

METRONIDAZOLE AND ACNE

Robert M. Bannatyne and Norma M. Harnett

From the Department of Bacteriology, the Hospital for Sick Children,
Toronto, Ontario, Canada

Abstract. The strong activity of metronidazole against obligate anaerobes suggested that the organism *Propionobacterium acnes* and the disease acne vulgaris might respond to treatment with this drug. Thirty-three clinical isolates of *P. acnes* were tested and found to be highly resistant to metronidazole. Prospects for its successful use in acne are remote.

Key words: Metronidazole; Acne

Metronidazole (Flagyl, Poulenc Ltd.) is best known for its anti-trichomonad activity but its effectiveness in the anaerobic infection Vincent's angina was noted by Shin (7) as long ago as 1962. Its potential usefulness against other obligate anaerobic bacteria was not fully realised at that time. Interest in metronidazole in this regard was re-awakened by recent findings of its powerful activity against a wide variety of anaerobic organisms (4, 5, 9).

Propionobacterium acnes is fundamentally implicated in the pathogenesis of acne vulgaris (2, 3). This organism is an obligate anaerobe and might be expected to respond to metronidazole if it were sensitive. The sensitivity of 33 strains of *P. acnes* to metronidazole is reported.

MATERIALS AND METHODS

Strains

Twenty-four clinical isolates of *P. acnes* were derived from blood cultures in which they represented skin contaminants. A further seven strains (origin unspecified) were obtained from the Ontario Central Public Health Laboratory. The remaining two strains were isolated from a skin swab and an intravenous solution respectively. All strains were Gram-positive bacilli, obligate anaerobes, catalase-positive and indole-positive (*P. acnes* group I).

Sensitivity tests

The agar dilution method using the Steers (8) replicator was used. Susceptibility to metronidazole was determined on brain-heart infusion agar enriched with 5% horse blood. Duplicate serial dilutions of metronidazole solution were added. The solution was prepared by dissolving 0.1 g of metronidazole powder in 5 ml methanol, adding 5 ml 0.02 M phosphate-buffered saline to give a concentration of 10000 µg/ml, dispensing in 2.0 ml aliquots and storing at -70°C. Working standards from 5.0 to 100 µg/ml were prepared by further dilution in 0.02 M phosphate-buffered saline. A 48-hour subculture of the *P. acnes* in cooked meat medium was adjusted to an optical density of 85 at 620 nm (corresponding to a count of 1.75×10^8 cfu/ml) on a Spectronic 20 spectrometer (Bausch & Lomb). Inocula of 7×10^6 cfu were delivered with a Steers replicator. Control plates without antibiotic, and a control organism, *Bacteroides fragilis* of known sensitivity, were included in each test series. Plates were incubated at 37°C for 48 hours in anaerobic jars after air had been evacuated and replaced with a gas mixture containing approximately 95% N₂ and 5% CO₂. The MIC was determined as the lowest concentration of metronidazole permitting no visible growth.

RESULTS

All thirty-three strains of *P. acnes* were highly resistant to metronidazole (>100 µg/ml) at levels well beyond the therapeutic range of 10-20 µg/ml. The control strain of *B. fragilis* was sensitive to <5 µg/ml.

DISCUSSION

With the discovery that many obligate anaerobes are highly sensitive to metronidazole the potential activity of this drug against *P. acnes*, the possible aetiological anaerobe in acne, was greeted with welcome anticipation. Metronidazole possessed other attributes which suggested its usefulness in acne

vulgaris. It is given by mouth. It is safe, non-toxic and virtually without side effects (10). Its serum half-life is around 8.7 hours and it is not protein-bound (6). Yet these pharmacologic qualities cannot be taken advantage of, for the work described here confirms the recent observation by Chow et al. (1) of metronidazole resistance in *P. acnes* and makes the prospects for the successful use of this drug in acne remote.

REFERENCES

1. Chow, A. W., Pattern, V. & Guze, L.: Susceptibility of anaerobic bacteria to metronidazole: relative resistance of non-spore-forming Gram-positive bacilli. *J Infect Dis* 131: 182, 1975.
2. Marples, R. R.: The microflora of the face and acne lesions. *J Invest Dermatol* 62: 326, 1974.
3. Marples, R. R., Leyden, J. J., Stewart, R. N., Mills, O. H. & Kligman, A. M.: The skin microflora in acne vulgaris. *J Invest Dermatol* 62: 37, 1974.
4. Nastro, L. J. & Finegold, S. M.: Bactericidal activity of five antimicrobial agents against *Bacteroides fragilis*. *J Infect Dis* 126: 104, 1972.
5. Prince, H. N., Grunberg, E., Titsworth, E. & De Lorenzo, W. F.: Effects of 1-(2-nitro-1-imidazolyl)-3-methoxy-2-propanol and 2-methyl-5-nitroimidazole-1-ethanol against anaerobic and aerobic bacteria and protozoa. *Appl Microbiol* 18: 728, 1969.
6. Ralph, E. D., Clarke, J. T., Libke, R. D., Luthy, R. P. & Kirby, W. M. M.: Pharmacokinetics of metronidazole as determined by bioassay. *Antimicro. Agents Chemother* 6: 691, 1974.
7. Shin, D. L. S.: Metronidazole in acute ulcerative gingivitis. *Lancet* II: 1191, 1962.
8. Steers, E., Foltz, E. L., Graves, B. S. & Riden, J.: An inocula replicating apparatus for routine testing of bacterial susceptibility to antibiotics. *Antibiot Chemother* 9: 307, 1959.
9. Whelan, J. P. F. & Hale, J. H.: Bactericidal activity of metronidazole against *Bacteroides fragilis*. *J Clin Path* 26: 393, 1973.
10. Willis, A. T., Bullen, C. L., Ferguson, I. R., Jones, P. H., Philips, K. D., Tearle, V. D., Williams, K., Young, S. E. J., Bretnall, G. C. et al.: Metronidazole in the prevention and treatment of bacteroides infections in gynaecological patients. *Lancet* I: 1540, 1974.

Received September 26, 1975

R. M. Bannatyne, M.B.
Department of Bacteriology
The Hospital for Sick Children
555 University Avenue
Toronto, Ontario M5G 1X8
Canada