A review of safety studies

In his review of the toxicological data, Dr Francis Roe writes that no grounds exist for concern that short courses of metronidazole, for example against anaerobic bacteria or for trichomoniasis, carry any cancer risk.

During the 29 years since the introduction of metronidazole (Flagyl) in 1953 into clinical medicine for the treatment of trichomoniasis, the drug has established a reputation as being remarkably safe. The gastrointestinal tract and nervous system are the main targets for metronidazole toxicity, both in laboratory animals and in humans. A few patients exposed to prolonged and/or a high dosage of metronidazole have exhibited neurotoxicity that has been slow to disappear after withdrawal of the drug. However, this reaction is exceptional, and most side-effects disappear rapidly after treatment stops.

Today, general prudence dictates that drug treatment should be avoided during the first trimester of pregnancy, but women who were treated with metronidazole during this period have been identified, and no evidence of teratogenicity was found. This negative result accords well with the negativity found in 10 out of 11 teratogenicity tests in animals. (The results of the eleventh study are uninterpretable because of unconventional design and inadequate control.)

Mutagenicity

The mechanism whereby metronidazole kills anaerobic bacteria is imperfectly understood, but it almost certainly involves nitroreduction which results in the formation of short-lived highly reactive cytotoxic metabolites. The fact that mutagenicity has been observed in strains of bacteria that possess nitroreductase activity is therefore not surprising. Of more relevance to the prediction of mutagenic and carcinogenic risk to humans are the results of mutagenicity tests on mammalian cells such as human lymphocytes and *in vivo* tests.

A variety of such tests have given convincingly negative results, and no excess of chromosome aberrations in circulating lymphocytes was seen in 22 patients with Crohn's disease given prolonged metronidazole therapy. Normal mammalian cells do not appear to exhibit nitroreductase activity *in vivo*, and consequently they are not prey to either the cytotoxic or

mutagenic potential of metronidazole. On the other hand, some evidence suggests that anoxic cells at the centres of cancerous growths may possess nitroreductase activity, which would explain the isolated reports that have appeared of benefit of metronidazole in patients with cancer.

Carcinogenicity

Metronidazole has been tested for carcinogenicity in rats, mice and hamsters. In each of two tests in hamsters, unequivocally negative results were obtained. In one of the three tests in rats, a treatment-related increased incidence of various kinds of tumour was reported. However, the increases were virtually entirely due to the fact that metronidazole markedly increased the numbers of rats which survived into old age, when tumours most commonly arise.

The only effect that might have been relevant was a raised incidence of liver tumours in female rats exposed daily throughout their lives to 0·6 per cent metronidazole in the diet. This would be equivalent to humans consuming 20 to 25g metronidazole every day of their lives. In three studies in mice, metronidazole in very high dosage for prolonged periods consistently increased the incidence of adenomatous tumours of the lung. This kind of tumour is peculiar to the mouse as a species, and its incidence is readily increased by overfeeding.

There is no evidence from laboratory studies that metronidazole at the dosage levels used in general practice carries any carcinogenic risk whatsoever. Consistent with this conclusion were the results of a follow-up of 771 women treated between 1960 and 1969 with metronidazole at the Mayo Clinic. No excess of cancer attributable to metronidazole treatment was seen in these women.

Conclusion

No grounds exist for concern that short courses of metronidazole prescribed, for instance, for the treatment or prophylaxis of anaerobic bacterial disease or trichomoniasis carry any cancer risk, and, in my opinion, it would be very wrong to withhold the drug for these purposes solely for fear of cancer risk. Safety is, as it is for virtually all drugs, less assured in relation to treatment that extends over months or years, particularly with high doses. □

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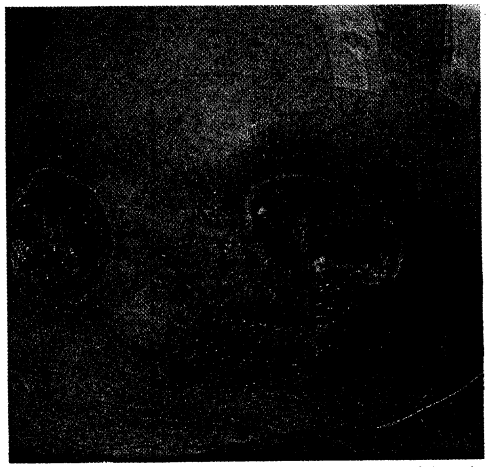
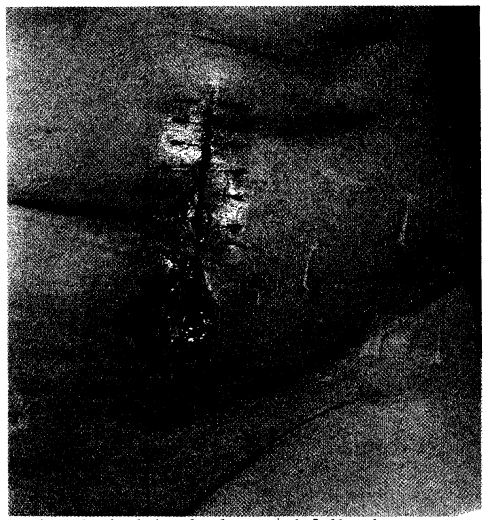


Infected bed sores may respond to metronidazole



A sloughed abdominal wound following surgery