The interaction between methotrexate and probenecid in man

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The pharmacokinetics of methotrexate (MTX) has been extensively studied in various mammalian species including man (Bischoff, Dedrick, Zaharko & Longstreth, 1971) and its main feature is the rapid elimination of unchanged drug from the body. Because of this, high doses are needed in order to maintain high serum concentrations of the drug, so that there is an increase in the risk of toxicity. As MTX is rapidly eliminated, some active renal transport of the drug is indicated. The co-administration of a drug, such as probenecid, which inhibits tubular transport, may delay the disappearance of MTX, and so prolong concentrations in the body. Smaller doses of MTX may then be given, so reducing its toxicity. This present report describes the effect of probenecid on the disappearance of MTX from the body over 24 h in patients receiving the drug.

Two groups of four patients with neoplastic disorders were studied. One group received MTX alone, whilst the other group received MTX with probenecid. MTX was administered as an intravenous bolus (200 mg/m^2) and samples of blood were obtained at various times following its administration. Urinary excretion of MTX was also studied and drug concentration were determined by radioimmunoassay.

Results indicated that the disappearance of MTX over 24 h could be resolved into two phases. The first phase represented a rapid distribution phase and there was no significant difference in the distribution of MTX between the two groups of patients. In those patients receiving MTX alone, the mean distribution half-life was 0.29 $\pm$ 0.06 h, and in those patients receiving the combination, it was 0.22 $\pm$ 0.04 hours. The second phase represented the elimination phase, and it was found that in those patients receiving MTX and probenecid, there was a less rapid elimination of MTX. Thus, the mean elimination half-life of MTX increased to 5.5 $\pm$ 0.75 h from a value of 3.75 $\pm$ 0.28 h as determined in control patients. The urinary excretion of MTX was also delayed following probenecid administration. Probenecid therefore delayed the elimination of MTX, so that at 24 h the serum concentration of MTX was 0.40 mg/l, which was four times that following MTX alone, where the serum concentration was 0.09 mg/l.

It was shown by Bourke, Chheda, Bremer, Watanabe & Tower (1975), using monkeys, that following various doses of probenecid, plasma levels of MTX were double comparable levels of drug in control animals given similar doses of MTX over the 4 h period of their study. In man, this difference was maintained for at least 24 hours. Because higher serum concentrations of MTX were achieved, there may be an increase in toxicity. In these cases, however, a smaller dose of MTX can be administered following probenecid treatment, so that similar serum concentrations are achieved as when MTX is given alone.

References

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A comparison of the metabolism and pharmacokinetics of intravenously administered theophylline and aminophylline in man

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Theophylline is a useful smooth muscle relaxant, of particular value in the treatment of asthma. Since it is poorly soluble in aqueous media, it is commonly combined with agents to enhance its solubility, the most widely used being ethylenediamine, to give aminophylline. It is frequently assumed that theophylline and aminophylline are pharmacologically equivalent, but in view of the considerable chemical differences between them, this may not be so. We now report on the metabolism and pharmacokinetics of aminophylline in man, and compare these findings