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Antibacterial Activity of GO 10213, a Nitroimidazole Derivative

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Compound GO 10213, a 5-nitroimidazole substituted at the 2 position, is more active against aerobic, microaerophilic, and anaerobic bacteria than metronidazole. The MICs for *Salmonella typhimurium* (2 to 128 μg/ml), *Campylobacter* spp. (0.06 to 16 μg/ml) and *Bacteroides* spp. (0.03 to 0.25 μg/ml) are definitely lower than those of metronidazole. Niridazole, a 5-nitrothiazole, is still more active.

The antitrichomonal activity of metronidazole has been known (2) long before its inhibitory effect on anaerobic bacteria (1, 3). Other 5-nitroimidazoles, such as tinidazole and ornidazole, which display different side chains at the 1 position, do not differ markedly in their antimicrobial activity. Modifications at the 2 position, however, are known to interfere with both the activity and the microbial spectrum (4). Compound GO 10213 [1-methylsulfonyl-3-(1-methyl-5-nitro-2-imidazolyl)-2-imidazolidinone], which has an imidazolidinone ring structure at the 2 position (7) (Fig. 1), exerts stronger antitrichomonal activity than metronidazole (9, 10). In this communication the antibacterial activities of compound GO 10213 are described and compared with those of metronidazole and niridazole, a 5-nitrothiazole derivative (Fig. 1) which possesses pronounced antibacterial activities (5, 6).

The antimicrobial susceptibility of anaerobic bacteria (*Bacteroides* spp.), microaerophilic campylobacters (*Campylobacter jejuni* and *Campylobacter coli*), and aerobic bacteria (*Salmonella typhimurium*) was tested by an agar dilution method. The anaerobic bacteria were grown in thioglycolate broth. The MICs of the three nitro compounds (Fig. 1) (metronidazole, Clont, Bayer AG, Leverkusen, Federal Republic of Germany; GO 10213, Ciba-Geigy AG, Basel, Switzerland; niridazole, Ambilhar, Ciba-Geigy AG) were determined under anaerobic atmosphere provided by a GasPak system (BBL Microbiology Systems, Cockeysville, Md.). Wilkins Chalgren nutrient agar was used (12). The aerobic bacteria were tested on Mueller-Hinton agar plates (13). The microaerophilic bacteria were grown in alkaline peptonic water. They were inoculated by means of a multipoint inoculator on Mueller-Hinton agar plates supplemented with 7% sheep blood which were incubated in a microaerophilic atmosphere (Campy Pak; BBL) as described previously (5).

Compound GO 10213 is highly active against anaerobic bacteria, even more so than metronidazole but less than niridazole (Table 1). The MIC of this new agent for strain ATCC 25285 of *Bacteroides fragilis* is 0.03 μg/ml, which is much lower than that of metronidazole (0.25 μg/ml). Thus, indeed the modification of the 5-nitroimidazole at the 2 position increases not only its antitrichomonal activity (9, 10) but also its antibacterial activity. Whereas among the anaerobic bacteria no resistant strains are detected, in the group of the microaerophilic bacteria few strains are relatively resistant (for example, strain NCTC 11168 of *C. jejuni* with a MIC of 16 μg/ml), whereas most campylobacter strains, like strain NCTC 11353 of *C. coli*, show low MICs (0.06 μg/ml). A similar distribution pattern is found with metronidazole and niridazole, albeit the absolute values are high and lower, respectively (Table 1) (5). The aerobic bacteria are definitely less susceptible to GO 10213 (Table 1). The control strain for aerobic bacteria, i.e., ATCC 25285 of *Escherichia coli*, is completely resistant to GO 10213 (MIC, 128 μg/ml). Few strains of *S. typhimurium*, however, are rather susceptible. Strains TA1538 and TA98 of *S. typhimurium* display low MICs (4 and 2 μg/ml, respectively), whereas the original strain LT2 is resistant (MIC, 64 μg/ml). Both derivatives differ from their parent strain by their deep rough character, which possibly facilitates penetration of the antimicrobial agent. Furthermore, they have undergone a mutation in the *uvr* gene. UvrB strains are in general more sensitive to DNA damage. On the other hand, the nitroreductase-deficient mutant TA98NR (11) is substantially less susceptible. These observations indicate that compound GO 10213 acts like other nitroheterocyclic substances. Therefore, reduction of the nitro group by bacterial nitroreductases is a prerequisite for antimicrobial activity producing labile intermediates which are able to damage bacterial DNA (4).

Although compound GO 10213 is well tolerated in experimental animals (8) and highly active against both trichomonads (9, 10) and bacteria (Table 1), we doubt whether this drug can be used clinically. Like niridazole, compound GO 10213 yields an imidazolidinone ring in its side chain (Fig. 1). This molecular configuration more than its nitro group has been found to contribute to the carcino-

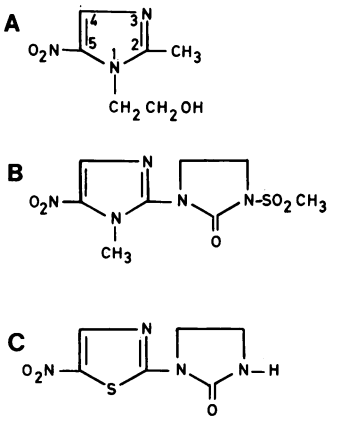

FIG. 1. Chemical structures of nitro compounds. A, Metronidazole (5-nitroimidazole); B, GO 10213 (5-nitroimidazole); C, niridazole (5-nitrothiazole).

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TABLE 1. MICs of nitro compounds

Species (n = 10)	Antimicrobial agent	MICs (μg/ml)		
		Range	50% MIC	90% MIC
Bacteroides spp.	Metronidazole	0.06–0.5	0.25	0.5
	GO 10213	0.03–0.25	0.015	0.125
	Niridazole	0.0037–0.03	0.0075	0.015
Campylobacter spp.	Metronidazole	0.25–128	0.5	32
	GO 10213	0.06–16	0.06	8
	Niridazole	0.0037–1	0.0075	0.5
S. typhimurium	Metronidazole	>128		
	GO 10213	2–>128	64	>128
	Niridazole	0.125–>128	4	>128

genic properties of niridazole, since during the oxidative metabolism an unstable epoxide is formed in mammalian tissues (L. T. Webster, J. W. Tracy, J. L. Blumer, B. A. Catto, and D. L. Sissors, *in Proceedings of the IUPHAR 9th International Congress Symposium on New Strategies in Anti-Parasitic Chemotherapy*, in press).

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