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Editorial

# The nitroimidazole family of drugs

In 1955 an antibiotic complex isolated from a strain of Streptomyces on the island of Reunion was found by research workers of Rhône-Poulenc in Paris to contain a trichomonacidal antibiotic—azomycin. It had previously been isolated in Japan (Maeda *et al.*, 1953) and identified as 2-nitroimidazole (Ia see Table) (Nakamura, 1955). At the time, and for some years after, this remarkably simple compound defied synthesis, but it stimulated the workers at Rhône-Poulenc to prepare and test the activity of the more readily accessible isomeric 5-nitroimidazoles (II). It was their good fortune in 1957 to find that these isomers were more active antiprotozoal agents than the natural product (Cosar and Julou, 1959). In a series of 150 related compounds, the one with a β-hydroxyethyl group in the 1-position gave the best compromise between activity and toxicity and this brand of metronidazole was introduced as Flagyl.

By the end of the decade, metronidazole was well established as the first agent systemically effective against *Trichomonas vaginalis* and *Trichomonas foetus*. In this subsequent period other protozoa—such as, *Giardia lamblia* and *Entamoeba histolytica*—which share with trichomonad species a parallel sensitivity to various drugs, were shown to be susceptible. Through the 1960s the potential of the drug as treatment for the serious tropical disease amoebiasis was explored and established in both the intestinal and extra-intestinal forms, including symptomless cyst passers.

During this period, many additional therapeutic claims were made in an astonishing variety of conditions, ranging from alcoholism to haemorrhoids, but of the few that stood the test of time the most significant was the treatment of acute ulcerative gingivitis, Vincent's angina, after acute clinical observation by a British dental surgeon (Shinn, 1962).

A much more recent development, which followed the recognition of the importance of certain groups of non-sporing anaerobic bacteria and especially *Bacteroides fragilis* in a wide range of infections, has been the establishment of metronidazole as a specific highly effective drug for the treatment of these infections. It is also useful in preventing post-operative infection caused by susceptible anaerobes, particularly in gynaecological surgery, appendicectomy, and colonic surgery.

Real innovations in chemotherapy, such as metronidazole, always attract attention from other research groups. Although interest was slow to develop, research workers have sought analogous, structurally-modified compounds which might afford some advantage in clinical use—for example, greater potency, better tolerance and freedom from side effects, a broader spectrum of action, a longer duration of action, or in some other characteristic. This effort has been concerned with important veterinary uses of 5-nitroimidazoles as well as the applications in human medicine.

Metronidazole has been a difficult target to improve upon, but several other drugs of this chemical family have been introduced to clinical practice and many more have been described in various stages of research. The main purpose of this editorial is briefly to review these newer drugs and their relationships.

It is worth noting that the first direct challenge to metronidazole as a systemically effective trichomonacide was not a 5-nitroimidazole. The Italian discovery nifuratel (Magmilor), marketed in the United Kingdom in 1960, is a nitrofuran, a series that includes such drugs as nitrofurantoin and nitrofurazone (but, as such, is outside the scope of this article).

The second nitroimidazole to be introduced was nimorazole (IIb) (Naxogin), previously known as nitrimidazine. This was also discovered in Italy, by the research workers of Carlo Erba (de Carneri *et al.*, 1969), and it was introduced in Britain in 1970. By the middle of 1977 no other member of this class had been marketed in this country for use in human medicine. Two others are however in use on the Continent, these being tinidazole (IIc) (Fasigyn, Pfizer) (Miller *et al.*, 1969), which has been available for about six years, and ornidazole (IId) (Tiberal, Hoffmann-La Roche), a recent introduction. Three other products which have attracted recent interest are secnidazole (IIe) (see page 77), carnidazole (IIf), and a 2-nitroimidazole, Ro 07-0582 or misonidazole (Ib), which has been

the subject of recent investigations in a different field, that of radiosensitisation.

The close structural relationships of these compounds are demonstrated in the Table, which shows that the above products, apart from misonidazole, differ only in the groups attached to the ring nitrogen adjacent to the nitro group. Secnidazole is a simple homologue of metronidazole; orinidazole differs from it only by having a hydrogen replaced by chlorine. These modest changes in structure, as well as the basic substituent, morpholine, in nimorazole, the sulphone group in tinidazole, and the thiocarbamate system in carnidazole may be expected to modify various physicochemical and biochemical characteristics—such as, distribution between aqueous and lipid media, transport across membranes, metabolic pathways, tissue distribution, routes of excretion, and other properties. They probably have little effect on the essential antiprotozoal or antibacterial action, which appears to be a function of the nitro group associated with the imidazole ring.

Comparisons of the anti-infective activity of related drugs are notoriously misleading when they are based on results from different laboratories using different strains of pathogen and different experimental techniques. Broad generalisations alone are possible from a review of the literature. The first is that *in vitro* activities of the five 5-nitro drugs against *T. vaginalis* or *T. foetus* are of the same order, and minimal inhibitory concentrations range from 0·12 to 6·0 μg/ml. There are minor variations in activity against *G. lamblia* and *E. histolytica*, metronidazole being among the most potent; and somewhat more variation against Gram-negative anaerobic bacteria, where nimorazole is slightly less active than the others.

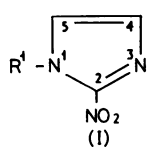
The comparative trichomonacidal activity of these drugs in experimental animals differs with the host and infecting species used; ornidazole has an $ED_{50}$ of 3 mg/kg against *T. foetus* but 37 mg/kg against *T. vaginalis* in the mouse (Grunberg *et al.*, 1970). It has been shown in some reports that nimorazole and tinidazole have lower $ED_{50s}$ than metronidazole but other reports have not substantiated this. It is doubtful whether differences in the values are often of much therapeutic significance.

All these drugs are absorbed efficiently from the digestive tract after oral administration, but they differ in their pharmacokinetic properties in humans. The serum half-life of tinidazole (12·5 h) is nearly twice that for metronidazole (7·3 h), while that of secnidazole (17 h) is half as long again. Nimorazole is more rapidly absorbed and excreted than metronidazole and it may be some advantage that its two main urinary metabolites retain antiprotozoal activity. It is also claimed that this compound is more effectively absorbed from pessaries (de Carneri *et al.*, 1969).

Are these modest differences of practical relevance in clinical practice? Again it is not easy to draw clear-cut conclusions by a review of published work. Cure rates for trichomoniasis are usually good (85 to 95%) but they are complicated by the number of relapses and by whether or not these are reinfections: the concomitant treatment of consorts always gives better results. When studies on metronidazole and on each of the other drugs have been compared, using similar dosage schedules, the results have been similar.

The subject of dosage schedules has received much attention, with shorter schedules being sought for the newer drugs which would be an advantage in the type of patient often seeking treatment.

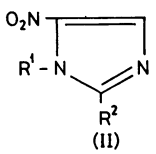
Table *Structures of nitroimidazoles studied in human medicine*



(I)

(Ia) $R^1 = H$

(Ib) $R^1 = -CH_2.CH(OH).CH_2.OCH_3$ misonidazole



(II)

(IIa) $R^1 = -CH_2CH_2OH$ ; $R^2 = CH_3$

(IIb) $R^1 = -CH_2CH_2$(morpholine) ; $R^2 = H$ nimorazole

(IIc) $R^1 = -CH_2CH_2SO_2.CH_2CH_3$; $R^2 = CH_3$ tinidazole

(IId) $R^1 = -CH_2.CH(OH).CH_2Cl$; $R^2 = CH_3$ ornidazole

(IIe) $R^1 = -CH_2.CH(OH).CH_3$; $R^2 = CH_3$ secnidazole

(IIf) $R^1 = -CH_2CH_2NH-CS-OCH_3$ $R^2 = CH_3$ carnidazole

Whereas the standard course originally established for metronidazole was 200 mg thrice daily for seven days, nimorazole was introduced in regimens of three 1 g doses at 12-hourly intervals or even as a single 2 g dose. Metronidazole has since been shown to be effective in these regimens.

The single-dose treatment has obvious clinical attractions and there is evidence that all five drugs give a good cure rate after such a schedule. Ornidazole has been shown to give successful cures in 87% of cases after a single course of four 500 mg pessaries (Hillström *et al.*, 1977; Sköld *et al.*, 1977). The high success rate after a single 2 g dose of secnidazole is reported, see page 77, but it is perhaps too early to say the longer the half-life in serum the higher the cure rate after a single dose. The only information on carnidazole is that given by Notowicz *et al.* (1977) who showed that a high cure rate was achieved in women with a single 2 g dose.

Resistance to metronidazole among trichomonads has been induced in laboratory experiments but it has very rarely, if ever, been responsible for therapeutic failure of which the commonest cause is reinfection. Cross-resistance in trichomonads is shown in the laboratory between nitroimidazoles, as might be expected between drugs probably acting by the same mechanism, but it may be incomplete.

Studies of the newer products in amoebiasis have been limited and conclusions must be tentative. Powell and Elsdon-Dew (1972), of the amoebiasis research unit in Durban, compared four of these drugs in the treatment of amoebic liver abscess. Ornidazole came nearest to the performance of metronidazole, but tinidazole was slower in action, and nimorazole failed to eradicate the intestinal infection, as shown by the number of cyst passers after treatment. Insufficient activity in the gut is a weakness of all the 5-nitroimidazoles. Indian workers however obtained equal results with metronidazole and tinidazole when they compared five-day courses of 400 mg three times a day of the former with 600 mg twice a day of the latter (Misra and Laiq, 1974; Prakash *et al.*, 1974).

In clinical reports, the effectiveness of metronidazole against Gram-negative anaerobic infections is well established. While there is no reason to doubt the potential efficacy of the newer drugs, clinical evidence has not yet been published.

The 2-nitroimidazole, misonidazole, also developed by Hoffmann-La Roche, is of interest in a different connection. In 1973, Dr R. L. Willson of Brunel University demonstrated that metronidazole, probably because of its marked electron-affinity character, was able to render hypoxic tumour cells more sensitive to radiotherapy (Foster and Willson, 1973). This has been confirmed by clinical trials at Mount Vernon Hospital, Northwood (Deutsch *et al.*, 1975) and also by North American investigators (Urtasun *et al.*, 1975, 1976). In a search for related compounds with higher electron-affinity, 2-nitroimidazoles were found to be promising and misonidazole was selected for its high potency. Unfortunately the doses used were still very large: this experimental drug shows signs of being too toxic for regular use for this radiosensitising purpose.

In this special field therefore there is much scope for a more satisfactory compound; in the traditional fields significant improvement on existing agents will probably be extremely difficult to attain.

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