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Absence of Pharmacokinetic Interaction Between Orally Co-administered Naproxen Sodium and Diphenhydramine Hydrochloride

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ABSTRACT: The potential for a pharmacokinetic interaction between naproxen and diphenhydramine was examined in a randomized three-way crossover design with a 1-week washout between dosing. Single oral doses of 220 mg of naproxen sodium and 50 mg of diphenhydramine hydrochloride were given separately and together to 30 healthy male and female subjects. Heparinized blood samples obtained for 48 h postdose were assayed for plasma naproxen and diphenhydramine concentrations using validated high-performance liquid chromatography (HPLC) and gas chromatography (GC) assay methods, respectively. The area under the plasma concentration–time curve (AUC), maximum plasma concentrations (C_{max}), time of C_{max} (T_{max}) and terminal exponential half-life ($t_{1/2,z}$), were analysed for significant treatment differences by analysis of variance (ANOVA). Based on absence of significant treatment effects on AUC and C_{max}, single-dose oral co-administration of 220 mg of naproxen sodium with 50 mg of diphenhydramine hydrochloride does not alter the pharmacokinetics of either naproxen or diphenhydramine. Significant treatment differences seen for naproxen T_{max} (0.3 h, males only) and diphenhydramine $t_{1/2,z}$ (0.8 h, females only) were minor and are unlikely to have therapeutic consequences. Thus, efficacy and safety of concomitant naproxen and diphenhydramine should not be altered due to a pharmacokinetic interaction. Copyright © 2000 John Wiley & Sons, Ltd.

Key words: diphenhydramine; human; interaction; naproxen; pharmacokinetics

Introduction

Recently, over-the-counter (OTC) products combining analgesics with sleep aids have appeared or are under development for effective nighttime pain relief. Implicit in this strategy is that the medicines given together will not alter the effectiveness of the individual components. Potential pharmacokinetic interactions between the two combined drugs could impact on the effectiveness of the combination.

Naproxen is a member of the sodium arylacetic group of non-steroidal anti-inflammatory drugs (NSAIDs) and is available as Aleve®, an approved OTC analgesic containing 220 mg of naproxen sodium. Naproxen sodium was developed as an analgesic because it is more rapidly absorbed than naproxen, achieving maximum systemic concentrations by 1 h postdose compared with 2 h for naproxen [1]. Oral absorption of naproxen is rapid and essentially complete [2]. Terminal exponential half-life is approximately 12–15 h. Elimination of naproxen is through renal excretion of oxidative and conjugative metabolites, with only minor amounts excreted unchanged [3]. Extensive protein binding of approximately 99% [4] results in a small apparent volume of distribution for naproxen. Saturable protein binding within the clinical

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dose range has shown to increase naproxen clearance.

Diphenhydramine is a potent antihistaminic agent with anticholinergic, antitussive, antiemetic and sedative effects, and is available as Sominex®, an approved OTC sleep aid containing 50 mg of diphenhydramine hydrochloride. Diphenhydramine is almost completely absorbed, but bioavailability is 72% due to substantial first-pass metabolism [5]. Maximum systemic concentrations are achieved by approximately 2 h postdose and the terminal exponential half-life is approximately 9 h, with oral forms exhibiting a somewhat longer half-life attributed to delayed absorption. Diphenhydramine is eliminated almost entirely through metabolic transformation [6].

Naproxen pharmacokinetics have been shown to be affected by concomitant administration of other drugs. Oral absorption of naproxen is changed by co-administration of diazepam [7] but not sucralfate [8]. Probenecid and cimetidine have been shown to interfere with naproxen elimination through alterations in clearance [9,10]. This study was conducted to assess the potential for a pharmacokinetic interaction between naproxen sodium and diphenhydramine hydrochloride. Since a combined formulation was not available for the study, co-administration was used to assess the potential for a pharmacokinetic interaction.

Materials and Methods

Subjects

The 30 subjects for this study were to be male or female, between the ages of 18 and 40 years and within 10% of ideal body weight. Subjects had to be in good health based on medical history, prestudy physical examinations and clinical laboratory tests, and could not have had an acute illness within 2 weeks of the study. Subjects were not allowed to take any other medications for 1 week prior to and during the study. Subjects were excluded if they had a history of hypersensitivity, allergy or serious adverse reaction to naproxen, diphenhydramine or related compounds. Subjects were also excluded based on tobacco use or prior use of drugs thought to interfere with the objectives of the study. The protocol was approved by the Institutional Review Board at the clinical site and all subjects gave informed consent after receiving an explanation of the nature and purpose of the study.

Study Design and Drug Administration

The study was a three-way crossover design with dosing 7 days apart in randomized sequences. Subjects received oral doses of a 220-mg naproxen sodium tablet (Aleve®) alone, a 50-mg diphenhydramine hydrochloride caplet (Sominex®) alone or the two medications given together. Doses were given with 240 mL of water (room temperature) after an overnight fast with subjects fasting for 4 h postdose. Subjects remained upright (sitting or standing) for 2 h postdose.

Blood Sampling

Serial blood samples (10 mL) were collected in Vacutainer® blood collection tubes using sodium heparin as the anticoagulant at 0 (predose), 10, 20, 30, 40 and 50 min postdose, and at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h postdose. Plasma samples obtained by centrifugation were stored frozen at $-20°C$ or lower until assayed for naproxen and diphenhydramine content, as appropriate.

Analysis of Plasma Samples

Plasma samples (0.2 mL) were analysed for naproxen content by a validated high-performance liquid chromatography (HPLC) assay method consisting of liquid–liquid extraction of naproxen and internal standard (β-naphthoxyacetic acid) followed by reverse-phase HPLC separation and fluorescence detection at 230 nm excitation and 370 nm emission. Standard curves were linear from 0.50 μg/mL, the lower limit of quantification, to 40 μg/mL. Assay batch acceptance was judged by having four of six quality control samples within 20% of nominal values, with at least one acceptable value at each of the three concentration levels. Replicate analyses were used to further verify acceptable assay performance. Inter- and intra-batch accuracy

were within 12.3% and 10% of nominal concentrations, respectively, with 13% precision or better.

Plasma samples (1.0 mL) were analysed for diphenhydramine content by a validated gas chromatography (GC) assay method consisting of liquid–liquid extraction of diphenhydramine and internal standard (orphenadrine) followed by GC separation and nitrogen–phosphorus detection. Standard curves were linear from 0.10 ng/mL, the lower limit of quantification, to 100 ng/mL. Assay batch acceptance was judged by having four of six quality control samples within 20% of nominal values, with at least one acceptable value at each of the three concentration levels. Replicate analyses were used to further verify acceptable assay performance. Inter- and intra-batch accuracy were within 10% and 8% of nominal concentrations, respectively, with 12% precision or better.

Pharmacokinetic Analysis

The highest observed plasma concentrations and the corresponding sample times were defined as C_{max} and T_{max}, respectively. The area under the plasma concentration versus time curve (AUC) was calculated using the linear trapezoidal rule with extrapolation to infinite time using the last observed quantifiable plasma concentration and the apparent first-order terminal rate constant λ_z. Terminal exponential half-life ($t_{1/2,z}$) was obtained as $0.693/\lambda_z$.

Statistical Methods

The effect of co-administration on the pharmacokinetics of naproxen and diphenhydramine was assessed using analysis of variance (ANOVA) with $\alpha = 0.05$. Data for AUC and C_{max} were log-transformed prior to analysis. Results for T_{max} and $t_{1/2,z}$ were assessed for normality and were subsequently analysed as appropriate. Carryover and period-by-gender interaction effects that were not significant at $\alpha = 0.10$ were dropped from the ANOVA model. Analyses were performed separately by gender when significant treatment-by-gender effects were observed ($\alpha = 0.10$).

Results and Discussion

The 30 human volunteers (15 female, 15 male) who entered the study were determined to be in good health based on medical history, prestudy physical examinations and clinical laboratory tests. None of the subjects had a history of disease anticipated to affect the outcome of the study. Subjects ($n = 30$) had a mean $\pm$ S.D. age of 26 ± 6 years (range 19–40 years), weight of 66.6 ± 8.2 kg (range 50.6–81.4 kg) and height of 172 ± 9 cm (range 158–189 cm). Twenty-eight of the 30 subjects who entered the study were evaluable for effects of co-administration on diphenhydramine pharmacokinetics. Twenty-seven subjects were evaluable for effects of co-administration on naproxen pharmacokinetics.

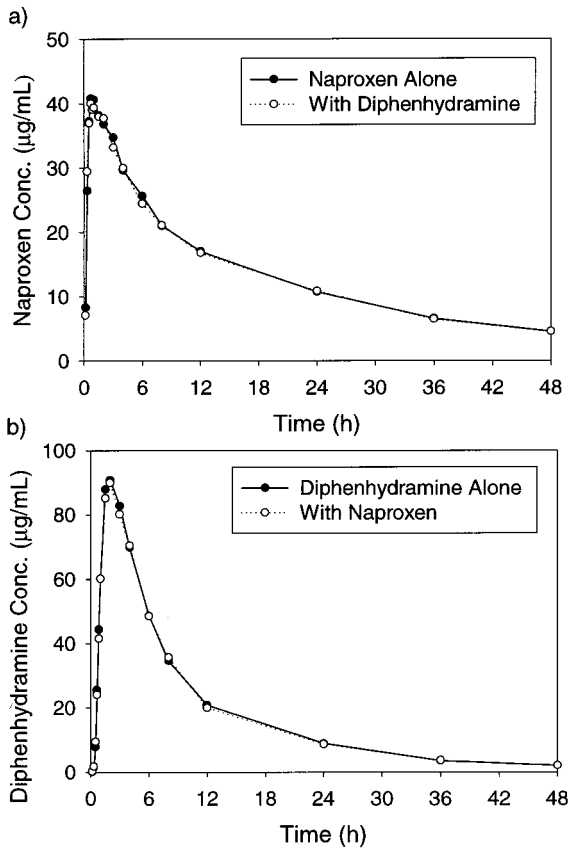

Figure 1. Mean plasma concentration–time profiles for (a) naproxen and (b) diphenhydramine following single-dose oral administration of 220 mg of naproxen sodium and 50 mg of diphenhydramine hydrochloride alone or together to healthy volunteers

One subject voluntarily withdrew for personal reasons. Two subjects were dropped due to positive predose caffeine screening results.

Pharmacokinetic parameter values observed for naproxen and for diphenhydramine in this study were in good general agreement with results from earlier studies [5,7]. As shown in Figure 1(a), mean plasma naproxen concentration–time profiles were superimposable for naproxen sodium alone and with diphenhydramine hydrochloride. Mean treatment values for naproxen AUC for separate versus concurrent administration were within 1% and were not significantly different (Table 1). A significant gender-by-treatment interaction was identified for naproxen C_{max}. Although not significantly different, mean naproxen C_{max} values were 10% lower and 15% higher for males and females, respectively, for naproxen sodium alone versus with diphenhydramine hydrochloride. Although treatment differences achieved significance for naproxen T_{max} in males, the 0.4 h postdose value for naproxen with diphenhydramine is not expected to be clinically relevant.

Diphenhydramine concentration–time profiles (Figure 1(b)) were superimposable for diphenhydramine hydrochloride alone and with naproxen sodium. Mean treatment values for diphenhydramine AUC, C_{max} and T_{max} for separate versus concurrent administration were within 1% and were not significantly different (Table 1). The gender-by-treatment interaction term in the ANOVA model was significant for $t_{1/2,z}$. Therefore, a separate analysis by gender was performed for this parameter. Diphenhydramine $t_{1/2,z}$ for males was unaffected by naproxen administration. Although $t_{1/2,z}$ differences for females achieve statistical significance, the 0.8 h longer $t_{1/2,z}$ value (less than 10% change) for diphenhydramine when given with naproxen sodium in females should not be of therapeutic importance.

Based on AUC and C_{max}, single-dose oral co-administration of 220 mg of naproxen sodium with 50 mg of diphenhydramine hydrochloride does not alter the pharmacokinetics of either naproxen or diphenhydramine when co-administered. Significant treatment differences seen for naproxen T_{max} and diphenhydramine $t_{1/2,z}$ were minor and are unlikely to have therapeutic consequences. Thus, the efficacy and safety of concomitant naproxen and diphenhydramine

Table 1. Pharmacokinetic parameters for naproxen and diphenhydramine following single-dose oral administration of 220 mg of naproxen sodium and 50 mg of diphenhydramine hydrochloride alone or together to healthy volunteers

Parameter	Gender	Least-squares means[a]		Point estimate[b]	p Value[c]	95% CI
		Co-administered (test)	Alone (reference)			
Naproxen						
AUC (μg · h/mL)	Both	776.2	777.4	99.8	NS	97.3, 102.4
C_{max} (μg/mL)	Males	41.6	46.1	90.3	NS	80.7, 101.1
	Females	55.2	48.0	115.0	NS	98.4, 134.4
T_{max} (h)	Males	1.14	0.74	154.5	0.0127	111.8, 213.6
	Females	0.76	1.10	68.8	NS	40.1, 117.9
$t_{1/2,z}$ (h)	Both	18.75	18.70	0.049	NS	−0.786, 0.882
Diphenhydramine						
AUC (ng · h/mL)	Both	778.1	775.1	100.4	NS	94.5, 106.6
C_{max} (ng/mL)	Both	86.9	87.6	99.2	NS	91.7, 107.3
T_{max} (h)	Both	2.191	2.194	−0.003	NS	−0.338, 0.333
$t_{1/2,z}$ (h)	Males	9.83	9.83	0.001	NS	−0.354, 0.355
	Females	10.6	9.81	0.807	0.0077	0.266, 1.348

[a] Geometric means for naproxen AUC, C_{max} and T_{max} and for diphenhydramine AUC and C_{max}. Arithmetic means for naproxen $t_{1/2,z}$ and for diphenhydramine T_{max} and $t_{1/2,z}$.
[b] Point estimate as test/reference (%) for AUC, C_{max} and T_{max} and for diphenhydramine AUC and C_{max}. Point estimate as test-reference for naproxen $t_{1/2,z}$ and for diphenhydramine T_{max} and $t_{1/2,z}$.
[c] NS, not significant ($p > 0.05$).

should not be altered due to a pharmacokinetic interaction. This outcome supports further work to assess whether a formulation-specific affect might exist when these drugs are given as a true combination product.

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