A study of bioavailabilities and dissolution rates of commercial tablets of nitrofurantoin

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An investigation was undertaken to compare the bioavailabilities (BA) of a number of tablet formulations (100 mg) of the urinary antibacterial nitrofurantoin (NFT) with dissolution data on the same lots.

Preliminary studies showed that (1) An aqueous suspension of NFT of particle size 180–75 μm was a well absorbed and reproducible control dose. (2) Blood concentration profiles (8 sampling times in 6 h) reflected urinary excretion curves and (3) No drug was detected in the urine after 14 h. Peak blood concentrations occurred within 1 h after ingestion and were in the range 0·7 to 1·5 μg/ml. Each of 6 tablet formulations B through G and the control suspension A were given at weekly intervals to 7 volunteers. A standard regimen was adhered to before and during the trial and the sequence of administration followed a 7 × 7 latin square design. Urine was voided at 1, 2, 3, 4, 5, 6, 8, 10 and 14 h after the drug was taken and analysed for NFT by the method of Conklin & Hollifield (1963). The ranking of BA relative to control A demonstrated that formulation B was lowest (Tukey's allowable difference at 95% confidence level). Formulation D war lower than highest ranked G. For the first 6 h after administration formulation D gave significantly lower (95% confidence level) NFT excretion than control, while that of C was lower for 5 h. The observed urinary excretion rate constant was about $1{\cdot}0\,h^{-1}$, $t_{\frac{1}{2}} = 0{\cdot}7$ h and the mean excretion curves for each formulation reflected the individual data. Approximate absorption rates were calculated using the Wagner-Nelson equation (1964) for a single compartment model (which appeared to fit the data). Compared to control, formulations B, C and D were more slowly absorbed (A, mean $t_{\frac{1}{2}}$ abs. = 0·5 h; B, mean $t_{\frac{1}{2}}$ abs. = 1·2 h).

The urinary NFT concentration of 30 μg/ml has been cited in clinical reports as sufficient to eradicate most sentive strains of infecting organisms while less sensitive strains may respond to 75 μg/ml. A comparison of the time required to attain and maintain 30 and 75 μg/ml indicated that formulation B was poorest.

The USP XVIII methods for disintegration and dissolution were used to obtain data for each formulation. The stated limit is not greater than 30 min for disintegration and the time required for 60% (T 60%) of NFT to dissolve should not be *less* than 1 h. The formulations of higher BA than control, E, F and G released the drug rapidly and gave T 60% less than 60 min. This dissolution standard was apparently designed to prevent rapid drug release in efforts to reduce nausea associated with NFT which may be accentuated with rapid absorption. The test may lead to formulations exhibiting lower bioavailabilities than control; B and D are two such dosage forms. B has a T30% of 55 min and a disintegration time of 7 min and D, a T60% of 140 min and a disintegration of 1·3 min. These experiments suggest that formulation of NFT is difficult and a suitable test that reflects BA is required.

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On the effect of pharmaceutical formulation on thioridazine absorption

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Mellinger (1965) showed that when thioridazine was given orally the resultant blood concentions were affected by the type of preparation administered, a syrup giving higher blood concentrations than a crushed tablet. Ingredients of an oral liquid preparation can affect absorption of a drug from the gastrointestinal tract (Wagner, 1968). Male Wistar rats (body weight 100–250 g) were given thioridazine (10 mg base/150 g body weight) by stomach tube as a soluble salt in a syrup or as a suspension of the insoluble base. The syrup contained 2·25% thioridazine, calculated as base. The suspension (I) contained 2·25% micronized thioridazine base, polysorbate 80, sucrose and water. Mean blood concentrations (determined according

to Pacha, 1969) were compared after appropriate time intervals by the *t*-test. Only at 1 h after administration, did suspension (I) give different (higher) blood concentrations than did the syrup. To obtain information on the absorption of thioridazine oral preparations in man, a single dose, 3-way cross-over study was carried out with six male adults. The preparations used were the syrup, suspension (I), and suspension (II) which contained 2·25% micronized thioridazine base and pharmaceutical formulating agents (Patent application no: 118–3076). The three preparations were given in a latin square order, with three weeks between successive administrations for elimination of thioridazine. Blood samples were taken at appropriate time intervals. Differences in thioridazine blood concentrations between subjects after the same preparation were greater than differences in a single subject after the three preparations. A modified *t*-test (Moroney, 1953) was therefore used to compare the differences in individuals after the three preparations. There was no significant difference between the blood concentrations after suspension (I) and suspension (II), but both these were consistently higher ($P < 0{\cdot}01$) than those after the syrup. Adjuvants added to suspension (II) had not reduced absorption. Thioridazine is a base and would be expected to be well-absorbed from the intestine and poorly absorbed from the stomach. The free base in suspension (I) and (II) will dissolve in the stomach. If solution is rapid and neither syrup nor suspension formulation affects absorption, the drug should be equally well absorbed from syrup and suspension. The superior absorption found for the suspensions could be due either to an ingredient included in both suspensions (but not the syrup) that increased thioridazine absorption, or to an ingredient in the syrup that reduced thioridazine absorption.

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Human volunteer studies of the antitussive activity of dropropizine

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The production of cough and its assessment is possible with reasonable accuracy in laboratory animals but it is much more difficult in human subjects. A series of experiments was designed to induce cough in order to measure the effects of antitussives. The purpose was the verification of the antitussive property of 1-(2,3-dihydroxypropyl)-4-phenylpiperazine (dropropizine). In this study cough was induced by inhalation of citric acid aerosol using a modification of the method of Bickerman, German, Cohen & Itkin (1957).

In the first phase of the experiment, healthy volunteers were screened for response to citric acid inhalation using concentrations from 2% to 16%. The apparatus consisted of Rybar inhalers attached to a constant air supply of 14 p.s.i. so that each would deliver 0·175 ml/min of aqueous solution in atomized form. Initial screening was of 25 volunteers of ages ranging from 19 to 48 years and including both smokers and non-smokers. Of these, 14 were selected as positive cough responders on the basis of inability to tolerate a given threshold concentration of citric acid aerosol for 30 s or following 30 s inhalation to cough persistently for at least 30 s. The selected volunteers were rechecked to establish constancy of tussigenic threshold.

In the second phase, 9 of the selected volunteers were used in a double-blind study comparing a single dose of 20 mg codeine phosphate with a single dose of 60 mg dropropizine. After verification of the sensitivity threshold to citric acid inhalation for each volunteer, the first capsule was administered and the threshold redetermined 1½ h later. 4 h after ingestion of the first capsule, the second capsule was given and a further redetermination of the threshold made after 1½ h. The selection of medication was radomized and the subjects were unaware of the concentrations of citric acid that they were inhaling. Results showed that after dropropizine 6 subjects showed an increased threshold of response while after codeine phosphate 7