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Bioavailability of Digoxin Tablets in Healthy Volunteers

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The bioavailability of digoxin generic tablets manufactured in Korea (formulations A & B) were compared to a standard (formulation C; Lanoxin brand digoxin, Burroughs Wellcome, USA) in 12 healthy Korean male volunteers (mean age 31.4 years) in a single dose, randomized, complete block crossover study. Using a Latin square design, each of the subjects was randomized to the order number and allocated to each of the three treatments of 0.5mg oral digoxin. Digoxin concentrations in serum and urine samples collected for 48 hours after dosing were measured by fluorescence polarization immunoassay and radioimmunoassay, respectively. Treatments were compared by using nonlinear least squares regression analysis to evaluate the following pharmacokinetic parameters: maximum serum concentration (C_{max}); time of maximum serum concentration (T_{max}); area under the serum concentration-time curve for 0-12 hours (AUC_{0-12}); and cummulative urinary excretion for 0-48 hours (CUE_{0-48}). Mean AUC_{0-12}, C_{max}, and CUE_{0-48} values for formulations B and C were significantly different from formulation A ($p<0.001$), but not significantly different from each other. Based on AUC_{0-12} and CUE_{0-48}, respectively, the relative availability of formulation B was 87.5% and 89.6% and the relative availability of formulation A was 43% and 35% when compared to formulation C (the standard).

Key words: Digoxin, Bioavailability, Pharmacokinetic parameters

INTRODUCTION

Bioavailability is defined as the fraction of a dose of a drug product that enters the systemic circulation in unchanged form after oral administration of the product. This concept also includes the rate at which this entry occurs (Koch-Weser, 1974a). Bioavailability is but the first of many factors that determine the relation between drug dosage and intensity of drug action in the body.

Physicians and pharmacists must be concerned about bioavailability of drugs whenever it influences the therapeutic or toxic effects of their drug therapy (Koch-Weser, 1974b). Differences in bioavailability between oral dosage forms of digoxin have also been demonstrated (Lindenbaum *et al.*, 1971). Variations in bioavailability of digoxin tablets can have potential serious clinical implications (Shaw *et al.*, 1972; Heizer *et al.*, 1971). Thus, having a predictable uniform bioavailability from oral digoxin tablets is important in order to optimize individual patient therapy.

For the past several years the Clinical Pharmacokinetic Service, Baptist Hospital, Pusan, Korea, has been predicting and measuring digoxin serum concentrations and generating computer-assisted consults for dosage adjustments for pediatric and adult patients. Experience in using pharmacokinetic calculations to predict serum digoxin concentrations suggested that the bioavailability of the digoxin tablet being used in the hospital was about 45% (the Korean manufacturer did not publish, not provide any dissolution rate or bioavailability data). In a previous study at Baptist Hospital, four different pharmacokinetic methods of predicting steady state digoxin serum concentration were compared retrospectively with measured steady state digoxin serum concentrations in ten adults with normal renal function undergoing digoxin therapy. Estimating a bioavailability of 45% for the generic digoxin tablet used, the correlation between predicted and measured steady state concentrations was statistically significant (Kim *et al.*, 1987). A study to confirm this observation was felt to be justified. The rusults would potentially be clinically applicable to all patients in Korea taking digoxin tablets. Thus, the purpose of this study was,

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in normal healthy male Korean subjects, to determine the relative bioavailability of two Korean generic digoxin tablets in comparison with Lanoxin brand digoxin tablet (Burroughs Wellcome, USA).

MATERIALS AND METHODS

Sample Size

For the purpose of calculating an adequate sample size the response variable considered most important for comparison was the area under the serum drug concentration versus time curve (AUC). Variability of this measurement was estimated from previously published data to be 25% (Bustrack *et al.*, 1984). A difference in 20% of the AUC was considered significant (Rodda *et al.*, 1980). A sample size was calculated to detect a 20% difference in AUC with 80% power at the 0.05 significance level (Weiner, 1981).

Subject Selection

Twelve healthy Korean male volunteers with a mean age of 31.4 years (range, 20~40 yrs) who were within plus or minus 15% of their Korean ideal body weight (Shin and Song, 1987) (mean 60.5 kg; range, 56~72 kg) were recruited from among hospital employees; all completed the study. Each subject received a complete physical examination, EKG, and a battery of laboratory tests of hemopoeitic, hepatic and renal function. Exclusion criteria included a history or presence of cardiovascular, hepatic, renal, hematological of significant gastro-intestinal disease, alcoholism of drug abuse, psychiatric disorders, hypersensitivity or idiosyncratic reaction to digitalis glycosides, abnormal diet (defined as anything other than a normal Korean diet) during the month preceding the study, and smoking.

Informed Consent

Prior to enrollment, the purpose of the study, all procedures, and potential hazzards were described to the subjects in nontechnical terms. They were assured that they could withdraw from the study at anytime and each read and signed the concent form.

Study Design

The trial was conducted as a single-dose, randomized, complete block crossover design, bioavailability study. There were three treatment levels: (1) generic digoxin tablet A (formulation A: 0.25 mg/tablet, Lot No. DG03804, H. Co. Korea), (2) generic digoxin tablet B (formulation B: 0.25 mg/tablet, Lot No. DI8013, I. Co. Korea), and (3) Lanoxin brand digoxin tablet (formulation C: 0.25 mg/tablet, Lanoxin, Lot No. 513087, Burroughs Wellcome, USA). In each case two 0.25 mg tablets plus 240 ml water were administered. Using a Latin square design, each of the 12 subjects was randomized to the order number and allocated to each of the three treatments.

The subjects fasted from midnight prior to dosing until four hours following treatment administration at which time a standardized light Korean lunch was served. Each subject was given 120ml of water one hour before dosing on the morning of each test day to provide hydration after the overnight fluid restriction. Dosing for each treatment began at approximately 8 : 00 AM and blood and urine collections were made over the next 48 hours.

Blood samples (5 ml) were obtained by standard venipuncture techniques in vacuum tubes without additives at the following times: just prior to dosing (0 hr), 0.25, 0.5, 0.75, 1.0, 2, 3, 4, 6, 8, 12, 24, and 48 hours after dose administration. The blood samples were allowed to clot and were then immediately centrifuged, the serum separated, aliquoted into duplicate, properly labeled containers, and stored at −20℃ until the time of analysis.

Urine was collected prior to drug administration, 0~24 hours and 24~48 hours after drug administration. At the end of each 24 hour interval the urine samples were thoroughly mixed, the volumes and pH measured and recorded, and duplicate aliquots were placed in properly labeled containers, and frozen at −20℃ until analysis.

Following drug administration the subjects were ambulatory, however, no strenous of abnormal physical activity was permitted. A two week wash out period followed each treatment.

Sample Analysis

Digoxin concentration in each serum sample was measured in duplicate by fluorescence polarization immunoassay (TDX, Abbott Diagnostics). This assay was linear from 0~5 ng/ml, and the minimum detectable quantity (sensitivity) was 0.2 ng/ml. The digoxin concentration in the urine sample was measured in duplicate by a modified radioimmunoassay (Christenson *et al.*, 1982; Marwha and Johnson, 1984). Both procedures were performed in the Department of Clinical Pathology, Baptist Hospital.

Pharmacokinetic and Statistical Analysis

Serum concentration versus time data were evaluated using SIPHAR/Base (SIMED, Creteil, Cedex-France). The following compartment model dependent and noncompartment parameters were determined for each subject for each treatment regimen: (1) observed maximum serum concentration (C_{max}), (2) time to C_{max} (T_{max}) and (3) area under the serum concentration-time curve 0-12 hours ($AUC_{0\text{-}12}$) by trapezoidal rule. In addi-

tion, the cumulative urinary excretion of digoxin out to 48 hours after dose was determined (CUE_{0-48}). The relative bioavailability of formulations A and B when compared to the industry standard (formulation C) were determined using AUC_{0-12} and CUE_{0-48} data. ANOVA for a crossover design was used to statistically analyze these parameters. The pharmacokinetic and statistical analyses were performed at the Samford University Pharmacokinetic Center, Birmingham, Alabama, USA.

RESULTS

The mean serum digoxin concentration-time profiles (0~12 h) for the three treatments are presented graphically in Fig. 1. The cumulative urinary excretion of digoxin during the first 48 hours following digoxin administration is presented in Fig. 2.

The individual subject values for area under the serum concentration-time curves 0-12 hours (AUC_{0-12}) (ng/ml·hr) and the cummulative urinary digoxin excretion (CUE_{0-48}) (mcg/48 hr) are listed in Tables I and II. AUC_{0-12} hours was used instead of AUC_{0-48} hours because the majority of the serum concentrations for formulation A after 12 hours following single-dose digoxin administration were below the level of assay sensitivity.

Table III presents a summary of the derived pharmacokinetic parameters: mean AUC_{0-12} (ng·h/ml), mean C_{max} (ng/ml), mean t_{max} (hours), and mean CUE_{0-48} (ng). The relative bioavailability (F-rel AUC_{0-12} and F-rel CUE_{0-48}) are presented in Table IV. Based on AUC_{0-12} and CUE_{0-48} respectively, formulation B was 87.5% to 89.6% as bioavailable as formulation C (the standard). However, the relative bioavailability of formulation A was significantly lower: 43% using AUC_{0-12} and 36% using CUE_{0-48}. The statistical analyses (ANOVA) of pharmacokinetic parameters based on the means of serum digoxin concentration and cumulative urinary excretion data are presented in Table V.

Mean AUC_{0-12} values for formulations B and C were significantly different from formulation A ($p<0.001$, ANOVA, log transfer). The value for mean AUC_{0-12} for formulation B was not significantly different from formulation C. The symmetrical 95% confidence interval for the difference in mean AUC_{0-12} when comparing formulation A and B with C, expressed as a percentage, was 60.9% and 18.5%, respectively.

Mean C_{max} values for formulations B and C were not significantly different from each other but were both significantly different from formulation A ($p<0.001$, ANOVA, log-transfer). The symmetrical 95% confidence interval for the difference in C_{max} when comparing formulations A and B with C, expressed as a percentage, was 68.5% and 22.7%, respectively. Mean T_{max} values for all three formulations were not significantly different. Mean CUE_{0-48} values for formulations B and C were not significantly different from each other but both were significantly different from formulation A ($p<0.001$, ANOVA, log-transfer). When comparing formulations A and B with C, the symmetrical 95% confidence interval for the difference in CUE_{0-48}, expressed as a percentage, was 69.3% and 21.9%, respectively.

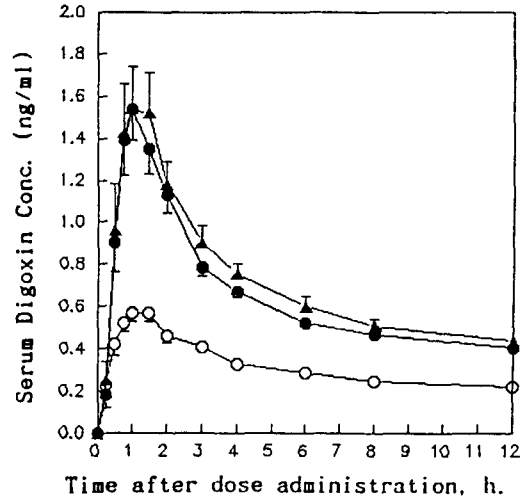

Fig. 1. Mean serum concentration-time curves during the first 12 h following oral administration of 0.25 mg digoxin tablet Vertical bar means the standard error of the mean (n=12). Key: (○) Tablet A: (●) Tablet B: (▲) Tablet C.

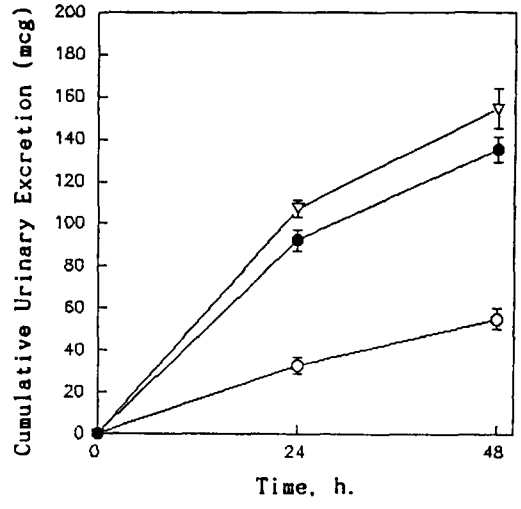

Fig. 2. Mean cumulative urinary excretion curves of digoxin during the 24 and 48 hours following oral administration of 0.25 mg digoxin tablet. Vertical bar means the standard error of the mean (n=12).
Key: (○) Tablet A: (●) Tablet B: (▽) Tablet C.

Table I. Area under the serum drug concentration-time curve 0-12 h (ng/ml·hr)

Subject	Formulation		
	A	B	C
1	3.82	8.96	10.76
2	4.06	7.42	10.48
3	5.08	7.45	8.86
4	3.36	6.42	7.27
5	4.94	7.41	9.83
6	3.08	7.93	7.95
7	3.81	6.03	6.50
8	3.74	9.93	10.05
9	3.62	9.10	9.48
10	2.89	6.34	4.82
11	3.07	7.84	8.48
12	2.29	5.68	6.71
Mean	3.65	7.55	8.43
SEM	0.23	0.38	0.53

SEM=standard error of the mean

Table II. Cumulative urinary Digoxin excretion (mcg/48 h)

Subject	Formulation		
	A	B	C
1	74.4	149.2	153.2
2	53.4	122.9	184.0
3	68.0	147.4	178.1
4	91.2	138.9	174.4
5	69.5	171.7	179.3
6	54.6	121.4	206.2
7	51.2	118.9	107.8
8	43.9	148.1	151.1
9	46.9	131.7	139.8
10	27.2	95.8	93.5
11	34.3	157.5	153.8
12	46.2	116.5	130.1
Mean	55.1	135.0	154.3
SEM	5.2	6.1	9.3

SEM=standard error of the mean

Table III. Pharmacokinetic Summary Statistics

Parameter	Formulation		
	A	B	C
Mean C_{max} (ng/ml± SEM)	0.65± 0.04	1.67± 0.15	1.90± 0.20
Mean T_{max} (h± SEM)	1.15± 0.11	1.29± 0.15	1.31± 0.20
Mean AUC_{0-12} (ng/ml·h± SEM)	3.65± 0.23	7.55± 0.38	8.43± 0.53
Mean CUE_{0-48} (ng± SEM)	55.1± 5.2	135.0± 6.1	154.3± 9.5

SEM=standard error of the mean

Table IV. Comparative Bioavailability

Relative Bioavailability	Formulation		
	A	B	C
F-rel AUC_{0-12}	0.4329	0.8956	1.0
F-rel CUE_{0-48}	0.3571	0.8749	1.0

F-rel AUC_{0-12}=relative bioavailability by comparison of the area under the serum concentration-time curve 0-12 hours of formulation A and with the standard (formulation C).
F-rel CUE_{0-48}=relative bioavailability by comparison of the cumulative urinary excretion 0-48 hours of formulation A and B with the standard (formulation C).

Table V. Pharmacokinetic parameters and urinary excretion data ANOVA

Formulation	AUC_{0-12}	C_{max}	T_{max}	CUE_{0-48}
A versus B	p<0.001	p<0.001	NSD	p<0.001
	56.8%[a]	64.7%	33.0%	65.4%
A versus C	p<0.001	p<0.001	NSD[b]	p<0.001
	56.8%	68.5%	32.3%	69.4%
B versus C	NSD	NSD	NSD	NSD
	18.5%	22.7%	32.4%	21.9%

[a]The symmetrical 95% confidence interval, expressed as a percentage.
[b]NSD: not significant different.

DISCUSSION

The clinical significance of differences in the bioavailability of digoxin was first investigated by Lindenbaum *et al.* (1970) in the United States (Lindenbaum *et al.*, 1971). Shaw *et al.* (1972) found clinically significant differences in serum digoxin concentrations produced by the administration of several different brands to patients on a maintenance schedule. They concluded that the brand of digoxin tablet can have a significant effect on the biological availability of digoxin for some patients and that this difference could be a cause of treatment failure (or in some cases toxicity). Subsequently there appeared in the literature a number of articles reviewing the appropriate interpretation of digoxin bioavailability studies (Sanchez *et al.*, 1973; Sorby and Tozer, 1973; Greenblatt *et al.*, 1973; Huffman *et al.*, 1974a). Koch-Weser produced the first of his classic discussions of the bioavailability of drugs in 1974a and 1974b. This was followed by a series of studies on variability in absorption of digoxin tablets (Binnion, 1974a, 1974b; Greenblatt *et al.*, 1974a; Preibisz *et al.*, 1974). In this same year the New York Heart Association Task Force on Digitalis Preparations published an article describing what physicians should know about digoxin bioavailability and how the new US FDA regulations would possibly affect the physician's clinical practice (Butler and Fox, 1974). Other

investigators continued to study the problem of digoxin bioavailability (Binnion, 1974b; Huffman *et al.*, 1974 b) and some suggested that intravenous digoxin be used as a bioavailability standard (Greenblatt *et al.*, 1974b; Stoll and Wagner, 1975).

New pharmacy standards for in vitro dissolution rate of digoxin tablets were established in the United States in late 1973 including a lot-by-lot certification program carried out by the US FDA (Kim, 1976). The clinical significance of the bioavailability of oral digoxin tablets slowly began to be recognized and many articles on the subject began to be published (Doherty, 1973; Lindenbaum, 1975; Johnson *et al.*, 1976; Greenblatt *et al.*, 1976; Huffman, 1976). Beginning in 1975, many studies have appeared demonstrating greater bioavailability of digoxin solution in capsules (Mallis *et al.*, 1975; Binnion, 1986; Marcus *et al.*, 1976; Colaizzi *et al.*, 1977; Lindenbaum, 1977; Lloyal *et al.*, 1978; Astorri *et al.*, 1979; Rund *et al.*, 1983; Doherty *et al.*, 1984; Johnson *et al.*, 1986).

At the time of this present study, the Korean pharmaceutical companies supplying digoxin tablets did not provide information on dissolution rates of bioavailability data. Thus Korean physicians and pharmacists had no direct knowledge of the exact bioavailability of the digoxin tablets available on the market.

At the Baptist Hospital in Pusan, our initial interest in this problem was generated with the creation of a clinical pharmacokinetic service. In 1985, we began predicting and measuring digoxin serum concentrations and generating computer-assisted consults for dosage adjustments. Clinical experience suggested that the bioavilability of the digoxin tablet being used in the hospital was only about 45%. Thus the present bioavailability study was performed to confirm this clinical impression.

In this study, based on both $AUC_{0\text{-}12}$ and $CUE_{0\text{-}48}$, formulation B (which was not in use at Baptist Hospital) was 87.5% to 89.6% as bioavailable as the standard (Burroughs Wellcome brand Lanoxin). This difference would not be expected to produce large clinically significant bioavailability problems in the treatment of patients. However, the comparative bioavailability of formulation A (which was in use at Baptist Hospital) was significantly lower (43.3% by $AUC_{0\text{-}12}$; 35.7% by $CUE_{0\text{-}48}$). If we assume the absolute bioavailability of the standard to be 70%~80% (Colaizzi *et al.*, 1977), this would suggest that the absolute bioavailability of formulation A would be even less than the value of 45% predicted by the clinical pharmacokinetic service. This would help to account for our clinical observations, prior to having facilities to measure serum drug concentrations, that many elderly patients with slightly incresed serum creatinine values were maintained on oral digoxin maintenance doses of 0.25 mg daily without signs or symptoms of toxicity. Likewise in many cases there was lack of therapeutic effect, especially in young otherwise healthy adults. Despite this, we do not ever recall a patient, regardless of body weight, receiving daily oral digoxin doses greater than 0.25 mg, which considering the poor bioavailability of formulation A, is a dose that in some cases would have been required to reach the normal therapeutic serum drug concentration range. Digoxin toxicity in adults was a rare occurance and limited to patients with renal failure in which the dose had not been adequately adjusted downward. The results of the present digoxin bioavailability study clearly suggest the reason for these clinical observations. As a result the pharmacy and therapeutics committee of the Baptist Hospital changed the brand of digoxin tablet from formulation A to formulation B (Burroughs Wellcome brand Lanoxin is not commercially available in Korea).

Since the discovery of the digoxin bioavailability problem in 1970 by Lindenbaum, much progress has been made in understanding the clinical significance of these differences. It is urgent that all physicians and pharmacists in Korea administering digoxin in any of its formulations (intravenous injection, elixir, tablets, capsules) be aware of the specific bioavailability of the particular formulation being used and the clinical implications and problems associated with changing from one commerical product to another, one formulation to another, and possible lot-to-lot differences.

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