A MULTICENTER, OPEN-LABEL PHARMACOKINETIC, PHARMACODYNAMIC, CLINICAL SYMPTOMS, AND SAFETY STUDY OF PANTOPRAZOLE DELAYED-RELEASED GRANULES ADMINISTERED AS A SUSPENSION IN NEONATES AND PRETERM INFANTS WITH A CLINICAL DIAGNOSIS OF GASTROESOPHAGEAL REFLUX DISEASE

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Primary: To determine whether or not consistent exposures can be achieved in neonates and preterm infants with presumed GERD receiving oral doses of pantoprazole. Secondary: PK and PD assessment after single dose and steady state. Determination fo...

Ethical review	Approved WMO
Status	Pending
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON30569

Source
ToetsingOnline

Brief title
PK-PD study of Pantoprazole in neonates with GERD.

Condition

- Gastrointestinal inflammatory conditions

Synonym
gastroesophageal reflux

Research involving
Human

Sponsors and support

Primary sponsor: Wyeth
Source(s) of monetary or material Support: Wyeth Pharmaceuticals

Intervention

Keyword: Neonates, Pantoprazole, PK-PD, Reflux

Outcome measures

Primary outcome

PK : The single-dose concentration versus time data will be analyzed initially

for the areas under the concentration versus time curves from time 0 to the

time T, at which time the last measurable concentration is obtained, for

patients from Group A (AUCT,A) and Group B (AUCT,B).

Concentrations of pantoprazole obtained following at least 5 consecutive doses

of pantoprazole will be summarized using descriptive statistics, while the

limited comparison of concentrations at 3 and 6 hours between the first and the

last doses may be made for the assessment of drug accumulation following

repeated dose administration.

PD Analyses: On each of the pH-metry days the following data will be collected

on the eCRF

· Mean and median intraesophageal pH

· Mean and median intragastric pH

· Percentage of time intragastric pH >4

· Percentage of time intragastric pH >3

· Percentage of time esophageal pH <4 (reflux index)

· Number of reflux episodes

· Number of episodes > 5 minutes

· Duration of longest episode

· AUC of gastric H+ concentration over time

Secondary outcome

GERD and respiratory symptoms will be collected at baseline and daily

throughout the study based upon nursing observations on a worksheet

Buccal cells for pharmacogenomic (PG) analysis of cytochrome P450 (CYP) enzymes

and CYP2C19 and CYP3A4 phenotypes will be collected with the parents/legal

guardian*s (PARENT) permission before the patient completes the study.

Study description

Background summary

Acid suppression therapy is being widely used in neonates and preterm infants to treat various conditions, including the prevention or treatment of upper gastrointestinal (GI) bleeding, and gastroesophageal reflux disease (GERD) among other indications. However, no specific pantoprazole pharmacokinetic (PK), pharmacodynamic (PD), clinical symptoms, safety, or dose information is available in neonates and preterm infants. This study is designed to determine the single- and multiple-dose PK, pharmacodynamic profile, change in clinical symptoms, and safety of pantoprazole delayed-release granules administered as a suspension in neonates and preterm infants with a clinical indication for acid suppression to treat a presumptive diagnosis of GERD.

Study objective

Primary: To determine whether or not consistent exposures can be achieved in neonates and preterm infants with presumed GERD receiving oral doses of pantoprazole.
Secondary: PK and PD assessment after single dose and steady state. Determination fo Gerd and respiratory symptoms. Safety evaluation.

Study design

This is a multicenter, open-label, randomized, single- and multiple-dose study that will assess PK, clinical GERD and respiratory symptoms and safety of 2 dose levels of pantoprazole (1.25 mg and 2.5 mg) and the PD at one dose level (2.5 mg) in neonates and preterm infants with a clinical indication for acid suppression to treat a presumptive diagnosis of GERD. At least 6 days of treatment. A follow-up contact day 23 ± 5 (approximately 15 ± 3 days after the last dose of test article) or possibility to enroll in study 3001B3-335-WW (open-label safety study with 6 weeks treatment).

Intervention

Single-dose PK Profiling: Each patient will have four blood samples (0.25 mL/sample) drawn.
Multiple-dose PK Profiling: Two multiple-dose (steady-state) PK samples collected at 3 and 6 hours after administration of the final dose of test article.
pH-metry: LES location may be verified by an LES Locator: fluoroscopy, x-ray, or by calculation based upon Strobel*s formula in infants over 40 cm in length.
Multiple-dose PD assessment:First on screening/baseline, second on study day 6, approximately 1 hour before the final dose of test article, the pH probe will be inserted. pH-metry during 24 hours.

Study burden and risks

Hospitalization during study period (5 to 7 days). Daily physical examination and daily 1 oral dose of pantoprazol. Twice ECG and once buccal cell collection.
For PK and PK/PD patients : 4 bloodsamples on day 1.
All patients : 2 bloodsamples on day 6. (Total amount of blood less than 3 - 4 mL). The patient may have pain, swelling, or bruising where his/her blood is collected.
PD and PK/PD patients: Twice pH-metry: First during screening and second on day6. pH-metry last 24 hours. The doctor will place a pH probe through one nostril down the back of the throat, and into the stomach. Location by radiography or fluoroscopy. Risks associated with the pH probe are nose bleeding, sinus discomfort and sore throat. Common (1-10 %) adverse events are headache and diarrhea.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Male or female hospitalized patients admitted to a neonatal intensive care unit (NICU) or special care nursery, at the time of enrollment. 2. Have a clinical indication for acid suppression to treat a presumptive diagnosis of GERD based on clinical symptoms suggestive of GERD and/or objective tests diagnostic of GERD. NOTE: Disorders associated with or worsened by GERD, objective tests suggestive of GERD, and/or aspiration in conjunction with GERD should also be noted. These are considered supportive documentation of the clinical diagnosis 3. Be either term or post-term infants within the neonatal period (not older than 28 days), or be preterm infants with a corrected age of less than 44 weeks.4. Have a body weight of at least 1500 grams. 5. Patients must be able to tolerate oral feeding and swallow the test article.

Exclusion criteria

1. Cardiovascular instability, life-threatening arrhythmia, previous cardiopulmonary arrest, or mechanical ventilation.2. Known human immunodeficiency virus (HIV) or clinical manifestations of acquired immune deficiency syndrome (AIDS) or other significant immunodeficiency disorder or malignancy.3. Clinically significant laboratory test abnormality:a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level 2 times upper limit of normal (ULN).b. Alkaline phosphatase 2 times ULN (age-corrected).4. Known history of positive serologic test for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody or RNA.5. Known hypersensitivity to proton pump inhibitors (PPIs), including pantoprazole.6. For PK Patients: History of treatment with PPIs within 24 hours before the first (1st) dose of test article.For PK/PD or PD Patients: History of treatment with PPIs within 7 days before the first (1st) dose of test article.7. For PK Patients: Use of histamine-2-receptor antagonists (H2RAs) within 24 hours before the first (1st) dose of test article. For PK/PD or PD Patients: Use of H2RAs within 3 days before the first (1st) dose of test article.8. Use of antacids within 2 hours before or after test article administration. Use of antacids is also prohibited 2 hours before or during pH-metry.9. Use of warfarin, carbamazepine, or phenytoin as well as rifampin for any disorder from at least 24 hours before the 1st dose of test article until after the final study procedure.10. Significant renal or hepatic disease.11. Any life-threatening condition that would make it unlikely for the patient to be discharged from the hospital.12. Participation in any other investigational study within 30 days before the administration of test article without prior approval of the Wyeth Research, (WR) Medical Monitor.13. PD or PK/PD patients receiving 24-hour continuous enteral feeding or any feeding more frequently than every 3 hours.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2007

Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	5-(difluoromethyoxy)-2(((3,4,-dimethoxy-2-pyridinyl)-methyl)-sulfinyl)-1H-benzimidazole
Generic name:	Pantoprazole
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-04-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-10-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2006-001473-24-NL
CCMO	NL15488.078.07