INFLUENCE OF SOFT GELATIN ON DIGOXIN ABSORPTION

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1 The influence of encapsulation in soft gelatin on the absorption of digoxin from a solvent mixture of polyethylene glycol 400 90% w/w, ethanol 6% w/w, propylene glycol 3% w/w and water 1% w/w was studied in eight healthy volunteers.

2 Each volunteer received 0.6 mg digoxin as solution alone, as three intact capsules containing digoxin solution, as three capsules containing digoxin solution sectioned in half and as three capsules containing digoxin solution dissolved in water prior to administration.

3 There was no significant difference between the four treatments in terms of area under the plasma concentration-time curves for 7 h, peak plasma concentrations, time to peak or in the cumulative urinary excretion for 6 days.

4 It is suggested that a constituent of the solvent rather than the presence of or encapsulation within soft gelatin may be the determining factor in enhanced absorption of digoxin from soft gelatin capsules as compared to aqueous solution or tablets of rapid dissolution rate.

Introduction

It has been shown that the bioavailability of digoxin is greater from soft gelatin capsules containing a solution of digoxin in polyethylene glycol than from either an aqueous solution of digoxin or from tablets of rapid dissolution rate (Mallis, Schmidt & Lindenbaum, 1975; Johnson, Bye, Jones & Sabey, 1976). It has been suggested that digoxin absorption might be facilitated by the solvent or by a factor in the capsule wall or that encapsulation might protect digoxin from inactivation by gastric acid or increase the local concentration at the intestinal absorption site (Mallis *et al.*, 1975; Johnson *et al.*, 1976).

The present study was designed to investigate the influence of encapsulation and of the co-administration of soft gelatin on the absorption of digoxin from solution.

Method

Eight healthy volunteers, four male and four female, were studied. Age ranged between 19-53 years and weight between 56.5-99 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 0.6 mg digoxin in a solvent mixture containing 90% w/w polyethylene glycol 400

(U.S.P., S.G. 1.11-1.14, viscosity 6.8-8.0 centistoke, Union Carbide Ltd), 6% w/w ethanol, 3% w/w propylene glycol and 1% w/w water on four separate occasions with a minimum of 2 weeks between occasions. The sequence of receiving treatments was randomized, and all subjects received the digoxin solution, after fasting overnight, in the form of:

- A. three intact soft gelatin capsules each containing 0.2 mg digoxin, followed by 100 ml water
- B. three soft gelatin capsules each containing 0.2 mg digoxin cut in half immediately before administration, followed by 100 ml water.
- C. a solution of digoxin containing 0.6 mg digoxin, followed by 100 ml water
- D. three soft gelatin capsules each containing 0.2 mg digoxin, dissolved in 100 ml water by heating to 37°C for a 5 min period immediately prior to administration.

An indwelling Braunula cannula was inserted into a forearm vein and blood samples collected at the following times after digoxin administration: control, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 3.0, 5.0 and 7.0 h.

Urine was collected for 6 days following each treatment occasion as separate 24 h urine collections.

Plasma was quickly separated from blood samples collected in lithium heparin tubes and stored at 4°C. Aliquots of urine were obtained and similarly stored as

soon as available. Digoxin was determined in all samples in triplicate by radioimmunoassay using the commercially available Lanoxitest – gamma Kit (Wellcome Reagents Ltd), in which the tracer is an iodinated tyrosine derivative of digoxin. Standards and reference plasma or urine were included in each assay run.

Statistical significance of differences was assessed by parametric analysis of variance. Non-parametric Friedman analysis of variance was used to compare the times of peak plasma concentrations.

Results

The plasma concentrations are shown in Table 1. When the areas under the plasma concentration–time

curves (Table 2) were compared there was no significant difference between the regimes, nor were the peak concentrations (Table 3) or times to peak (Table 4) significantly different. There was no significant difference in the cumulative urinary excretion over 6 days nor in the cumulative urinary excretion at any of the collection time intervals (Table 5).

Discussion

It is apparent that in this study neither encapsulation of digoxin solution in soft gelatin nor the co-administration of soft gelatin in solid or dissolved form altered the extent of absorption of digoxin from the solution. These findings differ from those of Mallis *et*

Table 1 Mean $\pm$ s.e. mean ($n=8$) plasma concentrations of digoxin on the four separate occasions

Time (h)	Preparation			
	Intact capsules	Cut capsules	Filling solution	Dissolved capsules
	Plasma digoxin (ng/ml)			
0	0.05 $\pm$ 0.01	0.04 $\pm$ 0.01	0.04 $\pm$ 0.01	0.08 $\pm$ 0.01
0.5	5.03 $\pm$ 1.04	6.67 $\pm$ 0.69	6.01 $\pm$ 0.96	6.92 $\pm$ 0.60
0.75	5.65 $\pm$ 1.30	6.00 $\pm$ 0.64	6.31 $\pm$ 0.60	5.99 $\pm$ 0.44
1	4.75 $\pm$ 0.70	5.03 $\pm$ 0.53	4.93 $\pm$ 0.42	4.90 $\pm$ 0.30
1.25	4.18 $\pm$ 0.49	3.98 $\pm$ 0.41	4.08 $\pm$ 0.38	4.09 $\pm$ 0.31
1.5	3.63 $\pm$ 0.45	3.50 $\pm$ 0.38	3.67 $\pm$ 0.41	3.40 $\pm$ 0.24
2	2.56 $\pm$ 0.31	2.61 $\pm$ 0.33	2.70 $\pm$ 0.26	2.39 $\pm$ 0.28
3	1.62 $\pm$ 0.24	1.42 $\pm$ 0.13	1.70 $\pm$ 0.20	1.75 $\pm$ 0.18
5	0.97 $\pm$ 0.12	0.94 $\pm$ 0.10	0.93 $\pm$ 0.14	0.84 $\pm$ 0.12
7	0.84 $\pm$ 0.09	0.71 $\pm$ 0.08	0.78 $\pm$ 0.10	0.77 $\pm$ 0.10

Table 2 Mean $\pm$ s.e. mean ($n=8$) area under plasma concentration–time curve (7 h) on the four separate occasions

	Preparation			
	Intact capsules	Cut capsules	Filling solution	Dissolved capsules
	Area under plasma concentration–time curve (ng ml ⁻¹ h)			
	14.02 $\pm$ 1.395	14.23 $\pm$ 1.384	14.67 $\pm$ 1.480	14.61 $\pm$ 1.220

Table 3 Mean $\pm$ s.e. mean ($n=8$) peak observed plasma digoxin concentration on the four separate occasions

	Preparation			
	Intact capsules	Cut capsules	Filling solution	Dissolved capsules
	6.56 $\pm$ 0.84	6.89 $\pm$ 0.71	6.78 $\pm$ 0.67	7.10 $\pm$ 0.59

Table 4 Mean time to peak observed plasma digoxin concentration on the four separate occasions

Preparation			
Intact capsules	Cut capsules	Filling solution	Dissolved capsules
Time to peak plasma concentration (h)			
0.73	0.56	0.59	0.56

Table 5 Mean $\pm$ s.e. mean ($n=8$) cumulative urinary excretion of digoxin

Time (days)	Preparation			
	Intact capsules	Cut capsules	Filling solution	Dissolved capsules
Cumulative urinary excretion of digoxin (μ g)				
1	138.2 $\pm$ 9.5	146.6 $\pm$ 12.7	157.5 $\pm$ 8.5	145.2 $\pm$ 13.6
2	190.0 $\pm$ 14.4	205.6 $\pm$ 15.7	213.8 $\pm$ 10.3	202.7 $\pm$ 19.0
3	226.5 $\pm$ 16.5	242.7 $\pm$ 17.5	254.0 $\pm$ 11.9	240.1 $\pm$ 21.6
4	248.1 $\pm$ 18.9	264.9 $\pm$ 19.1	278.3 $\pm$ 12.4	263.5 $\pm$ 24.2
5	264.8 $\pm$ 19.4	284.6 $\pm$ 20.0	296.9 $\pm$ 13.7	279.8 $\pm$ 25.7
6	278.1 $\pm$ 19.7	295.6 $\pm$ 20.5	309.3 $\pm$ 15.3	290.5 $\pm$ 26.5

al., 1975, who reported that the extent of absorption of digoxin from a solution in polyethylene glycol encapsulated in soft gelatin was significantly greater than from the non-encapsulated solution or from paediatric elixir, although the two liquid preparations did not differ significantly from each other. Johnson *et al.* (1976), showed that the absorption of digoxin from soft gelatin formulations of digoxin in solution was significantly greater than from an aqueous solution of digoxin.

Our results would therefore suggest that a solvent factor is responsible for the enhanced absorption of digoxin from this formulation. Previous studies from these laboratories demonstrated a greater extent of absorption of digoxin from paediatric elixir than from tablets of high dissolution rate (Johnson & Bye, 1975), and that hard gelatin encapsulation of a solid form of digoxin did not increase bioavailability (Johnson & Lader, 1974). Further studies of the effect of solvents on digoxin absorption may well be rewarding and

might have wider applicability to other drugs which are incompletely absorbed.

References

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