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

I. J. MCGILVERAY, G. L. MATTOK AND R. D. HOSSIE
The Research Laboratories, The Food and Drug Directorate, Ottawa, Ontario, Canada

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.

REFERENCES

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On the effect of pharmaceutical formulation on thioridazine absorption

CHRISTINE A. HIRST* AND R. C. KAYE
Division of Pharmacy, Department of Pharmacology, University of Leeds, Leeds, U.K.

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