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METABOLISM OF DIGOXIN AND ABSORPTION SITE

JAN OLOF MAGNUSSON & BJÖRN BERGDAHL
Departments of Clinical Pharmacology and Internal Medicine, Division of Cardiology, University Hospital, S-581 85, Linköping, Sweden

CONNY BOGENTOFT & ULF E. JONSSON
AB Hässle, Research Department,
S-431 83 Mölndal, Sweden

After oral intake of enteric-coated granules containing [^{3}H]-digoxin extensive metabolism was observed. Maximum 66% of the 24 h urinary excretion was identified as [^{3}H]-dihydrodigoxin, using high performance liquid chromatography for the analysis. It is suggested that metabolism of digoxin may depend on the absorption site.

Introduction

Bioavailability of tablet brands of digoxin is considered to be related to dissolution-rates (Bertler *et al.*, 1972). *In vitro* highly available tablets release more than 70% of the glycoside in 60 min. Most of the absorption occurs in the stomach and in the upper parts of small intestine (Beermann *et al.*, 1972). We now present evidence for metabolism of digoxin as a consequence of more distal absorption.

Methods and Results

To overcome acid degradation of digoxin in the stomach a capsule preparation with a large number of small enteric-coated granules containing digoxin was developed. In a previous study a delayed absorption was demonstrated (Bergdahl *et al.*, 1980). During further studies on digoxin metabolism, using tritiated glycoside a granule preparation with an *in vitro* dissolution-rate of about 80% in 60 min at pH 6.5 was compared with the digoxin solution. A randomized, cross-over design was used. Drug analysis was performed by high-performance liquid chromatography combined with liquid scintillation counting (Eriksson *et al.*, 1981). Results from four young, healthy volunteers, none of whom had received antibacterial agents during the recent months, are given in Table 1.

Discussion

These data show that some individuals may metabolize digoxin to dihydrodigoxin. This ability is enhanced when they are given a preparation which releases its

Table 1 Relative amounts of [^{3}H]-digoxin and [^{3}H]-dihydrodigoxin excreted in urine 0–24 h in four healthy men after oral intake of 1.5 mg [^{3}H]-digoxin as either a solution or a capsule.

Subject		*Digoxin (% excreted)*	*Dihydrodigoxin (% excreted)*	*Total radioactivity (% of dose)*
1	Solution	72.9	27.1	31.5
	Capsule	33.6	66.4	31.5
2	Solution	77.1(36.8)*	22.9(63.2)*	23.0(21.9)*
	Capsule	41.6	58.4	25.1
3	Solution	99.4	0.6	25.7
	Capsule	99.2	0.8	16.4
4	Solution	98.8	1.2	24.8
	Capsule	98.6	1.4	17.7

* values within brackets refer to recoveries after drug infusion into the jejunum

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digoxin in the more distal small intestine. The influence of the absorption site was verified in subject 2 who, several weeks after the first experiment had the digoxin solution infused into the jejunum at the level of the ligamentum (Table 1).

The mechanism for this metabolic reduction is unknown but the possibility of conversion by bacteria exists (Herrmann & Repke, 1969; Lindenbaum *et al.*, 1981a,b). Thus low bioavailability from tablet brands of digoxin, especially from tablets with slow dissolution-rates, may in some individuals not only depend on incomplete absorption but also on metabolism of the glycoside in the distal intestine. This will not be recognized by non-specific assay methods.

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