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<b>Study No.:</b> GR120008/901	
<b>Title:</b> A Study to Evaluate the Effect of a High Fiber and a High Fat Meal on the Pharmacokinetics of LANOXIN† (digoxin) Elixir Pediatric in Healthy Adults	
<b>Rationale:</b> There is evidence that meals high in bran fiber may result in a reduction in area under the concentration time curve (AUC), although most studies did not show clinically significant changes in exposure to digoxin when administered with various sources of fiber. Since no formal food effect study has been conducted for digoxin formulated as digoxin Elixir Pediatric, and a review of the published literature failed to reveal definitive data, this study was performed to evaluate the effect of food on the pharmacokinetics of the elixir formulation.	
<b>Phase:</b> I	
<b>Study Period:</b> 12 September 2003 to 07 November 2003	
<b>Study Design:</b> This was an open-label, randomized, three-period, period balanced, crossover study.	
<b>Centers:</b> 1 center in United States	
<b>Indication:</b> None	
<b>Treatment:</b> Commercially available digoxin, Elixir Pediatric, was administered as 10mL of 0.05mg/mL solution (i.e., 0.5 mg dose). Subjects were randomized to treatment sequences ABC, ACB, BAC, BCA, CAB, or CBA in accordance with a randomization schedule. Following an overnight fast of at least 10 hours, subjects received either a single oral dose of 0.5mg digoxin in the fasted state (Regimen A), or after consuming a high fiber (Regimen B) or high fat (Regimen C) breakfast separated by a washout of at least 14 days between treatments. Subjects ingested breakfast 30 minutes prior to administration of digoxin and consumed the meal in 30 minutes or less.	
<b>Objectives:</b> The primary objective was to evaluate the effect of a high-fiber meal and a high-fat meal on the pharmacokinetics of digoxin following oral administration of digoxin Elixir Pediatric in healthy adults. The secondary objective was to evaluate the safety and tolerability of a single oral dose of 0.5mg digoxin Elixir Pediatric administered under fasting conditions and following a high-fiber meal and a high-fat meal in healthy adults.	
<b>Statistical Methods:</b> The pharmacokinetic parameters of digoxin were assessed by determining maximum drug concentration (C <sub>max</sub> ), time of maximal plasma concentration (T <sub>max</sub> ), AUC(0-t) following the collection of blood samples prior to dosing and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, 96, 120, and 144 hours following dose administration. The primary comparisons of interest were the ratios of "fed:fasted" for both the high fat regimen (C:A) and the high fiber regimen (B:A). For each pharmacokinetic parameter separately, subjects were included in the formal statistical analyses provided they received study medication and contributed evaluable pharmacokinetic data from at least two regimens. All subjects who received at least one dose of study medication were included in the evaluation of tolerability.  After log <sub>e</sub> -transformation, AUC(0-t) and C <sub>max</sub> of digoxin were separately analyzed by analysis of variance (ANOVA) using a mixed effects model with terms for sequence, period, and regimen (included as fixed effects) and subject (sequence) (included as a random effect). Point estimates and associated 90% confidence intervals for the differences C-A and B-A were constructed using the residual variance. These point estimates and confidence intervals were then exponentially backtransformed to obtain point estimates and associated 90% confidence intervals for the ratios C:A and B:A. T <sub>max</sub> was analyzed nonparametrically using the Wilcoxon's Matched Pairs Method. The point estimates and 90% confidence intervals for the median differences were calculated for the differences C-A and B-A.	
<b>Study Population:</b> Healthy adult males and females between 18 and 55 years of age, inclusive with a body weight >50 kg (110 pounds) and body mass index between 19 and 30kg/m <sup>2</sup> and Creatinine clearance of ≥80ml/min. Individuals with any clinically relevant abnormalities and ECG abnormalities were excluded from the study.	
<b>Disposition</b>	<b>Number of Subjects</b>
Total Screened	42
Total Screened But Not Used	18
- Did Not Meet Criteria	7
- Positive Urine Drug Screen	3
- Decided Not to Participate	6
- Study No Show	2

- Total Randomized/Enrolled	24			
- Total Withdrawn Prior to Dosing	0			
	<b>Regimen</b>			
	<b>A</b>	<b>B</b>	<b>C</b>	<b>Total</b>
Total Dosed	20	23	20	24
Total Completed	20	23	20	18
Total Withdrawn After Dosing	1	4	1	6
	<b>Demographics</b>			
	<b>All Subjects</b>			
Females: Males	12:12			
Mean Age, years (SD)	33 (11.4)			
White, n (%)	14 (58)			
	<b>Regimen</b>			
	<b>A</b>	<b>B</b>	<b>C</b>	<b>Total</b>
Safety Population	20	23	20	24
Pharmacokinetic Population	19	21	20	
<b>Pharmacokinetic Results:</b>				
When LANOXIN Elixir Pediatric was administered with a high fiber meal, both the rate and extent of absorption of digoxin were reduced relative to the fasted state. On average, AUC(0-t) and Cmax were reduced 21% and 46%, respectively, with a high fiber meal. When LANOXIN Elixir Pediatric was administered with a high fat meal, the rate of absorption of digoxin was reduced with no change in extent of absorption. On average, Cmax was decreased by 31% with a high fat meal.				
	<b>Regimen A N=19</b>	<b>Regimen B N=21</b>	<b>Regimen C N=20</b>	
AUC(0-t) (ng.h/mL) Geometric Mean (range)	28.2 (12.1-49.2)	22.4 (11.1-46.9)	30.3 (20.4-55.8)	
Cmax (ng/mL) Geometric Mean (range)	3.72 (1.60-5.28)	2.01 (1.16-3.05)	2.55 (1.42-3.74)	
Tmax (h) Median (range)	0.75 (0.50-1.50)	0.75 <sup>1</sup> (0.50-4.00)	0.75 <sup>2</sup> (0.50-2.00)	
<sup>1</sup> N=19, <sup>2</sup> N=18				
	<b>Comparison</b>	<b>Point Estimate</b>	<b>90% CI</b>	<b>CVw%</b>
AUC(0-t)	B:A	0.79	0.66, 0.94	32.4
Cmax	B:A	0.54	0.48, 0.62	24.8
Tmax	B-A	0.25 h	0.13 h, 0.50 h	
AUC(0-t)	C:A	1.07	0.90, 1.27	
Cmax	C:A	0.69	0.60, 0.79	
Tmax	C-A	0.13 h	-0.13 h, 0.38 h	
<b>Safety Results: Safety Population</b>				
	<b>Regimen A N=20</b>	<b>Regimen B N=23</b>	<b>Regimen C N=20</b>	
<b>Most Frequent Adverse Events (AEs) – On-Therapy</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	
Subjects with any AE(s), n (%)	3(15)	5 (22)	8 (40)	
Headache	2(10)	2 (9)	2 (10)	
<b>Serious Adverse Events (SAEs) - On-Therapy</b>				
<b>n (%) [n considered by the investigator to be related to study medication]</b>				
	<b>Regimen A</b>	<b>Regimen B</b>	<b>Regimen C</b>	
Subjects with non-fatal SAEs, n (%)	0	0	0	
	<b>n (%) [related]</b>	<b>n (%) [related]</b>	<b>n (%) [related]</b>	
	0	0	0	
Subjects with fatal SAEs, n (%)	0	0	0	
	<b>n (%) [related]</b>	<b>n (%) [related]</b>	<b>n (%) [related]</b>	
	0	0	0	
<b>Publications:</b> No Publications				

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