THE INFLUENCE OF DIGOXIN PARTICLE SIZE ON ABSORPTION OF DIGOXIN AND THE EFFECT OF PROPANTHELINE AND METOCLOPRAMIDE

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1 The influence of particle size on absorption of digoxin was studied in ten healthy volunteers who received 0.5 mg digoxin as two standard Lanoxin tablets, or tablets containing micronized digoxin or large particle size digoxin. Tablets were given 30 min after 15 mg propantheline, 10 mg metoclopramine or a placebo tablet, and following an overnight fast.

2 The overall mean cumulative 4 day urinary excretion of digoxin was significantly lower ($P < 0.01$) after large particle size digoxin than after standard or micronized digoxin. Mean cumulative urinary excretion following large particle size digoxin was reduced when administered after metoclopramide and increased after propantheline, the difference between these two treatments being significant ($P < 0.05$). There was a significantly lower ($P < 0.05$) overall mean cumulative excretion following standard by comparison with micronized digoxin. However, by comparison with placebo, neither metoclopramide nor propantheline significantly altered mean cumulative excretion after standard or micronized digoxin. Propantheline and metoclopramide affect absorption of digoxin from formulations of large particle size and slow dissolution rate only.

Introduction

Particle size is one of the factors that determines the rate and extent of absorption of digoxin. Shaw & Carless (1974) showed in patients that when administered within a rice paper cachet, absorption was more rapid and complete with digoxin particles of 12 and 3.7 μm size than with particles of 22 μm , and that 7 days treatment with the 3.7 μm material produced significantly higher steady state plasma digoxin levels than with 22 μm particles. Florence, Salole & Stenlake (1974) reported increased dissolution rate of digoxin after milling to reduce particle size. Shah, Pytelewski, Eisen & Jarowski (1974) confirmed that milling of digoxin enhanced its dissolution rate and also demonstrated significantly increased peak blood levels of digoxin in rats following oral administration of digoxin milled with lactose as compared to unmilled digoxin and lactose. Jounela, Pentikäinen & Sothman (1975) have also demonstrated significantly lower bioavailability from digoxin tablets of large particle size material given to healthy volunteers.

It has been reported that propantheline and metoclopramide may affect digoxin absorption. Manninen, Melin, Apajalah & Karesoja (1973) demonstrated in patients on maintenance digoxin that prior administration of propantheline significantly increased and metoclopramide decreased serum

digoxin levels. In healthy volunteers, pretreatment with propantheline significantly reduced the peak plasma digoxin levels after tablets but not after ingestion of digoxin in solution. It was pointed out by Medin & Nyberg (1973) that the tablets used in the latter study had a slow dissolution rate (30% at 4 h), and that slow dissolution rate might be a prerequisite for absorption of digoxin to be affected by metoclopramide and propantheline.

The present study was designed to confirm the effect of alteration of particle size on absorption of digoxin from tablets and to investigate whether the effect of pretreatment with metoclopramide and propantheline was related to particle size and dissolution rate.

Method

Ten healthy volunteers (one female, nine males) were studied. Ages ranged between 22 and 36 years and weight between 55.1 and 79.5 kg. Informed consent was given. Subjects had no history of renal or hepatic disease and plasma creatinine and urea were within normal limits. Each subject received repeated single doses of 0.5 mg digoxin as two tablets of standard Lanoxin (Batch 1484X), dissolution rate 98%/1 h; of micronized digoxin (experimental batch HG/W/173/14) particle size $< 10 \mu\text{m}$, dissolution rate 100%/7.5 min and of large particle size digoxin (ex-

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perimental batch HG/W/173/5), particle size 90–106 μm , dissolution rate 34%/1 hour. The between tablet variation in weight of digoxin in the specially prepared batches was 2% for micronized digoxin and 7% for large particle size digoxin.

Subjects received each of the digoxin formulations after an overnight fast on three repeated occasions with either 15 mg propantheline, 10 mg metoclopramide or placebo tablets being given 30 min before digoxin. The sequence of administration of the nine digoxin formulation/pretreatment combinations was randomized using a balanced block design with a minimum of 2 weeks between treatments.

Urine was collected in 24 h periods for 4 days and stored at 4°C. The total volume for 4 days was pooled and an aliquot taken. Digoxin was determined in all samples in triplicate by radioimmunoassay using the commercially available Lanoxitest-Gamma Kit (Wellcome Reagents Limited) in which the tracer is an iodinated tyrosine derivative of digoxin. Standards and reference human urine were included in each assay run.

Statistical analysis

The analysis of variance used was that appropriate to a 3×3 factorial design. Since it was of interest to determine whether the pretreatments affected any of the digoxin preparations individually, the

formulation/pretreatment combinations were also compared with each other. Individual comparisons between means were assessed using Duncan's Multiple Range Test. A square root transformation was used to stabilize variances, and analyses were made on transformed data.

Results

The results are shown in Table 1. The overall mean cumulative 4 day urinary excretion following large particle size digoxin was significantly lower ($P < 0.01$) than following either of the other crystal types. A smaller but nonetheless significant difference ($P < 0.05$) was shown for overall mean excretion between standard and micronized digoxin preparations.

The comparison of all nine formulation/pretreatment combinations indicated that there were no significant differences between any of the six combinations involving standard and micronized digoxin. All three combinations using large particle size digoxin differed significantly ($P < 0.01$) from these six. Mean urinary excretion after large particle size digoxin with propantheline differed significantly ($P < 0.05$) from that after large particle size digoxin with metoclopramide.

Table 1 Cumulative 4 day urinary excretion of digoxin (μg) for subjects following each formulation of digoxin administered after propantheline (15 mg, P), metoclopramide (10 mg, M) or placebo

	Cumulative urinary excretion of digoxin (mg)								
	P	Standard M	Placebo	P	Micronized M	Placebo	P	Large crystal M	Placebo
PS	160.5	208.0	148.5	185.3	303.4	107.6	97.0	86.0	158.0
NMCH	268.2	157.2	259.5	285.1	224.9	158.1	56.8	58.7	89.0
FN	95.2	159.0	103.0	129.5	131.1	185.2	77.5	55.9	64.6
JD	106.8	210.5	92.7	225.1	197.3	197.5	85.5	34.1	97.9
TE	267.6	101.5	167.8	259.7	167.4	191.0	99.9	78.7	81.4
AS	115.0	188.3	171.1	196.4	237.0	163.5	142.4	47.2	75.2
AD	194.7	118.3	202.8	155.2	198.3	213.5	122.9	24.5	44.3
CF	114.4	134.8	197.2	196.4	247.2	213.1	107.7	97.6	71.3
RMcl	187.3	198.9	216.6	197.5	215.1	237.9	64.2	60.0	82.1
GG	241.6	163.3	229.7	145.0	202.6	243.5	77.3	56.3	54.9
Mean	175.1	164.0	178.9	197.5	212.4	191.1	93.1	59.9	81.9
s.e. mean	21.28	11.94	16.90	15.50	14.69	12.83	8.36	7.12	9.83
coefficient of varia- tion (%)	38	23	30	25	22	21	28	38	38
Overall: Mean		172.7			200.3			78.3	
s.e. mean		9.62			8.18			5.39	
coefficient of varia- tion (%)		31			22			38	

Discussion

Propantheline decreases the motility of the gastrointestinal tract (Schwartz, Lehman, Ostrove & Seibel, 1953), while metoclopramide stimulates gastrointestinal activity and increases rate of transit (Eisner, 1968; Margieson, Sorby & Williams, 1966; James & Hume, 1968). It is likely that their effects upon absorption of digoxin from formulations of large particle size are secondary to altered rate of transit of digoxin through the intestine, which must affect the time available for dissolution of digoxin particles in intestinal fluids. The lack of effect of these drugs on absorption of digoxin from the standard and micronized formulations probably reflects their rapid dissolution rates, as a much shorter time for dissolution and absorption would be necessary. This is supported by the finding (Manninen *et al.*, 1973) that propantheline does not affect the absorption of digoxin administered in liquid forms. Hence propantheline does not have a direct effect in promoting digoxin absorption.

It has been suggested (Thompson, 1973) that the apparent effect of propantheline on digoxin absorption might be attributable to a decrease in bile flow and biliary digoxin excretion. However, this would seem unlikely as propantheline did not affect the absorption of digoxin administered either in solution (Manninen *et al.*, 1973) or as tablets of standard or micronized digoxin.

It is generally accepted that between-subject variation in intestinal absorption is lower for completely absorbed than for incompletely absorbed drugs. Pharmaceutical attempts to enhance ab-

sorption of incompletely absorbed drugs like digoxin are primarily aimed at improving the consistency of absorption, which may be conveniently calculated as the coefficient of variation of individual quantitative determinations of intestinal absorption. As expected, in the placebo pretreatment phases, tablets of high bioavailability were associated with a reduced coefficient of variation. It had been anticipated that drug-induced alteration in intestinal motility might exaggerate this difference, and might provide a more powerful system for demonstrating improved consistency of absorption from new formulations. However, this did not appear to be the case, as overall coefficients of variation determined for each formulation with all pretreatments were remarkably similar to those for the formulations without active pretreatment.

It is apparent that absorption from a formulation of large particle size is reduced as compared to micronized or standard digoxin, and that metoclopramide increases and propantheline decreases this difference. The small but significant difference between the overall mean cumulative urinary excretion following standard or micronized digoxin may reflect a tendency for values after metoclopramide to be different. However, metoclopramide and propantheline are without significant effect on the extent of absorption of digoxin from tablets prepared with standard or micronized digoxin. It may be inferred that oral digoxin preparations of high bioavailability may be used concurrently with drugs affecting gastrointestinal motility without special precautions.

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(Received June 24, 1977)