Metabolism, distribution and excretion of orphenadrine in man

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A quantitative g.l.c. method was developed for the routine analysis of orphenadrine in urine and blood plasma, and its mono-*N*-demethylated metabolite and *N*-oxide [after reduction (Beckett, Mitchard & Shihab, 1971)] in urine.

The total *o*-tolyl phenyl methyl moiety excreted was determined quantitatively by oxidation, with alkaline $KMnO_4$, of the unchanged drug and its metabolites to *o*-methyl benzophenone which was then assayed by g.l.c.

Preliminary investigation showed that the excretion of orphenadrine in urine was dependent upon urine output as well as pH. Seven healthy male volunteers were given the drug while the urine was maintained at pH 5 $\pm$ 0·5 (Beckett & Tucker, 1966) and the intake of fluid increased to give a steady urine output (Beckett & Wilkinson, 1965). Under these conditions, the reabsorption of orphenadrine and its basic metabolites in the kidney tubules was reduced and the fluctuations in the excretion rates of orphenadrine virtually eliminated. Inter and intra subject variations were then minimal and therefore the excretion data could be used to study the absorption distribution and metabolism of orphenadrine from different preparations and from different routes of administration.

Under these controlled conditions, less than 30% of the drug after an oral dose was excreted unchanged while the mono-*N*-demethylated metabolite represented about 5% and the *N*-oxide about 4% of the administered dose. The *o*-tolyl phenyl methyl moiety excreted in the urine intact accounted for about 50% of the dose indicating that metabolism involving the aromatic rings was a major route for orphenadrine.

Under the controlled conditions, there was a direct relation between concentration of drug in plasma and the urinary excretion rates. Urinary excretion data was therefore used to propose a three-compartmental mathematical model to describe the kinetics of absorption distribution and metabolism of orphenadrine, the validity of which was examined using an analogue computer.

REFERENCES

BECKETT, A. H. & WILKINSON, G. R. (1965). *J. Pharm. Pharmac.*, **16**, 256–257.
BECKETT, A. H. & TUCKER, G. T. (1966). *Ibid.*, **18**, *Suppl.*, 72S–75S.
BECKETT, A. H., MITCHARD, M. & SHIHAB, A. A. (1971). *Ibid.*, **23**, 347–352.

Metabolism and excretion of guanoxan in man

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Guanoxan, 2-guanidinomethyl-1,4-benzodioxan, is an antihypertensive drug, the metabolism of which in man has not been reported. In urine samples (24 h) from 6 hypertensive patients receiving guanoxan (20 to 200 mg/day orally) only free guanoxan or 7-hydroxyguanoxan was detected. The level of 7-hydroxyguanoxan varied from 12 to 53% with little correlation with administered dose. Only in urine from the patient on the highest dose (200 mg/day) was a trace of guanoxan also found. Exceptionally, urine from one severely hypertensive female patient (50 mg/day dose) consistently contained no 7-hydroxyguanoxan and only guanoxan (39%). In the absence of faeces samples from this patient it is not possible to conclude the reason for this difference. Rapid metabolism and excretion, however, was generally evident as in the 24 h after an initial dose of guanoxan, up to 43% was found in the urine as free 7-hydroxyguanoxan.

The relation of urinary with faecal excretion was studied in the 24 h excreta from a non-hypertensive male subject following a single oral dose (20 mg). In urine no guanoxan was detected and 7-hydroxyguanoxan excretion (18%) was complete in 8 h. In faeces, guanoxan excretion was low (7·8%) and protracted (over 48 h) while 7-hydroxyguanoxan (4%) was

excreted only in the second 24 h. As the total recovery was only 30% a further study was made. The same subject took guanoxan (20 mg daily) for 7 days and collected excreta during a 24 h period following the final dose. A recovery of 59·5% based on one dose was obtained and as with hypertensive patients only 7-hydroxyguanoxan (51·5%) was excreted in urine. Faecal excretion was again low, the guanoxan concentration falling to 2% with 7-hydroxyguanoxan at 6%.

Despite the strong basicity of the guanidine group, guanoxan readily crosses body membranes and is extensively hydroxylated in the aromatic ring in man. Other work in this laboratory has shown guanoxan to be similarly hydroxylated by animal liver preparations. There was no indication of conjugation of guanoxan or 7-hydroxyguanoxan and the renal rather than biliary clearance of the latter would be anticipated. Although not all of an oral dose was accounted for, there was no evidence in excreta for degradation of the guanidine moiety of guanoxan. This is in agreement with the generally observed biological stability of the guanidine group in non-endogenous compounds, but in contrast to the major route of metabolism of guanoxan in the dog (Cañas-Rodriguez, 1966), in which the guanidine group underwent transamidination.

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REFERENCE

CAÑAS-RODRIGUEZ, A. (1966). *Experientia*, **22**, 472–473.

Interactions between phosphatidylethanolamine monolayers and phenols in relation to antibacterial activity

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Considerable evidence already exists suggesting that damage to the bacterial cytoplasmic membrane occurs in the presence of phenols. This evidence has been reviewed by Proudfoot (1971). One question has not so far been conclusively answered:—is cytoplasmic membrane damage a direct or an indirect effect of phenols? The answer may be sought by determining whether phenols affect those molecular interactions which maintain the integrity of the cytoplasmic membrane.

To determine whether phenols do so affect lipid-lipid interactions the effects of phenol, *o*-cresol, *p*-cresol and 2,6-xylenol on monolayers of phosphatidylethanolamine (obtained from *E. coli*) at the liquid-gas interface have been examined using a film balance technique.

One observed effect of the phenols was a reduction in the total lateral cohesion between adjacent phosphatidylethanolamine molecules. For example, a subphase concentration of $4{\cdot}2 \times 10^{-3}$ mol/dm^3 phenol was found to reduce the total lateral cohesion of a phosphatidylethanolamine monolayer to the point where desorption of phosphatidylethanolamine molecules and disruption of the monolayer occurred at surface pressures greater than 15·2 mN/m.

The relative abilities of four phenols to disrupt monolayers of phosphatidylethanolamine was assessed by noting the mean highest surface pressure to which the lipid monolayers spread on sub-phases containing $2{\cdot}1 \times 10^{-3}$ mol/dm^3 of each phenol could be compressed before disruption occurred. On this basis, the relative disruptive abilities of phenol, *o*-cresol, *p*-cresol and 2,6-xylenol were 1·0, 2·0, 2·2 and 3·5 respectively. These values have the same order and relative magnitudes as the published phenol coefficients of these chemicals. If lipid-lipid interactions contribute to the maintenance of the integrity of the bacterial cytoplasmic membrane, the experimental observations suggest that phenols are capable of physically impairing this integrity. The observed similarity between the relative disruptive effects of the phenols and their phenol coefficients suggests that the antibacterial action of phenols involves disorganization of phospholipid molecules present in bacterial cytoplasmic membranes.

REFERENCE

PROUDFOOT, S. G. (1971). Ph.D. Thesis. University of Leeds.

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