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.

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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