SAFETY OF NITROIMIDAZOLES

Francis J.C. Roe, D.M., D.Sc., F.R.C.Path.

  Independent Consultant in Toxicology,
  19 Marryat Road, Wimbledon Common,
  London, SW19 5BB, England.

Indexing words: Carcinogenicity
                  Metronidazole
                  Mutagenicity
                  Ornidazole
                  Teratogenicity
                  Tinidazole
                  Toxicity

Running Title: Safety of nitroimidazoles

+ Addendum
& additional
references

Abstract

In general, the nitroimidazoles used in the treatment of anaerobic infection are well-tolerated by patients. The main targets for toxicity are the gastrointestinal tract and nervous system. With the possible exception of neurotoxic effects associated with high dosage, signs and symptoms of toxicity are transient and disappear soon after withdrawal of treatment. Teratogenicity tests in animals have given negative results in the case of metronidazole and tinidazole, and in the case of metronidazole no evidence of any adverse effect on the outcome of pregnancy was seen in women treated for trichomoniasis at various times during gestation, including the first trimester.

Nitroimidazoles are active against trichomonads and against anaerobic bacteria by a mechanism that involves nitroreduction and the generation of electrophiles capable of binding to DNA. Not surprisingly, therefore, these agents can be shown to give rise to mutagenic metabolites under circumstances in which nitroreduction can occur. Such conditions probably do not exist anywhere in the healthy mammalian body. The observed low general toxicity of nitroimidazoles is consistent with the non-occurrence of nitroreduction, as is the absence of chromosonal abberation in the circulating lymphocytes of patients receiving prolonged metronidazole therapy for Crohn's disease.

Carcinogenicity tests involving the prolonged exposure of rats, mice and hamsters to a range of doses of metronidazole have given mixed results. In response to high doses, mice exhibited an increased risk of developing lung tumours, and female rats developed more liver tumours than controls. However, these effects may have been non-specific consequences of prolonged high dosage. No excesses of tumours were seen in response to lower doses and two tests in hamsters gave negative results. A follow-up of 771 women treated, 10 or more years previously, with metronidazole revealed no excess cancer risk.

Thus the available information suggests that metronidazole, tinidazole and other 5-nitroimidazoles effective against anaerobic micro-organisms are very safe both in the short-term and in the long-term.

Note

All correspondence and requests for reprints to Dr. Francis J.C. Roe, 19 Marryat Road, London, SW19 5BB, UK.

Introduction

During the last decade, knowledge of the role of anaerobic
organisms in the causation of disease in humans has expanded extremely
rapidly. One consequence of this has been an increasing recognition
of the potent antimicrobial activity of metronidazole and other
nitroimidazoles in the treatment of patients with infections caused
wholly or partly by obligate anaerobes. Starting in the UK
spreading rapidly to other countries, has been the realisation that
metronidazole, given as an umbrella during the course of surgery of
the intestinal tract and female genital tract, can cut down quite
drastically the incidence of post-operative wound infection and
inflammatory complications affecting the pelvis. In the light of
these developments, which have led to a considerable expansion in the
use of nitroimidazoles, it is appropriate that one should keep under
review the question of the safety of these agents from a toxicological
viewpoint.

There are three main perspectives against which the safety of
drugs, such as the nitroimidazoles, need to be viewed. Firstly, it
has to be borne in mind that their use may be life-saving and offers
the likelihood of materially reducing the duration and extent of
suffering of patients who require intestinal and pelvic surgery.
Secondly, one needs to consider the efficacy and safety of alternative
drugs. And, thirdly, one needs to distinguish between reports of
actual toxicity or lack of toxicity in humans and the results of
laboratory tests designed to predict possible toxicity in humans.

Among antimicrobial agents as a class, the nitroimidazoles in
general, and metronidazole in particular, are unique in that they have
been in widespread clinical use for a quarter of a century for the
treatment of trichomoniasis. By comparison, other agents of clinical
value against anaerobic infections have a much shorter history of
use. For this reason, one is able to attach more weight to evidence of
safety derived from the clinic in the case of the nitroimidazoles
than in the cases of other anaerobic antimicrobials.

I have on several previous occasions reviewed the safety of metronidazole both in terms of clinical observations and of the results of laboratory tests (1, 2, 3, 4). Much less has been published concerning the safety aspects of tinidazole and ornidazole. Such information as there is, suggests that they are of the same order of toxicity as metronidazole and share the same targets for toxicity (i.e. the gastrointestinal tract and the nervous system). The results of mutagenicity tests on microorganisms are similar for all three compounds, but I have found no reports of in vivo tests of either tinidazole or ornidazole for mutagenicity or clastogenicity. There is published laboratory evidence of lack of teratogenicity in the case of tinidazole, but not apparently for ornidazole. Figure 1 illustrates the chemical structures of metronidazole, ornidazole, secnidazole and tinidazole and, in the next section, I summarise available data relevant to the safety of tinidazole.

Safety evaluation data for Tinidazole

The list of clinical side-effects reported for tinidazole is generally similar to that for metronidazole. Varhegyi (5) reported a 4% incidence of adverse reactions among 2037 patients given a 7-day course of tinidazole for trichomoniasis at a dose rate of 150 mg twice daily. The effects included nausea, vomiting, headaches, furred tongue, itching and skin rash. Most of them were mild and all of them disappeared shortly after the course of treatment ended. Only in two patients was it necessary to discontinue treatment, in one because of severe vomiting and in another because of a skin rash. Inza et al (6) reported transient disturbances of liver function in one patient and Schmör (7) noted that 9 out of 50 patients given a single dose of 2g. tinidazole for trichomoniasis noticed that their urine was dark on the day after treatment. Packard (8) reported a low incidence of side-effects attributable to tinidazole among over 1400 patients given the drug by the oral or intravenous routes for anaerobic infections. A metallic taste in the mouth was the

commonest side-effect in the orally-exposed patients (13 out of 599)
and thrombophlebitis was the commonest side-effect in the intra-
venously-dozed subjects (16 out of 834). Nausea, vomiting, diarrhoea,
headache and/or lassitude occurred in a total of 14 of the subjects.
One subject developed a skin rash and one exhibited a transient
leukopenia and thrombocytopenia. Sawyer et al (9) pointed out that,
like metronidazole, tinidazole crosses the placenta. However, in
their review of the literature up to 1976, they encountered no
reports of harm to the fetus. The same authors refer to the
possibility of disulfiram-like alcohol intolerance and to neuro-
toxicity as a complication of tinidazole therapy. However, I am aware
of no published reports of these effects.

Acute and subacute toxicity studies in rats and mice have
indicated that tinidazole, like metronidazole is of low general
toxicity (10). In both species the single dose oral or intraperitoneal
LD50 doses were in excess of 2,000 mg/kg, while in rats and in monkeys
twice daily doses of 150 mg/kg for 30 days gave rise to no observed
changes either clinically or at necropsy. Maternal deaths occurred
in response to daily doses of 2000 mg/kg given to pregnant rats for
6 days during the period of organogenesis and increased fetal death
rates were seen both at this dosage and in response to 500 mg/kg/day.
However, no evidence of teratogenicity was seen in either rats or
mice at the highest dose levels tested, namely 2500 mg/kg/day (mice)
or 2000 mg/kg/day (rats) (11).

Unlike metronidazole, tinidazole has apparently not been subjected
formally to carcinogenicity tests in rats and mice. The results of
a limited number of tests for mutagenicity and clastogenicity are
summarized in Table . Lindmark and Muller (12) reported that
tinidazole, like metronidazole, induced mutations in a nitroreductase-
positive strain of Salmonella typhimurium (namely, TA100). This
finding strengthened their view that reduction of the nitro-group
is necessary both for antitrichomonad activity and for mutagenic
activity. Voogd et al (13) reported positive results
in other bacterial test systems (Klebsiella pneumoniae, Escherichia
coli, and Citrobacter freundii). In all these tests, tinidazole

behaved like other 5-nitroimidazoles.

Toxicological profile of metronidazole

There are no fundamentally new data relevant to the toxicological
evaluation of metronidazole since I reviewed the topic in 1983 (4).
In the present paper, I will therefore merely summarise the important
information under the following 8 sub-headings:-

(i)   Clinically-observed side effects.

(ii)   Lack of embryotoxicity in humans.

(iii)   Lack of cytogenicity in humans.

(iv)   Lack of evidence of carcinogenicity in humans.

(v)   The results of laboratory tests for mutagenicity
        and carcinogenicity.

(vi)   The beneficial effects of metronidazole on the
        survival of mice, rats and hamsters.

(vii)   The effects of prolonged exposure to high doses in
        mice, rats and hamsters on tumour incidence.

(viii) Experimental evidence that metronidazole is not a teratogen.

(i)   Clinically-observed side effects of metronidazole

According to Catterall (14), the main side effects of metronidazole
in women treated with it for trichomoniasis (600-500 mg per day for
7 days) involve the gastro-intestinal tract (nausea, bad taste in
the mouth, furring of the tongue, disulfiram-like effect) and
nervous system (headache, dizziness and sleepiness). Metronidazole
in the prolonged high dosage, as has been used in the treatment
of Crohn's disease (15) has been reported to produce more severe
neurotoxic effects (peripheral neuropathy, paraesthesiae, epileptiform
seizures). Prompt recovery, after the withdrawal of treatment, for all
symptoms is the rule although in isolated cases recovery of peripheral
neuropathy has taken several months to disappear. Transient
neutropenia was reported among a group of 386 patients treated for

trichomoniasis by Lefebvre & Hesseltine (16) and, more recently, a
solitary case of bone marrow aplasia attributed to metronidazole
(600 mg daily for 10 days) has been reported (17).

(ii) Lack of embryotoxicity of metronidazole in humans

Morgan (18) reported no evidence of embryotoxicity or teratogenicity
among 597 women given metronidazole for trichomoniasis during pregnancy
(62 during the first trimester, 284 during the second and 251 during
the third) (see Table 1).

*Table 1
non
from*

(iii) Lack of cytogenicity of metronidazole in humans

Mitelman et al (19) found no evidence of cytogenicity attributable
to metronidazole in an 8-month double-blind cross-over study in which
Crohn's disease patients were given either metronidazole (0.8g daily)
or sulphasalazine (3.0g daily). Negative results have also been
reported by Hartley-Asp (20) in 12 Women given a 7-day course
(600 mg/day) metronidazole for trichomoniasis.

(iv) Lack of evidence of carcinogenicity of metronidazole in humans

Beard et al (21) at the Mayo Clinic followed up 771 who were
treated between 1960 and 1969 with metronidazole for trichomoniasis.
They also followed up 237 women who were treated for the same disease,
but not with metronidazole. Incidence of carcinoma in situ of the
uterine cervix was higher than among the general population among
both groups of women. This is not surprising since the risk of
cervical cancer is known to be enhanced by poor sexual hygiene.
The only statistically significant finding was an observed incidence
of 4 cases of lung cancer versus 0.6 cases expected. However, all
four women were smokers and this renders the observation difficult
to interpret.

Further evidence of the non-carinogenicity of metronidazole in
humans is provided by the results of the follow-up of patients in
the Kaiser-Permanente program (22).

(v) The results of laboratory tests of metronidazole for mutagenicity and clastogenicity

There is now a huge literature concerning tests of metronidazole and other nitroimidazoles for mutagenicity and clastogenicity (12, 13, 23, 24, 25). Positive results have been recorded in bacterial systems under conditions in which nitro-reduction can occur (12). The picture as far as mammalian cells is concerned is unclear. There have been reports of cytotoxicity and chromosomal damage in cultured mammalian cells maintained under hypoxic conditions, though not under normal aerobic conditions (26, 27). Prosser and Priseman (28) showed that metronidazole and another nitroimidazole, misonidazole, enhanced the cytogenetic activity of X-irradiation under anoxic conditions, but had no such effect in the absence of irradiation. Lambert et al (29) saw no increase in sister-chromatid exchanges in human lymphocytes exposed either to metronidazole itself or to two of its major urinary excretion metabolites, at concentrations of up to 1000 μg/ml for 75 hours, and Dunlop et al (30) saw no excess of sister-chromatid exchanges in Chinese hamster ovary cells exposed to concentrations of up to 1000 μM metronidazole under anoxic conditions. Tests for unscheduled DNA synthesis in mammalian cells gave negative results (31).

In general, the results of in vivo laboratory tests for mutagenicity and clastogenicity have given negative results. A test for heritable translocation in mice (32) gave a negative result. Bost (31) reported negative results in dominant lethal tests in the rat and mouse. Hartley-Asp (20) recorded a negative result in a micronucleus test in mice.

Table 2 summarizes the results of in vivo tests for mutagenicity   Table
and carcinogenicity in animals and humans.

(vi)   The beneficial effects of metronidazole on the survival
         of mice, rats and hamsters

     There have been reported no less than 8 long-term toxicity studies
on metronidazole in rodents: 3 in mice, 3 in rats and 2 in hamsters
(33, 34, 35, 36, 37, 38). A crude measure of chronic toxicity is
survival. It is noteworthy that in all 3 rodent species chronic
exposure to metronidazole has been associated with improved survival
(see Table 3 and 4, Figures 2 - 5).

Table 2?
Figs 2 - 5
near here

(vii)   The effects of prolonged exposure of mice, rats and hamsters
         to metronidazole on tumour incidence

     In mice (3 separate studies) prolonged high-dose oral exposure
to metronidazole has resulted in relatively small increases in
lung tumour incidence (33, 34). The first of the three studies (34)
was flawed in several ways, particularly in so far as it was not
properly controlled. For this reason, an equivocally increased
incidence of lymphoreticular neoplasms reported for females in this
study, but not seen in either of the other two later studies, can
be ignored. With regard to the increase in lung tumours, which
was seen in all three studies, the most likely explanation is that
the increase reflected a non-specific response to an effect on
nutritional status secondary to the effects of metronidazole on
the gut flora. It is well-established that overfeeding predisposes
to increased lung tumour incidence in mice (39, 40).

     Much prominence has been given to the results of the carcinogenicity
study in rats reported by Rustia and Shubik (36). However, the
report of this study is very seriously flawed. In both sexes,
prolonged exposure to metronidazole had a dose-related beneficial
effect on survival which was not taken into account by the authors
in their comparisons of tumour incidence in the different groups.
For most tissue sites in all species, the risk of tumour development
increases logarithmically with age. It is, therefore, no wonder
that the control rats in Rustia and Shubik's study which died much
earlier than the treated rats had fewer tumours. It has not been
possible for me to carry out an age-standardized analysis of the

data because the records of the study have been lost. However, I have no doubt that, with possibly one exception, metronidazole was without effect on the incidence of any type of tumour in the Rustia and Shubik experiment. The possible exception is the liver in high-dose females. A theoretical explanation of this effect, if it was real, is that at the very high doses of metronidazole involved, there was a sufficient production of acetamide, a minor metabolite formed by intestinal bacteria, to increase liver tumour risk (41). In any case, the relevance of the observation to humans exposed for much shorter periods to much lower doses of metronidazole is very dubious.

Negative results in two carcinogenicity tests in hamsters (37, 38) are consistent with the view that metronidazole poses no carcinogenic risk for man.

(viii)   Experimental evidence that metronidazole is not a teratogen

There is abundant evidence that metronidazole is not a teratogen in rabbits (4 studies), rats (5 studies) and mice (1 study) (42, 43). The only discordant finding was reported by Ivanov (44), who claimed to have seen adverse effects in rats, mice and guinea pigs. However, the studies in question were of unconventional and poor design, without adequate control of important variables. In my opinion, there is absolutely no reason for concern with regard to teratogenic risk from metronidazole.

Discussion and conclusions

There is much more information, both from the clinic and from the laboratory, relevant to the safety evaluation of metronidazole than to that of tinidazole or ornidazole. However, wherever parallel information is available, it seems that the 3 compounds are very similar in toxicological profile. The main feature of this toxicological profile of the nitroimidazoles may be summarized as follows:-

1. Low acute general toxicity.

2. No tendancy to cause pseudomembranous colitis.

3. Lack of teratogenicity (evidence for metronidazole and tinidazole).

4. Cytotoxicity and mutagenicity for microorganisms that possess nitroreductase activity and possibly for mammalian cells maintained in culture under hypoxic or anoxic conditions but lack of mutatagenic or clastogenic activity <u>in vivo</u>.

5. Ability to prolong the life of laboratory rats, mice and hamsters associated with increased lung tumour risk in mice and possibly liver tumour risk in female rats (evidence for metronidazole only). The latter effects are probably laboratory artefacts.

In relation to choice of drug for the treatment of anaerobic infections, it is relevant to point out that metronidazole (and probably tinidazole and ornidazole also) carries less risk of serious side effect than other drugs commonly used for the same purpose see <u>Table 5</u>.

References

1. Roe FJC. Metronidazole: review of uses and toxicity. J Antimicrobial Chemotherapy 3: 205-212, 1977.

2. Roe FJC: A critical appraisal of the toxicology of metronidazole. *In* Phillips I, Collier J, editors: Metronidazole: proceedings of the Second International Symposium on Anaerobic Infection, Geneva, April, 1979. New York, 1979, Grune & Stratton, Inc, pp 214-22

3. Roe FJC: Safety evaluation of metronidazole from the view point of general toxicity and carcinogenicity: 1981 appraisal. *In* Finegold SM, McFadzean JA, Roe FJC, editors: Metronidazole—proceedings of the International Metronidazole Conference, Montreal, Quebec, Canada.

4. Roe FJC. Toxicologic Evaluation of metronidazole with particular reference to carcinogenic, mutaginic and teratogenic potential. Surgery 93: 158-164, 1983.

5. Varhegyi MT. Results of a field study with the trichomonacide, Simplotan. Therapiewoche 23: 723-   , 1973.

6. Inza R, Comparatu M, Abizandra LC. Comparative study between nimorazole and a new derivative: tinidazole. Revista Argentina de Ginecologia y Obstetrica 5: 277-   , 1974.

7. Schmör J. Single-dose treatment with tinidazole: progress in therapy of trichomoniasis. Current Medical Research & Opinion 2: 138, 1974.

8. Packard RS. Tinidazole: a review of clinical experience in anaerobic infections. J Antimicrobial Chemotherapy 10: Suppl.A, 65-78, 1982.

9. Sawyer PR, Brogden RN, Pinder RM, Speight TM, Avery GS. Tinidazole: a review of its antiprotozoal activity and therapeutic efficiency. Drugs 11: 423-440, 1976.

10. Miller MW, Howes HL, English AR. Tinidazole, a potent new antiprotozoal agent. Antimicrobial Agents and Chemotherapy 3: 257-260, 1969.

11. Owaki Y, Momiyama H, Sakai T , Nabala H. Effects of tinidazole on the fetuses and their post-natal development in mice and rats. Pharmacometrics 8: 421-427, 1974.

12. Lindmark DG , Müller M. Antitrichomonad action, mutagenicity and reduction of metronidazole and other nitroimidazoles. Antimicrobial agents and Chemotherapy 10: 476-482, 1976.

13. Voogd CE, Van der Stel JJ, Jacobs JJJAA . The mutagenic action of nitroimidazoles III Tinidazole, Ipronidazole, Panidazole and Ornidazole. Mutation Res 48: 155-162, 1977.

14. Catterall RD: Fifteen years' experience with metronidazole. In Finegold SM, McFadzean JA, Roe FJC, editors: Metronidazole—proceedings of the International Metronidazole Conference, Montreal, Quebec, Canada. Amsterdam, 1977, Excerpta Medica, pp 107-11

15.

16. Lefebvre Y, Hesseltine HC. The peripheral white blood cells and metronidazole. JAMA 194: 15-18, 1965.

17. White CM, Price JJ , Hunt KM. Bone marrow aplasia associated with metronidazole. Brit med J 1: 647, 1980.

18. Morgan IFK: Metronidazole treatment in pregnancy. Int J Gynaecol Obstet 15:501-2, 1978

19. Mitelman F, Strombeck B, Ursing B: No cytogenetic effect of metronidazole. Lancet 1:1249-50, 1980

20. Hartley-Asp B: Metronidazole: Absence of mammalian cytogenicity. Scand J Infect Dis (supp) 26:72-4, 1981

21. Beard CM, Noller KL, O'Fallon WM, Kurland LT, Dockerty MB: Lack of evidence for cancer due to use of metronidazole. N Engl J Med 301:519-22, 1979

22. Friedman GD, Ury HK: The initial screening for carcinogenicity of 53 commonly used drugs. Natl Cancer Inst 65:723-31, 1980

23. Mohn GR, Ong T-M, Callen DF, Kramers PGN & Aaron CS. Comparison of the genetic activity of 5-nitroimidazole derivatives in Escheridia coli, Neurospora crassa, Saccharomyces cerevisiae and Dropsophila melanogaster. J Environ Path Toxicol 2: 657-670, 1979.

24. Voogd CE, Van der Stell JJ, Jacobs JJJAA. The mutagenic action of several nitroimidazoles and some imidazoles. Mutation Res 66: 207-221, 1979.

25. Andersen M, Binderup M-L, Kiel P, Larsen H. Mutagenicity of metronidazole. Arch Pharm Chemi Sci Ed 10: 25-44, 1982.

26. Mahood JS, Willson RL: Cytotoxicity of metronidazole (Flagyl) and misonidazole (Ro-07-0582): Enhancement by lactate. Br J Cancer 43:350-4, 1981

27. Korbelik M, Horvat D: The mutagenicity of nitroaromatic drugs. Effect of metronidazole after incubation in hypoxia in vitro. Mutat Res 74:190-1, 1980

28. Prosser JS, Priseman SJ. The influence of two radio sensitizers on the induction of chromosone aberration in human lumphocytes. Brit J Radiol 53: 228-232, 1980.

29. Lambert B, Lindblad A, Ringborg U: Absence of genotoxic effects of metronidazole and two of its urinary metabolites on human lymphocytes in vitro. Mutat Res 67:281-7, 1979

30. Dunlop JR, Mahood JS, Willson RL: Metronidazole and misonidazole: Absence of cytogenetic effects in a euoxic bacterial and a mammalian cell system in vitro. In Breccia A, Cavalleri B, Adams GE, editors: Nitroimidazoles: Chemistry, pharmacology and chemical applications. NATO Advanced Study Institutes, Series A, Life Sciences, Vol. 40, pp 171-9

31. Bost RG. Metronidazole: Mammalian mutagenicity. In: Finegold SM, McFadzean JA, Roe FJC, eds. Metronidazole - proceedings of the International Metronidazole Conference, Montreal, Quebec, Canada, Amsterdam, Exerpta Medica, 126-131, 1977.

32. Jorgenson TA, Rushbrook CJ. Heritable translocation study of metronidazole. Stanford Research Institute (unpublished data), 1977.

33. Rust JR: An assessment of metronidazole tumorigenicity studies in mouse and rat. *In*. Finegold SM, McFadzean JA, Roe FJC, editors: Metronidazole—proceedings of the International Metronidazole Conference, Montreal, Quebec, Canada.

34. Rustia M, Shubik P: Induction of lung tumours and malignant lymphomas in mice by metronidazole. J Natl Cancer Inst 48:721-9, 1972

35. Cohen SM, Enturk E, Von Esch AM, Crovetti AJ, Bryan GT: Carcinogenicity of 5-nitrofurans, 5-nitroimidazoles, 4-nitrobenzenes and related compounds. J Natl Cancer Inst 51:403-17, 1973

36. Rustia M, Shubik P: Experimental induction of hepatomas, mammary tumors and other tumors with metronidazole in non-inbred sas:MRC(WI)BR rats. J Natl Cancer Inst 63:863-8, 1979

37. Lowe CY, Ingham B. Metronidazole (Flagyl[R]): Tumorigenicity study in Syrian hamsters. Document RES/2415, May & Baker Ltd., Dagenham, Essex, RM19 7XS, England, 1974.

38. Roe FJC: Metronidazole: Tumorigenicity studies in mice, rats and hamsters. *In* Finegold SM, McFadzean JA, Roe FJC, editors: Metronidazole—proceedings of the International Metronidazole Conference, Montreal, Quebec, Canada. Amsterdam, 1977, Excerpta Medica

39. Tucker MJ: The effect of long-term food restriction on tumours in rodents. Int J Cancer 23:803-7, 1971

40. Conybeare G: Effect of quality and quantity of diet on survival and tumour incidence in outbred Swiss mice. Food Cosmet Toxicol 18:65-75, 1980

41. Koch RL, Chrystal EJT, Beaulieu BB, Goldman P: Acetamide—a metabolite of metronidazole formed by the intestinal flora. Biochem Pharmacol 28:3611-5, 1979

42. . Bost RG: Metronidazole: Toxicology and teratology. *In* Fine-gold SM, McFadzean JA, Roe FJC, editors: Metronidazole—proceedings of the International Metronidazole Conference, Montreal, Quebec, Canada. Amsterdam, 1977, Exerpta Medica, pp 112-8

43. Cella PL: Experimental studies on the teratology of metronidazole. Rev Patolog Clin 24:529-37, 1969

44. Ivanov I: The effect of "trichomonacid" on pregnancy in experimental animals. Akush Ginekol 8:241-4, 1969
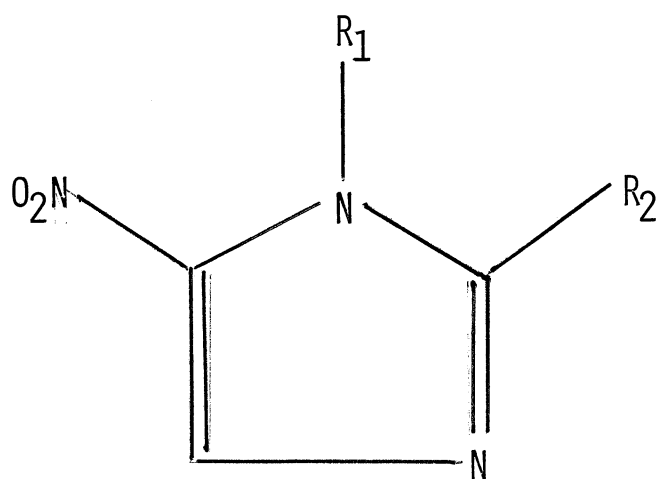
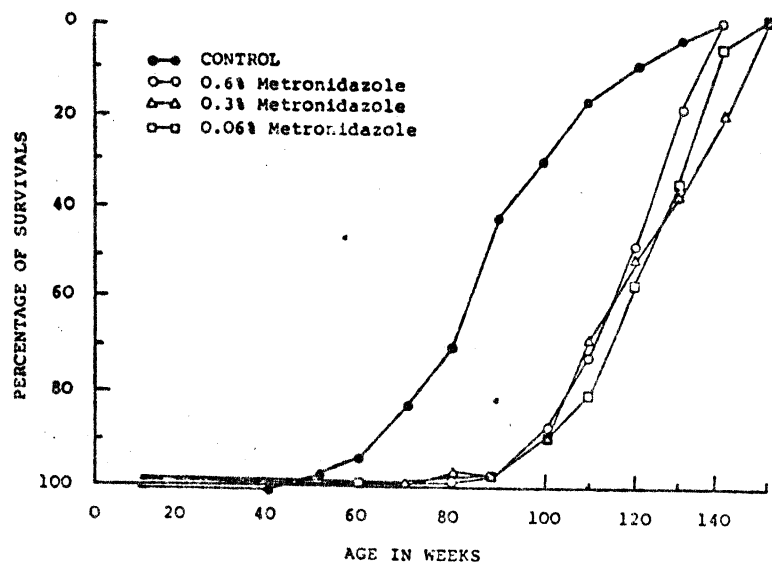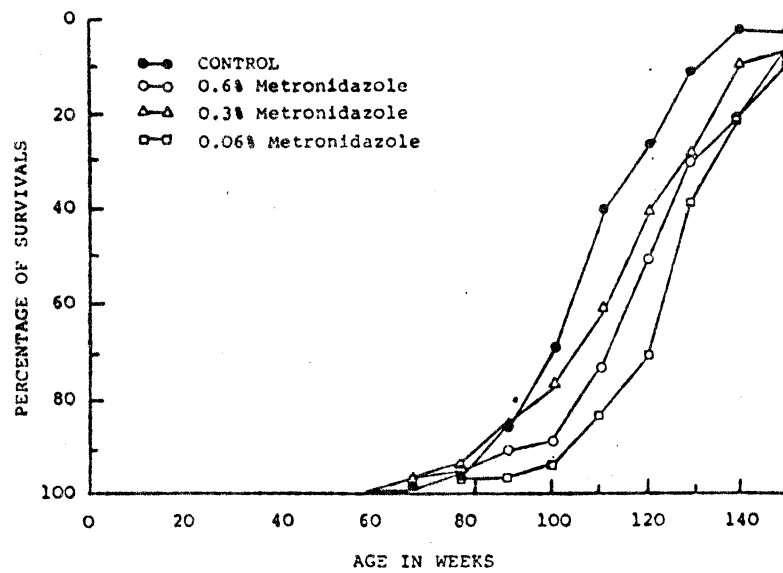| 5-Nitroimidazole	R_1	R_2
Metronidazole	- CH_2CH_2OH	- CH_3
Ornidazole	- $CH_2CHOHCH_2CL$	- CH_3
Secnidazole	- $CH_2CHOHCH_3$	- CH_3
Tinidazole	- $CH_2CH_2SO_2CH_2CH_3$	- CH_3

Figure 1:   Structures of certain 5-nitroimidazoles

Rustia and Shubik (1979) rat study: beneficial effect of metronidazole on survival of male animals.

Rustia and Shubik (1979) rat study: beneficial effect of metronidazole on survival of females
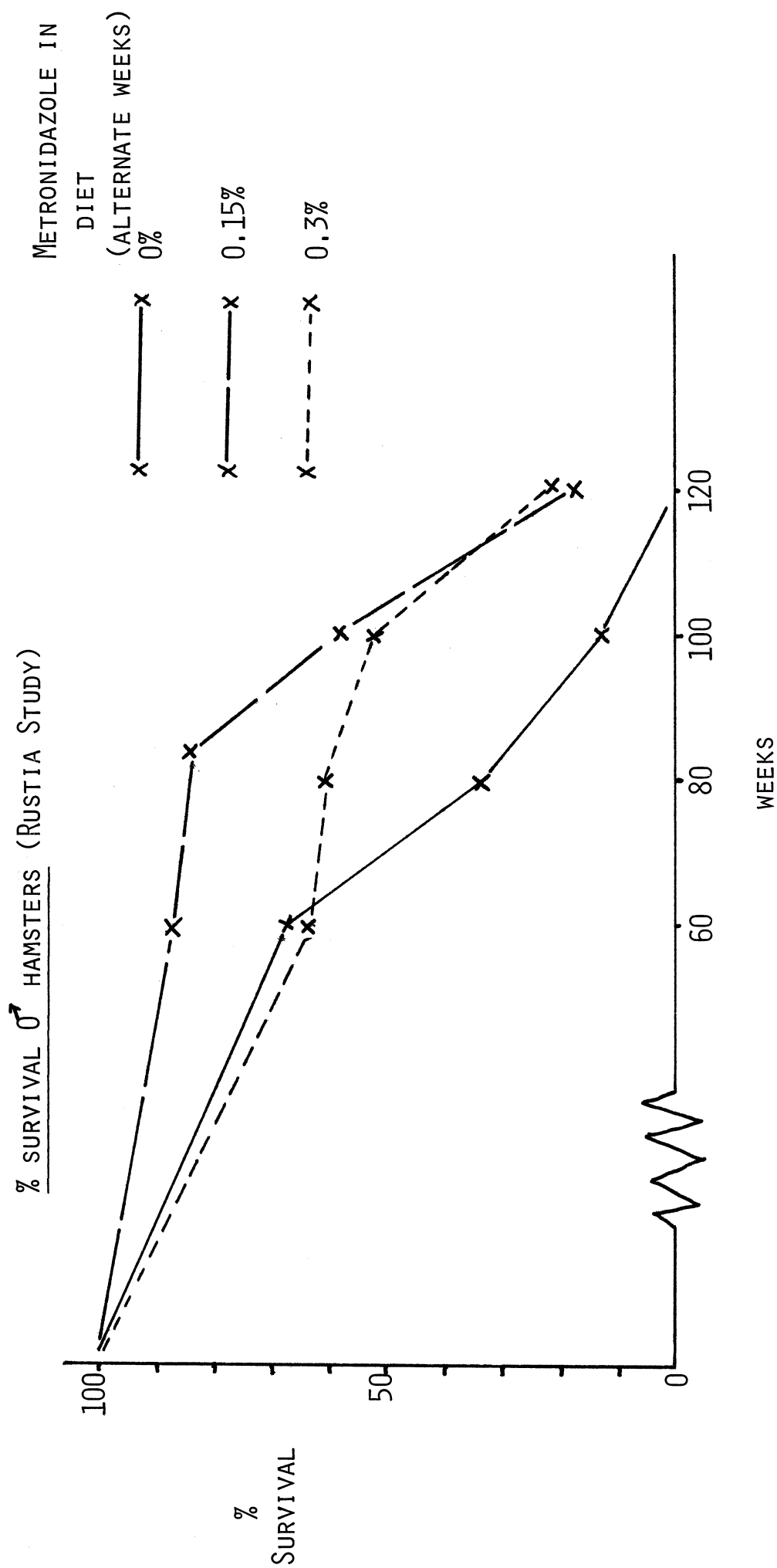
FIGURES 2 & 3

FIGURE 4

% SURVIVAL ♂ HAMSTERS (RUSTIA STUDY)

METRONIDAZOLE IN
DIET
(ALTERNATE WEEKS)

x———x 0%

x———x 0.15%

x----x 0.3%

% SURVIVAL

WEEKS

TABLE 1

Hammersmith Hospital study of effects of metronidazole treatment for trichomoniasis during pregnancy

	Trichomoniasis untreated	Trichomoniasis treated with metronidazole	All deliveries 1971-76
No. of women	283	597	9,629
No. of babies	287	605	9,757
Small-for-dates babies (nineteenth percentile)	11.8	9.6%	—
Premature infants	4.5%	5.3%	—
Twins (% of pregnancies)	0.011%	0.013%	—
Stillbirths*	1.7%	0.5%	1.2%
Congenital abnormalities			
Major	1.7%	1.2%	1.0%
Minor	1.0%	0.8%	0.8%

Table modified from Morgan.[21]
*Excluding those associated with severe rhesus incompatibility.

Table 2: The results of in vivo tests of metronidazole for mutagenicity and clastogenicity

			Reference
Heritable translocation	Mouse	Negative	32
Dominant lethal	Mouse	Negative	31
	Rat	Negative	31
Micronucleus	Mouse	Negative	20
Peripheral lymphocytes	Man	Negative	19, 20

TABLE 3

EFFECT OF METRONIDAZOLE ON SURVIVAL IN
92-WEEK CARCINOGENICITY STUDY IN MICE

(RUST, 1977)

DAILY DOSE OF METRONIDAZOLE (MG/KG/D)	MEAN SURVIVAL (DAYS)	
	MALES	FEMALES
0	457	432
75	467	474
150	442	515
300	479	517

TABLE 4

EFFECT OF METRONIDAZOLE ON SURVIVAL IN LOWE &
INGHAM HAMSTER STUDY

METRONIDAZOLE MG/KG/D		0	30	80
♂ % SURVIVAL TO 60 WEEKS		72	83	92
80 "		40	47	67
93 "		26	36	50
♀ % SURVIVAL TO 60 WEEKS		68	75	81
80 "		20	36	36
93 "		0	0	0

TABLE 5 : MODERATELY SERIOUS AND SERIOUS SIDE-EFFECTS FROM VARIOUS ANAEROBIC ANTIMICROBIAL AGENTS

	MODERATELY SERIOUS	SERIOUS
CHLORAMPHENICOL	° PMC*	° BONE MARROW HYPER- PLASIA ° LEUKAEMIA ° DEATHS IN PREMATURE INFANTS
CLINDAMYCIN/LINCOMYCIN	° PMC ° HEPATOTOXICITY ° HYPERSENSITIVITY REACTIONS	
CEFOXITIN	° PMC	° RENAL FAILURE
MOXALACTAM	° PMC ° HEPATOTOXICITY ° HYPERSENSITIVITY REACTIONS	° PROLONGED BLEEDING FROM HYPOPROTHROMBINAEMIA
METRONIDAZOLE (HIGH DOSES ONLY)	° NEUROTOXICITY ° MARKED ANOREXIA	

*PMC = PSEUDOMEMBRANOUS COLITIS DUE TO CLOSTRIDIUM DIFFICILE. NOT ONLY DOES METRONIDAZOLE NOT CAUSE PMC, BUT IT IS EFFECTIVE AGAINST PMC CAUSED BY OTHER AGENTS.

Addendum

After the above paper had been submitted for publication, I obtained the following information.

Voogd (45) provided a substantial and detailed review of the mutagenicity of the nitroimidazoles. In this he discusses structure-activity relationships within this group of substances and distinguishes some nitroimidazoles which pose much more mutagenic risk than others. Metronidazole, tinidazole and ornidazole are not among his high-risk group. Coulter and Turner (46) report the results of mutagenicity studies specifically on tinidazole and Lee et al (47) report negative results for ornidazole in a micronucleus test in mice.

Further evidence of the lack of teratogenicity of metronidazole in humans was provided by Berget and Weber (48). Their survey of 24 papers covering 1469 pregnant women treated with metronidazole included 206 treated during the first trimester without evidence of teratogenic effect.

Richle et al (49) discuss the efficacy of ornidazole as indicated by studies in mice, rats and hamsters infected with trichomonads, amoebae or anaerobic bacteria. They also report the occurrence of neurotoxicity in dogs exposed to ornidazole; evidence of its mutagenicity for various strains of bacteria in vitro and in a host-mediated assay; negative results in an in vitro test for clastogenicity in human lymphocytes; a negative result in a micronucleus test in mice; and a negative result in a dominant lethal test in mice. In addition, the authors report negative results in teratogenicity tests in mice, rats and rabbits and a negative result in a carcinogenicity test of 2 years duration in rats.

Additional References

45. Voogd CE. On the mutagenicity of nitroimidazoles. Mutation Res 86: 243-277, 1981.

46. Coulter JR, Turner JV. Tinidazole (TNZ) (ethyl(2-(2-methyl-5-nitro-1-imidazolyl)ethyl)-sulphone) is mutagenic in a Salmonella typhimurium assay, Mutation Res 57: 97-101, 1978.

47. Lee SY, Paik SG, Byeon WH. Mutagenic potential of trichomonacides. Toxicol Let Suppl 1: 249, 1980.

48. Berget A, Weber T. Metronidazole in pregnancy. Ugeskr Laeg 134: 2085-2089, 1972.

49. Richle VR, Scholer HJ, Angehrn P, Fernex M, Hummler H. Jeunet F, Schärer K, Schüpbach M, Schwartz DE. Grundlagen der Chemotherapie von Trichomoniasis and Amoebiasis mit Ornidazol. Arzneim-Forsch/ Drug Res 28 (1), 4: 612-625, 1978.