Cardiotoxicity and the plasma digoxin concentration profile in conscious dogs

D.J. CHAPPLE*, R. HUGHES & B.F. JOHNSON

Pharmacology Laboratory & Department of Clinical Pharmacology, The Wellcome Research Laboratories, Beckenham, Kent

Some oral digoxin preparations of high bioavailability produce relatively high peak plasma concentrations and it has been suggested that this could be associated with an increased incidence of toxicity in man (Harter, Skelly & Steers, 1974). The frequency of nausea after oral digoxin at the time of peak plasma concentration supports this concern (Falch, Teien & Bjerkelund, 1973). However, maximal inotropic and chronotropic effects occur several hours after digoxin administration to man, presumably after tissue-plasma equilibrium has been established (Ganz, Fujimori, Penna, Greiner & Gold, 1957; Shapiro, Narahara & Taubert, 1970). It was therefore decided to examine the relationship between cardiac toxicity and plasma digoxin concentration.

The toxic effects on the heart of oral doses of digoxin were determined indirectly at various times after administration to eight conscious dogs by recording the intravenous doses of acetyl-strophanthidin necessary to induce cardiotoxic changes. One of the following changes in e.c.g. (Lead II) was accepted as indicative of cardiotoxicity: multifocal ectopics, ectopics representing one in every two beats, ventricular tachycardia or complete heart block. Acetyl-strophanthidin (infused at 0.095 mg/min) was used because its rapid elimination from the body permitted separate estimates to be made 45, 180 and 360 min after administration of digoxin. Each dog underwent four studies with 0.05, 0.1, 0.2 and 0.4 mg/kg digoxin given in an alcoholic solution (1.4-14%), allowing at least ten days between each test. Samples of venous blood were taken at intervals for the measurement of plasma digoxin levels by a modified radioimmunoassay technique.

Digoxin reduced the amount of acetyl-strophanthidin required to cause toxic changes in the e.c.g. the increase in cardiac sensitivity being dose-dependent. Plasma concentrations of digoxin were maximal 30-60 min after dosing and then declined rapidly (Figure 1). However, sensitivity to acetylstrophanthidin thereafter was maximal between 3 and 6 h after administration of digoxin (Figure 1). At each dose of digoxin there was no correlation between plasma levels and maximal sensitivity to acetylstrophanthidin (Figure 1). These results suggest that there is little or no increased risk of cardiotoxicity during periods of transient increase in plasma digoxin concentration.

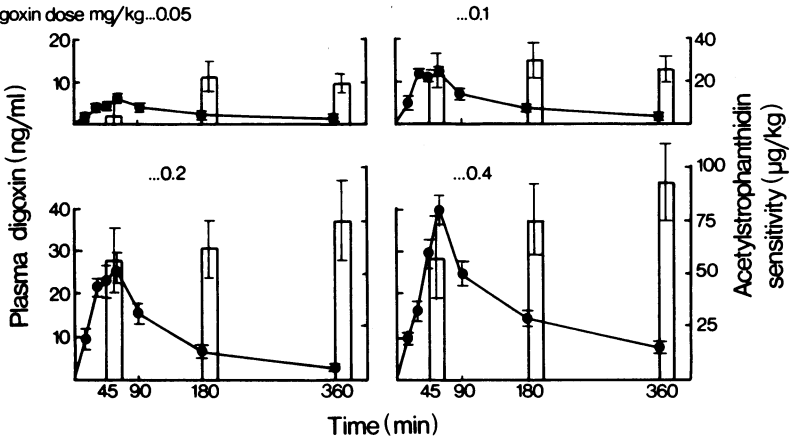

Figure 1 Comparisons of mean plasma digoxin concentration and mean acetylstrophanthidin sensitivity for four oral doses of digoxin administered to eight unanaesthetized dogs. Acetylstrophanthidin sensitivity was calculated as the difference between the amounts of acetylstrophanthidin required to induce cardiotoxicity in the digoxin and control phases.

The plasma digoxin levels are shown by the curves while acetylstrophanthidin sensitivity is represented by the columns. Bars represent standard error about the mean.

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