CORRELATION OF DIGOXIN-TABLET DISSOLUTION-RATE WITH BIOLOGICAL AVAILABILITY

Clinically important differences in biological availability among various tablet preparations of digoxin are well established. Both authorities responsible for the safe use of pharmaceutical compounds and the manufacturers need a simple and reliable method for testing the bioavailability and stability of digoxin tablets. Absorption tests on humans, especially if done during maintenance therapy, provide the most reliable estimate of digoxin bioavailability and stability of various products (Preibisz, Butler & Lindenbaum, 1974). Such testing on humans, even in single-dose experiments (Greenblatt, Duhme, Koch-Weser & Smith, 1973), is, however, extremely tedious and is suitable only for investigational purposes of clinical pharmacology. Less troublesome methods for predicting digoxin bioavailability would be welcome.

In several studies a rapid tablet dissolution rate has been associated with high bioavailability of digoxin (Manninen, McLin & Reissell, 1972; Johnson, Greer, McCrerie, Bye & Fowle, 1973; Lindenbaum, Butler, Murphy & Cresswell, 1973). The present experiments were undertaken to establish if dissolution tests could be used to predict the clinical bioavailability of digoxin from tablets with a wide range of dissolution rates (Figure 1).

Dissolution rate was studied in accordance with U.S.P. XVIII. In the absorption studies six healthy volunteers of both sexes, 18-29 years of age, served as experimental subjects. Digoxin was administered in a single dose of 0.5 mg on the

morning of the trial. The tablets were ingested in the fasting state with 100 ml water. Eating was allowed 2 h later. A random cross-over technique was used. The time interval between administration of different tablets was at least 1 week. Digoxin concentrations in serum and urine were determined by radioimmunoassay. The coefficient of variation was 3.6% and the recovery from urine was 98%.

In single-dose experiments excretion of digoxin in urine over 24 h and areas under serum concentration curves both give a reliable estimate of digoxin bioavailability (Greenblatt *et al.*, 1973). When the excretion of digoxin in urine over 24 h and the percentage of tablet dissolution at 30 and 60 min were correlated a good linear correlation could be seen between these parameters with the exception of product B (Figure 2). Because urinary digoxin excretion and areas under 24 h serum concentration curves were closely correlated ($r = 0.998$) the present result holds even for areas under serum concentration curves.

Dissolution of digoxin tablets in a good dissolution test should closely mimic dissolution in the upper gastrointestinal tract. The dissolution test of U.S.P. XVIII is often recommended for testing digoxin tablet dissolution. Authors controlling the quality of marketed pharmaceutical products are well aware of its disadvantages (Harter, Skelly & Steers, 1974), though better methods have not been available for official use. We tried also the Sartorius dissolution method (Membranfilter,

Figure 1 Dissolution of seven different brands of digoxin tablets.

Figure 2 Correlation between dissolution at 30 (closed symbols) and 60 min (open symbols) and the urinary 24 h digoxin excretion.

Göttingen). With that method correlation obtained between dissolution rates and bioavailability was poor.

Serum digoxin concentration peaks occur at about 30 to 60 min after digoxin intake. Therefore dissolution achieved later than at 30 min would not be used in predicting digoxin bioavailability.

Among the tablets tested by us one product (B) with good bioavailability dissolved very slowly. In earlier experiments (Reissell, Manninen, Ojala & Karjalainen, 1974) tablets from a different batch of the manufacturer B dissolved very rapidly and had a good bioavailability. Deviation of product B in the present work from the others indicates that dissolution tests in their present form cannot always be used to predict digoxin bioavailability. However, if the tablets are manufactured in a

suitable way, this simple test can be used in the control of the stability of digoxin tablets between different batches of tablets and to predict the bioavailability, thus diminishing the need for cumbersome testing of bioavailability in man.

P. REISELL & KAARINA OJALA

Kivelä Hospital, Helsinki 26, Finland

V. MANNINEN

First Department of Medicine, University of Helsinki, Helsinki 29, Finland

A. SOTHMAN

Research Laboratories of Orion Pharmaceutical Manufacturers, Mankkaa, Finland

Received July 19, 1976

References

- GREENBLATT, D.J., DUHME, D.W., KOCH-WESER, J. & SMITH, T. W. (1973). Evaluation of digoxin bioavailability in single-dose studies. *New Engl. J. Med.*, 289, 651-654.
- HARTER, J.G., SKELLY, J.P. & STEERS, A.V. (1974). Bioavailability of digoxin—The regulatory viewpoint. *Circulation*, 49, 395-398.
- JOHNSON, B.F., GREER, H., MCCRERIE, J., BYE, C. & FOWLE, A. (1973). Rate of dissolution of digoxin tablets as a predictor of absorption. *Lancet*, i, 1473-1475.
- LINDENBAUM, J., BUTLER, V.P. Jr., MURPHY, J.E. & CRESSWELL, R.M. (1973). Correlation of digoxin tablet dissolution rate with biological availability. *Lancet*, i, 1215-1217.
- MANNINEN, V., MELIN, J. & REISELL, P. (1972). Tablet disintegration: A possible link with bioavailability of digoxin. *Lancet*, i, 490-491.
- PREIBISZ, J., BUTLER, V.P. Jr. & LINDEBAUM, J. (1974). Digoxin tablet bioavailability: Single-dose and steady state assessment. *Ann. int. Med.*, 81, 469-474.
- REISELL, P., MANNINEN, V., OJALA, K. & KARJALAINEN, J. (1974). Non-equivalence of digoxin tablets. *Ann. clin. Res.*, 6, Suppl. 11, 4-8.

EFFECT OF VITAMIN C SUPPLEMENT ON ANTIPYRINE DISPOSITION IN MAN

Previous studies have shown that concomitant administration of vitamin C with certain drugs can inhibit the rate at which the drug undergoes

biotransformation (Houston & Levy, 1975; Houston & Levy, 1976a; Houston & Levy, 1976b). This may result in a potentiation of the pharma-