ANTIPYRINE METABOLITE KINETICS IN RATS

P. N. Shaw, J. C. Rhodes and J. B. Houston, Department of Pharmacy, University of Manchester, Manchester M13 9PL.

Antipyrine clearance or half-life is frequently used as an index of an individuals drug metabolising capacity (Vesell 1979). It has been suggested that the potential of antipyrine as a marker compound could be increased if the kinetics of the individual metabolite pathways were determined rather than the kinetics of total elimination. Determination of metabolite formation kinetics requires both information on the total elimination rate of parent drug (elimination half-life or clearance) and the characterisation of the metabolic pattern (fm, fraction of the dose metabolised by a specific primary pathway). As part of a program to evaluate the usefulness of antipyrine metabolite kinetics, we have investigated the role of dose and time dependent factors.

Male Sprague-Dawley rats received [N-methyl-^{14}C]-antipyrine (50mg/kg; 10μCi/kg; i.p.) and were housed in all-glass metabolism cages which allowed collection of $^{14}CO_2$ and urine (Houston *et al* 1981). The half-life of antipyrine was estimated from the $^{14}CO_2$ exhalation rate (CER)-time profile. Studies involving both plasma antipyrine concentration and CER monitoring established a strong, statistically significant correlation between CER half-life and plasma half-life ($r=0.973$, $p < 0.01$). Urinary metabolite pattern for 4-hydroxy-, 3-hydroxymethyl; and norantipyrine was determined by h.p.l.c. following conjugate hydrolysis and chloroform extraction.

Interanimal variation in the above parameters was found to be substantial (mean with range for 80 rats) -CER half-life 142, 80-190 min; fm(4H)0.21, 0.12-0.33; fm(3HM)0.21, 0.10-0.32; fm(N)0.22,0.12-0.30) - after administration of 50mg/kg antipyrine. Administration of 25, 50 and 100 mg/kg antipyrine to the same animals on three separate occasions showed no statistically significant dose effect.

In order to investigate the feasibility of both cross-over and longitudinal experimental design in antipyrine metabolite kinetic studies, a group of animals were tested on a number of occasions within a 7 day period. The data obtained are shown in the Table expressed in terms of % change from day 1 value.

Time dependence in antipyrine metabolite kinetics over a 7 day period

Test days	Half-life	fm (4H)	fm (3HM)	fm (N)
1,7 (n=8)	4 ± 2	7 ± 6	6 ± 4	8 ± 7
1,3,5 (n=4)	1 ± 1	6 ± 8	6 ± 6	5 ± 4
1-7 (n=6)	23 ± 9	50 ± 19	35 ± 17	4 ± 25

Good reproducibility was observed when either 6 or 1 day was allowed between tests; CER half-life altering by 10 min and the fm values by 0.03 at maximum under these conditions. In contrast daily administration resulted in moderate enzyme induction (significant reduction in CER half-life, $p < 0.01$) which was manifested mainly in the 4H and N pathways. Thus it is concluded that 50mg/kg antipyrine is suitable for cross-over experiments but 25mg/kg is required when longitudinal studies involving daily testing is necessary.

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