Journal of Clinical Pharmacy and Therapeutics (2002) **27**, 7–12

Absence of a pharmacokinetic interaction between digoxin and levofloxacin

S.-C. Chien MS, M. C. Rogge* PhD, R. R. Williams MD, J. Natarajan PhD, F. Wong MS and A. T. Chow PhD

Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ, USA

SUMMARY

Background: **Levofloxacin, a broad-spectrum fluoroquinolone, may enhance digoxin bioavailability by eliminating intestinal flora that metabolize digoxin. Moreover, levofloxacin, which is eliminated primarily by glomerular filtration and active tubular secretion, may alter the elimination rate of digoxin. Because of the narrow therapeutic index of digoxin, it is important to evaluate the potential for interaction with levofloxacin when administered concomitantly.**

Methods: **This was a placebo-controlled, randomized, double-blind, two-phase crossover study. Twelve healthy subjects (six males and six females) received 500 mg twice/day oral doses of levofloxacin or placebo for 6 days and a single oral dose of 0·4 mg digoxin on the morning of study day 5 along with levofloxacin or placebo.**

Results: **There was no significant effect of levofloxacin on the pharmacokinetics (C_{max}, AUC, and other disposition parameters) of oral digoxin. Steady-state levofloxacin absorption and disposition kinetics were also similar in the presence or absence of digoxin.**

Conclusions: **Results of this study suggest that an important pharmacokinetic interaction between levofloxacin and digoxin is unlikely to occur when administered concomitantly.**

Keywords: **digoxin, levofloxacin, pharmacokinetics**

Received 28 September 2001, Accepted 22 October 2001

Correspondence: A. T. Chow, Global Clinical Pharmacokinetics and Clinical Pharmacology Division, Johnson & Johnson Pharmaceutical Research & Development, L.L.C., 1000 Route 202, Raritan, NJ 08869, USA. Tel.: +1 908 704 4057; fax: +1 908 253 0448; e-mail: achow @prdus.jnj.com

*Current address: Immunex Corporation, Seattle, WA, USA

INTRODUCTION

Digoxin (Lanoxicaps®, GlaxoWellcome Inc., Research Triangle Park, NC, U.S.A.) is a preferred cardiac glycoside used in pharmacotherapy of congestive heart failure and severe chronic heart failure, and in atrial fibrillation with rapid ventricular response (1–3). Evaluation of potential drug interactions with digoxin is important because of its narrow therapeutic index. Antiarrhythmic drugs, such as quinidine and amiodarone, can markedly increase steady-state serum digoxin levels by reducing the renal clearance of digoxin (4, 5). Certain calcium channel-blocking drugs, particularly verapamil, have a similar effect (6). Drugs such as cholestyramine, antacid gels, kaolin-pectate, and certain chemotherapeutic agents have been found to decrease digoxin bioavailability (7–12).

Levofloxacin (Levaquin®, Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ, U.S.A.) is a broad-spectrum fluoroquinolone antibacterial approved for marketing in the United States and indicated for the treatment of acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, uncomplicated and complicated skin/skin structure infections, uncomplicated and complicated urinary tract infections, and acute pyelonephritis.

Antimicrobials may enhance digoxin bioavailability in some patients by eliminating intestinal flora that metabolize digoxin (13, 14). In addition to their potential interactions through disruption of intestinal flora, both digoxin and levofloxacin are primarily cleared by the kidneys, and the mechanism of renal clearance involves both glomerular filtration and tubular secretion (15, 16). Given the potential for interaction between these two drugs, which may be used concomitantly in some patients, this study was conducted to investigate potential drug interaction between levofloxacin and digoxin.

© 2002 Blackwell Science Ltd

MATERIALS AND METHODS

Subjects

Twelve normal, healthy subjects (six males and six females) between the ages of 18 and 55 were admitted to the study. Subjects had normal findings in pre-study medical history and physical examinations performed within 2 weeks of study entry, negative urine toxicology screen, and negative hepatitis B surface antigen. Haematologic, serum chemistry, urinalysis laboratory values, and electrocardiogram (ECG) findings were all within normal limits. All participants were within 30% of their ideal body weights. Key exclusion criteria included any presence of a significant gastrointestinal condition that could interfere with the absorption or disposition of the study medications, a history of allergy to a fluoroquinolone or cardiac glycoside, use of an investigational agent within 30 days of study entry, pregnancy or nursing. Potential subjects were also excluded if they used any medication, including over-the-counter drugs, within 3 days prior to administration of the first study dose, or suffered from an acute illness within 1 week of study entry. All subjects signed an informed consent form approved by the investigational review board. All procedures were in accord with the Helsinki Declaration of 1975.

Study design and treatment assignment

A placebo-controlled, randomized, double-blind, crossover Phase I study was conducted. Subjects (three males and three females in each sequence) were randomly assigned to one of two treatment sequences according to a computer-generated randomization schedule prepared by The R.W. Johnson Pharmaceutical Research Institute. At each treatment period, each subject received either 500 mg every 12 h of levofloxacin for 6 days or matching placebo every 12 h for 6 days. On study day 5, all subjects received a single 0·4-mg oral dose of digoxin as Lanoxicaps® with the morning dose of levofloxacin or placebo. Following a 6-day washout period, subjects were crossed over to receive the alternate treatment of levofloxacin or placebo. The total study duration was 21 days.

Each dose was administered with 8 oz of water. Subjects fasted for at least 8 h prior to and 4 h after administration of each dose on study days 4 and 5 of each treatment period; water was allowed *ad libitum* 2 h after dosing. Ingestion of alcohol or caffeine was not permitted during the study period. A normal diet was served throughout the study. Subjects were confined for the entire duration of the study.

Sample collection

Samples (5 mL) of venous blood for determination of plasma digoxin concentrations were collected from an indwelling catheter starting on day 5 of each treatment period, immediately prior to dosing (0 h), and then at the following times after the morning dose on day 5: 0·5, 1·0, 1·5, 2·0, 2·5, 3·0, 4·0, 6·0, 8·0, 12·0, 24·0, 36·0, 48·0, 72·0, and 96·0 h. On study day 5 of each treatment period, quantitative urine samples were collected pre-dose (−8 to 0 h) and at the following time intervals after the morning dose administration: 0–12, 12–24, 24–48, 48–72, and 72–96 h. A 20-ml aliquot from each collection was frozen at −20 °C until determination of urine digoxin concentrations.

In addition, on study days 4 and 5 of each treatment period, blood samples were collected for levofloxacin determination immediately prior to the morning dose and at the following times after the morning dose administration: 1·0, 1·5, 2·0, 4·0, 8·0, and 12·0 h. Blood samples were collected in heparinized tubes and centrifuged; the plasma was separated and stored at −20 °C until assayed. On study days 4 and 5 of each treatment period, urine was collected pre-dose (−8 to 0 h) and 0–12 h after administration of study medication in the morning to determine levofloxacin concentration.

Safety analysis

Subjects were monitored for adverse events throughout the study. Each treatment-emergent adverse event was assessed by the investigator as to severity (mild, moderate, or severe) and relationship to the study drug (definite, probable, possible, remote, or unlikely). A physical examination, including vital signs, was performed at baseline prior to treatment initiation and on day 9 of each treatment period. Routine clinical laboratory tests (haematology, chemistry, urinalysis) were performed pre-study and on days 1 and 9 of

each treatment period. On day 5 of each treatment period, ECG, blood pressure, and pulse rate were monitored at 0 h (immediately prior to dosing) and at 4, 8, 12, and 24 h after the digoxin dosing. Baseline ECG was obtained before the administration of digoxin in both periods (within 2 weeks prior to study day 1 in period I and 1 day prior to treatment initiation in period II).

Analytical procedures

Serum and urine samples were assayed for digoxin according to a specific and validated radioimmunoassay procedure (17). For plasma, the range of detection was linear from 0·10 to 4·80 ng/mL; the interday assay precision values (as percent coefficient of variation) for digoxin were consistently <4% and accuracy values were within 3% of target concentrations over the assay concentration range. For urine, the range of detection was linear from 0·10 to 5·24 ng/mL; the interday assay precision values were consistently <12%, and accuracy values were within 11% of target concentrations over the assay concentration range.

The concentration of total levofloxacin in plasma and urine was determined by a high-pressure liquid chromatography (HPLC) method (18). The procedure utilized a single step liquid–liquid extraction. A reversed phase C_{18} column was used to separate levofloxacin and the internal standard (ciprofloxacin). Elution was accomplished using a mobile phase consisting of copper (II) sulphate pentahydrate (5 mmol/L) containing isoleucine (10 mmol/L) : methanol (87·5 : 12·5, v : v) at a flow rate of 1·0 mL/min. Ultraviolet detection (330 nm) was used to measure peak area. For plasma, the range of detection was linear from 0·08 to 5·12 μg/mL; both the inter- and intra-assay precision values (as percentage coefficient of variation) for levofloxacin were <6%. For urine, the range of detection was linear from 25 to 2000 μg/mL; the inter- and intra-assay precision values for levofloxacin were each <9%. In both matrices, the accuracy was within 6% of target value over the assay concentration range.

Pharmacokinetic analysis

Plasma and urine concentration data for both digoxin and levofloxacin were analysed using standard non-compartmental methods on a Digital Equipment Corporation VAX 8600 computer system (Maynard, MA, U.S.A.). The individual peak plasma digoxin and levofloxacin concentrations (C_{max}) and time to reach peak concentrations (T_{max}) values were obtained by visual inspection of the plasma concentration vs. time. For single-dose digoxin, with and without levofloxacin, the following pharmacokinetic parameters were estimated: area under the plasma concentration–time curve measured by trapezoidal summation method with terminal phase extrapolation to infinite time ($AUC_{0-\infty}$), apparent total body clearance (CL/F) calculated as dose/$AUC_{0-\infty}$, elimination half-life at terminal disposition phase ($t_{1/2}$), cumulative amount recovered in the urine at 96 h post-dose (Ae_{0-96}), and renal clearance (CL_R) calculated as $Ae_{0-96}/AUC_{0-\infty}$ assuming urinary excretion of digoxin was essentially completed by 96 h post-dose. For levofloxacin, pharmacokinetic parameters, without (day 4) and with (day 5) concomitant digoxin, were determined: AUC_{0-12}, CL/F calculated as dose/AUC_{0-12}, $t_{1/2,}$ Ae_{0-12}, and CL_R calculated as Ae_{0-12}/AUC_{0-12}.

Statistical analysis

Comparison of digoxin pharmacokinetic parameters with and without concomitant levofloxacin was made using analysis of variance (ANOVA) models. The analysis of $AUC_{0-\infty}$ and C_{max} was performed on log-transformed data. The analysis of T_{max} was carried out on ranked values, and the remaining parameters were analysed in their original units. ANOVA models were fitted to the data with treatment sequence group, gender, treatment sequence group by gender interaction, subjects nested within treatment sequence group by gender interaction, treatment, period, and gender by treatment interaction. The treatment sequence group effect was tested at the 10% level. Period and treatment effects were tested at the 5% level. As gender by treatment interaction was not significant, the data were pooled and the ANOVA model was refitted without gender by treatment interaction term. The levofloxacin pharmacokinetics with or without concomitant administration of digoxin were summarized and compared descriptively.

Clinical safety data (adverse events, clinical laboratory tests, vital signs) were analysed using

the SAS statistics software package (SAS Institute, Cary, NC, U.S.A.). The overall incidence of adverse events was summarized by body system and by primary and secondary terms, by treatment. ANOVA for the crossover design was used to test for post-baseline changes in haematology, serum chemistry, and urinalysis parameters as well as for ECG readings. Post-baseline physical examination abnormalities, including vital sign abnormalities, were summarized and reviewed for possible clinical relevance. All statistical inferences regarding safety analyses were based on a Type I error rate of 0·05.

RESULTS

Population demographics

Twelve subjects (six males and six females) were enrolled, randomized, and treated, and completed the study. Ten subjects were Caucasian and two were African-American. Ages ranged from 19 to 54 years (mean ± SD = 32·9 ± 13·4 years) and weights ranged from 137 to 211 lb pounds (mean ± SD = 167·9 ± 25·2 lb). Demographic and baseline characteristics of the two treatment sequence groups were similar. All 12 subjects were included in the pharmacokinetic and safety analyses.

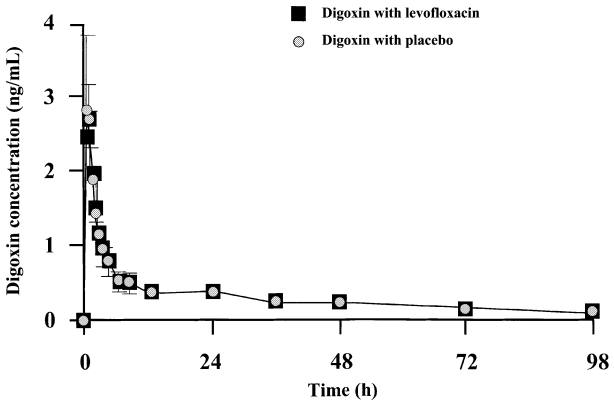

Fig. 1. Mean (±SD) serum digoxin concentration vs. time profiles in 12 healthy subjects receiving a single oral dose of 0·4 mg digoxin with concomitant administration of levofloxacin (■) or placebo (◎).

Pharmacokinetics

Because there was no significant treatment interaction by gender, pharmacokinetic parameter estimates for both genders were pooled for subsequent evaluations. Examination of mean plasma digoxin concentration vs. time profiles, with and without levofloxacin, reveal that the two curves are practically superimposable (Fig 1). Mean ± SD digoxin C_{max} concentrations with concomitant levofloxacin were 3·04 ± 0·68 ng/mL compared with 3·31 ± 1·02 ng/mL following concomitant placebo administration (Table 1). Mean digoxin T_{max} values were also not significantly different between the two treatments. Mean ± SD digoxin $AUC_{0-\infty}$ values, following the levofloxacin and placebo treatment periods, were 36·6 ± 8·48 and 37·0 ± 6·76 ng h/mL, respectively, and were nearly identical. Except for T_{max} values, all other digoxin pharmacokinetic estimates when given concomitantly with levofloxacin were within 8% of the corresponding values for digoxin administered with placebo (14% for T_{max}). There were no statistically significant differences in mean digoxin pharmacokinetic distribution and elimination parameters, with or without concomitant levofloxacin administration.

Table 1. Summary of digoxin pharmacokinetic parameter estimates in 12 healthy subjects[a]

	Digoxin with levofloxacin	Digoxin with placebo
C_{max} (ng/mL)	3·04 ± 0·68	3·31 ± 1·02
T_{max} (h)	0·8 ± 0·3	0·7 ± 0·3
$AUC_{0-\infty}$ (ng h/mL)	36·6 ± 8·48	37 ± 6·76
$t_{1/2}$ (h)	43·8 ± 6·8	43 ± 7·7
CL/F (mL/min)	195 ± 66·9	186 ± 35·2
CL_R (mL/min)	103 ± 19·1	99·2 ± 27·2
Ae_{0-96} (% dose)	55 ± 12	54 ± 17

[a]There were no statistically significant differences between the two treatment groups.

Mean levofloxacin plasma concentration–time curves in 12 subjects with and without concomitant digoxin administration are illustrated in Fig 2. Observed mean C_{max} and T_{max} values of 8·3 μg/mL and 1·3 h, respectively, were found following concomitant digoxin therapy compared with 8·0 μg/mL and 1·4 h, respectively, without digoxin administration. Mean $AUC_{0–12}$, CL/F, and $t_{1/2}$-values were also similar during the two treatment periods (Table 2). Overall, the pharmacokinetics of levofloxacin appeared to be similar, with or without concomitant digoxin administration.

Safety evaluation

Only one possibly drug-related adverse event was reported among the 12 subjects participating in the two-way crossover. One subject receiving levofloxacin reported a mild headache on study day 2, which disappeared without therapeutic intervention. No other adverse events reported were considered by the investigator to be related to levofloxacin or placebo administration.

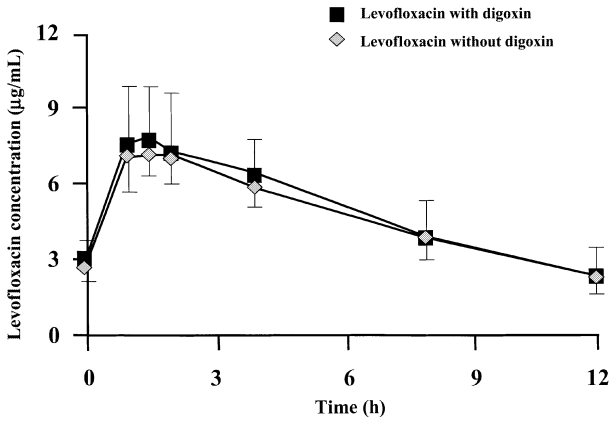

Fig. 2. Mean (±SD) deviation observed plasma levofloxacin concentration vs. time profiles following multiple twice daily doses of 500 mg levofloxacin with (■) or without (◇) concomitant administration of 0·4 mg digoxin.

DISCUSSION

Digoxin is metabolized to dihydrodigoxin and its corresponding aglycone, dihydrodigoxigenin; both are relatively inactive. The two metabolites appear to be made exclusively by bacteria in the gastrointestinal tract, probably in the colon (13). After certain antimicrobial therapy, these metabolites essentially disappear from the stool and urine, leading to an increase in the bioavailability of digoxin (14). Digoxin is mainly excreted into the urine by glomerular filtration and active tubular secretion.

Levofloxacin is a fluoroquinolone with a broad spectrum of antimicrobial activity. Levofloxacin as a zwitterion undergoes glomerular filtration as well as active cation and anion channels of renal tubular secretion (16). Therefore, it is possible that levofloxacin could influence the bioavailability and/or the elimination rate of digoxin. Absorption of levofloxacin is rapid and essentially complete as unchanged drug. The potential of digoxin influencing the pharmacokinetics of levofloxacin is highly unlikely and therefore is only a secondary objective of the study.

This study was mainly conducted to evaluate the pharmacokinetic drug interaction between levofloxacin and digoxin. To examine the potential of levofloxacin altering the bioavailability of digoxin, subjects were pre-treated with levofloxacin 500 mg twice daily for 4 days prior to co-administration of

Table 2. Summary of levofloxacin pharmacokinetic parameter estimates in 12 healthy subjects

	Levofloxacin without digoxin	Levofloxacin with digoxin
C_{max} (μg/mL)	8·03 ± 2·77	8·29 ± 1·54
T_{max} (h)	1·4 ± 0·4	1·3 ± 0·4
$AUC_{0–12}$ (μg h/mL)	9·6 ± 19·9	62·5 ± 12·2
$t_{1/2}$ (h)	8·3 ± 6·1	6·9 ± 0·9
CL/F (mL/min)	181 ± 156	138 ± 27
CL_R (mL/min)	186 ± 64	194 ± 61
$Ae_{0–12}$ (% dose)	74 ± 34	97 ± 26

digoxin with levofloxacin on day 5. The potential of competitive active tubular secretion of digoxin by levofloxacin was also examined under steady-state multiple dosing conditions of levofloxacin. In this study, C_{max}, AUC, CL/F and $t_{1/2}$-values of digoxin were almost identical following concomitant therapy of either levofloxacin or placebo (Table 1). The digoxin pharmacokinetics determined in this study, with concomitant levofloxacin or placebo, were comparable with those reported in the literature given as a monotherapy (19) or in combination with other fluoroquinolones (20, 21). The plasma concentration vs. time profile of levofloxacin also appeared superimposable, with or without the concomitant therapy of digoxin (Fig 2). Results of this study thus suggest that a clinically important pharmacokinetic interaction between levofloxacin and digoxin is unlikely to occur when administered concomitantly.

REFERENCES

1. Smith TW, Braunwald E. (1984) The management of heart failure. In: Braunwald, E, ed. *Heart Disease: a Textbook of Cardiovascular Medicine*. 2nd edn. Philadelphia: W.B. Saunders, 503–559.
2. Jaeschke R, Oxman A, Guyatt G. (1990) To what extent do congestive heart failure patients in sinus rhythm benefit from digoxin therapy? A systematic overview and meta-analysis. *American Journal of Medicine*, **88,** 279–286.
3. Smith TW. (1988) Digitalis. Mechanism of action and clinical use. *New England Journal of Medicine*, **318,** 358–365.
4. Ejvinsson G. (1978) Effect of quinidine on plasma concentrations of digoxin. *British Medical Journal*, **1,** 279–280.
5. Moysey JO, Jaggarao NSV, Grundy EN, Chamberlain DA. (1981) Amiodarone increases plasma digoxin concentrations. *British Medical Journal*, **282,** 272.
6. Klein HO, Lang R, Weiss E, Di Segni E, Libhaber C, Guerrero J, Kaplinsky E. (1982) The influence of verapamil on serum digoxin concentration. *Circulation*, **65,** 998–1003.
7. Caldwell JH, Greenberger NJ. (1971) Interruption of the enterohepatic circulation of digitoxin by cholestyramine. *Journal of Clinical Investigation*, **50,** 2626–2637.
8. Smith TW. (1973) New approaches to the management of digitalis intoxication. In: Storstein O, ed. *Symposium on Digitalis*. Oslo: Glydenal Norsk Forlag, 312–323.
9. Binnion PF. (1973) Absorption of different commercial preparations of digoxin in the normal human subject and the influences of antacid, antidiarrhoeal, and ion-exchange agents. In: Storstein O, ed. *Symposium on Digitalis*. Oslo: Glydenal Norsk Forlag, 216–223.
10. Brown DD, Juhl RP, Warner SL. (1978) Decreased bioavailability of digoxin due to hypocholesterolemic interventions. *Circulation*, **58,** 164–172.
11. Brown DD, Juhl RP. (1976) Decreased bioavailability of digoxin due to antacids and kaolin-pectin. *New England Journal of Medicine*, **295,** 1034–1037.
12. Kuhlmann J, Zilly W, Wilke J. (1981) Effects of cytostatic drugs on plasma level and renal excretion of B-acetyl digoxin. *Clinical Pharmacology and Therapeutics*, **30,** 518–527.
13. Lindenbaum J, Maulitz RM, Butler VP Jr (1976) Inhibition of digoxin absorption by neomycin. *Gastroenterology*, **71,** 391–404.
14. Lindenbaum J, Rund DG, Butler VP Jr, Tse-Eng D, Saha JR. (1981) Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. *New England Journal of Medicine*, **305,** 789–794.
15. Alderman CP, Allcroft PD. (1997) Digoxin–itraconazole interaction: possible mechanisms. *Annals of Pharmacotherapy*, **31,** 438–440.
16. Fish DN, Chow AT. (1997) The clinical pharmacokinetics of levofloxacin. *Clinical Pharmacokinetics*, **32,** 101–119.
17. Khan M, Pham K. (1994) Radioimmunoassay validation report for the determination of digoxin in human plasma/urine. Data on File: Phoenix International, Montreal, Canada and The R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ.
18. Wong FA, Juzwin SJ, Flor SC. (1997) Rapid stereospecific high-performance liquid chromatographic determination of levofloxacin in human plasma and urine. *Journal of Pharmaceutical and Biomedical Analysis*, **15,** 765–771.
19. Peter HH, Hartmann D. (1991) Pharmacokinetics of digoxin and main metabolites/derivatives in healthy humans. *Therapeutic Drug Monitoring*, **13,** 381–401.
20. Johnson RD, Dorr MB, Hunt TL, Conway S, Talbot GH. (1999) Pharmacokinetic interaction of sparfloxacin and digoxin. *Clinical Therapeutics*, **21,** 368–379.
21. Vousden M, Allen A, Lewis A, Ehren N. (1999) Lack of pharmacokinetic interaction between gemifloxacin and digoxin in healthy elderly volunteers. *Chemotherapy*, **45,** 485–490.