Leading article

Testicular atrophy in animals—an effect of methylthiotetrazole-containing antibiotics

Methylthiotetrazole (MTT)-containing antibiotics, including cefamandole, latamoxef, and cefoperazone, have, in humans, previously been associated with two side effects which are directly related to the pharmacological activity of the MTT group, namely, hypoprothrombinemia (Smith & Lipsky, 1983) and a disulfiram effect (Buening & Wold, 1982). The finding of an additional side effect of MTT on testicular function in animals (Anon., 1984) gives cause to review what is known about these antibiotics, and the bearing of this on the new observations.

The MTT group leaves the antibiotic molecule when the β-lactam bond of the antibiotic is broken (Boyd & Lunn, 1979). This separation occurs when the β-lactam bond is subjected to chemical attack as a result of the antibiotic binding to proteins, or the antibiotic being degraded by β-lactamases, or the antibiotic dissolving into solution. Indeed, free MTT has been detected in the serum of patients who were receiving MTT-containing antibiotics (Black, Buening & Wolen, 1983) as well as in a solution of the antibiotic which had been prepared for intravenous administration (Wise & Dent, 1983).

One demonstrated side effect of MTT is that of the development of hypoprothrombinemia, although this suggestion was initially controversial. There is now strong evidence from in-vitro systems (Lipsky, 1983, 1984), from animal studies (Lipsky, Lewis & Novick, 1984), and more recently from investigations in man (Bechtold et al., 1984), that this side effect is directly related to the ability of the MTT group to inhibit the vitamin K dependent step in clotting factor synthesis, which is the γ-carboxylation of glutamic acid. This effect may involve the formation of an active metabolite of the MTT group, and this possibility becomes important when the other previously known side effect of the MTT group, the disulfiram effect, is considered.

Disulfiram is used for aversion therapy in the treatment of alcoholism (Eneanya et al., 1981). It inhibits alcohol metabolism at the level of the enzyme aldehyde dehydrogenase. Therefore, when alcohol is ingested while a patient is taking disulfiram, there is an accumulation of acetaldehyde and a toxic reaction occurs. MTT-containing antibiotics have been found to produce a disulfiram effect in humans and both MTT and MTT-containing antibiotics have been shown to alter alcohol metabolism in animals (Buening & Wold, 1982). In contrast, MTT was found to be inactive in inhibiting aldehyde dehydrogenase in vitro (Kitson, 1984). However, when a potential metabolite of MTT, its disulphide dimer, was examined in vitro, it was found to be a very potent inhibitor of this enzyme. The disulphide dimer of MTT has also been shown in vitro to be a potent inhibitor of the vitamin K dependent step in clotting factor synthesis, the carboxylation of glutamic acid (Lipsky, 1984). These results suggest that the disulfiram effect of MTT, like the hypoprothrombinemia effect, is likely to be due to the presence of an active metabolite of MTT, although it is not clear whether or not this is the disulphide dimer itself.

Recently it has been reported that both MTT and MTT-containing antibiotics have produced adverse effects in the testes of neonatal rats (Anon., 1984). Effects detected have included testicular atrophy, the formation of abnormal spermatocytes, and a reduction of spermatogonia. In order for this effect to occur, it appears that either MTT or MTT-containing antibiotics must be administered to the rats during the first two weeks of life. Effects may be seen at doses of antibiotics as low as 50 mg/kg body wt/day. It is not known whether these effects are reversible.

The mechanism of this effect is as yet unknown, but if a comparison can be made with the other two toxic effects of MTT, then it is possible that an active metabolite of MTT may be involved. The reason for the existence of a time period of susceptibility to the effect is also unknown, although it may be related to the endocrine status of the developing rat. Another, and not necessarily mutually exclusive, possibility is that it may be associated with the ability of the young rat to form, or its inability to remove, a toxic metabolite of MTT.
There have been no published reports of testicular abnormalities occurring in humans as a result of the use of MTT-containing antibiotics, although this side effect has probably not been well examined in human neonates. It is of course entirely possible that this effect has no relevance for humans. However, until the situation is clarified, the risk of this side effect should be weighed against the benefit of the use of MTT-containing antibiotics in the neonate.

JAMES J. LIPSKY
Division of Clinical Pharmacology,
Departments of Medicine and Pharmacology
and Experimental Therapeutics,
The Johns Hopkins Hospital,
Baltimore, Maryland 21205 U.S.A.

References