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A Critical Appraisal of the Toxicology of Metronidazole

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Clinical Toxicology

Since there is abundant experience of the clinical use of metronidazole, it is appropriate to begin a consideration of its toxicology by reviewing reports of side-effects in man. Until a few years ago the use of metronidazole in clinical medicine was more or less confined to the treatment of patients with trichomoniasis. For this purpose the oral administration of 200 mg three times per day for 5-7 days was commonly prescribed, although it is now clear that 95% cure rates can be equally well achieved by a single dose of 2 g, provided that male consorts are treated simulataneously. At the First International Metronidazole Conference, on the basis of his experience of treating over 15,000 women and 4,000 men for trichomoniasis over a period of 15 years, Dr Catterall (1977) listed the toxic side-effects associated with the use of metronidazole in decreasing order of frequency, as follows: mild nausea, a bad taste in the mouth, furring of the tongue, headache, dizziness, sleepiness, depression, transient skin eruptions (usually maculopapular on trunk and neck) and a disulfiram effect on taking alcohol. A transient leucopenia was reported in less than 2% of subjects when, in the early days of its use, it was customary to carry out white cell counts on patients receiving metronidazole. All the side effects quickly disappeared after treatment stopped, if not before, and Dr Catterall regarded them as negligible.

During the past few years metronidazole has been used increasingly in the treatment of, or for the prevention of, diseases other than trichomoniasis and in relation to some of these new uses the doses given have been higher, and the duration of treatment longer, than for trichomoniasis. Thus, metronidazole has been used in high dosage as a radiosensitizer in conjunction with radiotherapy, and also by itself in the treatment of cancer. Rather more severe side effects have from time to time been reported in patients receiving these higher doses of the drug. Urtasun *et al.* (1977) reported that single doses of 2.5 g/m^2 , giving maximum blood concentrations of $250 \ \mu\text{M}$ were apt to give rise to moderate or severe anorexia, a bitter taste in the mouth, nausea and vomiting, although the vomiting could to some extent be controlled by antiemetic medication. They saw no evidence of liver, kidney or bone marrow damage during a 6–24 month follow-up of six patients given 6 g/m² thrice weekly for 3 weeks. Willson (1974) reported transient leucopenia, and Deutsch *et al.* (1975) reported severe nausea persisted for up

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to 48 h in patients given doses of up to 300 mg/kg. They concluded that doses of 180 mg/kg, which reliably produce peak serum concentrations of 200 μ g/ml, are on the borderline of tolerance and cannot be repeated more than two or three times per week. Frytak et al. (1978) gave doses of 0.5-1.0 g/m² thrice daily for 7 days once every 6 weeks to 32 patients with advanced cancer of the colon or rectum. Severe nausea and vomiting limited dosage in 24 of the patients, myalgia was recorded in two, mild paraesthesiae of the extremities in one and a convulsion attributable to transient encephalopathy in one. Transient encephalopathies have been recorded in two other patients receiving metronidazole in high dosage (10 g daily on alternate days), according to Frytak et al. (1978), and there have been several other reports of peripheral neuropathies. Thus, Ramsay (1968) reported reversible numbress and tingling of the arms and legs in a 43 year old man treated empirically with oral metronidazole, 400 mg thrice daily, for 113 days. Ursing (1977) saw three cases of paraesthesiae among 30 Crohn's disease patients given 1.2 g metronidazole a day for up to 6 months. In all three the symptom disappeared on reducing the dose or stopping treatment. More persistent and distressing paraesthesiae were experienced by a 40 year old man given 800 mg metronidazole thrice daily for 63 days (Coxon and Pallis, 1976). Similar cases have been reported by Ingham et al., 1975; Ursing and Kamme, 1975; and Bradley et al., 1977). Typically, paraesthesiae disappear after cessation of treatment, but a case in which the condition persisted for at least two years was reported by Karllson and Hamlyn (1977). Also, Schipper et al. (1976) reported only slow improvement of ataxia and a peripheral neuropathy affecting the arms and legs of a female patient after a 42 day course of metronidazole, 3 g daily, was terminated. The picture that emerges from these reports is that the gastro-intestinal tract and the central and peripheral nervous systems are the main targets for toxicity when humans are given metronidazole in high doses. The gastrointestinal toxicity is always reversible and the neurotoxicity is nearly always so. The same is true for another nitroimidazole compound which has been used as a radiosensitizer, namely, misonidazole (Dische et al., 1977; Saunders et al., 1978).

Animal Tests for Acute and Chronic Toxicity

The results of standard toxicological tests in four species of animls were reviewed by Bost (1977a) at the First International Metronidazole Conference. The main targets for toxicity are the same in animals as man, namely, the gastro-intestinal tract and the nervous system. In addition reduced testicular weight and reduced spermatogenesis have been recorded in rats and mice in response to high doses of metronidazole (Bost, 1977a). A reduction in thyroid weight was seen in dogs in one small early experiment (Hambourger et al., 1960), but no effect on the thyroid was seen in two studies in rats involving the i.v. administration of metronidazole at a dose level of 30 mg/kg/day for 4 weeks (Life Science Report, 1975; Lowe et al., 1976). No histopathological changes were seen in the central nervous system or other tissues of eight dogs given 225 mg/kg metronidazole orally daily until they developed neurological signs (Hambourger et al., 1961). Dogs given up to 50 mg/kg/day metronidazole for 4 weeks remained perfectly healthy and responded normally in tests of neurological, hepatic, renal and thyroid function (May and Baker Internal Reports, 1969 and 1976). Monkeys exposed to very high doses of metronidazole (e.g. 225 mg/kg/day) either by the oral route (Bost, 1977a) or by the i.v. route (Reno and Voelker, 1974) exhibited non-specific degenerative changes in the liver associated with inappetance and loss in body weight. The results of the many animal tests that have been carried out have, thus, not revealed any target for metronidazole toxicity other than has already been recognised by clinicians as a target in man.

Toxicology of Metronidazole

Effects of Metronidazole Administered During Pregnancy: Clinical and Experimental Experience

At the 1976 Conference, Catterall (1977) stated that metronidazole, which readily passes the placental barrier, had been used extensively during pregnancy for the treatment of trichomoniasis without evidence of deleterious effect on the fetus. Earlier, Rodin and Hass (1966) had concluded that there was enough published evidence (Perl, 1965; Petersen et al., 1966; Robinson et al., 1966; Scott-Gray, 1964) to be sure that metronidazole can safely be given for trichomoniasis during the second and third trimesters. Recently Morgan (1978) (see also p. 000) reported no increased incidences of low birth-weight infants, still births or congenital abnormalities among the progeny of 597 women given standard courses (200 mg thrice daily for 7 to 10 days) or oral metronidazole for trichomoniasis during pregnancy as compared with 283 women with trichomoniasis left untreated throughout pregnancy. The total of 597 treated women included 62 treated during the first trimester, 284 during the second and 251 during the third. Although there have been no reports of harm to the fetus from metronidazole given during the first trimester, on grounds of common sense caution most clinicians prefer to withhold all drugs during this period and therefore, to defer treatment of trichomoniasis until the second trimester (Catterall, 1977; Morgan, 1978). There is nothing new to add to Bost's (1977a) review of the substantial evidence from animal studies that metronidazole is neither a teratogen nor embryotoxic. The only evidence to the contrary stemmed from poorly and unconventionally designed, and inadequately controlled, studies (Ivanov, 1969).

Evaluation of Metronidazole for Mutagenic Potential

Bacterial tests

The development during recent years of very sensitive tests for bacterial mutagenicity (e.g. those of Ames et al., 1975) has led to many chemicals, previously regarded as safe, coming under the cloud of suspicion not only of mutagenicity, but also of carcinogenicity. The problem is that such tests may be both qualitatively and quantitatively misleading. The test-tube conditions under which such tests are carried out purposely exclude all the defenses which exist in vivo to prevent electrophilic compounds coming into contact with the DNA of stem cells. Furthermore, the artificiality of the test conditions render it impossible to extrapolate meaningfully and quantitatively from the test-tube to the situation in the whole animal. Metronidazole is just one of many chemicals that has been caught in this trap. Rosenkranz and Speck (1977) reviewed this topic at the 1976 Conference. Their own studies had indicated that metronidazole can be activated metabolically by mammalian tissues to substances which are mutagenic for strains of Salmonella typhimurium which posess nitro-reductase activity (e.g. strain TA100) and that the urine of patients given metronidazole either orally or by the vaginal route contains such substances. However, the work of Rosenkranz and his colleagues was open to the criticism that they did not record the number of replicate plates or the significance levels of revertant frequencies. Moreover, the particular test system they used did not take into account the survival of bacteria on the plate. More recently, Connor et al. (1977) compared the activities of metronidazole and two of its metabolites against five tester strains of Salmonella, with and without

liver microsomes from rats medicated with a microsomal enzyme inducer (i.e. phenobarbitone or aroclor). Metronidazole itself and one of the metabolites was found to be active against two of the five strains, and against one of the strains (TA 1535) this same metabolite was five to ten times more active than the parent compound. However, it was not established by the authors that the in vitro conditions under which mutations were seen ever exist in mammalian cells under in vivo conditions. The overall picture which has emerged from the work of Connor et al. (1977), Lindmark and Müller (1976), Salem and Cartier (1976) and Bost and Stolt (1977) is that the mutagenic effects of metronidazole and its principle metabolite depend on reduction of the 5-nitro group to a hydroxylamine group. Such reduction occurs in obligate anaerobic bacteria and to a lesser extent in facultative anaerobes. Except possibly in hypoxic or anoxic tumour tissues, the conditions do not normally exist in vivo for nitro-reduction. The reversible binding of metronidazole to neural DNA and RNA, which according to Bradley et al. (1977) may be responsible for the neurotoxicity of the drug, probably relies on a different mechanism, since the highly reducing environment required for nitro-reduction of metronidazole is unlikely to arise in mammalian neurones.

Clearly there are some important questions remaining to be answered. Obviously it does not matter what happens to the DNA of a bacterium which is killed. But is it possible for bacteria with nitro-reductase activity to survive and, if so, might metronidazole-resistant mutants evolve? I find it rather comforting that, so far, there is no evidence, even where prolonged metronidazole therapy has been given, that metronidazole-resistant obligate anaerobes have evolved. Secondly, we do not at present know whether the reactive electrophiles produced as a result of nitro-reduction escape from the vicinity of the enzymes required for their production and, if so, whether they could reach the DNA of normal cells in patients treated for anaerobic infections or other conditions. Further research is needed in these areas.

Cytogenetic effects

Shortly after the first International Metronidazole Conference, Mitelman et al. (1976) reported a higher incidence of chromosomal aberrations in the circulating lymphocytes of Crohn's disease patients who had been receiving metronidazole in fairly high dosage for periods ranging from 1-24 months than in untreated patients or normal individuals. Unfortunately, the incidence of chromosomal abnormalities in the affected individuals before they started on metronidazole treatment was not ascertained. A further study of Crohn's disease patients, controlled for initial incidence of chromosomal abnormalities is presently in progress in Sweden. Dr Hartley-Asp describes the results of recent studies later in this publication (see p. 237) Inter alia she reports that no meaningful increase in chromosomal aberrations was seen in any of 12 women given a 7 day course of treatment for vaginal trichomoniasis (Hartley-Asp, 1979). Lambert et al. (1979) examined the effects of metronidazole and its two main oxidative metabolites for genotoxic activity on cultures of human lymphocytes. Exposure to concentrations of between 10 and 100 μ g/ml for 48 h did not increase the frequency of chromosomal abnormalities. Moreover, neither metronidazole nor its metabolites had any inhibitory effect on DNA synthesis in unstimulated peripheral lymphocytes nor did they evoke DNA repair synthesis. Prosser and White (1978) showed that metronidazole increased the yield of chromosomal abnormalities in lymphocytes produced by irradiating anoxic blood but had no such enhancing effect when fully oxygenated blood was irradiated.

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Other tests

Bost (1977b) considered that a slight increase in pre-implantation loss seen in a dominant lethal test in the rat was indicative of toxicity rather than mutagenicity, while metronidazole at dose levels up to 1 g/kg/day for 5 weeks produced no lethal dominant effect in the mouse. Tests for unscheduled DNA synthesis in mammalian cells reported by Bost (1977b) to be in progress were subsequently completed. No unscheduled synthesis of DNA was seen in human fibroblasts of the cell line, WI-38, irrespective of whether metabolizing enzymes were present or not (Mitchell, 1976). Finally two separate tests for heritable translocation in mice (Jorgenson and Rushbrook, 1977; Mitchell *et al.*, 1977) gave negative results. Mice in both these studies were given 190, 375 or 750 mg/kg/day for 8 consecutive weeks.

Evaluation of Metronidazole for Carcinogenic Potential

Animal studies

No further accounts of carcinogenicity of metronidazole in laboratory animals have been reported since the 1976 Conference. The position at that time (summarized in Table 1) was that increased incidences of lung tumours in one or both sexes have been seen in three experiments in mice, but two experiments in hamsters and two in rats have given negative results except for a non-significant increase in incidence of mammary tumours in female rats. I have pointed out earlier (Roe 1977a, 1977b) that the kinds of tumour that have been seen in excess in metronidazole-exposed mice (lung tumours and lympho-reticular neoplasms) are the same kinds as arise in excess under conditions of

Animal tests for carcinogenicity of metronidazole				
Species	Dose-levels	Duration	Observations	Reference
Mouse	0, 0.06, 0.15, 0.3, 0.5% in diet	Life-span	Lung tumours in both sexes Lympho-reticular neoplasms in females	Rustia and Shubik (1972)
Mouse	0, 75, 150, 600 mg/kg/day	78 weeks	Lung tumours in males but not females	Rust (1977)
Mouse	0, 75, 150, 600 mg/kg/day	92 weeks	Lung tumours in both sexes	Rust (1977)
Rat	0.135% in diet (females only)	80 weeks	Negative	Cohen et al. (1973)
Rat	0, 75, 150, 300 mg/kg/day	80 weeks	Non-significant increase in mammary tumours	Rust (1977)
Hamster	0, 30, 80 mg/kg/day	Life-span	Negative	Lowe and Ingham (1975)
Hamster	0, 0·15, 0·30% in diet	Life-span	Negative	Rustia (see Roe, 1977)

Table 1

overfeeding (Roe and Tucker, 1974; Tucker, 1979; Conybeare, 1979). In view of the hint of an increase in incidence of mammary tumours in response to metronidazole in rats, it is perhaps worth noting that overfeeding in rats is associated with increased mammary tumour risk (Tucker, 1979). Since metronidazole causes profound changes in the gut flora, it is to be expected that its administration would change nutritional status. Secondary effects on tumour incidence are therefore not surprising, particularly in response to prolonged exposure to metronidazole in high dosage. I would summarize the present position as follows: there is no evidence from animal studies that metronidazole is a primary carcinogen; and there is no evidence from such studies that, at dose levels used for most clinical purposes (e.g. treatment of trichomoniasis, prophylaxis during abdominal surgery), it has increased tumour incidence by either a direct or an indirect mechanism.

Studies in humans

Later in this publication (see p. 243) Dr Beard of the Mayo Clinic describes a study by her colleagues and herself designed to assess whether metronidazole enchances cancer risk in humans. To date, their follow-up of over 750 women treated with metronidazole for trichomoniasis between 1 January, 1960 and 31 December, 1969, has revealed no meaningful excess risk of cancer of any kind or site. A higher than expected incidence of lung cancer was thought to be associated with heavy smoking by the women concerned.

Conclusions

At the dose levels used for the treatment of trichomoniasis, metronidazole gives rise to only trivial side effects. Where high doses are given for prolonged periods gastrointestinal toxicity and neurotoxicity may be troublesome although reversibility on reduction of dosage or drug withdrawal are the rule. Metronidazole is not teratogenic but common prudence dictates that it should not normally be administered during the first trimester of pregnancy. It selectively kills obligate anaerobic bacteria after nitro-reduction of the molecule. The lethal effect is probably dependent on a reaction between an electrophilic metabolite of the drug with nucleic acids. Where nitroreduction occurs, but the reaction with DNA is not completely lethal, mutation may occur. Positive results in certain bacterial mutagenicity tests which arise in this way, may well be laboratory artefacts in the sense that the conditions under which mutations occur never arise in vivo except possibly in facultatively anaerobic tumour cells. Conventional mammalian tests for mutagenicity have given negative results. At the dose levels required for treating trichomoniasis, metronidazole is without cytogenetic effect in humans and there is no evidence that it is a primary carcinogen. Increased incidences of lung tumours and lymphoreticular neoplasms in mice and suggestive increased incidences of mammary tumours in rats are probably secondary to the effects of metronidazole on gut flora and nutritional status.

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Summary

Eighteen years clinical experience of the use of metronidazole in the treatment of trichomoniasis has revealed a low incidence of trivial and temporary side effects such as nausea, headache and dizziness. With higher and more prolonged dosage regimens used for radiosensitization, more severe gastrointestinal symptoms, transient encephalopathies and peripheral neuropathies have been encountered. Properly conducted teratogenicity tests in animals (rats, mice, rabbits) have given uniformly negative results and no adverse effects on the fetus have been observed in humans despite extensive use of metronidazole during pregnancy. In mice, huge doses of metronidazole increased lung tumour incidence (three out of three studies) and malignant lymphoma incidence (one out of three studies), but the interpretation of these findings is obscure because both kinds of neoplasm occur frequently in mice, and non-specific factors readily affect their occurrence. Two long-term studies in hamsters gave unequivocally negative results and two rat tests equivocally increased incidences of benign mammary tumours. Dominant lethal studies in rats and mice and heritable translocation studies in mice gave negative results. Metronidazole is clearly an eminently safe drug in terms of acute toxicity. However, the possibility that prolonged high dosage poses a very small risk of carcinogenicity and/or mutagencity to humans cannot be completely excluded by presently available test methods. In most clinical situations the predictable benefits from the use of metronidazole far outweigh the possibility of hazard to health.