Cancer Chemother Pharmacol (1987) 20: 181–182

Cancer Chemotherapy and Pharmacology

Letter to the editors

Dear Sir,

We should like to congratulate Dubois et al. [1] on having successfully measured the primary metabolite of hexamethylmelamine (HMM) in vivo for *N*-hydroxymethylmelamine pharmacokinetics in vivo per se [7], but the problems associated with HMM pharmacokinetics are well known, and this is an extremely valuable contribution to the literature. We would, however, take issue with their suggestion that these data show that HMM would be rapidly and completely transformed to HMPMM in humans. These studies were performed in mice, and the assumption that the findings can be extrapolated to man is probably invalid.

Ames' group at the Mayo Clinic performed a pharmacokinetic analysis of their new clinical i.v. formulation of HMM using gas chromatography [4]. The were unable to measure *N*-hydroxymethylmelamines, but they did show almost complete metabolism, in that all of the demethylated metabolites were demonstrated. Nevertheless, some parent compound was detected in the urine, and the terminal half-life of HMM was 622 min, the elimination being fitted by a three-compartment model. It would appear that the metabolism of HMM in man is not all that rapid. D'Incalci et al. [2] demonstrated the variability of plasma levels in man following oral administration, which did not appear to be due entirely to poor bioavailability.

Whilst we would give credit to Atassi's group for having approached the methodology correctly, in that they have paid due attention to temperature and pH [7], there are a number of things which we would question. First, they fail to consider the possibility of species differences in metabolism, which were, in fact, the subject of the paper by Rutty et al. [6] referred to be Dubois et al. [1]. This dealt with the comparative pharmacokinetics of pentamethylmelamine (PMM), rather than HMM. Marked differences were demonstrated which raise serious doubts concerning the ability of humans to metabolise PMM, and probably HMM, rapidly.

Rutty also showed a significant difference between mouse and rat liver microsomes in their ability to metabolise HMM and PMM [5]. The kM values for HMM and PMM were 0.17 m*M* and 0.39 m*M* for mouse liver, and 0.38 m*M* and 1.14 m*M* for rat liver. Metabolic activation of melamines takes place in the liver and bowel wall. Hence, it is important to consider the possibility of variations in first-pass metabolism in relation to route of administration. This issue is also not addressed by Dubois et al. In these experiments HMM was given i.p., so that one may assume optimal delivery of the drug to the liver for metabolic activation. A different result may have been obtained using the i.v. route, although it is difficult to administer HMM i.v. to mice in order to investigate this.

Before confident statements concerning the metabolism of HMM in man can be made, it will be necessary to perform a pharmacokinetic analysis of HMM which includes the measurement of the metabolite N^2-monohydroxymethyl-pentamethylmelamine (HMPMM). Ideally this would be carried out following administration p.o. and i.v. Until such information is available, we suggest that the weight of current evidence indicates that HMM is unlikely to be metabolised as efficiently in man as it is in mice. The activity of HMM is likely to depend on the balance between metabolic activation and the rate of breakdown of *N*-hydroxymethyl metabolites; hence the importance of rapid metabolism. It is this hypothesis which underlies the decision to develop for clinical use an analogue of HMM which does not require metabolic activation, i.e. trimelamol [3]. The demonstration of useful clinical activity with this compound, unlike PMM, appears to have vindicated this approach.

References

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I. R. Judson
C. J. Rutty
Department of Biochemical Pharmacology
Institute of Cancer Research
Clifton Avenue
Belmont, Sutton, Surrey SM2 5PX
England

Received May 14, 1987/Accepted May 15, 1987