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

with those communicated previously (Caldwell, Lancaster, Monks & Smith, 1977).

[^{14}C]-Aminophylline injection was prepared from 8-[^{14}C]-theophylline and ethylenediamine as described in the British Pharmaceutical Codex (1963), sterilized by ultrafiltration and administered to three male volunteers by intravenous injection (125 mg; 10 μCi). The subjects kept their normal diets, and collection of urine samples, determination of urinary metabolites and pharmacokinetic analysis was performed as previously described (Caldwell *et al.*, 1977).

The metabolism of aminophylline was the same as that of theophylline; the excretion products being 3-methylxanthine, 1,3-dimethyluric acid and 1-methyluric acid in addition to theophylline and the pharmacokinetic model describing the disposition of aminophylline was identical with that previously described for theophylline (Caldwell *et al.*, 1977). However, the recovery of [^{14}C] in the 0–24 h urine was higher for aminophylline (theophylline, 76.3 ± 6.9% (mean ± s.d.); aminophylline, 87.0 ± 2.0; $P < 0.05$), and this was accompanied by significant increases in the first-order rate constant for 1,3-dimethyluric acid elimination (K_{el}^{DMU}, theophylline, 0.022 h^{-1}; aminophylline, 0.034 h^{-1}; $P < 0.05$) and in the V_{max} of the Michaelis–Menten expression for 3-methylxanthine elimination (V_{max}^{3MX}, theophylline, 0.94 mg h^{-1}; aminophylline, 1.66 mg h^{-1}; $P < 0.05$). The elimination $T_{1/2}$ of total urine [^{14}C] was reduced from 10.0 ± 2.8 h for theophylline to 7.4 ± 0.4 h for aminophylline ($P < 0.05$).

It is clear that there are significant differences between the metabolism and pharmacokinetics of aminophylline and theophylline in man. Thus, the complexation of theophylline and ethylenediamine alters its disposition when compared with theophylline alone, with increases in the rate and extent of conversion to, and elimination of, 1,3-dimethyluric acid and 3-methylxanthine. These increases account for the greater urinary excretion of [^{14}C] after aminophylline compared with theophylline. The reasons for this difference in behaviour between the two drugs is not clear, since aminophylline is commonly regarded as the ethylenediamine salt of theophylline.

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A radioimmunoassay for amitriptyline and nortriptyline

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Routine plasma level determinations are becoming increasingly important in antidepressant therapy (Montgomery, Braithwaite & Crammer, 1977). A sensitive radioimmunoassay for amitriptyline and nortriptyline, suitable for routine use, has been developed which requires no sample preparation other than a five-fold dilution of the plasma.

Using [^{3}H]-amitriptyline (sp.act. = 10.0 Ci/mmole) as the label the antiserum, raised in a sheep (Aherne, Piall & Marks, 1976) could be used at a final dilution of 1:1400. The antiserum avidity constant was 9.3×10^{7} l/mol and the assay sensitivity was 0.86 ng/ml.

Cross-reactivity studies demonstrated that the assay was specific for amitriptyline and nortriptyline, showing no cross-reactivity with their metabolites or any drugs likely to be given in combined therapy. The mean intra- and inter-assay coefficients of variation were 4.7% and 9.8% ($n = 10$) respectively.

Comparison of the assay with a routine gas–liquid chromatographic method for nortriptyline was made on plasma samples collected from three patient groups. For a controlled in-patient group the correlation coefficient, r, for the two methods was 0.9799 ($n = 83$), for an uncontrolled out-patient group r = 0.9528 ($n = 45$) and for a third group, receiving single doses prior to therapy, r = 0.9438 ($n = 25$).

Plasma amitriptyline levels in five volunteers fol-