Evaluation of the pharmacokinetics of digoxin in healthy subjects receiving etoricoxib

Jules I. Schwartz, Nancy G. B. Agrawal,¹ Martin Wehling,²
Bret J. Musser, Carol P. Gumbs, Nicole Michiels, Marina De Smet &
John A. Wagner

Merck Research Laboratories, Rahway, NJ and ¹Merck & Co., Inc., West Point, PA, USA, and ²University of Heidelberg, Heidelberg, Germany

Correspondence

Dr Jules I. Schwartz, Merck Research
Laboratories, 126 E. Lincoln Avenue, PO
Box 2000, RY34-A552, Rahway, NJ
07065-0900, USA.
Tel: + 1 732 594 5838
Fax: + 1 732 594 5405
E-mail: jules_schwartz@merck.com

Keywords

digoxin, etoricoxib, pharmacokinetics

Received

29 October 2007

Accepted

10 August 2008

Published OnlineEarly

24 September 2008

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Digoxin is a well-recognized inotropic agent with a narrow therapeutic index.
- Nonsteroidal anti-inflammatory drugs, including the selective cyclooxygenase-2 inhibitor etoricoxib, are very likely to be used in patients receiving digoxin due to the similar populations requiring the drugs.
- Digoxin drug interactions should be assessed and described to clinicians when new drugs become available.

WHAT THIS STUDY ADDS

- This study is the first to provide the practitioner with a detailed description of the influence of etoricoxib on the pharmacokinetics of digoxin.
- Due to the methods used, it shows that etoricoxib does not interfere with P-glycoprotein in the kidney, a method of digoxin disposition.
- In addition, this paper provides confidence to the practitioner that there will be no clinically important reason to avoid the combination of the two drugs.

AIMS

Digoxin is a commonly prescribed cardiac glycoside with a narrow therapeutic index. The aim was to investigate whether the cyclooxygenase-2 selective nonsteroidal anti-inflammatory drug etoricoxib affects the steady-state pharmacokinetics of digoxin.

METHODS

This was a double-blind, randomized, placebo-controlled, two-period cross-over study. In each period, 14 healthy volunteers ranging in age from 21 to 35 years received oral digoxin 0.25 mg daily and were randomized to either etoricoxib 120 mg or matching placebo tablets once daily for 10 days. Trough digoxin plasma concentrations were analysed by linear regression to examine digoxin accumulation over time.

RESULTS

The geometric mean ratios (etoricoxib/placebo) for AUC_{0-24hr} , C_{max} and urinary excretion were 1.06 (90% confidence interval 0.97, 1.17), 1.33 (1.21, 1.46) and 1.10 (1.00, 1.20), respectively. The median (range) for digoxin T_{max} (h) values with etoricoxib and placebo were 0.5 (0.5, 1.5) and 1.0 (0.5, 1.5), respectively. Steady-state digoxin plasma concentrations were achieved by day 7 in each treatment period. No serious adverse experiences were reported.

CONCLUSIONS

Although etoricoxib 120 mg did produce an approximately 33% increase in digoxin C_{max} , this increase does not appear to be clinically meaningful, as cardiotoxicity with digoxin has been associated with elevations in steady-state rather than peak concentrations. From these results, it appears that etoricoxib does not cause any changes in digoxin steady-state pharmacokinetics that would necessitate a dose adjustment.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are highly effective for the treatment of pain and inflammation and are one of the most widely prescribed classes of drug worldwide. It has been estimated that as many as 70% of people >65 years old take at least one dose of an NSAID each week. Approximately one-third of this age group takes at least seven doses of an aspirin or non-aspirin NSAID per week [1]. Cyclooxygenase-2 (COX-2)-selective NSAIDs were developed as a strategy to reduce the risk of gastrointestinal (GI) clinical events, such as bleeding ulcers, that are associated with the inhibition of COX-1 in the GI mucosa and COX-1-dependent platelet function by traditional NSAIDs.

Etoricoxib is a COX-2-selective NSAID [2] that is effective for the treatment of acute pain and the pain and inflammation associated with chronic conditions such as osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and lower back pain [3]. Because of its COX-2 selectivity, its long-term use is associated with a lower risk of upper GI clinical events compared with traditional NSAIDs [4–6].

Because of the potential widespread use of this COX-2-selective NSAID in patient populations with comorbid conditions who are also taking other therapies, it was important to evaluate potential pharmacokinetic interactions of etoricoxib with commonly prescribed medications having a narrow therapeutic index. Here we report the results of a study specifically designed to examine potential pharmacokinetic interactions of etoricoxib 120 mg with the cardiac glycoside digoxin, commonly prescribed for cardiac arrhythmias, mostly atrial fibrillation, and congestive heart failure, predominantly in the elderly population. Although no significant drug interactions were predicted, digoxin and etoricoxib are likely to be co-administered in this population, who commonly need both analgesic and cardiac medication. The elimination half-life of digoxin is approximately 36 h, and clearance is primarily via passive glomerular filtration and P-glycoprotein (P-gp)-mediated active tubular secretion in the kidney [7]. Traditional NSAIDs and COX-2-selective NSAIDs inhibit synthesis of prostaglandins and have been shown to have similar effects on renal function, as measured by minor dose-dependent changes in urinary prostaglandin secretion, glomerular filtration rate and sodium retention [8–13]. Due to digoxin's low therapeutic index

and the potential of etoricoxib to inhibit renal function, and thus affect digoxin clearance, it was necessary to determine whether co-administration of etoricoxib could alter the pharmacokinetics of digoxin.

Methods

Subjects

The protocol for this study was approved by the Institutional Review Board for the clinical study centre (Institut für Klinische Pharmakologie, Klinikum Mannheim, Germany). All subjects provided written informed consent prior to participation.

We enrolled 14 subjects, eight men and six women, with a mean age of 21.4 years (Table 1). All subjects were determined to be healthy based on their medical history, physical examination, vital signs, electrocardiogram (ECG) and routine laboratory tests. Subjects were required to be within 30% of ideal body weight based on a standard height and weight table [14]. Persons with a past history of GI abnormalities except for uncomplicated appendectomy, cholecystectomy or colorectal surgery for polyps, nonmalignant tumours or diverticular obstruction were excluded. Subjects were also excluded if their sitting systolic blood pressure (BP) was >140 mmHg or diastolic BP >90 mmHg. Women of child-bearing potential enrolled into the study were determined to be in the nongravid state based on serum β -human chorionic gonadotropin measurements and were instructed to use barrier contraceptives throughout the trial.

Subjects were not allowed to take nonstudy medications for 2 weeks prior to study start until the completion of the trial, except for paracetamol for minor ailments at the discretion of the investigator. Subjects were also instructed to avoid excess alcohol and strenuous physical activity for the duration of the study and follow-up period. Subjects were not allowed to drink beverages containing quinine or >6 cups of coffee or equivalent intake of caffeine per day.

Study design

This was a randomized, double-blind, placebo-controlled, two-period cross-over study (protocol 030). A wash-out of ≥ 14 days (equivalent to 7–9 half-lives, given the digoxin half-life of 1.5–2 days) between periods minimized the

Table 1

Baseline demographics of the study subjects

Group	Mean (range) Age (years)	Mean (range) Weight (kg)	Mean (range) Height (cm)
Men (<i>n</i> = 8)	26.3 (21–35)	75.4 (60.0–87.3)	179.5 (174.0–190.0)
Women (<i>n</i> = 6)	26.0 (23–29)	65.2 (54.0–72.0)	166.0 (160.0–172.0)
Total (<i>n</i> = 14)	26.1 (21–35)	71.0 (54.0–87.3)	173.7 (160.0–190.0)

possibility of any carryover effects. The study was specifically designed to test the primary hypothesis that the 90% confidence interval (CI) of the steady-state area under the plasma digoxin concentration–time curve (AUC_{0-24h}) ratio [(digoxin + etoricoxib)/(digoxin + placebo)] would be contained in the interval 0.8–1.25.

During each 10-day period, subjects received daily oral doses of digoxin 0.25 mg (Lanoxin™ tablets) and either etoricoxib 120 mg, given as one 60-mg and two 30-mg tablets, or matching placebo tablets once daily. A computerized allocation schedule was used to assign subjects to treatment groups. Subjects were required to fast from food or drink except water for 8 h preceding the first and last doses. Starting on day 1, all subjects received their study medication with 240 ml of water between 08.00 h and 09.00 h each morning under the supervision of study personnel. Breakfast and lunch were served 2 and 6 h after dosing, respectively, on days 1–9. On day 10, a lunch 4 h after dosing and dinner 10 h postdose were served. At the discretion of the investigator, subjects were allowed to leave the clinical research unit after the 6-h postdose ECG was performed on days 1–9. On day 10, subjects were required to remain in the clinical research unit until all procedures were completed over the 24-h postdose period.

ECGs and vital signs were monitored prior to and following dosing at predefined intervals on days 1–9. Serum electrolytes (potassium, magnesium, calcium) were measured on days 4, 7 and 9. Blood samples for plasma digoxin analysis were collected in heparinized glass tubes predose on days 1, 4, 7, 8, 9, 10 and 11 and at 0 h (predose digoxin), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h after the digoxin dose on day 10. Samples were centrifuged and plasma aliquoted into new containers and stored at -20°C until analysed. On day 4 only, plasma digoxin levels were determined as quickly as possible after the blood draw at a local laboratory. This was performed to ensure that plasma trough concentrations of digoxin had not exceeded 3 ng ml^{-1} .

The total urinary recovery of digoxin was determined for each subject. Urine samples were collected for the following intervals: 2 h predose on day 1 and 0–6, 6–12 and 12–24 h after the digoxin dose on days 10–11.

Concentrations of digoxin in urine and plasma were determined using a radioimmunoassay as previously described [15]. The lower limit of detection of the assay was 0.1 ng ml^{-1} . For measurements of digoxin in plasma, inter-day variation was assessed by preparing quality control (QC) standards of digoxin in plasma of approximately 0.5, 0.9 and 2 ng ml^{-1} ; these QC standards were divided into aliquots of 0.3 ml and stored frozen at -20°C until analysis. The mean concentrations of digoxin in plasma were determined by analysing replicate ($n = 6$) QC standards, giving $0.50 \pm 0.04\text{ ng ml}^{-1}$ (mean $\pm$ SD), coefficient of variation (CV) = 8.7% for 0.5 ng ml^{-1} , $0.89 \pm 0.06\text{ ng ml}^{-1}$, CV = 6.3% for 0.9 ng ml^{-1} , and $2.04 \pm 0.08\text{ ng ml}^{-1}$, CV = 3.8% for 2 ng ml^{-1} . QC standards in plasma were assayed daily

($n = 19$ days) with study samples, giving values of $0.54 \pm 0.04\text{ ng ml}^{-1}$, CV = 8.1%, $0.82 \pm 0.05\text{ ng ml}^{-1}$, CV = 6.2% and $2.20 \pm 0.08\text{ ng ml}^{-1}$, CV = 3.6%. For measurement of digoxin in urine, variation was assessed by preparing QC standards of digoxin in urine of approximately 1.6, 10 and 40 ng ml^{-1} ; these QC standards were divided into aliquots of 0.3 ml and stored frozen at -20°C until analysis. The controls of 10 and 40 ng ml^{-1} were diluted 10-fold. The mean concentration of digoxin in urine was determined by analysing replicate ($n = 6$) QC standards, giving $1.63 \pm 0.10\text{ ng ml}^{-1}$, CV = 6.4% for 1.6 ng ml^{-1} , $10.00 \pm 0.86\text{ ng ml}^{-1}$, CV = 8.6% for 10 ng ml^{-1} , and $36.68 \pm 1.57\text{ ng ml}^{-1}$, CV = 4.3% for 40 ng ml^{-1} . QC standards in urine were assayed daily ($N = 6$ days), yielding values of $1.60 \pm 0.08\text{ ng ml}^{-1}$, CV = 5.2%, $10.00 \pm 0.43\text{ ng ml}^{-1}$, CV = 4.3%, and $37.91 \pm 1.45\text{ ng ml}^{-1}$, CV = 3.8%.

Pharmacokinetic parameters

Actual sampling times relative to the timing for dosing on day 10 were used to estimate pharmacokinetic parameters for immunoreactive digoxin for each treatment: AUC_{0-24h} , maximum concentration of drug observed in the plasma ($C_{\max}$), and time to reach maximum concentration ($T_{\max}$). The AUC_{0-24h} was calculated using the linear trapezoidal method. The values for $C_{\max}$ and $T_{\max}$ were obtained by inspection of the concentration–time data during actual sampling times. Concentration values in concentration–time profiles that fell below the assay's limit of quantification (0.1 ng ml^{-1}) were replaced by concentration values of one-half of the limit of quantification (0.05 ng ml^{-1}) prior to pharmacokinetic analysis. Urinary concentrations and urine volumes from individual collection intervals were used to calculate the total recovery of immunoreactive digoxin in urine over 24 h.

Sample size and data analysis

Sample size calculations Sample size calculations relied on a pooled estimate of the within-subject SD of the AUC_{0-24h} of $0.153\text{ (ln } \mu\text{g h ml}^{-1})$. This was derived from three previous clinical trials that examined potential drug interactions with digoxin [16–18]. A sample size of 14 subjects provided at least 93.9% probability of yielding 90% CIs for the (etoricoxib + digoxin)/(placebo + digoxin) geometric mean ratio (GMR) for AUC_{0-24h} of 0.80–1.25 if the true GMR was 1.0. There was 80% power to detect a GMR within 0.94–1.07 with a 90% CI of 0.80–1.25.

Analysis of pharmacokinetic parameters Digoxin steady-state pharmacokinetic parameters were analysed using an ANOVA model appropriate for a two-period, crossover design. The ANOVA model included terms for sequence, subject-within-sequence, treatment, and period. A log transformation was applied to the AUC_{0-24h} data. The normality assumption was tested using the Shapiro–Wilk statistic; the homogeneity of variance assumption was evaluated using graphical methods. Similar methodology

was applied to $C_{\max}$, which was log transformed, and to $T_{\max}$, which was ranked prior to the ANOVA model. Slight nonconstant variance was apparent in a residual plot for $C_{\max}$. Transforming $C_{\max}$ to $1/(C_{\max})^2$ in the ANOVA produced a model that met all assumptions; however, the inference from that model was not substantially different from that using $\ln[C_{\max}]$, indicating that the initial ANOVA model was robust to the nonconstant variance. Thus, this model was not pursued, and only results from the log transformation of $C_{\max}$ are provided. To answer the primary hypothesis, a 90% CI based on the *t*-distribution was generated from the above ANOVA model for the AUC_{0-24h} GMR (digoxin + etoricoxib)/(digoxin + placebo). This interval was compared with the clinically meaningful bounds of (0.80, 1.25). A similar interval was constructed for $C_{\max}$.

Total urinary excretion of immunoreactive digoxin after concomitant use of either etoricoxib or placebo was compared using an ANOVA model similar to that used for AUC_{0-24h} . The normality assumption was tested using the Shapiro–Wilk statistic; the homogeneity of variance assumption was evaluated using graphical methods. The assumptions were satisfied. The achievement of steady state was assessed by determining the day after which the trough concentrations were approximately constant. For each day on which the trough concentration was measured (days 4 and 7–11), plasma concentrations were modelled as a linear function of time (i.e. using linear regression). This regression model was repeated by dropping each successive day (starting with dropping day 4) until the slope was not significantly different from 0.0. This analysis was done within each treatment group and used a model that included terms for subject [13 degrees of freedom (d.f.)] and day (1 d.f.).

Results

All 14 subjects completed the trial. The slope of the relationship between plasma trough concentrations of digoxin (predose) vs. study day on days 7, 8, 9, 10 and 11 for subjects in either treatment group did not differ from 0 ($P > 0.200$), indicating that steady-state digoxin concentrations in plasma were obtained prior to the pharmacokinetic evaluations on day 10. On average, steady-state plasma concentrations of immunoreactive digoxin were attained by day 7.

The mean plasma concentration–time profiles for immunoreactive digoxin in the presence and absence of concomitant treatment with etoricoxib 120 mg are displayed in Figure 1. The plasma immunoreactive digoxin geometric mean AUC_{0-24h} values for digoxin plus etoricoxib and digoxin plus placebo were 13.3 and 12.5 ng h ml⁻¹, respectively. The observed difference in the digoxin AUC_{0-24h} during etoricoxib treatment was not significant ($P = 0.246$). The GMR for AUC_{0-24h} was 1.06 with a 90% CI of (0.97, 1.17). The 90% CI was within the prespecified clinical

Figure 1

Mean ($\pm$ SD) concentrations of immunoreactive digoxin in plasma following administration of daily doses of 0.25 mg digoxin and 120 mg etoricoxib or placebo for 10 days. Etoricoxib (●); placebo (○)

interval of (0.80, 1.25), the limits generally accepted for bioequivalence. The highest GMR observed for this parameter was 1.26.

There was a modest but statistically significant ($P < 0.001$) increase in digoxin $C_{\max}$ concentration when administered with etoricoxib 120 mg (Figure 1, Table 2). The GMR for $C_{\max}$ was 1.33 (90% CI 1.21, 1.46). This increase in digoxin plasma concentration was no longer apparent beyond 4 h post dose. There was no difference in median $T_{\max}$ values for digoxin when administered with etoricoxib and placebo (0.5 h and 1.0 h, respectively; $P = 0.087$).

Total urinary excretion of immunoreactive digoxin on day 10 is summarized in Table 2. There was no difference in geometric mean excretion between the etoricoxib and placebo groups. The GMR for urinary excretion of digoxin was 1.10 (90% CI 1.00, 1.21; $P = 0.086$).

Safety

All patients received ECGs 6 h following dosing, and no clinically significant deviations were observed. Nine subjects experienced a total of 15 adverse experiences, nine (five etoricoxib, four placebo) of which were judged by the investigator to be possibly drug-related. These adverse events included headache, bitter taste sensation, and nausea.

Discussion

Digoxin is frequently used to treat arrhythmias, mostly atrial fibrillation, and heart failure. Because digoxin has a narrow therapeutic index and the possibility exists that both etoricoxib and digoxin may be prescribed to the same patients, this study was conducted to investigate the effect of etoricoxib 120 mg on the pharmacokinetics of digoxin. The 120-mg dose of etoricoxib is the dose recom-

Table 2

Summary statistics for digoxin AUC_{0-24h} , C_{max} , T_{max} and urinary excretion following a single dose of 0.25 mg oral digoxin in healthy volunteers ($n = 14$) receiving daily oral doses of etoricoxib 120 mg or placebo

Parameter Day 10	Digoxin + Etoricoxib	Digoxin + Placebo	CV*	GMR Etoricoxib/placebo	90% CI for GMR
AUC_{0-24h} (ng h ml ⁻¹)	13.3 ± 4.25‡	12.5 ± 2.38‡	13.6%	1.06	(0.97, 1.17)
C_{max} (ng ml ⁻¹)	1.76 ± 0.52‡	1.32 ± 0.18‡	14.4%	1.33	(1.21, 1.46)
T_{max} (h)	0.5 (0.5, 1.5)†	1.0 (0.5, 1.5)†			
Urinary excretion (µg)	119.5 ± 15.30‡	109.0 ± 16.90‡	13.1%	1.10	(1.00, 1.20)

AUC, Area under the plasma concentration–time curve; C_{max} , maximum concentration of drug observed in the plasma; T_{max} , time to reach maximum concentration; GMR, geometric mean ratio; CI, confidence interval. *Coefficient of variation (CV) = $100 \times \text{root mean square error from the analysis of variance (ANOVA) model (within-subject variation)}$. Ranges were 0.59–1.26 for AUC, 1.00–2.18 for C_{max} . †Median (min, max). ‡Geometric mean ± back-transformed SD. The SD was computed as follows: $SQRT(EXP(STD**2)*(EXP(STD**2)-1))$ (Back-Transformed Mean), where STD is the log-scale SD.

mended for the treatment of acute pain and active gouty arthritis. It is greater than the highest daily dose (90 mg) recommended for chronic use [3]. The 0.25-mg chronic oral dose of digoxin was expected to and did result in readily detectable plasma immunoreactive digoxin concentrations, with no serious adverse experiences. Digoxin was administered together with etoricoxib 120 mg in order to maximize the probability of detecting any drug interaction if patients took the two drugs simultaneously. No interaction was expected, as NSAIDs, including the COX-2-selective inhibitor rofecoxib, have not been shown to have clinically important interactions when administered concomitantly with digoxin [19, 20].

Examination of the mean concentration–time profiles and the individual pharmacokinetic parameters in the current study revealed that etoricoxib 120 mg has no clinically meaningful effect on immunoreactive digoxin pharmacokinetics. Steady-state AUCs of immunoreactive digoxin were similar between etoricoxib 120 mg and placebo treatments. Additionally, the individual digoxin AUC_{0-24h} GMR were similar, with the exception of one subject who had an AUC_{0-24h} GMR of 0.59. Excluding data from this subject resulted in a GMR for the remaining subjects combined of 1.12 (90% CI 1.08, 1.16), which was still within the prespecified 90% CI. No explanation is apparent for the decreased digoxin levels observed in this subject since all study drug doses were witnessed. The highest GMR for digoxin AUC_{0-24h} was 1.26. All other subjects had GMRs of ≤ 1.21 for this pharmacokinetic parameter.

Digoxin is a substrate for P-gp, an energy-dependent efflux pump that regulates the renal tubular secretion of digoxin. P-gp plays a significant role in excreting drugs into urine, so inhibition of the transporting function of P-gp can cause clinically significant drug interactions. Other drugs that inhibit P-gp, including ciclosporin, erythromycin, clarithromycin, propafenone, itraconazole, amiodarone, verapamil and diltiazem, can inhibit digoxin renal elimination and increase digoxin plasma concentration. [21] Whether etoricoxib is a substrate or inhibitor of P-gp has not been tested. Urinary recovery of immunoreactive

digoxin in the present study was similar between treatments, however, suggesting that etoricoxib 120 mg does not alter digoxin renal clearance and thus does not meaningfully influence P-gp-mediated transport.

Mean immunoreactive digoxin trough concentrations (days 7–11) were similar between placebo and etoricoxib treatments. Examination of the mean immunoreactive digoxin trough concentrations showed that steady state was achieved by day 7 of multiple dosing when either etoricoxib 120 mg or placebo were administered concurrently with digoxin.

Co-administration of etoricoxib 120 mg did produce a modest increase in digoxin C_{max} (approximately 33%). Although the reason for this increase is unclear, it could potentially be due to a faster rate of drug absorption. This increase in C_{max} was not seen in a similar study of the effect of rofecoxib, another COX-2-selective NSAID, on digoxin pharmacokinetics, so it does not appear to be a class effect [20]. This increase in plasma digoxin concentration observed during etoricoxib treatment was transient and no longer apparent beyond 4 h post dose. In fact, nearly identical plasma concentrations for digoxin were observed in the presence and absence of etoricoxib treatment over the 4–24 h postdose period. In clinical practice, blood samples for therapeutic drug monitoring of digoxin are drawn at least 6 h after administration of the last dose of digoxin in order to ensure adequate distribution between plasma and myocardial compartments [7, 22, 23]. Hence, samples obtained during distribution (<6 h) are thought not to be interpretable with regard to prediction of digoxin toxicity [7, 22, 23]. Also, evidence in dogs suggests that the cardiotoxic effect of digoxin is related to elevated steady-state serum concentrations and not to transient increase in peak concentrations, as seen here [24].

In the present study, the digoxin T_{max} value was ≤ 1.5 h post dose for all subjects in all treatment periods. Thus, in clinical practice, the modest transient increases in digoxin concentrations observed around T_{max} during etoricoxib treatment, without any clinically relevant accompanying increase in steady-state AUCs, are unlikely to result in digoxin toxicity or to be of clinical relevance.

Etoricoxib 120 mg, administered either alone or in combination with digoxin, was well tolerated in this study. In particular, no clinically significant deviations were observed in ECGs obtained 6 h after dosing, the time of peak pharmacodynamic activity of digoxin [7].

Once-daily co-administration of etoricoxib 120 mg and digoxin 0.25 mg was well tolerated in this small study performed in healthy volunteers. In the recently completed etoricoxib Multinational Etoricoxib and Diclofenac Long-term (MEDAL) clinical trials programme [25, 26] enrolling >34 000 patients with osteoarthritis or rheumatoid arthritis, daily etoricoxib 60 or 90 mg for a mean duration of 18 months was demonstrated to have comparable risk of thrombotic cardiovascular events vs. the traditional NSAID diclofenac 150 mg. However, in the MEDAL programme, important increases in renovascular end-points (e.g. fluid retention and blood pressure) were observed with etoricoxib compared with diclofenac. Specifically, the incidence of confirmed congestive heart failure (etoricoxib 90 mg) and discontinuations due to hypertension (etoricoxib 60 and 90 mg) were higher with etoricoxib [26]. Due to its effects on the renovascular system, etoricoxib use is contraindicated in patients with New York Heart Association grade II–IV congestive heart failure.

In conclusion, etoricoxib 120 mg co-administered with digoxin 0.25 mg does not produce clinically important effects on the steady-state plasma AUC_{0-24h} , T_{max} or urinary excretion of immunoreactive digoxin. Although co-administration of etoricoxib 120 mg did produce a modest increase in digoxin C_{max} (approximately 33%), this increase was not thought to be clinically meaningful, as plasma digoxin concentrations returned to the levels seen for co-administration with placebo over the 4–24-h post-dose period. Based on these pharmacokinetic data in healthy volunteers, no dose adjustment of digoxin appears necessary when co-administered with etoricoxib 120 mg for patients where the use of either agent is not contraindicated.

Competing interests

J.I.S. N.G.B.A., B.J.M., C.P.G., N.M., M.D.S. and J.A.W. are employees of Merck & Co., Inc. and may own stock or hold stock options in the company.

This study was supported by Merck Research Laboratories. The authors thank Paul Cavanaugh, Carolyn Hustad and Jennifer Pawlowski of Merck Research Laboratories for assistance with preparation of the manuscript.

REFERENCES

- 1 Talley NJ, Evans JM, Fleming KC, Harmsen WS, Zinsmeister AR, Melton LJ III. Nonsteroidal antiinflammatory drugs and dyspepsia in the elderly. *Dig Dis Sci* 1995; 40: 1345–50.
- 2 Dallob A, Hawkey CJ, Greenberg H, Wight N, De Schepper P, Waldman S, Wong P, DeTora L, Gertz B, Agrawal N, Wagner J, Gottesdiener K. Characterization of etoricoxib, a novel, selective COX-2 inhibitor. *J Clin Pharmacol* 2003; 43: 573–85.
- 3 Matsumoto AK, Cavanaugh PF Jr. Etoricoxib. *Drugs Today* 2004; 40: 395–414.
- 4 Laine L, Curtis SP, Cryer B, Kaur A, Cannon CP. Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2007; 369: 465–73.
- 5 Hunt RH, Harper S, Watson DJ, Yu C, Quan H, Lee M, Evans JK, Oxenius B. The gastrointestinal safety of the COX-2 selective inhibitor etoricoxib assessed by both endoscopy and analysis of upper gastrointestinal events. *Am J Gastroenterol* 2003; 98: 1725–33.
- 6 Hunt RH, Harper S, Callegari P, Yu C, Quan H, Evans J, James C, Bowen B, Rashid F. Complementary studies of the gastrointestinal safety of the cyclo-oxygenase-2-selective inhibitor etoricoxib. *Aliment Pharmacol Ther* 2003; 17: 201–10.
- 7 Mutnick AH. Digoxin. In: *Therapeutic Drug Monitoring*, ed Schumacher GE. Norwalk, CT: Appleton & Lange, 1995; 469–91.
- 8 Harris RC Jr. Cyclooxygenase-2 inhibition and renal physiology. *Am J Cardiol* 2002; 89: 10D–17D.
- 9 Gertz BJ, Krupa D, Bolognese JA, Sperling RS, Reicin A. A comparison of adverse renovascular experiences among osteoarthritis patients treated with rofecoxib and comparator non-selective non-steroidal anti-inflammatory agents. *Curr Med Res Opin* 2002; 18: 82–91.
- 10 Curtis SP, Ng J, Yu Q, Shingo S, Bergman G, McCormick CL, Reicin AS. Renal effects of etoricoxib and comparator nonsteroidal anti-inflammatory drugs in controlled clinical trials. *Clin Ther* 2004; 26: 70–83.
- 11 Schwartz JI, Vandormael K, Malice MP, Kalyani TN, Lasserter KC, Holmes GB, Gertz BJ, Gottesdiener KM, Laurenzi M, Redfern KJ, Brune K. Comparison of rofecoxib, celecoxib, and naproxen on renal function in elderly subjects receiving a normal-salt diet. *Clin Pharmacol Ther* 2002; 72: 50–61.
- 12 Swan SK, Rudy DW, Lasserter KC, Ryan CF, Buechel KL, Lambrecht LJ, Pinto MB, Dilzer SC, Obrda O, Sundblad KJ, Gumbs CP, Ebel DL, Quan H, Larson PJ, Schwartz JI, Musliner TA, Gertz BJ, Brater DC, Yao SL. Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet. *Ann Intern Med* 2000; 133: 1–9.
- 13 Schwartz JI, Thach C, Lasserter KC, Miller J, Hreniuk D, Hilliard DA, Snyder KM, Gertz BJ, Gottesdiener KM. Effects of etoricoxib and comparator nonsteroidal anti-inflammatory drugs on urinary sodium excretion, blood pressure, and other renal function indicators in elderly subjects consuming a controlled sodium diet. *J Clin Pharmacol* 2007; 47: 1521–31.

- 14** 1983 Metropolitan height and weight tables. *Stat Bull Metrop Life Found* 1983; 64: 3–9. PMID: 6623350.
- 15** Schwartz JI, De Smet M, Larson PJ, Verbesselt R, Ebel DL, Lins R, Lens S, Porras AG, Gertz BJ. Effect of rofecoxib on the pharmacokinetics of digoxin in healthy volunteers. *J Clin Pharmacol* 2001; 41: 107–12.
- 16** Snel S, Jansen JA, Pedersen PC, Jonkman JHG, van Heiningen PNM. Tiagabine, a novel antiepileptic agent: lack of pharmacokinetic interaction with digoxin. *Eur J Clin Pharmacol* 1998; 54: 355–7.
- 17** Harder S, Thürmann PA. Pharmacokinetic and pharmacodynamic interaction trial after repeated oral doses of imidapril and digoxin in healthy volunteers. *Br J Clin Pharmacol* 1997; 43: 475–80.
- 18** Awni WM, Hussein Z, Cavanaugh JH, Granneman GR, Dube LM. Assessment of the pharmacokinetic interaction between zileuton and digoxin in humans. *Clin Pharmacokinet* 1995; 29 (Suppl. 2): 92–7.
- 19** Rodin S, Johnson B. Pharmacokinetic interactions with digoxin. *Clin Pharmacokinet* 1988; 15: 227–44.
- 20** Schwartz JI, De Smet M, Larson PJ, Verbesselt R, Ebel DL, Lins R, Lens S, Porras AG, Gertz BJ. Effect of rofecoxib on the pharmacokinetics of digoxin in healthy volunteers. *J Clin Pharmacol* 2001; 41: 107–12.
- 21** Tanigawara Y. Role of P-glycoprotein in drug disposition. *Ther Drug Monit* 2000; 22: 137–40.
- 22** Reuning RH, Geraets DR. Digoxin. In: *Applied Pharmacokinetics*, 2nd edn, eds Evans WE, Schentag JJ, Jusko WJ. Spokane, WA: Applied Therapeutics, 1986; 570–623.
- 23** Williamson KM, Thrasher KA, Fulton KB, LaPointe NM, Dunham GD, Cooper AA, Barrett PS, Patterson JH. Digoxin toxicity: an evaluation in current clinical practice. *Arch Intern Med* 1998; 158: 2444–9.
- 24** Chapple DJ, Hughes R, Johnson BF. The relationship between cardiotoxicity and plasma digoxin concentration in conscious dogs. *Br J Pharmacol* 1976; 57: 23–7.
- 25** Cannon CP, Curtis SP, Bolognese JA, Laine L. Clinical trial design and patient demographics of the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Study Program: cardiovascular outcomes with etoricoxib vs. diclofenac in patients with osteoarthritis and rheumatoid arthritis. *Am Heart J* 2006; 152: 237–45.
- 26** Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, Reicin AS, Bombardier C, Weinblatt ME, van der Heijde D, Erdmann E, Laine L; MEDAL Steering Committee. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006; 368: 1771–81.