Mutagenicity Studies with Praziquantel, a New Anthelmintic Drug: Tissue-, Host-, and Urine-Mediated Mutagenicity Assays

J. Obermeier* and H. Frohberg
E. Merck, Institute of Toxicology, Frankfurter Straße 250, D-6100 Darmstadt, Federal Republic of Germany

Abstract. Praziquantel, a new anthelmintic drug with activity against all species of schistosomes pathogenic to man, and against a wide range of Cestodes, was tested for mutagenic potential. For the detection of both base substitutions and frameshift mutations, Salmonella typhimurium TA 100 and TA 98 were used as tester strains. Using the plate assay with and without added S-9, host-mediated assay and urine-mediated assay without and after incubation with β-glucuronidase/arylsulfatase, no mutagenic activity could be detected.

Key words: Praziquantel — Benzo(a)pyrene — Mutagenesis — Bacteria — Metabolic activation — Host-mediated assay — Urine-mediated assay.


Introduction

Praziquantel (Embay 8440) is a compound belonging to a new chemical class which emerged from joint research by E. Merck, Darmstadt and Bayer AG, Leverkusen. It

* To whom offprint requests should be sent
is a drug with a broad anthelmintic spectrum active against various tapeworms and all species of schistosomes pathogenic to man (Gönner and Andrews, 1977; Thomas and Gönner, 1977).

In animals, Praziquantel is quantitatively absorbed following oral administration. It is rapidly and virtually quantitatively eliminated as a variety of different metabolites after rapid and extensive biotransformation (Steiner et al., 1976). Following oral administration no unchanged drug is excreted neither in urine (the major route of excretion) nor in feces (Diekmann and Bühring, 1976).

Praziquantel was well tolerated in acute and subacute toxicity tests in various animals (Mürmann et al., 1976) and perhaps it may be argued that this low toxicity is likely to be due to the ease of its biotransformation and excretion (Diekmann and Bühring, 1976).

It has been demonstrated in investigations with human volunteers that Praziquantel has pharmacokinetics similar to those in animals. Again there is a marked "first-pass effect" and predominating excretion via the kidneys (Leopold et al., 1977).

In preliminary clinical trials with 1, 2, or 3 x 20 mg Praziquantel/kg in single-day treatment of human infections due to Schistosoma haematobium, patient’s tolerance was excellent. There was a high therapeutic effect against S. haematobium at all dose levels tested. Follow-up of the 80 treated patients for 6 months revealed only one parasitological failure. No adverse effects on the haematopoetic or other systems could be observed (Davis, 1977).

More than 200 million human subjects are infected with schistosomiasis, but none of the presently available schistosomicides appears to meet all criteria for use in mass treatment programs. About 100 million persons in the world are estimated to be infected with Cestodes. Moreover, loss through Cestode infections in animals is considerable (Isslip, 1973; Burrows, 1973).

Requirements for mass treatment include high efficacy against all the different stages and species of the parasites, only a small number of doses per treatment, and low toxicity, since even a low frequency of delayed serious complications caused by mutagenic, teratogenic, or carcinogenic actions of a drug, in this case can involve a large absolute number of individuals.

Some other antischistosomal agents representing different chemical classes, as Niridazole (Legator et al., 1975), Hycanthone (Hartman et al., 1971) and Furapromidium (Tong-Man Ong et al., 1977) have all been found to be mutagenic in Salmonella typhimurium. In addition, Niridazole (Urman et al., 1975) and Hycanthone (Haese et al., 1973) are carcinogenic in animals. This raises the question whether antischistosomal and mutagenic properties are necessarily associated. Evidence that this is not necessarily the case results from findings with Hycanthone and some analogs, which indicated a dissociation of mutagenic from antischistosomal activity (Hartman et al., 1971; Hulbert et al., 1974). These two activities therefore may be based on two different mechanisms.

Since Praziquantel represents a new chemical class with excellent antischistosomal activity, it was tested for possible mutagenic activity, using sensitive Salmonella tester strains containing R-factor plasmids.