T1972

Pharmacokinetics of Naproxen and Esomeprazole in PN400, a Single-Tablet, Multilayer Formulation of Enteric-Coated Naproxen Coupled with Immediate-Release Esomeprazole

Philip B. Miner, John R. Plachetka, Eric Orlemans, John G. Fort, Mark B. Sostek

Introduction: PN400 is a single-tablet formulation with an enteric-coated (EC) naproxen core surrounded by an immediate-release (IR) esomeprazole mantle designed for initial and rapid release of esomeprazole in the stomach followed by release of EC naproxen after esomeprazole absorption. The aim of this study was to determine levels of exposure of esomeprazole and naproxen when used in combination in PN400 and with EC esomeprazole + naproxen 500 mg. Methods: This randomized, open-label, 9-day, 4-way crossover, single-center study enrolled 28 healthy F H, non-smoking adults without a history of peptic ulcer/acid-related gastrointestinal symptoms. Subjects were randomized to different sequences of the following: A) PN400/E30 [EC naproxen 500 mg/IR esomeprazole 30 mg BID]; B) PN400/E20 [EC naproxen 500 mg/IR esomeprazole 20 mg BID]; C) PN400/E10 [EC naproxen 500 mg/IR esomeprazole 10 mg BID]; and D) EC/E20 [EC naproxen 20 mg QID + non-EC naproxen 500 mg BID]. Blood samples were taken on Days 1 and 9 before dosing and at various times up to 24 hours afterwards for pharmacokinetic assessments of esomeprazole and naproxen. Results: Esomeprazole was rapidly absorbed from all 3 doses of PN400 with measurable plasma concentrations as early as 10 minutes after the AM dose and at 20-30 minutes after the PM dose. Differences in Cmax and AUCs for esomeprazole from PN400 were generally dose-dependent. As expected, the Tmax for EC naproxen was delayed in relation to the Tmax for esomeprazole. Steady-state AUCs for naproxen monocomponent were comparable to all PN400 formulations. Tmax with non-EC naproxen occurred considerably earlier than with the EC naproxen component of the PN400 formulations. Esomeprazole and naproxen pharmacokinetic parameters for the AM dose on Day 9 of BID dosing for PN400 are provided in the Table. Conclusion: PN400 induced dose-dependent increases in plasma esomeprazole concentrations and similar naproxen concentrations to dosing with EC E20 + naproxen. The pharmacokinetics of esomeprazole administered as the PN400 formulation were consistent with immediate release, and Tmax for esomeprazole preceded that for EC naproxen.

T1973

Diagnostic Precision of Primary Care Electronic Database for Study of Gastrointestinal Bleeding and Its Ability to Detect the Influence of Aspirin

Matthew Leighton, Yana Vinogradova, Anthony Shonle, John C. Atherton, Richard F. Logan, Anthony Avery, Denise Kendick, Julia Hippley-Cox, Chris J. Hawley

INTRODUCTION: Large Primary Care electronic databases offer good opportunities for systematic epidemiological research. However, general practitioners do not necessarily code according to the gold-standard classification scheme and placed onto a thermostatically-controlled chamber. The chamber was mounted on a table. Results: There were no statistically significant sequence, period, or formulation effects in healthy subjects for either plasma concentrations or computed PK parameters for either IBU or FAM when administered via HZT-501 or via concurrent administration of commercially available IBU and FAM. The following table shows the PK parameters for both formulations in healthy and renally-impaired subjects. Both HZT-501 and concurrent administration of IBU 800 mg and FAM 26.6 mg in two treatment periods separated by at least a 1-week washout. Blood samples collected for pharmacokinetic analysis were obtained from the following: A) PN400/E30 [EC naproxen 500 mg/IR esomeprazole 30 mg BID]; B) PN400/E20 [EC naproxen 500 mg/IR esomeprazole 20 mg BID]; C) PN400/E10 [EC naproxen 500 mg/IR esomeprazole 10 mg BID]; and D) EC/E20 [EC naproxen 20 mg QID + non-EC naproxen 500 mg BID]. Values are mean (% coefficient of variation) for Cmax and AUC, and median (range) for Tmax.

<table>
<thead>
<tr>
<th>Naproxen</th>
<th>Cmax [μg/mL]</th>
<th>Tmax [hr]</th>
<th>AUC_{0-24hr} [μg hr/mL]</th>
<th>Cpeak [μg/mL]</th>
<th>Tmax [hr]</th>
<th>AUC_{0-24hr} [μg hr/mL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PN400/E30</td>
<td>2779 (45)</td>
<td>80.9 (23)</td>
<td>3.00 (0.00-8.00)</td>
<td>603 (21)</td>
<td>715 (57)</td>
<td>1216 (69)</td>
</tr>
</tbody>
</table>

Values are mean (% coefficient of variation) for C_{max} and AUC, and median (range) for T_{max}.

T1974

HVT-501, A Novel Combination of Ibuprofen (Ibu) and Famotidine (FAM), Provides Pharmacokinetics Comparable to That of Commercially Available Ibu and FAM in a Patient-Friendly Dosing Form: Evaluation in Healthy and Renally-Impaired Subjects

George Tulmarch, Susan B. Rodriguez

Background: Clinical studies have demonstrated that reducing gastric acid secretion with FAM during treatment with non-steroidal anti-inflammatory drugs (NSAIDs) decreases the risk of development of upper gastrointestinal (GI) ulceration. However, physician compliance is reported to be <30% in co-prescribing acid-reducing agents for patients on NSAIDs, and patient compliance with the differing dosing regimens for these various agents is reported to be only 37%. HVT-501, a combination product containing IBU 800 mg and FAM 26.6 mg, is designed both to improve patient compliance and to ensure that the time of gastric acid suppression coincides with the time of maximum vulnerability to NSAID-induced GI ulceration. Objective: To evaluate the bioequivalence of HVT-501 and concurrent administration of equivalent doses of commercially available IBU and FAM in healthy subjects and in subjects with renal impairment. Methods: Randomized, open-label, single-dose, 2-period crossover study in 24 healthy subjects and 5 subjects with moderate-to-severe renal impairment (creatinine clearance < 45 mL/min) (Cockcroft-Gault formula). Oral administration of HVT-501, and concurrent oral administration of IBU 800 mg and FAM 26.6 mg, in two treatment periods separated by at least a 1-week washout. Blood samples collected for pharmacokinetic analysis were obtained from the following: A) PN400/E30 [EC naproxen 500 mg/IR esomeprazole 30 mg BID]; B) PN400/E20 [EC naproxen 500 mg/IR esomeprazole 20 mg BID]; C) PN400/E10 [EC naproxen 500 mg/IR esomeprazole 10 mg BID]; and D) EC/E20 [EC naproxen 20 mg QID + non-EC naproxen 500 mg BID]. Blood samples were taken on Days 1 and 9 before dosing and at various times up to 24 hours afterwards for pharmacokinetic assessments of esomeprazole and naproxen. Results: Esomeprazole was rapidly absorbed from all 3 doses of PN400 with measurable plasma concentrations as early as 10 minutes after the AM dose and at 20-30 minutes after the PM dose. Differences in Cmax and AUCs for esomeprazole from PN400 were generally dose-dependent. As expected, the Tmax for EC naproxen was delayed in relation to the Tmax for esomeprazole. Steady-state AUCs for naproxen monocomponent were comparable to all PN400 formulations. Tmax with non-EC naproxen occurred considerably earlier than with the EC naproxen component of the PN400 formulations. Esomeprazole and naproxen pharmacokinetic parameters for the AM dose on Day 9 of BID dosing for PN400 are provided in the Table. Conclusion: PN400 induced dose-dependent increases in plasma esomeprazole concentrations and similar naproxen concentrations to dosing with EC E20 + naproxen. The pharmacokinetics of esomeprazole administered as the PN400 formulation were consistent with immediate release, and Tmax for esomeprazole preceded that for EC naproxen.

T1975

NSAIDs: A Direct Activator of Acid Secretion in Parietal Cells

Elizabeth Aretta, Nina Buchinger, Barbara Groitz, Sascha Kopic, Michael K. Murek, John P. Geibel

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used classes of drugs in the treatment of inflammatory and degenerative conditions. The side effects of NSAIDs, particularly the increased risk of gastrointestinal and renal complications, have caused concern in their widespread use. NSAID use increases the risk of peptic ulcer disease (PUD), particularly with prolonged duration of therapy or higher dose. Studies have demonstrated a key inhibitory role of NSAIDs in the cyclooxygenase pathway leading to inhibition of prostaglandin synthesis, an important mediator in the protection of gastrointestinal mucosal lining. Little is known, however, about the effect of NSAIDs directly on the parietal cell. This study aims to investigate the effect of NSAIDs on acid secretion in the parietal cell. Methods: Rats were fasted for 12-18 hrs prior to sacrifice to ensure basal acid secretion. Gastric glands were hand-dissected from the corpus, transferred to a coveslip, and placed onto a thermostatically-controlled chamber. The chamber was mounted on a microscope attached to a digital imaging system. The glands were incubated with the pH-sensitive dye BCECF. Intracellular pH changes were monitored using real-time video imaging. Data were collected as arbitrary intensity units every 15s and converted to absolute

rectal bleeding / melena, related to aspirin use. CONCLUSION: Coding impression limits the exactitude of conclusions but is not enough to obscure the impact of aspirin on event rates. The impact of aspirin is likely to be higher when coding and exposure impressions are allowed for.

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