ACTIVITY OF NITROFURANTOIN AND NIFURATEL AGAINST ANAEROBIC GRAM-NEGATIVE BACILLI

SIR,—Fusidic acid [1] and metronidazole [2] have, perhaps unexpectedly, been found to be active in vitro against non-sporing gram-negative anaerobic bacteria. However, it is becoming more widely appreciated that demonstrating in-vitro activity is only the first step in clinical application of new antimicrobial agents. Subsequent work must show not only that blood-levels exceed the minimum inhibitory concentration (M.I.C.) for the organism being tested but also that adequate concentration can be achieved at the site of infection.

Metronidazole has been very successful in protozoal infections, and in view of the close similarity between the nitroimidazoles (of which metronidazole is the most familiar example) and the nitrofurans, we thought it would be worth testing the activity of two nitrofurans against a representative selection of the more commonly encountered gram-negative anaerobic bacilli.

73 strains in all were tested; 24 were reference strains, the remainder were clinical isclates. All were either *Bacteroides* spp. or *Fusobacterium* spp. Strains were incubated for 22 hours at 37°C in liquid thioglycollate medium (B.B.L.) supplemented with yeast extract (1%), hæmin (5 μg. per ml.), and menadione (0·5 μg. per ml.) Such cultures were diluted 1/500 in sodium-phosphate buffer (0·06*M*, pH 7) containing 0·03% cysteine hydrochloride, and these dilutions used as inoculum. Nitrofurantoin (sodium salt) was dissolved in water, and nifuratel

IN-VITRO ACTIVITY OF NITROFURANTOIN AND NIFURATEL AGAINST ANAEROBIC GRAM-NEGATIVE BACILLI

—	No. of strains inhibited by indicated concentration (μg. per ml.)						
	≤0·25	0·5	1·0	2·0	4·0	8·0	16·0
Nitrofurantoin					5	67	1
Nifuratel ..	63	8	2				

('Magmilor') was dissolved in dimethyl sulphoxide; various amounts of each solution were added to plates to give the desired dilutions. The medium used was brucella agar (B.B.L.) supplemented with lysed horse blood (5%), hæmin (5 μg. per ml.) and menadione (0·5 μg. per ml.). 3 μl. volumes of inoculum were placed on each plate by means of a multiple inoculating device.[3] Plates were incubated for 42 hours at 37° using the 'GasPak' system (B.B.L.; 90% hydrogen and 10% carbon dioxide), and then read. End-points were clearcut.

Our results are shown in the accompanying table. Mean M.I.C.s were: nitrofurantoin 7·7 μg. per ml., nifuratel ≤0·28 μg. per ml. Thus, it is clear that nifuratel is much more active than nitrofurantoin against anaerobic gram-negative bacilli. A similar observation has been made for aerobic bacteria.[4] The only other report we have seen on the activity of nitrofurans against anaerobic organisms is that by Schoutens et al.,[5] who found that nitrofurantoin was inhibitory at 6·26 μg. per ml.

Nifuratel is generally regarded as being indicated for candidal and trichomonal vaginitis,[6] although some workers have suggested that it is less active than metronidazole.[7,8] Lately we [9] have obtained excellent results in the treatment of urinary-tract infections.

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Blood-level data are very scarce for nifuratel, partly because its use for systemic infections has never been contemplated and also because no effective assay system has been widely applied. However, in view of our findings, efforts should be made to study the pharmacokinetics of nifuratel to decide whether the M.I.C. for anaerobes falls within the therapeutically obtainable range. We are expanding this work, including the study of other nitrofurans which have become available.

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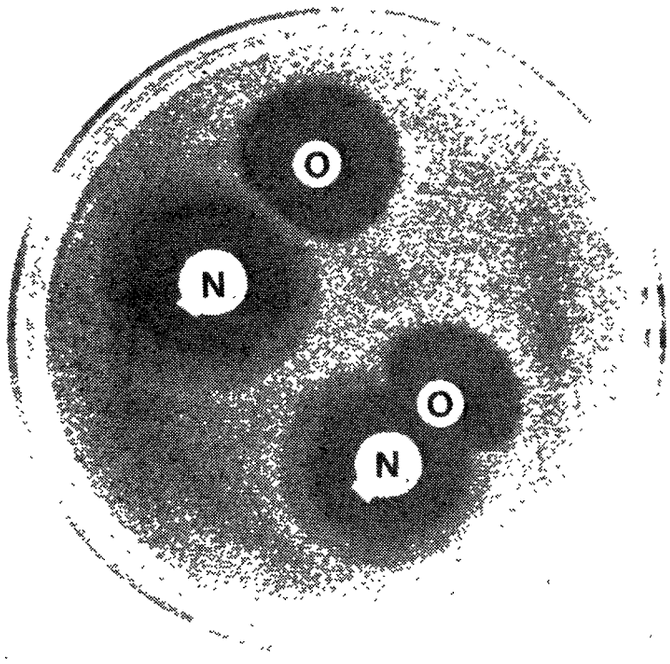
ANTAGONISM OF OXOLINIC ACID BY NITROFURANTOIN

SIR,—Oxolinic acid is now being marketed in the U.K. as a drug for the treatment of urinary-tract infections. The antibacterial spectrum of oxolinic acid is similar to that of nalidixic acid, except that it is claimed to be effective against some strains of *Staphylococcus aureus* and its minimum inhibitory concentration for *Escherichia coli* and *Proteus* spp. is smaller than for nalidixic acid, allowing it to be used in a twice-daily treatment regimen. During the course of antibacterial sensitivity testing it was noted that the presence of a nitrofurantoin disc near to the oxolinic-



Nitrofurantoin (N) inhibiting action of oxolinic acid (O) on Proteus mirabilis.

acid disc reduced the zone of inhibition of most non-lactose-fermenting organisms (see accompanying figure). This in-vitro effect has been reported in Germany, Japan, and France [1-3] with nalidixic acid but not as far as we are aware with oxolinic acid. Although antagonism may not occur in vivo, it would seem inadvisable to treat proteus, klebsiella, and non-lactose-fermenting coliform urinary-tract infections with oxolinic acid and nitrofurantoin concurrently, since the inhibitory effect has been observed with over 90% of these organisms tested in the laboratory.

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