Pharmacodynamic Effects of Nitroimidazoles Alone and in Combination with Clarithromycin on *Helicobacter pylori*

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Pharmacodynamic studies of *Helicobacter pylori* exposed to metronidazole and tinidazole alone and in combination with clarithromycin were performed by bioluminescence assay of intracellular ATP. The pharmacodynamic parameter control-related effective regrowth time (CERT) was used. CERT is defined as the time required for the resumption of logarithmic growth and a return of the level of growth to the preexposure inoculum in the test culture minus the corresponding time in the control culture. CERT measures the combined effects of the initial level of killing and postantibiotic effect. The incubation times and drug concentrations were chosen according to their half-lives and their clinically achievable concentrations. The study shows that the parameter CERT is useful for the testing of antibiotic combinations. The CERTs induced by clarithromycin, metronidazole, and tinidazole alone and in the combinations tested were concentration dependent, with no maximum response, indicating that the use of high doses may be preferable. The combinations with the highest concentrations induced synergistic effects and prevented regrowth. The use of tinidazole in combination with clarithromycin proved to give the longest CERTs, indicating that this is the most effective combination.

It is well established that *Helicobacter pylori* infection is strongly associated with duodenal ulcer disease (16). The regimen most widely used today to eradicate *H. pylori* is combination therapy with two antibiotics and bismuth (10, 20) or an acid pump inhibitor (3, 5).

In order to select an antibiotic for use against *H. pylori*, MICs (7) and minimal bactericidal concentrations (MBCs) (7) have generally been determined. These parameters are endpoints after a prolonged incubation and represent the final results of a complex interaction between a bacterium and a drug (11). MICs and MBCs fail to reveal important pharmacodynamic information about the time course of the bacterial response to antibiotics.

To obtain this information, parameters such as the initial level of killing and postantibiotic effect (PAE) (11), effective regrowth time (ERT) (2, 14), and control-related effective regrowth time (CERT) (9, 15, 26) must be studied. PAE describes the delayed regrowth after a brief exposure to an antibiotic. ERT describes the combined effects of the initial level of killing and PAE. By relating the ERT for the drug-exposed culture to the ERT for the control culture we have developed the CERT parameter, which is obtained independently of methods used to quantitate bacteria, antibiotic elimination, and growth rate (15). PAEs obtained by different methods sometimes give conflicting results (11, 14, 21). However, it has been shown that the use of ERT and CERT can circumvent these methodological problems (14, 15).

In a previous study we found a good concordance between bioluminescence and viable counts in the determination of CERT, which makes this the most reliable parameter in postexposure studies of antibiotics and acid pump inhibitors used against *H. pylori* (24).

The aim of this study was to compare the pharmacodynamic effects of nitroimidazoles alone and in combination with clarithromycin against *H. pylori*.

MATERIALS AND METHODS

Bacterial strain. *H. pylori* NCTC 11637 was used.

Antibiotics. Metronidazole and tinidazole were purchased from Sigma Chemical Co., St. Louis, Mo. Clarithromycin was kindly provided by Abbott Laboratories, Chicago, Ill.

Growth medium. Mueller-Hinton broth (Becton Dickinson, Cockeysville, Md.) supplemented with 50 µg of Ca^{2+} per ml, 25 µg of Mg^{2+} per ml, and 1% fetal calf serum was used as the growth medium.

MIC determination. MICs were determined by the Etest (AB Biodisk) after 72 h of incubation at 37°C under microaerobic conditions (5% oxygen, 10% carbon dioxide, 85% nitrogen) in an incubator box (ASSAB with CO_2 and O_2 regulators; Kebo Biomed, Spånga, Sweden).

Bioluminescence assay of intracellular ATP. The bioluminescence assay used in this study has been described elsewhere (24).

Assay procedure. The culture conditions and the assay procedure have been described elsewhere (24). The experiments were repeated three times.

The incubation times and drug concentrations were chosen according to the half-lives and the clinically achievable concentrations of clarithromycin (5), metronidazole (22), and tinidazole (22). When combinations were used, the testing times were chosen so that they corresponded to the half-life of each antibiotic included in the combination: 5 h for clarithromycin, 8 h for metronidazole, and 12 h for tinidazole.

Determination of CERTs. After the bacteria had been exposed to a single antibiotic or a combination of antibiotics, the drugs were eliminated by 1,000-fold dilution after 5, 8, or 12 h. The ATP levels in the cultures exposed to high antibiotic concentrations were below the detection limit immediately after dilution 10^{-3}. Therefore, the ATP level was measured before dilution, and the values obtained (divided by 10^3) were used as the starting values in these calculations. The CERT was calculated from the equation CERT = $T - C$, where T is the

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time required for the bacteria in the test culture to resume logarithmic growth and for the level of growth to return to the preexposure inoculum, and *C* is the corresponding time for the level of growth in the control culture to return to the preexposure inoculum after dilution. CERTs were calculated from growth curves obtained by the bioluminescence method. In order to obtain values for growth in the logarithmic phase, a value 10 times lower than the preexposure value was read from the curves due to the leveling off of the curve.

Definition of synergism. The CERT induced by the drug combination was defined as synergistic when the median CERT of the drug combination was longer than the sum of the median CERT of each of the drugs (i.e., $CERT_{A + B} > CERT_A + CERT_B$) (26). Cultures in which synergism was shown according to the definition given above were statistically evaluated by the two-tailed paired *t* test.

RESULTS

Single antimicrobial agents. The MICs of clarithromycin, metronidazole and tinidazole were 0.032, 0.094, and 0.094 µg/ml, respectively.

The CERTs induced by clarithromycin, metronidazole, and tinidazole were concentration and exposure time dependent (Table 1; Fig. 1 and 2). The relative lengths of the CERTs induced by single antimicrobial agents were as follows: tinidazole > metronidazole > clarithromycin.

None of the drugs prevented regrowth after 5 h of exposure (Fig. 2). Clarithromycin did not prevent regrowth after 8 h of exposure, but metronidazole prevented regrowth in 7% of the cultures at the five highest concentrations tested (Fig. 2). The corresponding figures for clarithromycin and tinidazole after 12 h of exposure were 33 and 53%, respectively (Fig. 2)

Combinations of antimicrobial agents. The CERTs induced by clarithromycin in combination with metronidazole and tinidazole were concentration and exposure time dependent (Table 1 and Fig. 1). The lengths of the CERTs induced by the combination of clarithromycin and tinidazole were longer than those induced by the combination of clarithromycin and tinidazole (Fig. 1 and Table 1)

Clarithromycin in combination with metronidazole prevented regrowth in 27% of the cultures at the five highest concentrations tested after 5 h of exposure and in 40% of the cultures after 8 h of exposure (Fig. 2). The corresponding values for clarithromycin in combination with tinidazole were 40% after 5 h of exposure and 73% after 12 h of exposure (Fig. 2).

DISCUSSION

The antibiotic dose regimens used today for the treatment of *H. pylori* infection are based on those developed for other bacterial infections. The other bacteria tested have much shorter generation times than *H. pylori*, however, which makes pharmacodynamic studies of *H. pylori* warranted. On the basis of the results of clinical studies (3, 19), the trends in the antibiotic treatment of *H. pylori* infection to minimize side effects, achieve better compliance, and improve eradication rates involve the use of lower doses with longer intervals between dosing and shorter courses of therapy.

Endpoint analyses such as MIC and MBC determinations (7) have been used to study the effects of antimicrobial agents on *H. pylori*. These analyses are the final results of a complex interaction between the bacteria and the drugs and fail to reveal important pharmacodynamic interactions related to the time course of the bacterial response to antibiotics (11). Pa-

rameters such as the initial level of killing, ERT (2, 14), and CERT (9, 15, 26) have been studied to obtain this information. PAE describes the delayed regrowth after a brief exposure to an antibiotic. ERT describes the combined effects of the initial level of killing and PAE. By relating ERT for the drug-exposed culture to ERT for the control culture we have developed the parameter CERT, which is independent of the methods used to quantitate bacteria, antibiotic elimination, and growth rate (15). Previous studies with *H. pylori* and other bacterial species have shown a good correlation between bioluminescence, viable counts, and microscopy results for determination of cell numbers (15, 23, 25, 27).

Following the administration of clarithromycin at doses of 250 or 500 mg, mean peak levels in plasma are about 1 to 2.5 mg/ml at 1 to 2 h, with plasma elimination half-lives of 3.5 to 5 h (5). Gustavson et al. (12) found the concentration of clarithromycin in gastric tissue to be three to six times higher than that in plasma. Metronidazole doses of 500 mg produce mean peak levels in plasma of 11.5 mg/ml, and the metronidazole half-life is 8 h (22). Veldhuyzen van Zanten et al. (28) found the metronidazole concentration to be much higher in gastric fluid than in plasma. In the present study, the incubation times and the drug concentrations were chosen according to the half-lives and the clinically achievable concentrations of clarithromycin (5), metronidazole (22), and tinidazole (22).

In this study clarithromycin, metronidazole, and tinidazole induced long time- and concentration-dependent CERTs without a maximum response (Fig. 1 and Table 1), indicating that the use of high doses may be preferable. These findings are in concordance with the results of our earlier study (24). Tinidazole induced the longest CERT of the drugs investigated, followed by metronidazole and clarithromycin (Fig. 1 and Table 1).

The pharmacodynamic parameters PAE and CERT have been used to study the effects of drug combinations on different bacterial species (13, 17, 26, 29). In this study the combination of metronidazole and clarithromycin induced long time- and concentration-dependent CERTs without a maximum response (Fig. 1 and Table 1). Tinidazole in combination with clarithromycin induced a longer CERT than the combination of metronidazole and clarithromycin (Fig. 1 and Table 1).

The term synergy is commonly used to describe the interaction of two antimicrobial agents when the effect produced by the drugs in combination is greater than the sum of the effects when the drugs are used alone (11, 18). When the combination of antibiotics induces a PAE or CERT longer than the sum of the PAEs or CERTs of the individual antibiotics, the activity has been considered synergistic (13, 17, 26). In this study clarithromycin in combination with metronidazole or tinidazole at high concentrations induced CERTs longer than the sum of the CERTs induced by the individual antibiotics (Fig. 1 and Table 1). Furthermore, at the highest concentrations tested the combinations prevented regrowth more frequently than the individual drugs did (Fig. 1 and 2 and Table 1). This indicates that there are synergistic effects. These synergistic effects were most pronounced for clarithromycin in combination with tinidazole (Fig. 1 and 2 and Table 1).

Other studies have been conducted to find the best combination of antibiotics for the treatment of *H. pylori* infections (1, 4, 6, 8). By using the checkerboard technique,

TABLE 1. CERTs induced by clarithromycin, metronidazole, tinidazole, clarithromycin combined with metronidazole and
clarithromycin combined with tinidazole after different incubation times

Antibiotic and culture no.	Concn (μg/ml)	Incubation times (h)	CERT[a] (h)	
			Ranges	Medians
Clarithromycin				
1	0.0075	5, 8, 12	4–6, 0–2, 0–5	4, 2, 2
2	0.015	5, 8, 12	0–3, 0–5, 0–12	2, 5, 4
3	0.03	5, 8, 12	0–6, 0–4, 0–7	3, 4, 2
4	0.06	5, 8, 12	7–7, 1–3, 0–25	7, 2, 5
5	0.125	5, 8, 12	9–16, 5–7, 7–88	12, 6, 43
6	0.25	5, 8, 12	23–26, 16–23, 30–77[c]	24, 23, 53[b]
7	0.5	5, 8, 12	16–32, 24–55, 87–>240[c]	24, 44, >240[c]
8	1	5, 8, 12	54–62, 70–94, 142–>240[c]	58, 86, >240[c]
Metronidazole				
1	0.06	5, 8	2–3, 1–9	2, 2
2	0.125	5, 8	2–3, 2–3	2, 2
3	0.25	5, 8	3–4, 1–3	3, 1
4	0.5	5, 8	6–6, 2–13	6, 7
5	1	5, 8	2–19, 7–52	11, 10
6	2	5, 8	19–28, 25–82	24, 40
7	4	5, 8	30–58, 58–109	44, 86
8	8	5, 8	53–74, 75–>240[b]	64, 79[b]
Tinidazole				
1	0.06	5, 12	1–3, 0–3	2, 2
2	0.125	5, 12	2–3, 0–3	2, 1
3	0.25	5, 12	3–6, 2–11	5, 6
4	0.5	5, 12	8–17, 10–38	16, 38
5	1	5, 12	25–48, 22–>240[b]	37, 49[b]
6	2	5, 12	32–60, 109–>240[c]	52, 240[c]
7	4	5, 12	65–84, >240[d]	71, >240[d]
8	8	5, 12	156, 125–>240[c]	156, >240[c]
Clarithromycin-metronidazole				
1	0.075 + 0.06	5, 8	0–9, 2–7	0, 2
2	0.015 + 0.125	5, 8	0–9, 2–7	0, 4
3	0.03 + 0.25	5, 8	0–10, 3–6	8, 3
4	0.06 + 0.5	5, 8	0–10, 6–12	3, 12
5	0.125 + 1	5, 8	6–20, 16–42	11, 28
6	0.25 + 2	5, 8	19–49, 60–>240[b]	39, 94[b] (S[e])
7	0.5 + 4	5, 8	85–167[b] (S), 135–>240[c] (S)	167[b] (S), >240[c] (S)
8	1 + 8	5, 8	>240[d] (S), >240[d] (S)[f]	>240[d] (S), >240[d] (S)[f]
Clarithromycin-tinidazole				
1	0.075 + 0.06	5, 12	1–4, 0–4	2, 2
2	0.015 + 0.125	5, 12	0–4, 2–19	1, 9
3	0.03 + 0.25	5, 12	0–18, 5–36	8, 21 (S)
4	0.06 + 0.5	5, 12	2–24, 18–>240[b]	13, 23[b] (S)
5	0.125 + 1	5, 12	13–100, 65–>240[b]	46, 72[b] (S)
6	0.25 + 2	5, 12	84–>240 (S), >240[c]	87[b] (S), >240[d] (S)
7	0.5 + 4	5, 12	>240[d] (S),[h] >240[d]	>240 (S),[h] >240[d]
8	1 + 8	5, 12	200–>240[c] (S),[g] >240[d]	>240[d] (S),[g] >240[d]

[a] The values are the means of three experiments.
[b] No regrowth in one of three experiments.
[c] No regrowth in two of three experiments.
[d] No regrowth in three of three experiments.
[e] S, synergism.
[f] $P < 0.005$ (two-tailed paired t test).
[g] $P < 0.01$ (two-tailed paired t test).
[h] $P < 0.001$ (two-tailed paired t test).

additive effects were found for the combination of clarithromycin and metronidazole (4). Another study found no difference in the effects of the combination of clarithromycin and metronidazole compared with the effects of the drugs used singly (1). The time-kill method has also been used to investigate the effects of antibiotic combinations (6, 8).

Coudron and Stratton (6) found that drug combinations had more pronounced effects than the drugs used singly. Maximum killing occurred when bismuth, metronidazole, and tetracycline were used in combination. Another study found that the combination of clarithromycin and metronidazole exhibited synergism against two of four strains susceptible to
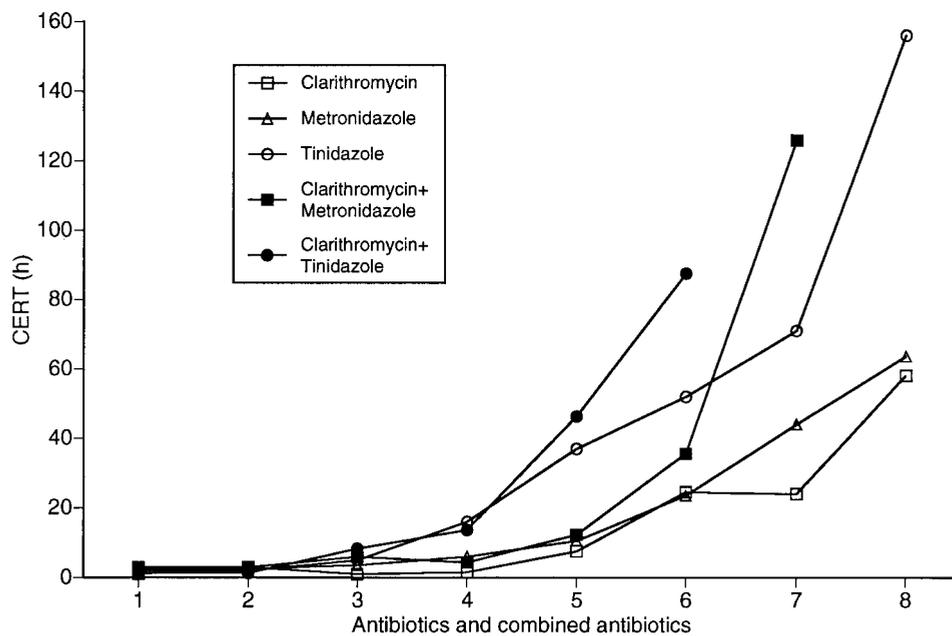
FIG. 1. CERTs for clarithromycin, metronidazole, tinidazole, clarithromycin in combination with metronidazole, and clarithromycin in combination with tinidazole after 5 h of exposure. The concentrations of the antibiotics singly and in the combinations in cultures 1 to 8 are given in Table 1.

both drugs (8). When a strain was resistant to one drug in the combination, no synergism was detected (8).

In conclusion, this study shows that the parameter CERT is of use for the testing of antibiotic combinations. Furthermore, the CERTs induced by clarithromycin, metronidazole, and tinidazole alone and in the combinations tested were concentration dependent, with no maximum response, indicating that the use of high doses may be preferable. At the highest concentrations tested, the combinations induced synergistic effects and prevented regrowth. Tinidazole in combination with clarithromycin proved to induce the longest CERTs, indicating that this is the most effective combination.
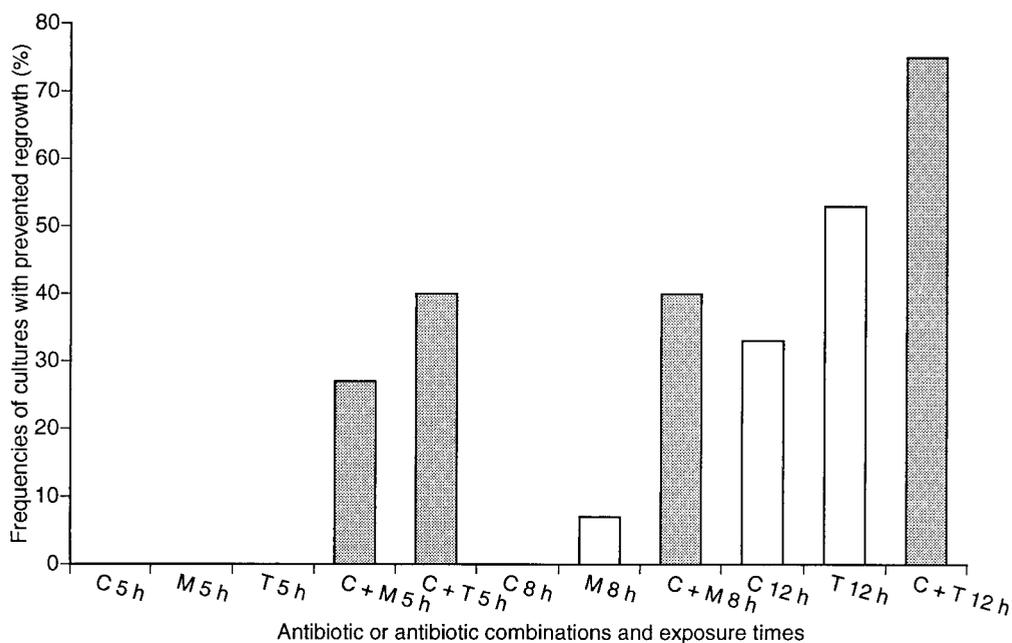

FIG. 2. Frequencies of prevention of regrowth in cultures after different times of exposure to the five highest concentrations of clarithromycin (C), metronidazole (M), tinidazole (T), clarithromycin in combination with metronidazole (C + M), and clarithromycin in combination with tinidazole (C + T).

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AUTHOR'S CORRECTION

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Volume 46, no. 7, p. 2244–2248, 2002. Page 2244: The article byline should read as given above.