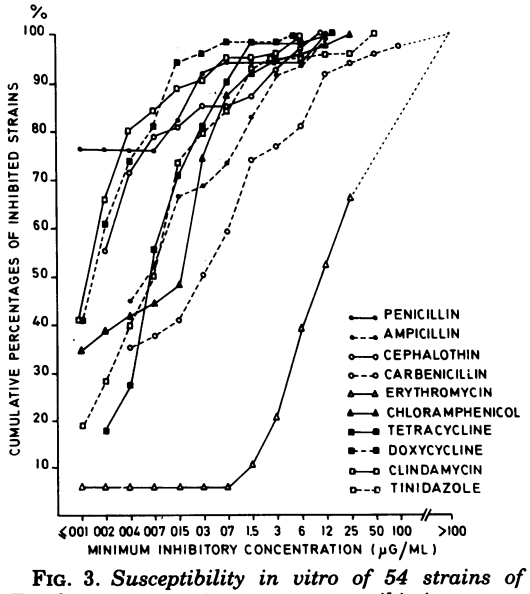

FIG. 3. *Susceptibility in vitro of 54 strains of Fusobacterium species to common antibiotics.*

Figure 4 shows the susceptibility of *Clostridium* species to the various antibiotics tested. It appears that the median MIC for all these antibiotics falls within levels attainable with regular doses; tetracycline was the least effective drug, with a 50% MIC equal to 2.2 μg/ml. Penicillin G and ampicillin appeared to be the most active antibiotics; these two drugs, as well as tinidazole, inhibited 100% of the *Clostridium* strains at a concentration of 12 μg/ml. Figure 5 shows the susceptibility to different antibiotics of gram-positive cocci, for which doxycycline and tetracycline were the least effective drugs; 100% of the strains could not be inhibited by high concentrations of these two antibiotics, and they could not be inhibited by 25 μg of tinidazole per ml, the median MIC of which was 0.15 μg/ml. On the other hand, penicillin G, ampicillin, clindamycin, and cephalothin appeared to be the optimal drugs, being active at low concentrations and inhibiting 100% of the strains tested at a concentration ≤3 μg/ml.

Clinical studies. The general characteristics of the population of patients studied are summarized in Table 1. It can be seen that the patients in the three study groups were comparable from the points of view of age, sex, and associated diseases or therapies. The distribution of the different types of infection was also similar among the three groups of patients.

Gram-negative anaerobic rods were responsible for most infections in this series, *B. fragilis* and *B. melaninogenicus* being the most frequently found pathogens. No specific relationship between the site of the infection and the type of offending pathogen could be demonstrated. Among these pathogens, 15 were susceptible to doxycycline (MIC <3 μg/ml), and all were inhibited by less than 1.0 μg of clindamycin or tinidazole per ml.

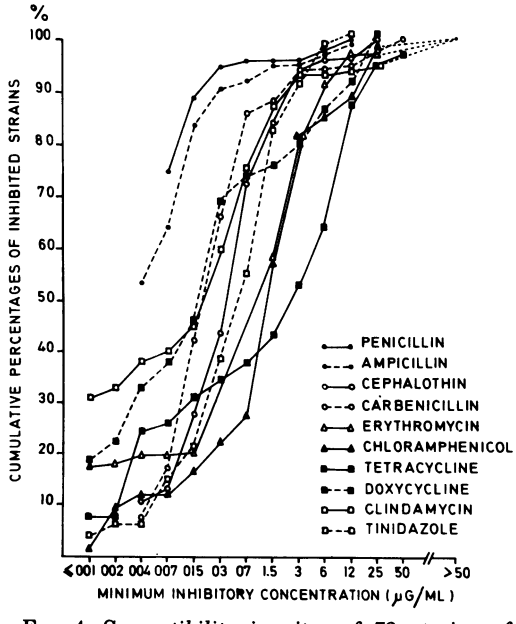

FIG. 4. *Susceptibility in vitro of 72 strains of Clostridium species to common antibiotics.*

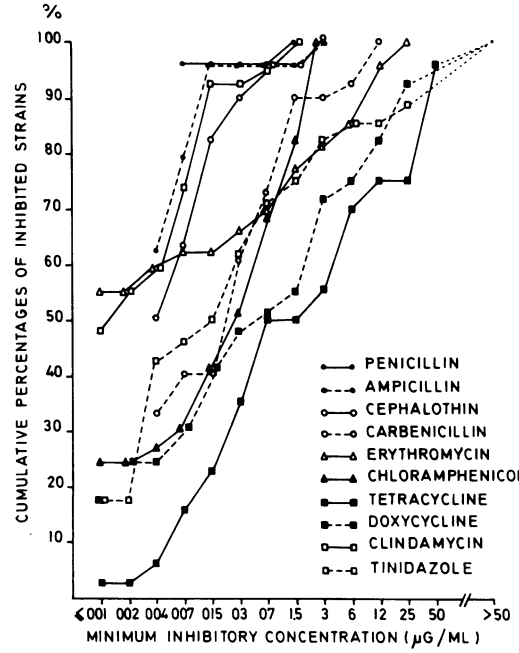

FIG. 5. *Susceptibility in vitro of 30 strains of anaerobic gram-positive cocci (peptococci and peptostreptococci) to common antibiotics.*

Aerobic microorganisms were found to be associated with anaerobes in the lesions of 12 patients who received doxycycline, 10 patients who received tinidazole, and 12 patients who received clindamycin. Most of them consisted of aerobic gram-negative bacilli (*Proteus* sp., *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella* in decreasing frequency); in some patients beta-hemolytic streptococci, staphylococci, and pneumococci were isolated in addition to the anaerobes. Five of the 12 strains of aerobic microorganisms isolated initially from doxycycline-treated patients were susceptible to doxycycline (MIC ≤3 μg/ml, Table 1). None of the aerobic microorganisms isolated from patients receiving tinidazole was susceptible to tinidazole, but three strains isolated from clindamycin-treated patients were susceptible to clindamycin (MIC ≤1 μg/ml).

It was extremely difficult to decide whether or not these aerobic microorganisms played an important part in the infections studied here.

TABLE 1. *Clinical and microbiological characteristics of the patients*

Determination	Doxycycline	Tinidazole	Clindamycin
General features			
No. of patients	19	18	19
Age (mean yrs)	56.2	53.9	55.6
Males	9	6	8
Females	10	12	11
Associated diseases[a]	8	5	6
Surgery[b]	9	4	6
Antibiotics[b]	5	3	7
Type of infection (no. of patients)			
Surgical wound	4	5	8
Infected tumor	8	5	8
Abcess	2	3	2
Tracheostomy	5	5	1
Types of anaerobes[c] (no.)			
B. fragilis	6	9	8
Fusobacterium species	3 (+1)	2	4 (+1)
B. melaninogenicus	5	4	5 (+2)
Gram-positive cocci[d]	2	0	1
Clostridium species	1 (+1)	1 (+1)	1
Others	2[e]	2[f]	(+1)[g]
Anaerobes susceptible to therapy[h] (no.)	15	18	19
Associated aerobes[i] (no.)	12 (5)	10 (0)	12 (3)
Clinical characteristics			
Temp (38°C)	12	11	13
Leukocytosis (10,000/mm^3)	8	8	9
Pus	17	18	19
Smell	13	15	13

[a] Associated diseases include (number of patients): chronic alcoholism, 4; chronic bronchitis, 3; cardiac failure, 2; diabetes, 3; tuberculosis, 3; thrombophlebitis, 1; silicosis, 1.
[b] Within 1 month before onset of present treatment.
[c] Numbers in parentheses indicate number of anaerobic strains considered as associated pathogens.
[d] Peptococci and peptostreptococci.
[e] *Veillonella* sp., 2.
[f] *B. capillosus*, 2.
[g] *Veillonella* sp., 1.
[h] MIC: 3 μg/ml for doxycycline and 1 μg/ml for tinidazole and clindamycin.
[i] Numbers in parentheses indicate number of aerobic strains susceptible to the therapy given.

In all cases, they were present in smaller numbers than the anaerobes, and in most cases they had not been seen on Gram-stained smears of the cultured material, although it may be impossible to distinguish between aerobic and anaerobic microorganisms on a morphological basis alone.

The clinical characteristics of the infections studied here are also summarized in Table 1. These characteristics were similarly distributed in the three study groups.

Temperature greater than 38.5°C was present initially in approximately two-thirds of the patients. Leukocytosis greater than 10,000 mm^3 was found in one-third. In all patients, pus was obtained from the wound, except in two patients who received doxycycline and in whom the infection was superimposed on a necrotic tumor. In 13 (68.4%), 15 (83.3%), and 13 (68.4%) patients, respectively, in the three study groups, an offensive smell was noted as a main characteristic of the infection. As a rule, this smell disappeared very early after the onset of treatment in those patients who responded. As a matter of fact, the disappearance of the unpleasant smell was the first indication of a favorable outcome.

Table 2 indicates the clinical results obtained in this series. Overall evaluation shows that 73.7% of the patients responded to clindamycin and 63.1 and 61.1% responded to doxycycline and tinidazole, respectively. If one takes into consideration those infections caused by *Bacteroides* species and *Fusobacterium* species only, the more frequent favorable outcome with clindamycin appears even more clearly: 76.5% responded to clindamycin, but only 57.2% responded to doxycycline and 58.3% to tinidazole. The respective figures for the three drugs were 73.3, 44.4, and 58.3% when only infections

caused by these two types of anaerobic microorganisms were considered, excluding the cases where aerobic infection, caused by an organism susceptible to the given drug, was also recovered from the wound.

If the same exclusion is made and all the anaerobic infections are taken into consideration, favorable results can be observed in 68.8% of the patients receiving clindamycin, 57.2% of those receiving and 61.1% of those treated with tinidazole. Finally, if one excludes the four infections caused by doxycycline-resistant microorganisms, one can see that the results with doxycycline (70%) are similar to those obtained with clindamycin (68.8%). It is noteworthy that among the four infections caused by anaerobes resistant to doxycycline (three *B. fragilis* and one *B. melaninogenicus*), therapy with doxycycline failed in three patients (75%).

Untoward effects of therapy were not frequently seen in this series (Table 3). Asymptomatic bacterial colonization by aerobes was observed in a similar number of patients in all three study groups (ca. 10 to 20% of them). In one patient receiving doxycycline, the asymptomatic colonization by a strain of *Klebsiella* resistant to doxycycline progressed into clinical infection and septicemia during therapy with doxycycline.

Side effects of the drugs were minimal in the doxycycline and tinidazole groups, where two patients in each series complained of nausea and occasionally vomited. The same symptoms appeared in 5 out of 19 (26.3%) patients receiving clindamycin. In none of these patients did therapy have to be discontinued because of these complaints, which could be managed with asymptomatic treatment. Moreover, it is often difficult, in patients with severe underlying diseases who often are receiving multiple drugs, to decide whether a symptom is really caused by a specific medication.

Finally, Table 3 also indicates the mean value of the bactericidal activity obtained in the serum 1 h after the administration of the drug. These assays were performed in 10 patients receiving doxycycline and in 10 and 11 patients, respectively, in the tinidazole and clindamycin groups. These values were relatively modest in the patients who received

TABLE 2. *Clinical results*

Parameter	Frequency of favorable responses (%)		
	Doxycycline	Tinidazole	Clindamycin
Overall evaluation (all patients)	12/19 (63.1)	11/18 (61.1)	14/19 (73.7)
Only infections caused by *Bacteroides* and *Fusobacterium* species	8/14 (57.2)	10/17 (58.3)	13/17 (76.5)
Only infections caused by *Bacteroides* and *Fusobacterium* species (susceptible aerobes excluded)[a]	4/9 (44.4)	10/17 (58.3)	11/15 (73.3)
All infections caused by anaerobes (susceptible aerobes excluded)[a]	8/14 (57.2)	11/18 (61.1)	11/16 (68.8)
All infections caused by anaerobes susceptible to the given drug[b]	7/10 (70.0)	11/18 (61.1)	11/16 (68.8)

[a] Infections possibly caused by aerobes that were susceptible to the drugs used were excluded.
[b] Four strains (*B. fragilis*, 3; *B. melaninogenicus*, 1) were resistant to doxycycline in vitro (MIC ≥6 μg/ml). Among the infections caused by these strains, three (75%) failed to respond.

TABLE 3. *Frequency of bacterial colonization and superinfection and untoward effects and bactericidal activity of the serum*

Determination	Doxycycline	Tinidazole	Clindamycin
Bacterial colonization[a]	3	2	4
Side effects	2	2	5
Bactericidal activity achieved in serum (geometric mean and range)[b]	1/4 (<1/2-1/32)	1/16 (1/2-1/128)	1/4 (<1/2-1/32)

[a] Doxycycline group: 2 *Proteus mirabilis*; 1 *Klebsiella* sp. (clinical superinfection). Tinidazole group: 1 *P. aeruginosa*; 1 *Streptococcus faecalis*. Clindamycin group: 2 *P. aeruginosa*; 1 *Enterobacter* sp.; 1 *Klebsiella* sp.
[b] Consisted of nausea and occasional vomiting.
[c] Mean peak activity: Serum was obtained 1 h after the administration of the antibiotics.

doxycycline and clindamycin (mean value, 1/4), but were higher in those who received tinidazole (mean value, 1/16).

The levels of bactericidal activity observed 8 h after the administration of the drugs (trough levels) were 1/2 in all study groups. No clear relationship could be found between the level of the bactericidal activity of the serum and the clinical results when each treatment group was studied separately, presumably due to the small number of patients studied. Such a relationship could, however, be suspected when all the cases were pooled. There were 14 patients in whom the peak bactericidal activity, expressed as the maximum bactericidal dilution, was $\leq 1/2$; among these patients only 6 (42.8%) had a favorable clinical course. On the other hand, among 17 patients whose peak bactericidal activity in serum was $\geq 1/4$, 12 (70.5%) responded well to therapy.

DISCUSSION

It is widely accepted that optimal antimicrobial therapy should be based on a study in vitro of the susceptibility of the specific offending microorganisms. On the other hand, in severely ill patients, especially in those with an underlying serious disease such as cancer, antimicrobial therapy is often started before the results of in vitro testing are available. Under these circumstances, periodic reviews of the susceptibility of pathogens commonly isolated in a given institution may be useful in the selection of initial therapy. The present in vitro studies indicate that clindamycin is a valuable drug (i.e., it can inhibit most or all the organisms tested at concentrations, multiples of which can easily be achieved and maintained in the blood of patients treated with regular doses) against the anaerobes studied here with the exception of *Clostridium* species. Its effectiveness against *B. fragilis* species is somewhat unique; no other drug tested here was as effective as clindamycin against these strains. These results are in complete accordance with those presented by Bartlett and coworkers (2). Doxycycline, which was reported to be distinctly more active than tetracycline against anaerobic bacteria (14), did not appear to be very effective here except on *Fusobacterium* species. On *B. fragilis* species, *Clostridium* species, and anaerobic gram-positive cocci its activity was poor. Tinidazole has a unique bactericidal action against *B. fragilis* and *C. perfringens* (10). In our studies, the drug appeared effective against all types of anaerobic microorganisms tested, with the exception of the anaerobic gram-positive cocci. Chow and co-workers reported also that the susceptibility to the parent compound metronidazole varied considerably for anaerobic bacteria other than *Fusobacterium, Clostridium,* and *B. fragilis* (4). However, for none of the five groups of anaerobic microorganisms examined here could tinidazole be considered the drug of choice; clindamycin was superior to it against *B. fragilis, B. melaninogenicus, Fusobacterium,* and anaerobic gram-positive cocci. Penicillin G was superior to it on all types of microorganisms, with the exception of *B. fragilis*; as a matter of fact, penicillin G appeared to be the drug of choice against all the anaerobic microorganisms examined here, except for *B. fragilis*. Chloramphenicol, a drug sometimes considered the therapy of choice for severe anaerobic infections, especially when *B. fragilis* are involved, appeared to be an active drug except for *Clostridium* sp. but could not be considered the drug of choice on a weight basis.

The type of analysis just made is necessarily limited because it does not take into account the differences that exist between antibiotics from the pharmacological point of view or the modes of action of the antibiotics and their possible toxicity. Nevertheless, it can serve as a basis for the choice of early therapy when it is needed before the susceptibility studies become available, and it is a stimulus for developing clinical trials to verify the value of predictions based on in vitro data.

The overall mortality rate in infections caused by *B. fragilis* in cancer patients is 50%, but might be lower for other species of *Bacteroides* (7, 11). Little data are available about the mortality of bacteremia caused by the other anaerobic microorganisms, with the exception of *Clostridium* species (1). As a rule, patients treated with adequate antimicrobial agents survived more often than untreated patients. When a bacteremia cannot be documented, as in our patients, the role of antimicrobial therapy in the outcome is extremely difficult to assess. Our data, although limited, nevertheless suggest that antimicrobial therapy is useful for the cure of infection: among four patients whose infection was caused by doxycycline-resistant strains of *Bacteroides,* three failed to respond. No statistically significant difference could be shown here between clindamycin and tinidazole. Both drugs were well tolerated, and none resulted in any serious untoward reactions. Further clinical studies are thus indicated to compare the respective advantages and disadvantages of these two therapies. Other investigators have reported favorable clinical results with clindamycin in anaerobic

infections; most strains are susceptible to that drug, although an occasional resistant strain may be encountered (2, 3, 6).

Although doxycycline was clinically as active as clindamycin in infections caused by doxycycline-susceptible anaerobes, the high numbers of resistant strains, especially *B. fragilis*, precludes its use as initial therapy. In vitro data showing the susceptibility of the pathogen to doxycycline are thus mandatory; in infections caused by susceptible strains, it may be suspected from these data and from other studies (11) that tetracycline or doxycycline may be effective forms of therapy.

Our data also indicate that the determination of the bactericidal activity of sera against the bacteria responsible for the infection is valuable in predicting the outcome. A similar conclusion had been reached previously in our laboratory in the case of infections caused by aerobic microorganisms (9). The determination of the antimicrobial activity of sera can be used not only to predict the outcome of infection, but also to compare different antibiotics presumed to be effective in anaerobic infections.

LITERATURE CITED

1. **Alpern, R. J., and V. R. Dowell.** 1969. Clostridium septicum infections and malignancy. J. Am. Med. Assoc. 209:385–388.
2. **Bartlett, J. G., V. L. Sutter, and S. M. Finegold.** 1972. Treatment of anaerobic infections with lincomycin and clindamycin. N. Engl. J. Med. 287:1006–1010.
3. **Chow, A. W., J. Z. Montqomerie, and L. B. Guze.** 1974. Parenteral clindamycin therapy for severe anaerobic infections. Arch. Intern. Med. 134:78–92.
4. **Chow, A. W., V. Pattern, and L. B. Guze.** 1975. Susceptibility of anaerobic bacteria to metronidazole: relative resistance of non-spore-forming gram positive bacilli. J. Infect. Dis. 131:182–185.
5. **De Haan, R. M., C. M. Metzeler, D. Schellenberg, et al.** 1973. Pharmacovinetic studies of clindamycin phosphate. J. Clin. Pharmacol. 13:190–209.
6. **Fass, R. J., J. F. Scholand, G. R. Hodges, et al.** 1973. Clindamycin in the treatment of serious anaerobic infections. Ann. Intern. Med. 78:853–859.
7. **Felner, J. M., and V. R. Dowell.** 1971. Bacteroïdes bacteremia. Am. J. Med. 50:787–796.
8. **Holdeman, L. V., and W. E. C. Moore (ed.).** 1975. Anaerobe laboratory manual. Virginia Polytechnic Institute and State University, Blacksburg.
9. **Klastersky, J., D. Daneau, G. Swings, et al.** 1974. Antimicrobial activity in serum and urine as a therapeutic guide in bacterial infections. J. Infect. Dis. 129:187–193.
10. **Ralph, E. D., and W. M. M. Kirby.** 1975. Unique bactericidal action of metronidazole against *Bacteroides fragilis* and *Clostridium perfringens*. Antimicrob. Agents Chemother. 8:409–414.
11. **Sinkovics, J. G., and J. P. Smith.** 1970. Septicemia with bacteroides in patients with malignant disease. Cancer 25:663–671.
12. **Steers, E., E. L. Foltz, and B. S. Graves.** 1959. An inocula-replicating apparatus for routine testing of bacterial susceptibility to antibiotics. Antibiot. Chemother. 9:307–311.
13. **Sutter, U. L., and S. M. Finegold.** 1975. Susceptibility of anaerobic bacteria to carbenicillin, cefoxitin and related drugs. J. Infect. Dis. 131:417–422.
14. **Sutter, V. L., F. P. Tally, Y. Y. Kuok, et al.** 1973. Activity of doxycycline and tetracycline versus anaerobic bacteria. Clin. Med. 80:31–38.
15. **Welling, P. G., and A. M. Mono.** 1972. The pharmacokinetics of metronidazole and tinidazole in man. Drug Res. 22:2128–2132.