Br. J. clin. Pharmac. (1983), **16**, 741–742

METABOLISM OF DIGOXIN AFTER ORAL AND INTRAJEJUNAL ADMINISTRATION

J. OLOF MAGNUSSON

Departments of Clinical Pharmacology and Internal Medicine, Division of Cardiology, University Hospital, S-581 85 Linköping, Sweden

To study the influence of administration site on metabolism of digoxin in the gut, urinary excretion of digoxin and its metabolites was compared after oral and intrajejunal administration of [^{3}H]-digoxin solution to eight healthy volunteers, using liquid chromatography for the drug analysis. Dihydrodigoxin was not excreted in higher amounts after the more distal administration. The excretions of hydrolytic and non-extractable metabolites were significantly greater after the oral administration.

Keywords digoxin metabolism oral administration intrajejunal administration

Introduction

A microencapsulated digoxin formulation, as compared to a fast dissolving tablet, delayed absorption of the glycoside without reducing the amount absorbed (Bergdahl *et al.*, 1980). During further studies, a microencapsulated preparation with more sustained dissolution properties was compared with a digoxin solution. A reduction of the hydrolytic cleavage and an unexpectedly large biotransformation to dihydrodigoxin was found after intake of the microencapsulated formulation. In a pilot study, a threefold increase of the excretion of dihydrodigoxin was demonstrated in one subject after intrajejunal administration of a digoxin solution (Magnusson *et al.*, 1982a). Thus, evidence suggested that metabolism of the glycoside might depend on a more distal absorption site in the intestine. The present study was performed to investigate whether the more distal absorption site *per se* is important for the metabolic inactivation of digoxin. The design also allowed an estimation of glycoside hydrolysis in the stomach.

Methods

In a randomized, cross-over study 50 ml 3% ethanol solution containing digoxin (0.5 mg) and 12α[^{3}H]-digoxin (100 μCi, New England Nuclear Chemical Corporation, G.F.R.) was given to eight healthy male volunteers, none of whom had received antibacterial drugs during the recent months. Approval was given by the Ethical committee and Isotope committee of the University Hospital, Linköping, Sweden. The dose of radiolabelled material was chosen to obtain sufficient sensitivity of the liquid chromatography (LC)-method. Radiochemical purity was determined with the same analytical procedure as used for the urine samples (Eriksson *et al.*, 1981). The solution contained 1.8% [^{3}H]-hydrolytic metabolites. The drug was given either orally or as a 15 min infusion into the jejunum about 120 cm from the mouth via a catheter previously found not to adsorb digoxin. The position of the catheter was checked by X-ray. At least 10 days elapsed between the trials. Urine was collected 0–72 h after drug administration and parts were kept frozen until assayed. Digoxin and its metabolites were determined by LC combined with liquid scintillation counting (Eriksson *et al.*, 1981). The urine samples were not pretreated with deconjugating enzymes.

Results

Results from the analysis of the 3 day urine collections from the eight subjects are given in Table 1. The absorbed amount, estimated from the total urinary radioactivity was the same after both modes of administration. The excretion of dihydrodigoxin did not increase after the distal infusion. Only one subject produced considerable amounts of the reduced metabolite after both oral and intestinal administration (6.3% and 9.6% of the dose). The excretion of hydrolytic and non-extractable metabolites was significantly greater ($P < 0.05$; Student's t-test) after the oral intake of digoxin (2.9% *vs* 0.6% and 11.4% *vs* 4.7% of the dose, respectively).

Table 1 Relative amounts of [^{3}H]-digoxin, [^{3}H]-dihydrodigoxin, and [^{3}H]-hydrolytic digoxin metabolites (mean and range) excreted in urine 0–72 h in eight healthy men after administration of 0.5 mg [^{3}H]-digoxin solution.

	Oral administration		*Intrajejunal infusion*
Total radioactivity (% of dose)	51.8 (44.8–63.3)		52.4 (41.1–62.9)
Recovery by LC (% of dose)	40.4 (35.4–50.6)	*	47.7 (34.9–62.3)
Digoxin (% excreted)	90.8 (81.8–97.2)	*	96.3 (82.2–98.6)
Dihydrodigoxin (% excreted)	2.0 (0.3–12.5)		2.3 (0.3–15.5)
Hydrolytic metabolites (% excreted)	7.2 (2.4–16.7)	*	1.4 (1.2–1.7)

* $P < 0.05$

Discussion

An explanation of the low production of dihydrodigoxin in the present study could be that the infusion of the glycoside was too proximal to allow exposition of the drug to bacteria possibly responsible for the metabolic process (Herrmann & Repke, 1969; Lindenbaum *et al.*, 1981a). It can also be argued that not only the distal absorption but also individual factors may be responsible for the inactivation since the recovery of dihydrodigoxin differs greatly in previous investigations (Peters *et al.*, 1978; Gault *et al.*, 1979; Lindenbaum *et al.*, 1981a, b; Magnusson *et al.*, 1982b).

The recovery of hydrolytic metabolites mainly after oral intake of digoxin is consistent with previous reports demonstrating intragastric hydrolysis of the glycoside (Beermann *et al.*, 1972; Gault *et al.*, 1980). Also consistent with a previous study (Magnusson *et al.*, 1982b) non-extractable metabolites, i.e. metabolites calculated as the difference between the total urinary radioactivity and the recovery of LC, were found in increased amounts when the hydrolysis was large.

The author is indebted to Miss Stina Gustavsson, AB Hässle, Mölndal, Sweden, for skilful technical assistance.

References

BEERMANN, B., HELLSTRÖM, K. & ROSEN, A. (1972). The absorption of orally administered (12α-^{3}H)-digoxin in man. *Clin. Sci.*, **43**, 507–518.

BERGDAHL, B., BOGENTOFT, C., JONSSON, U.E. & MAGNUSSON, J.O. (1980). Absorption of digoxin from a new microencapsulated formulation. *Eur. J. clin. Pharmac.*, **17**, 443–447.

ERIKSSON, B.-M., TEKENBERGS, L., MAGNUSSON, J.O. & MOLIN, L. (1981). Determination of tritiated digoxin and metabolites in urine by liquid chromatography. *J. Chromatogr.*, **223**, 401–408.

GAULT, M.H., SUGDEN, D., MALONEY, C., AHMED, M. & TWEEDDALE, M. (1979). Biotransformation and elimination of digoxin with normal and minimal renal function. *Clin. Pharmac. Ther.*, **25**, 499–513.

GAULT, H., KALRA, J., AHMED, M., KEPKAY, D. & BARROWMAN, J. (1980). Influence of gastric pH on digoxin biotransformation. I. Intragastric hydrolysis. *Clin. Pharmac. Ther.*, **27**, 16–21.

HERRMANN, I. & REPKE, K. (1969). Transformation of cardenolides by microorganisms in the intestine. *Symposium über Biochemische Aspecte der Steroid Forschnung*, pp. 115–119. Berlin Akademie Verlag.

LINDENBAUM, J., RUND, D., BUTLER, V.P., TSE-ENG, D. & SAHA, J.R. (1981a). Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. *New Engl. J. Med.*, **305**, 789–794.

LINDENBAUM, J., TSE-ENG, D., BUTLER, V.P. & RUND, D.G. (1981b). Urinary excretion of reduced metabolites of digoxin. *Am. J. Med.*, **71**, 67–74.

MAGNUSSON, J.O., BERGDAHL, B., BOGENTOFT, C. & JONSSON, U.E. (1982a). Metabolism of digoxin and absorption site. *Br. J. clin. Pharmac.*, **14**, 284–285.

MAGNUSSON, J.O., BERGDAHL, B., BOGENTOFT, C., JONSSON, U.E. & TEKENBERGS, L. (1982b). Excretion of digoxin and its metabolites in urine after a single oral dose in healthy subjects. *Biopharm. Drug. Disp.*, **3**, 211–218.

(Received May 23, 1983, accepted August 15, 1983)