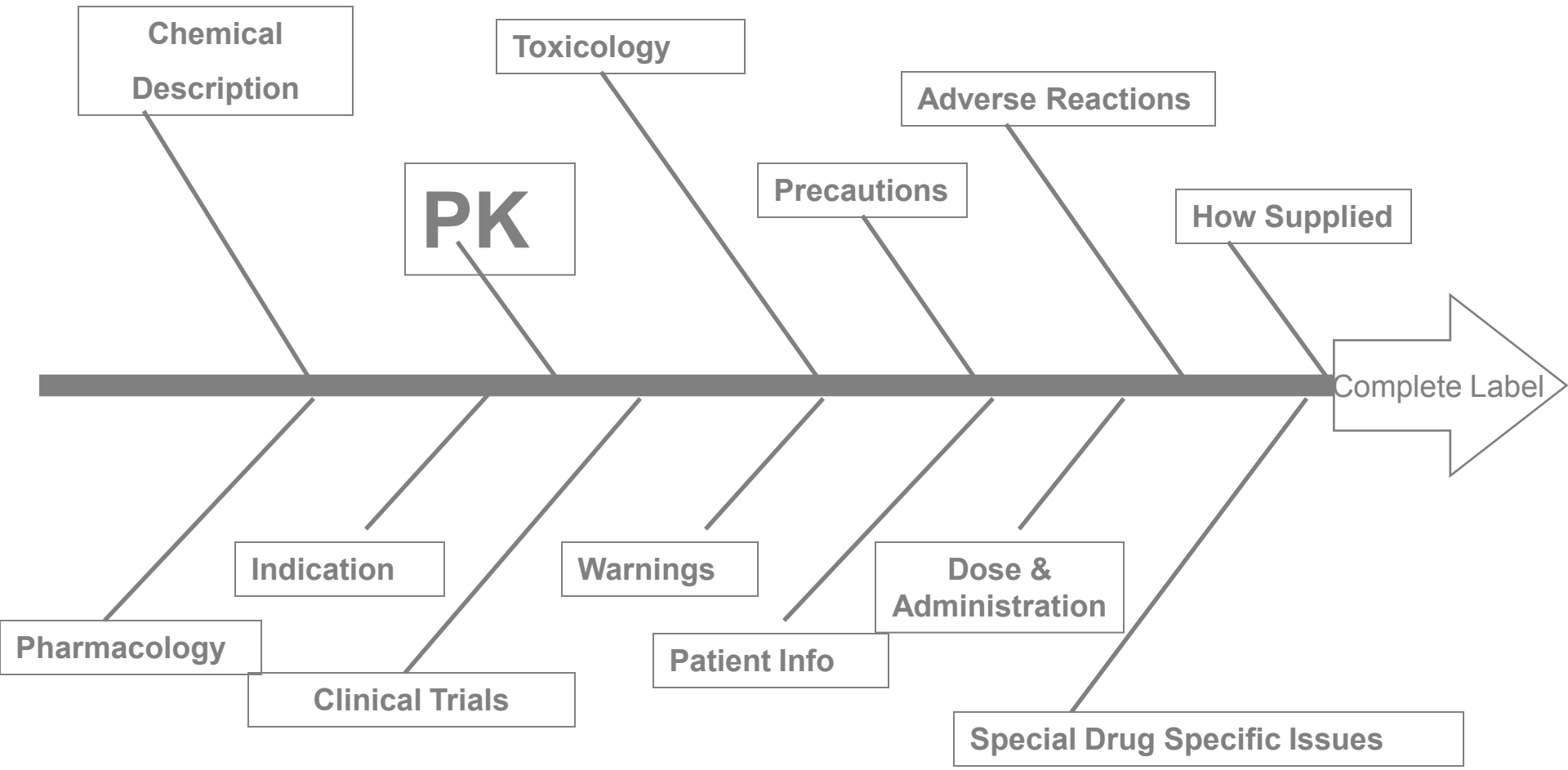
Developing the Clinical Pharmacology Section of a U.S. Package Insert-Protonix

Phil Mayer, PhD

General Requirements for Prescription Drug Labeling (21CFR201.56)

- Summary for the safe and effective use of the drug
- Informative and accurate
- Not promotional, false, or misleading
- No implied claims or suggestions for use if evidence of safety or effective is lacking
- Based whenever possible on data derived from human experience
- Updated when new information becomes available that causes the labeling to become inaccurate, false or misleading

Drug Label/Package Insert



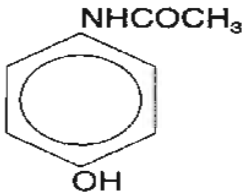
Reformatting Drug Labeling

First page of labeling

Old Format

BRAND NAME
(chemical name)

DESCRIPTION
The chemical structure is shown below:



The molecular weight is 201.70. The molecular formula is C10H15NO•HCl. Pseudoephedrine hydrochloride occurs as fine, white to off-white crystals or powder,having a faint characteristic odor. It is very soluble in water, freely soluble in alcohol, and Sparingly soluble in chloroform.

CLINICAL PHARMACOLOGY
Mechanisms of Action:
Pharmacokinetics:
Absorption:

Revised Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BRAND NAME safely and effectively. See full Prescribing information.

BRAND NAME® (chemical name)
Initial U.S. Approval: 2001

----------RECENT MAJOR CHANGES----------

----------INDICATIONS AND USAGE----------

----------DOSAGE AND ADMINISTRATION----------

----------DOSAGE FORMS AND STRENGTHS----------

----------CONTRAINDICATIONS----------

----------WARNINGS AND PRECAUTIONS----------

----------ADVERSE REACTIONS----------
To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

Example of Highlights for a Fictitious Drug

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Imdicon safely and effectively. See full prescribing information for Imdicon.

IMDICON® (cholinasol) CAPSULES
Initial U.S. Approval: 2000

WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Imdicon immediately if any of the following occur:

- **Neutropenia/agranulocytosis (5.1)**
- **Thrombotic thrombocytopenic purpura (5.1)**
- **Aplastic anemia (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Coronary Stenting (1.2)	2/200X
Dosage and Administration, Coronary Stenting (2.2)	2/200X

----------INDICATIONS AND USAGE----------

Imdicon is an adenosine diphosphate (ADP) antagonist platelet aggregation inhibitor indicated for:

- Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
- Reducing the incidence of subacute coronary stent thrombosis, when used with aspirin (1.2)

Important limitations:

- For stroke, Imdicon should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Stroke: 50 mg once daily with food. (2.1)
- Coronary Stenting: 50 mg onee daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)

Discontinue in renally impaired patients if hemorrhagic or hematopoietic problems are encountered (2.3, 8.6, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 50 mg (3)

----------CONTRAINDICATIONS----------

- Hematopoietic disorders or a history of TTP or aplastic anemia (4)
- Hemostatic disorder or active bleeding (4)
- Severe hepatic impairment (4, 8.7)

----------WARNINGS AND PRECAUTIONS----------

- Neutropenia (2.4 % incidence; may occur suddenly; typically resolves within 1-2 weeks of discontinuation), thrombotic thrombocytopenic purpura (TTP), aplastic anemia, agranulocytosis, pancytopenia, leukemia, and thrombocytopenia can occur (5.1)
- Monitor for hematological adverse reactions every 2 weeks through the third month of treatment (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence >2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- Anticoagulants: Discontinue prior to switching to Imdicon (5.3, 7.1)
- Phenytoin: Elevated phenytoin levels have been reported. Monitor levels. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Hepatic impairment: Dose may need adjustment. Contraindicated in severe hepatic disease (4, 8.7, 12.3)
- Renal impairment: Dose may need adjustment (2.3, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 5/200X18

FIGURE 6.1.1A. PANTOPRAZOLE CLINICAL PHARMACOLOGY STUDIES

General Pharmacokinetic Studies
First-In-Man IV FHP001
^{14}C-pantoprazole PO/IV FHP018E + A9916
Dose Proportionality IV FHP003
Multiple IV doses FHP002E
Long-term IV infusion FHP024E
Dose Proportionality PO A9907-GER
Multiple PO doses FK3029
Multiple PO doses FHP007E
IV and PO PD 3001A1-100

Bioavailability/ Bioequivalence Studies
F: A9915/GER
IV FHP027E
PO FHP014
PO FHP028E
PO FHP042
PO FHP041

Special Population Studies
Elderly FHP017E/2 + FHP017E
Severe renal impairment FHP020E
Severe renal impairment FHP022E
Renal impairment FHP023
Liver cirrhosis FHP008E
Hepatic impairment FHP045

Food Effect Studies
A9905-GER
FHP015

Drug Interaction Studies
Antipyrine A9903-GER + A9910-GER
Caffeine FHP032E
Ethanol FK3036
Theophylline FHP006E
Diazepam FHP004E
Carbamazepine FHP037
Phenytoin FHP026E
Digoxin FHP010 + FHP019
Metoprolol FHP035
Nifedipine FHP025
Warfarin A9920-UK+ FHP012E
Phenprocoumon FHP034E
Cisapride 3001A1-102
Antacids FHP021
Diclofenac FHP030
Glibenclamide FHP036E
Oral Contraceptive BGS 004

TABLE 6.1.1B NUMBER OF STUDY PARTICIPANTS WHO RECEIVED EACH DOSE OF PANTOPRAZOLE OR PLACEBO IN PHASE I CLINICAL PHARMACOLOGY STUDIES

	Pantoprazole Dose (mg)																		
Population	**1**	**2.5**	**5**	**6**	**10**	**15**	**20**	**30**	**40**	**45.5**	**60**	**80**	**91**	**100**	**120**	**232**	**240**	**Placebo**	**Total**
Healthy																			
Intravenous	4	4	4		16	8	22	66	119	12	17	54	12		5	6	12	104	465
Oral				2	12		106	12	669		6	39		2				244	1092
Elderly																			
Intravenous								32											32
Oral									32										32
Renal-Impaired																			
Intravenous									8										8
Oral									24										24
Hepatic-Impaired																			
Intravenous								12											12
Oral							16		44										60
Total	4	4	4	2	28	8	144	122	896	12	23	93	12	2	5	6	12	348	1725

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

PROTONIX IS PREPARED AS AN ENTERIC-COATED TABLET SO THAT ABSORPTION OF PANTOPRAZOLE BEGINS ONLY AFTER THE TABLET LEAVES THE STOMACH. PEAK SERUM CONCENTRATION (CMAX) AND AREA UNDER THE SERUM CONCENTRATION TIME CURVE (AUC) INCREASE IN A MANNER PROPORTIONAL TO ORAL AND INTRAVENOUS DOSES FROM 10 MG TO 80 MG. PANTOPRAZOLE DOES NOT ACCUMULATE AND ITS PHARMACOKINETICS ARE UNALTERED WITH MULTIPLE DAILY DOSING. FOLLOWING ORAL OR INTRAVENOUS ADMINISTRATION, THE SERUM CONCENTRATION OF PANTOPRAZOLE DECLINES BIEXPONENTIALLY WITH A TERMINAL ELIMINATION HALF-LIFE OF APPROXIMATELY ONE HOUR.

IN EXTENSIVE METABOLIZERS (SEE METABOLISM SECTION) WITH NORMAL LIVER FUNCTION RECEIVING AN ORAL DOSE OF THE ENTERIC-COATED 40 MG PANTOPRAZOLE TABLET, THE PEAK CONCENTRATION (CMAX) IS 2.4 µG/ML, THE TIME TO REACH THE PEAK CONCENTRATION (TMAX) IS 2.4 H AND THE TOTAL AREA UNDER THE PLASMA CONCENTRATION VERSUS TIME CURVE (AUC) IS 4.8 µG·HR/ML. WHEN PANTOPRAZOLE IS GIVEN WITH FOOD, ITS TMAX IS HIGHLY VARIABLE AND MAY INCREASE SIGNIFICANTLY. FOLLOWING INTRAVENOUS ADMINISTRATION OF PANTOPRAZOLE TO EXTENSIVE METABOLIZERS, ITS TOTAL CLEARANCE IS 7.6-14.0 L/H AND ITS APPARENT VOLUME OF DISTRIBUTION IS 11.0-23.6L.

Figure 1. Mean ± SD Serum Concentrations Following a Single IV Administration of Pantoprazole in 12 Healthy Volunteers (Protocol FHP003)

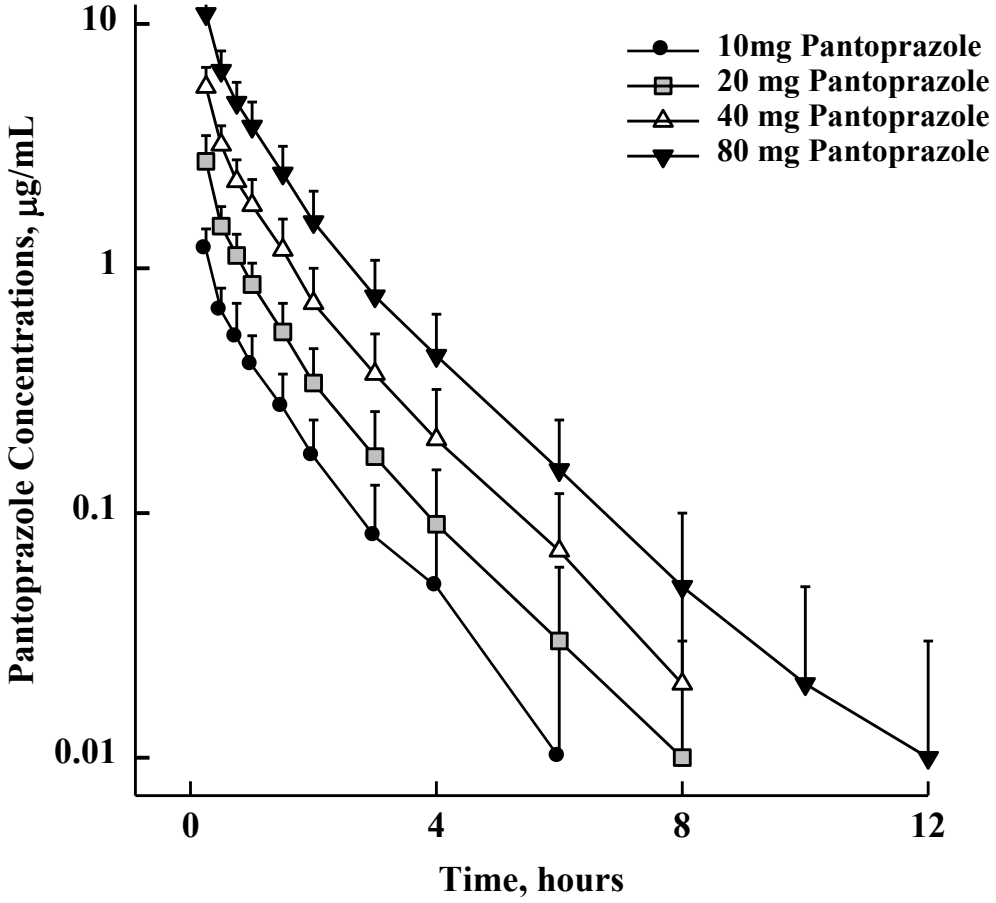


Figure 2. AUC after Intravenous Administration of Increasing Doses of Pantoprazole in 12 Healthy Volunteers (Protocol FHP003)

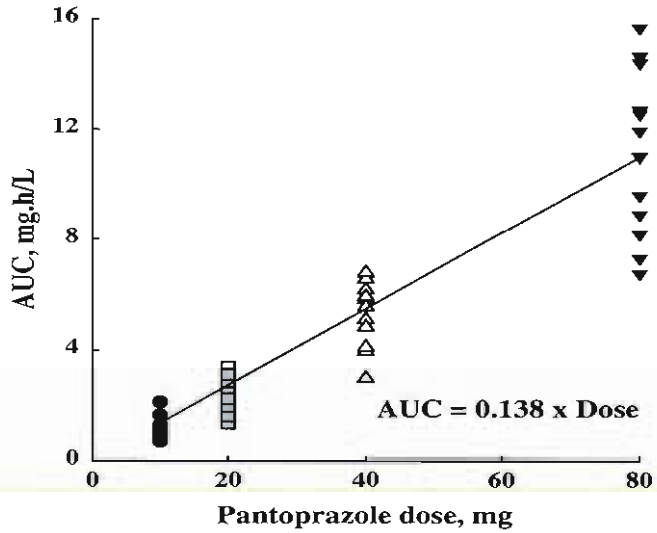
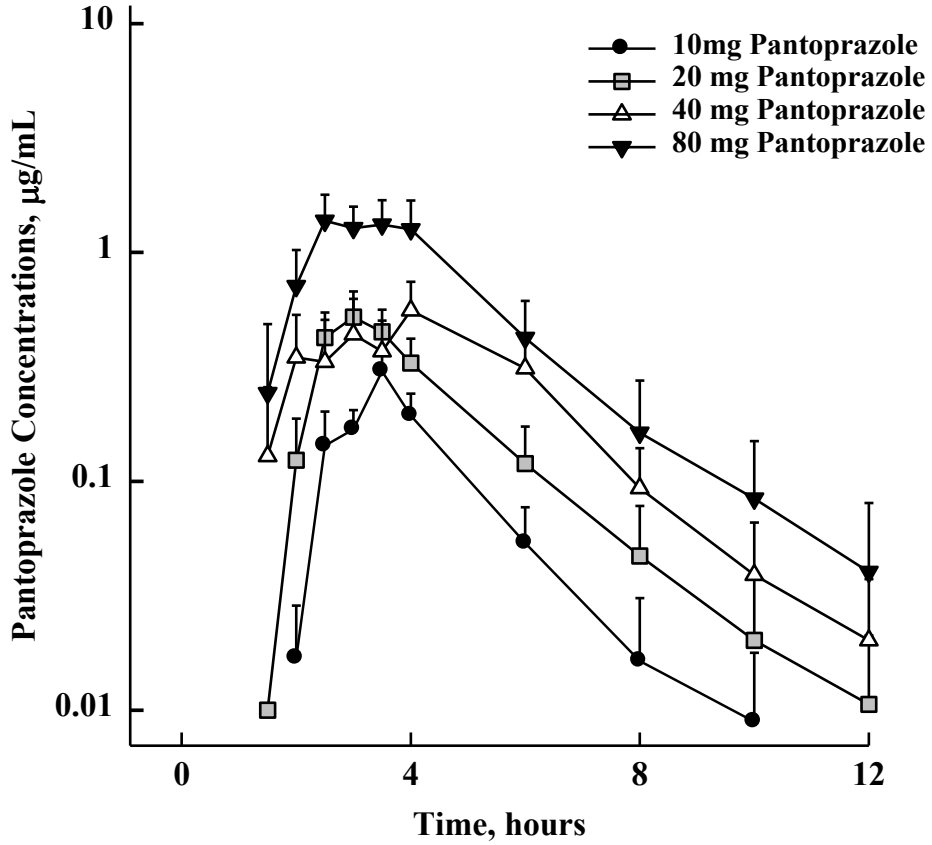


Figure 3. Mean ± SD Serum Concentrations Following a Single Oral Administration of Pantoprazole in 10 Healthy Subjects (Protocol A9907)



Individual pantoprazole concentration-time curve after a single oral pantoprazole (40-mg) administration in normal and slow CYP 2C19 metabolizer

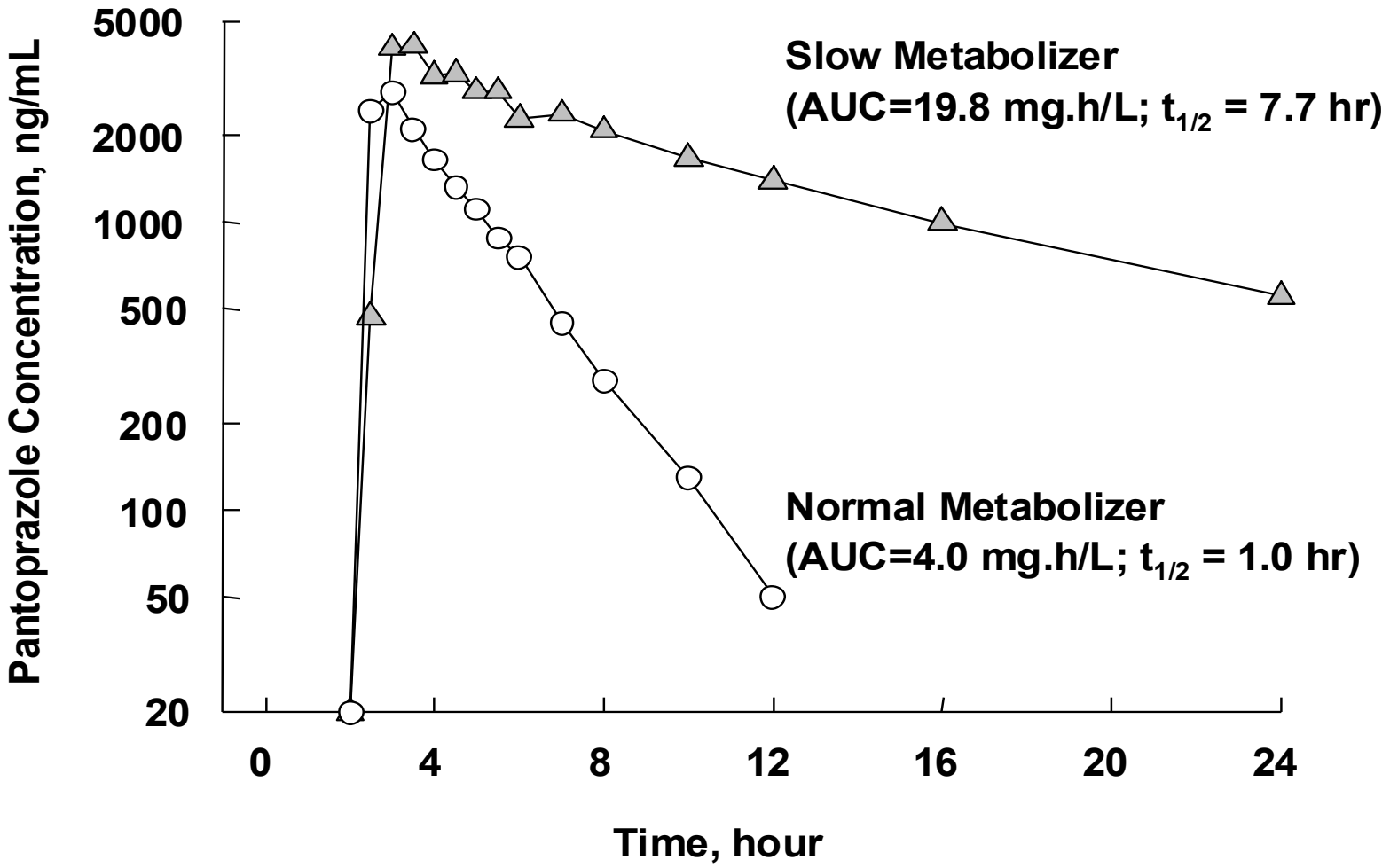
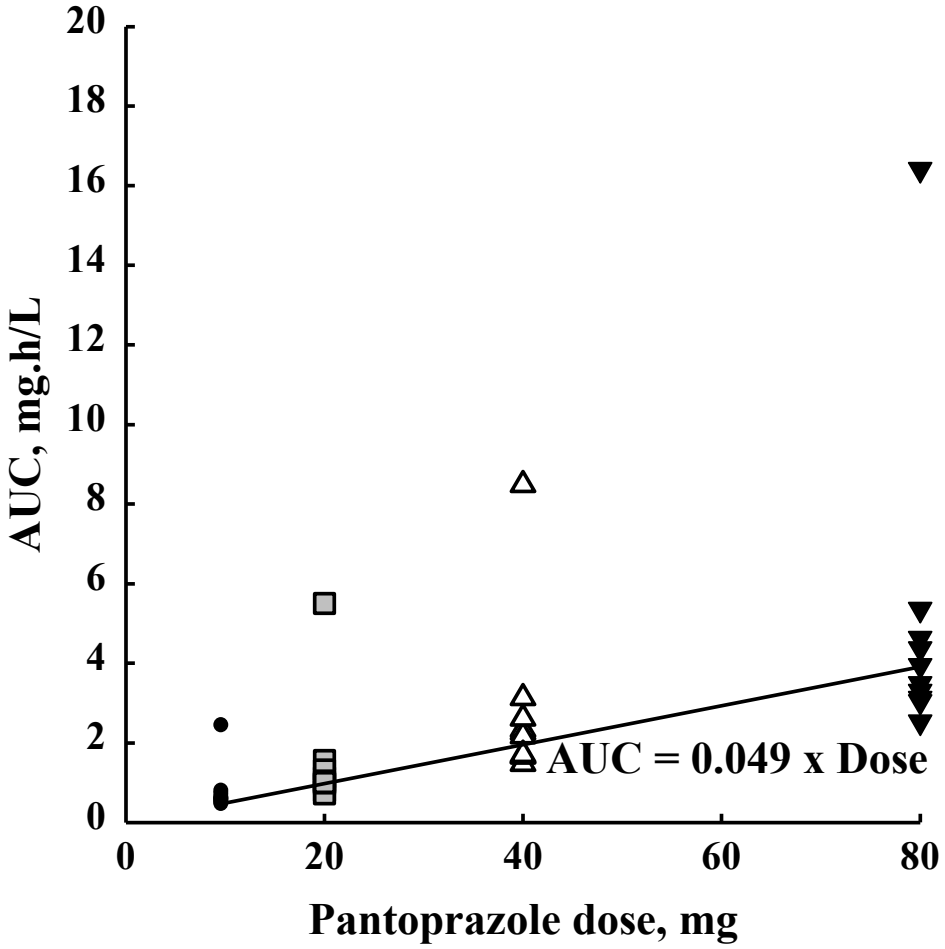


Figure 4. AUC after Oral Administration of Increasing Doses of Pantoprazole in 10 Healthy Volunteers (Protocol A9907)



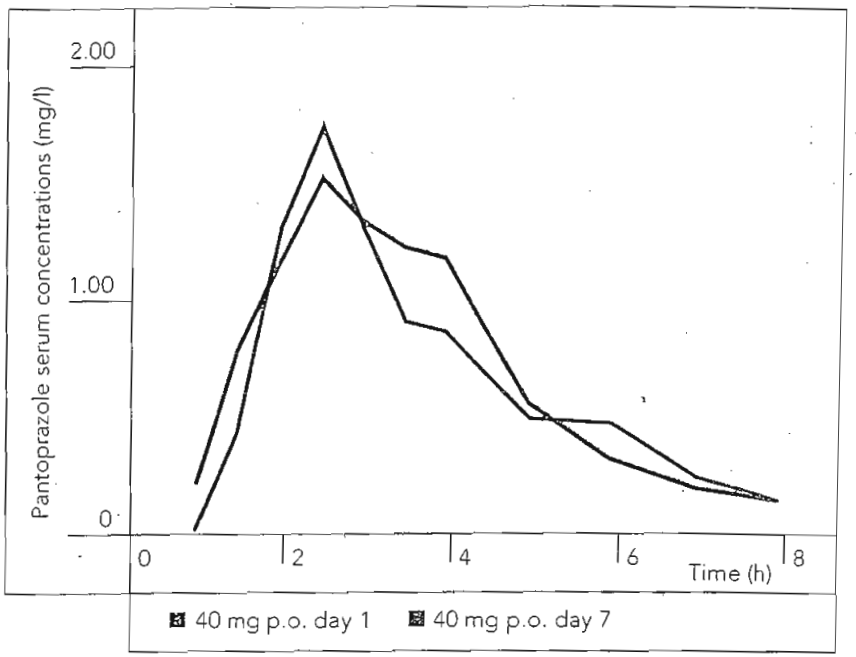
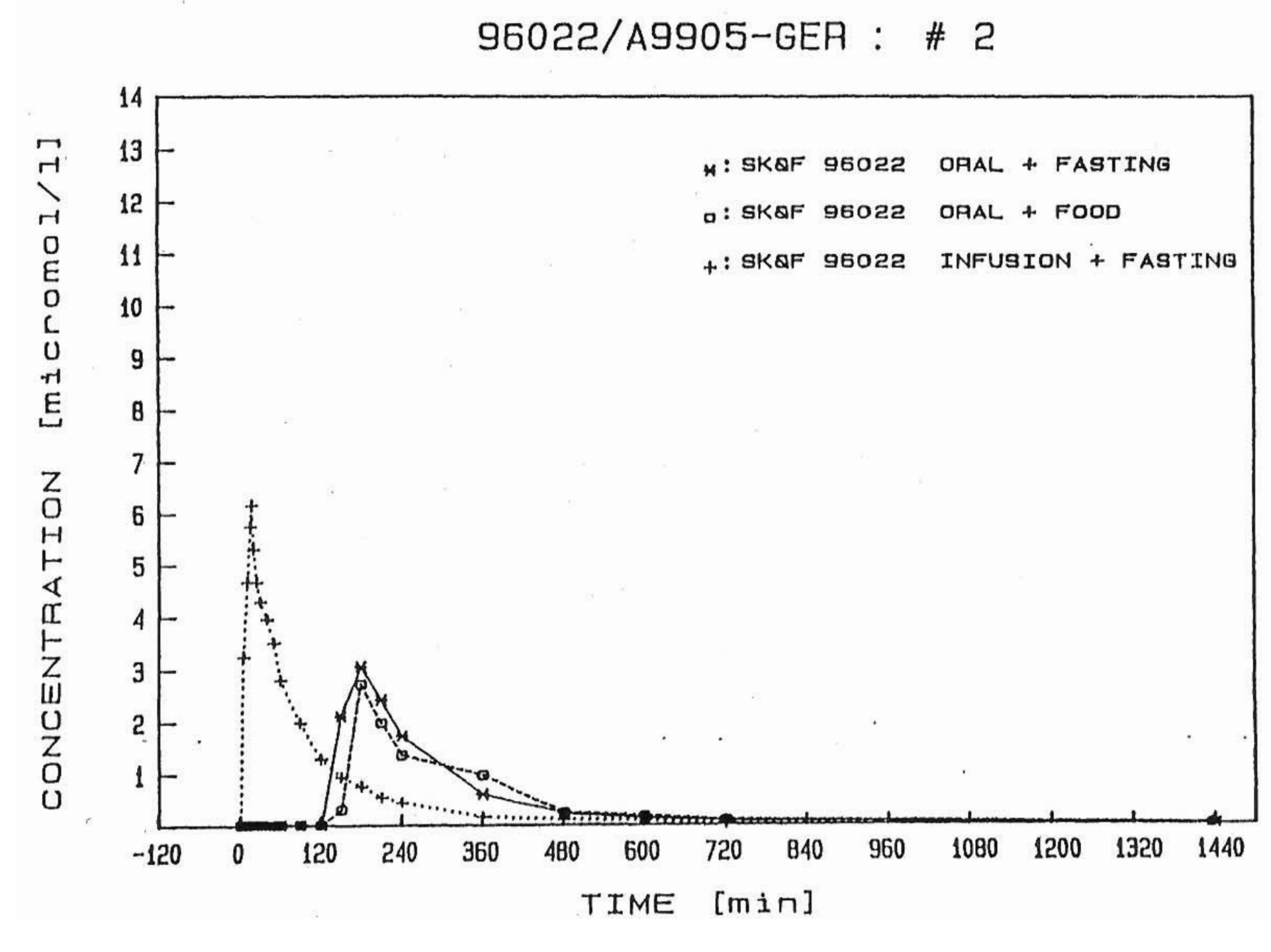


Figure 14 *Mean pantoprazole serum concentrations (n=12) following single (day 1) and repeated (day 7) oral intake of 40 mg.*

ABSORPTION

THE ABSORPTION OF PANTOPRAZOLE IS RAPID, WITH A CMAX OF 2.5 µG/ML THAT OCCURS APPROXIMATELY 2.5 HOURS AFTER SINGLE OR MULTIPLE ORAL 40-MG DOSES. PANTOPRAZOLE IS WELL ABSORBED; IT UNDERGOES LITTLE FIRST-PASS METABOLISM RESULTING IN AN ABSOLUTE BIOAVAILABILITY OF APPROXIMATELY 77%. PANTOPRAZOLE ABSORPTION IS NOT AFFECTED BY CONCOMITANT ADMINISTRATION OF ANTACIDS. ADMINISTRATION OF PANTOPRAZOLE WITH FOOD MAY DELAY ITS ABSORPTION UP TO 2 HOURS OR LONGER; HOWEVER, THE CMAX AND THE EXTENT OF PANTOPRAZOLE ABSORPTION (AUC) ARE NOT ALTERED. THUS, PANTOPRAZOLE MAY BE TAKEN WITHOUT REGARD TO TIMING OF MEALS


96022/A9905-GER : # 2
CONCENTRATION [micromol/l]
TIME [min]
14
13
12
11
10
9
8
7
6
5
4
3
2
1
-120
0
120
240
360
480
600
720
840
960
1080
1200
1320
1440
: SK&F 96022 ORAL + FASTING
: SK&F 96022 ORAL + FOOD
: SK&F 96022 INFUSION + FASTING

DISTRIBUTION

THE APPARENT VOLUME OF DISTRIBUTION OF PANTOPRAZOLE IS APPROXIMATELY 11.0-23.6L, DISTRIBUTING MAINLY IN EXTRACELLULAR FLUID. THE SERUM PROTEIN BINDING OF PANTOPRAZOLE IS ABOUT 98%, PRIMARILY TO ALBUMIN.

METABOLISM

PANTOPRAZOLE IS EXTENSIVELY METABOLIZED IN THE LIVER THROUGH THE CYTOCHROME P450 (CYP) SYSTEM. PANTOPRAZOLE METABOLISM IS INDEPENDENT OF THE ROUTE OF ADMINISTRATION (INTRAVENOUS OR ORAL). THE MAIN METABOLIC PATHWAY IS DEMETHYLATION, BY CYP2C19, WITH SUBSEQUENT SULFATION; OTHER METABOLIC PATHWAYS INCLUDE OXIDATION BY CYP3A4. THERE IS NO EVIDENCE THAT ANY OF THE PANTOPRAZOLE METABOLITES HAVE SIGNIFICANT PHARMACOLOGIC ACTIVITY.

CYP2C19 DISPLAYS A KNOWN GENETIC POLYMORPHISM DUE TO ITS DEFICIENCY IN SOME SUB-POPULATIONS (E.G. 3% OF CAUCASIANS AND AFRICAN-AMERICANS AND 17-23% OF ASIANS). ALTHOUGH THESE SUB-POPULATIONS OF SLOW PANTOPRAZOLE METABOLIZERS HAVE ELIMINATION HALF-LIFE VALUES OF 3.5 TO 10.0 HOURS, THEY STILL HAVE MINIMAL ACCUMULATION (≤ 23%) WITH ONCE DAILY DOSING.

Figure 6. Mean Pharmacokinetic Profiles of Pantoprazole and its Major Metabolites After IV or Oral Administration in Healthy Subjects

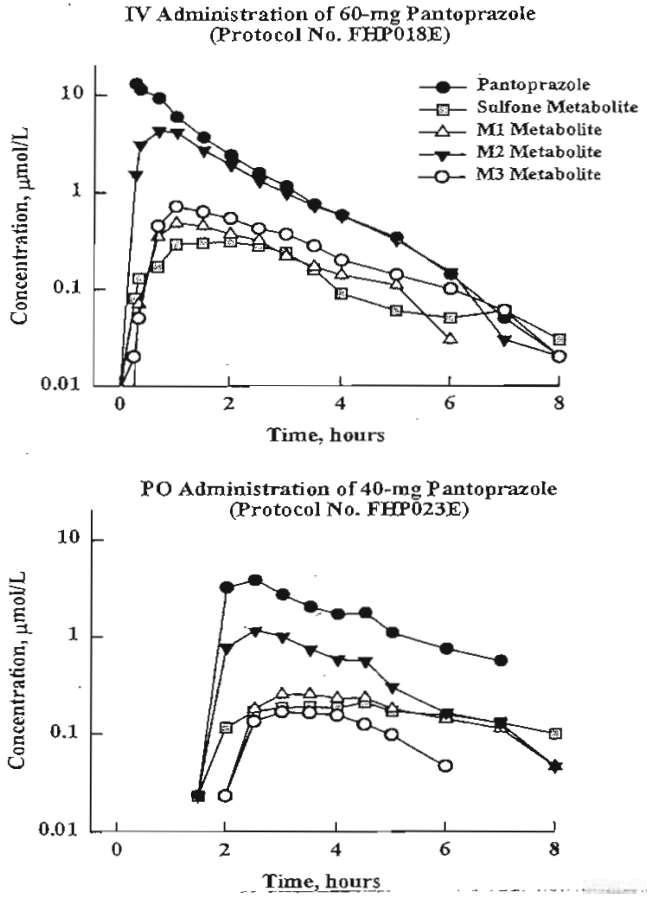
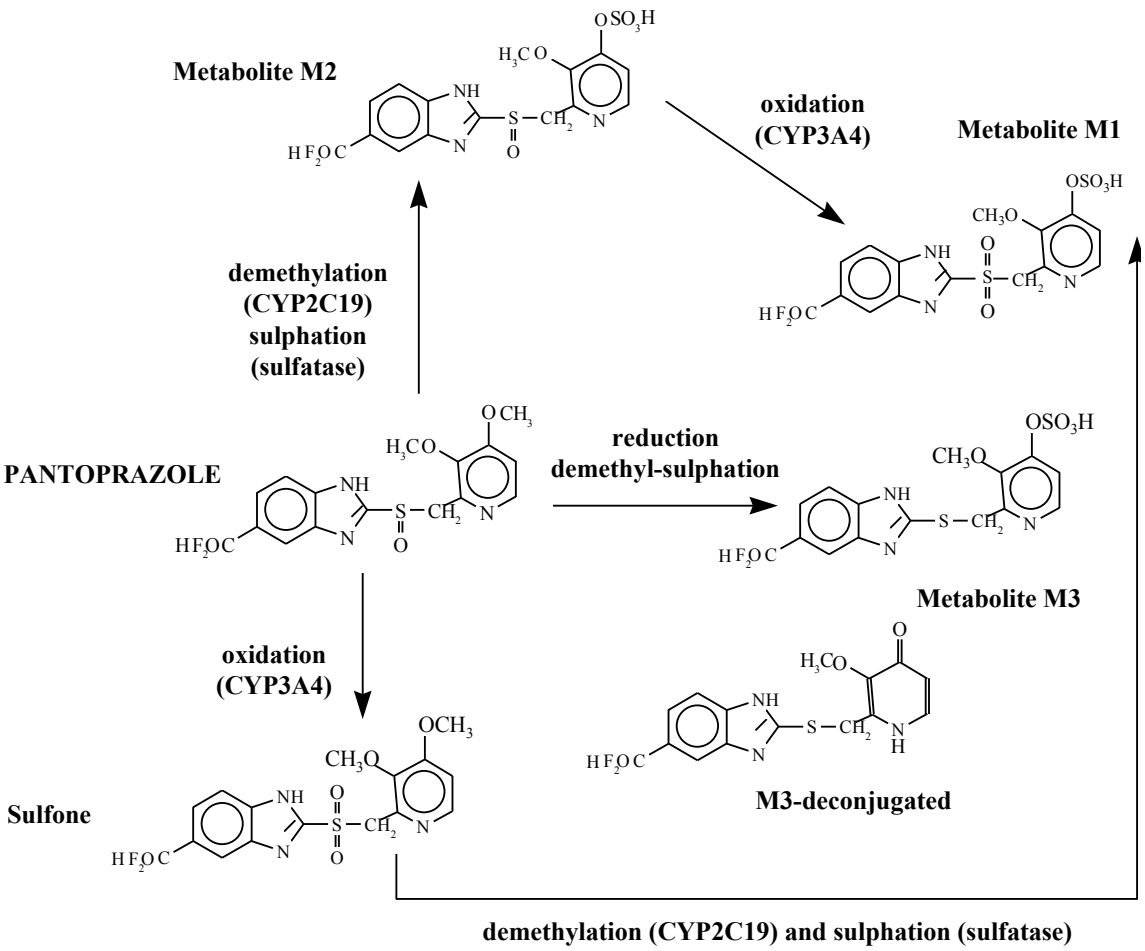


Figure 5. Metabolism of Pantoprazole in Human Subjects



ELIMINATION

AFTER A SINGLE ORAL OR INTRAVENOUS DOSE OF 14C-LABELED PANTOPRAZOLE TO HEALTHY, NORMAL METABOLIZER VOLUNTEERS, APPROXIMATELY 71% OF THE DOSE WAS EXCRETED IN THE URINE WITH 18% EXCRETED IN THE FECES THROUGH BILIARY EXCRETION. THERE WAS NO RENAL EXCRETION OF UNCHANGED PANTOPRAZOLE.

SPECIAL POPULATIONS

GERIATRIC

ONLY SLIGHT TO MODERATE INCREASES IN PANTOPRAZOLE AUC (43%) AND CMAX (26%) WERE FOUND IN ELDERLY VOLUNTEERS (64 TO 76 YEARS OF AGE) AFTER REPEATED ORAL ADMINISTRATION, COMPARED WITH YOUNGER SUBJECTS. NO DOSAGE ADJUSTMENT IS RECOMMENDED BASED ON AGE.

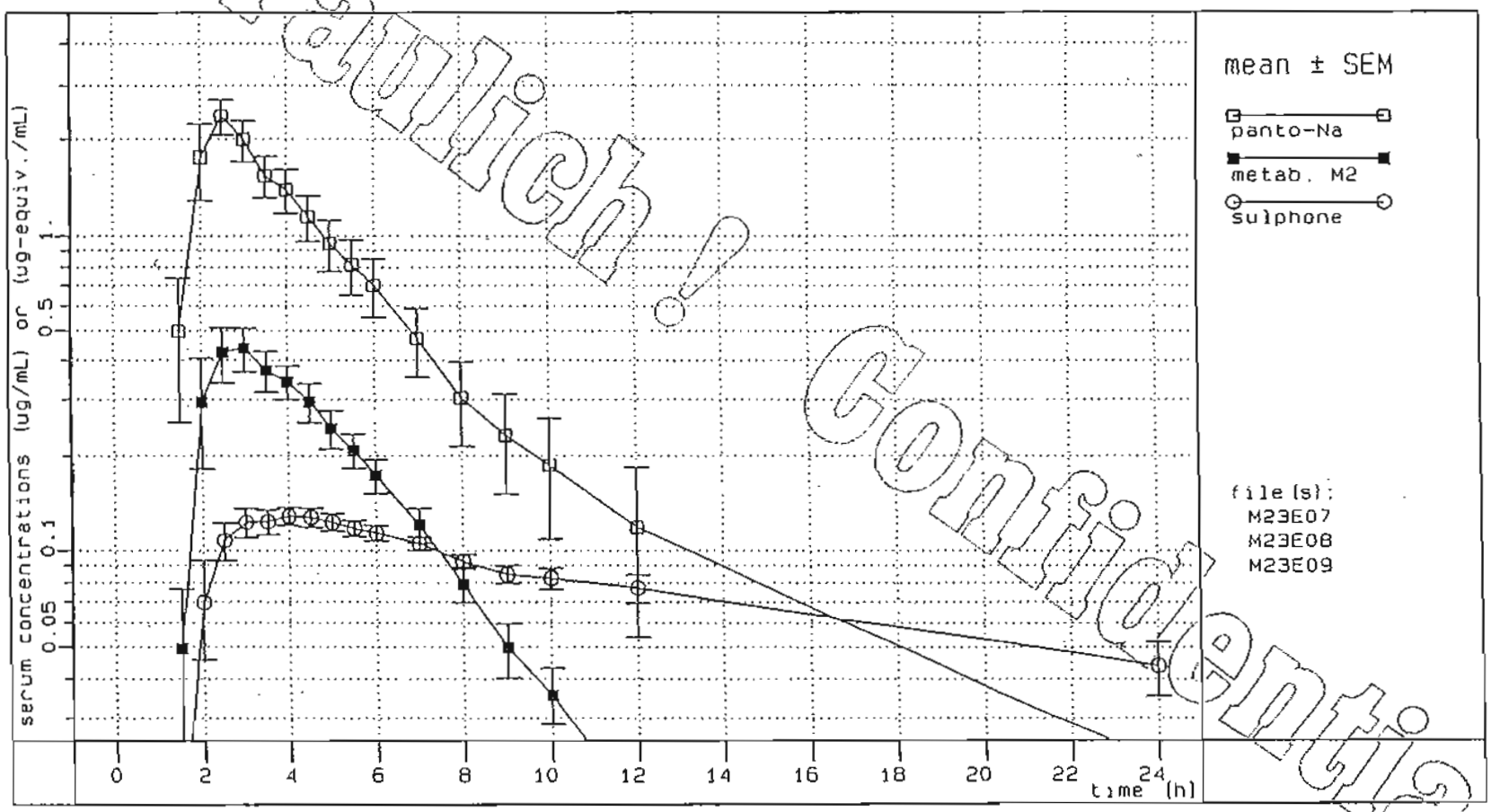


Fig. 5: mean (SEM) serum concentrations of pantoprazole-Na, metabolite M2 and the sulphone metabolite in elder healthy subjects after the 1st oral dose (day 1) of 40 mg (FHP017/II)

INN (Proiect / Compound)
Pantoprazole/BY1023

Report No.
120/93

SPECIAL POPULATIONS

PEDIATRIC

IN A POPULATION PHARMACOKINETIC ANALYSIS, CLEARANCE VALUES IN CHILDREN 1 TO 5 YEARS OLD HAD A MEDIAN VALUE OF 2.4 L/HR. FOLLOWING A 1.2 MG/KG DOSE, THE PLASMA CONCENTRATIONS OF PANTOPRAZOLE WERE HIGHLY VARIABLE AND THE MEDIAN TIME TO PEAK PLASMA CONCENTRATION WAS 3 TO 6 HOURS. THE SYSTEMIC EXPOSURE WAS HIGHER IN PATIENTS LESS THAN 1 YEAR OF AGE WITH GERD; THE APPARENT CLEARANCE INCREASED WITH AGE COMPARED TO ADULTS (MEDIAN CLEARANCE: 0.6 L/hr, RANGE 0.03 TO 3.2 L/HR).

THE GEOMETRIC MEAN AUC ESTIMATED FROM A POPULATION PK ANALYSIS AFTER A 40 MG PROTONIX TABLET WAS ABOUT 39% AND 10% HIGHER RESPECTIVELY IN 6 TO 11 AND 12 TO 16 YEAR-OLD CHILDREN, COMPARED TO ADULTS.

PK PARAMETERS IN CHILDREN AND ADOLESCENTS WITH GERD RECEIVING 40 MG PROTONIX TABLETS

	6-11 YEARS	12-16 YEARS
Cmax (ug/mL)	1.8	1.8
Tmax (h)	2.0	2.0
AUC (ug.h/mL)	6.9	5.5
CL/F (L/h)	6.6	6.8

GENDER

THERE IS A MODEST INCREASE IN PANTOPRAZOLE AUC AND CMAX IN WOMEN COMPARED TO MEN. HOWEVER, WEIGHT-NORMALIZED CLEARANCE VALUES ARE SIMILAR IN WOMEN AND MEN. NO DOSAGE ADJUSTMENT IS NEEDED BASED ON GENDER (ALSO SEE USE IN WOMEN).

RENAL IMPAIRMENT

IN PATIENTS WITH SEVERE RENAL IMPAIRMENT, PHARMACOKINETIC PARAMETERS FOR PANTOPRAZOLE WERE SIMILAR TO THOSE OF HEALTHY SUBJECTS. NO DOSAGE ADJUSTMENT IS NECESSARY IN PATIENTS WITH RENAL IMPAIRMENT OR IN PATIENTS UNDERGOING HEMODIALYSIS.

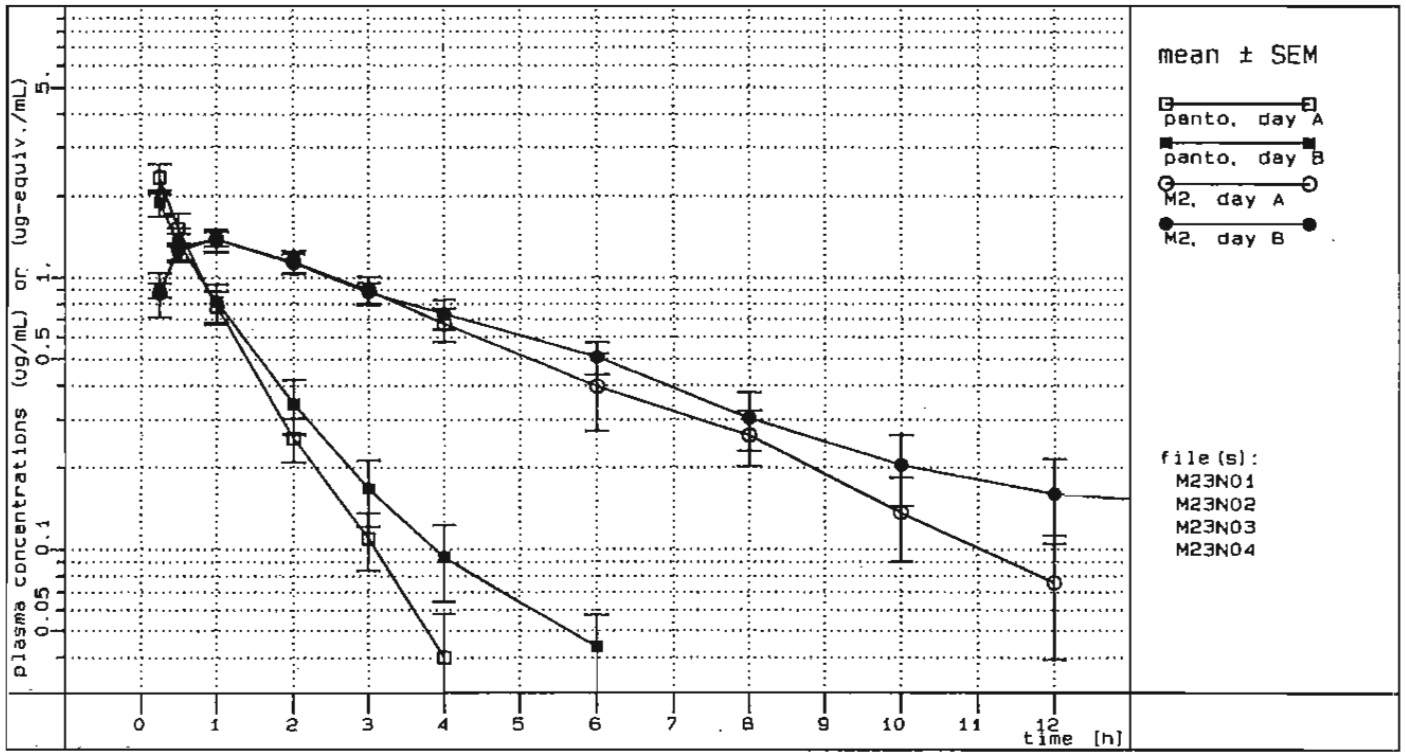


Fig. 1: plasma concentrations of pantoprazole-Na and metabolite M2 after single bolus injection of 40 mg to patients with renal impairment, without (day A) or with (day B) dialysis

HEPATIC IMPAIRMENT

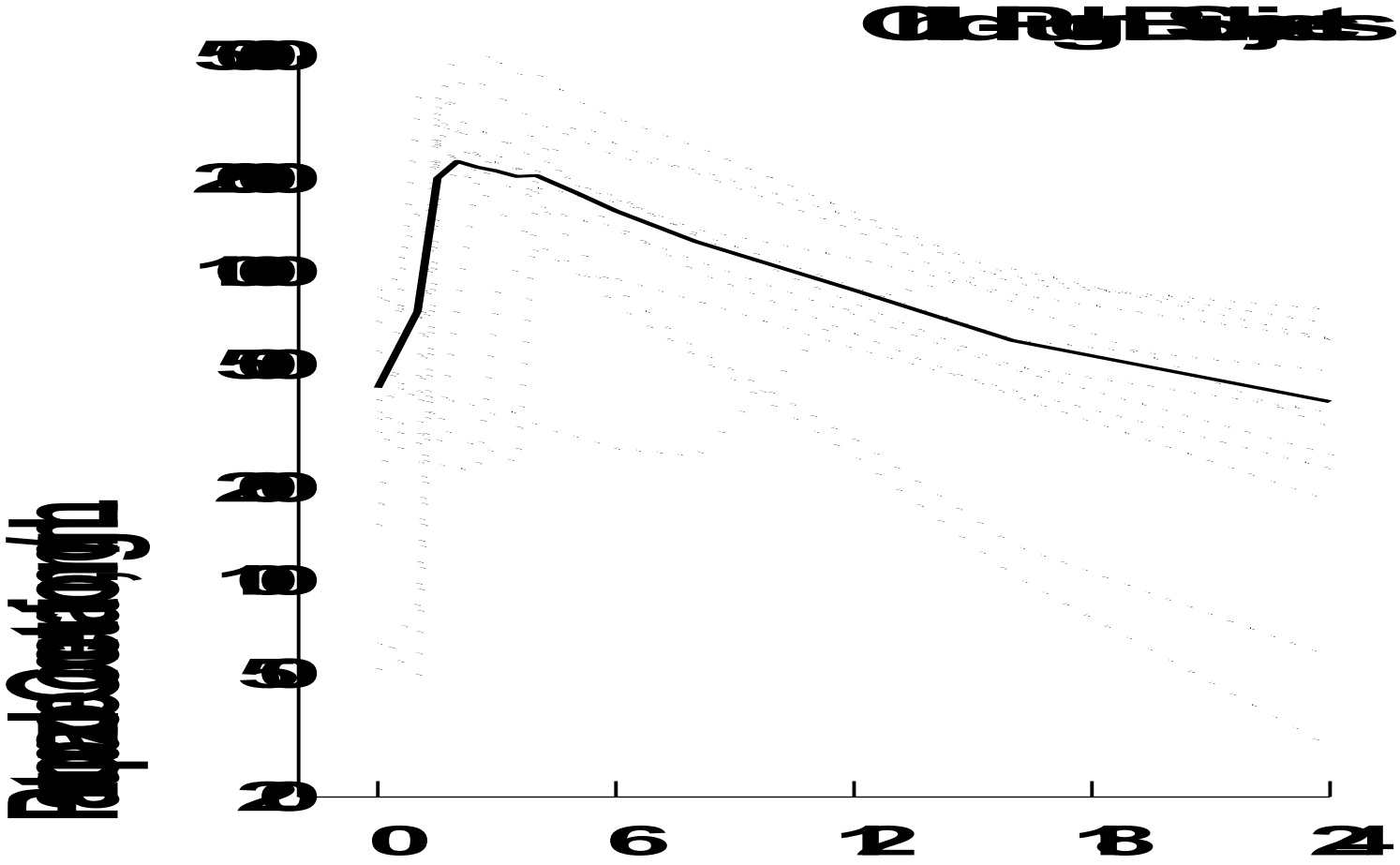
IN PATIENTS WITH MILD TO MODERATE HEPATIC IMPAIRMENT, MAXIMUM PANTOPRAZOLE CONCENTRATIONS INCREASED ONLY SLIGHTLY (1.5-FOLD) RELATIVE TO HEALTHY SUBJECTS. ALTHOUGH SERUM HALF-LIFE VALUES INCREASED TO 7-9 HOURS AND AUC VALUES INCREASED BY 5- TO 7-FOLD IN HEPATIC-IMPAIRED PATIENTS, THESE INCREASES WERE NO GREATER THAN THOSE OBSERVED IN SLOW CYP2C19 METABOLIZERS, WHERE NO DOSAGE FREQUENCY ADJUSTMENT IS WARRANTED. THESE PHARMACOKINETIC CHANGES IN HEPATIC-IMPAIRED PATIENTS RESULT IN MINIMAL DRUG ACCUMULATION FOLLOWING ONCE DAILY MULTIPLE-DOSE ADMINISTRATION.

SUBJECT CHARACTERISTICS

	Child-Pugh B	Child-Pugh C	Slow CYP 2C19 Metabolizers
N	13	9	17
Gender	11 M, 2 F	9 M	15 M, 2 F
Age, yr	52 ± 5.9[a]	48 ± 8.2	42 ± 18
Weight, kg	86 ± 14	83 ± 10	79 ± 8.1
Child-Pugh Score	8.2 ± 0.7	10.6 ± 0.9	--
Bilirubin, mg/L	13.2 ± 7.0	28.5 ± 14.4	--
Albumin, g/L	38.2 ± 4.7	27.8 ± 5.5	--
PT, sec	13.9 ± 2.2	16.2 ± 3.4	--
Ascites, severity[b]	2.8 ± 0.4	2.7 ± 0.5	--
Encephalopathy, severity [b]	1.8 ± 0.4	1.9 ± 0.3	--

a: mean ± SD
b: severity based on scale of 1 to 3 where 1 = none, 2 = slight and 3 = moderate to severe

Mean and Individual Concentration – Time Profile on Day 4 Following Daily Administration of 40 mg of Pantoprazole



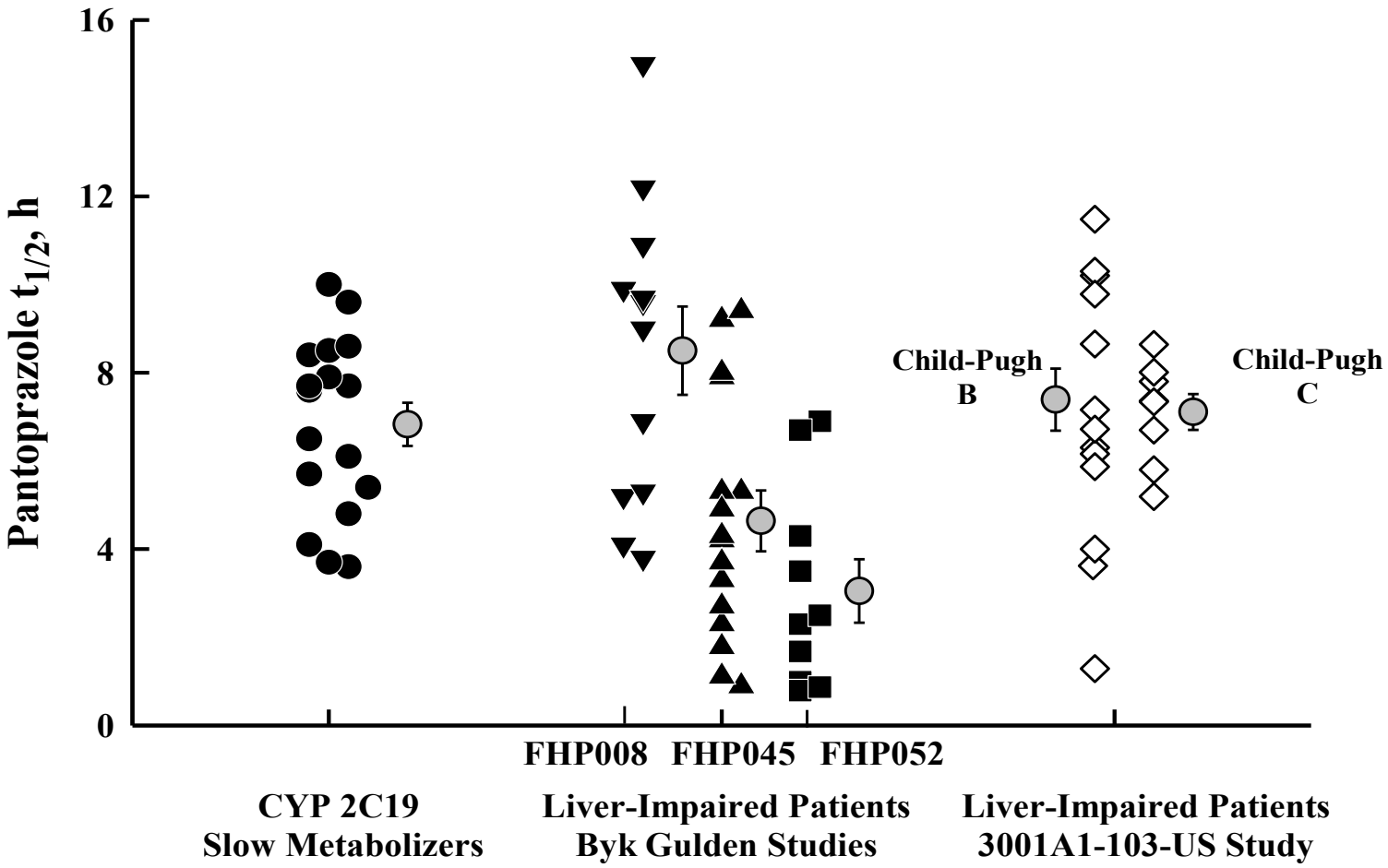
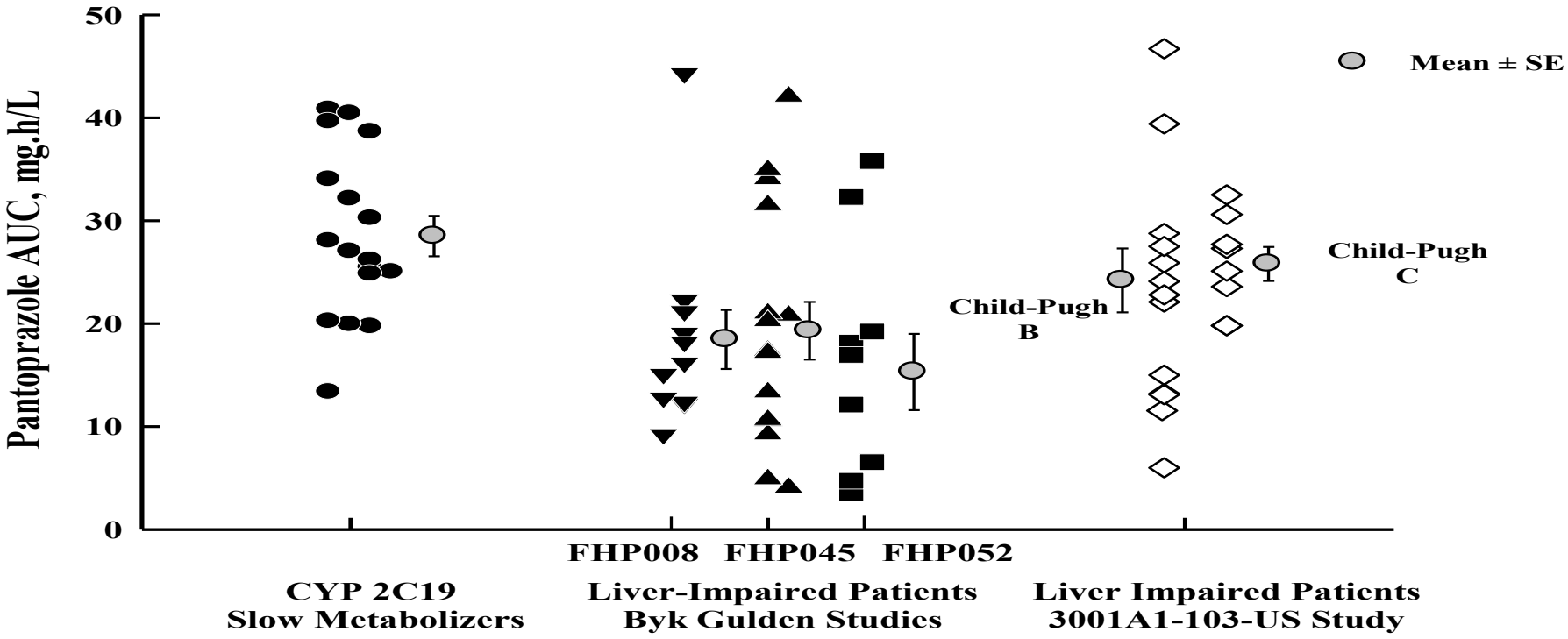

Pantoprazole $t_{1/2}$, h
16
12
8
4
0
Child-Pugh B
Child-Pugh C
FHP008
FHP045
FHP052
CYP 2C19 Slow Metabolizers
Liver-Impaired Patients Byk Gulden Studies
Liver-Impaired Patients 3001A1-103-US Study

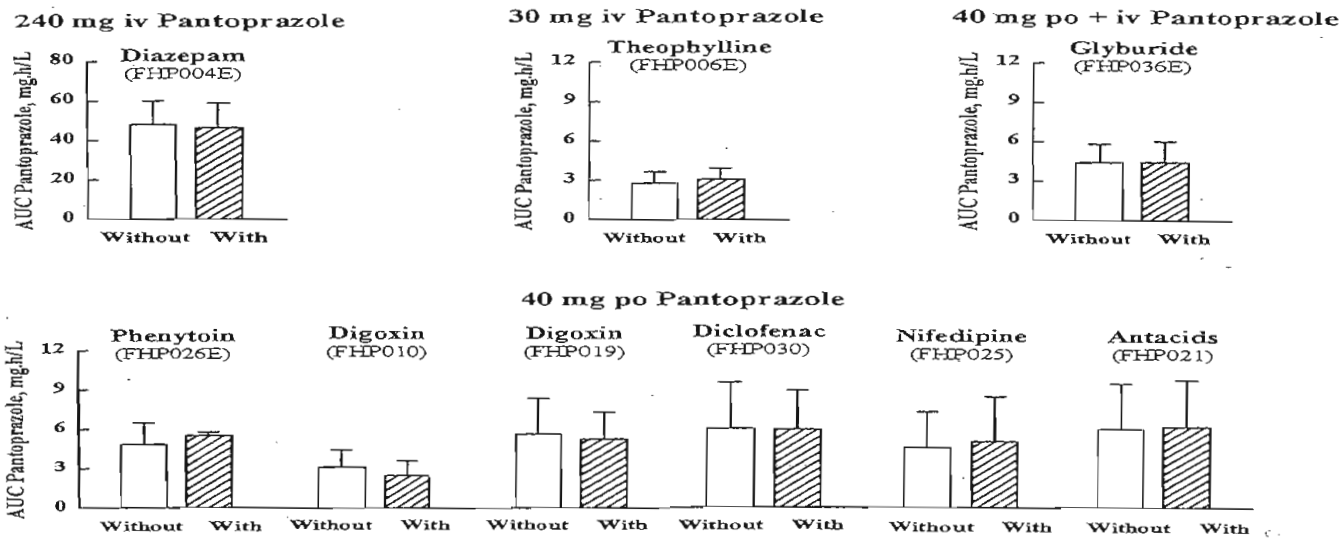
FIGURE 6.1.3.4B: Comparison of Pantoprazole Area Under the Concentration-Time Curve Values in Liver-Impaired Subjects and CYP 2C19 Slow Metabolizers Receiving 20 or 40 mg Oral Pantoprazole: Values Adjusted to a 40 mg Dose



DRUG-DRUG INTERACTIONS

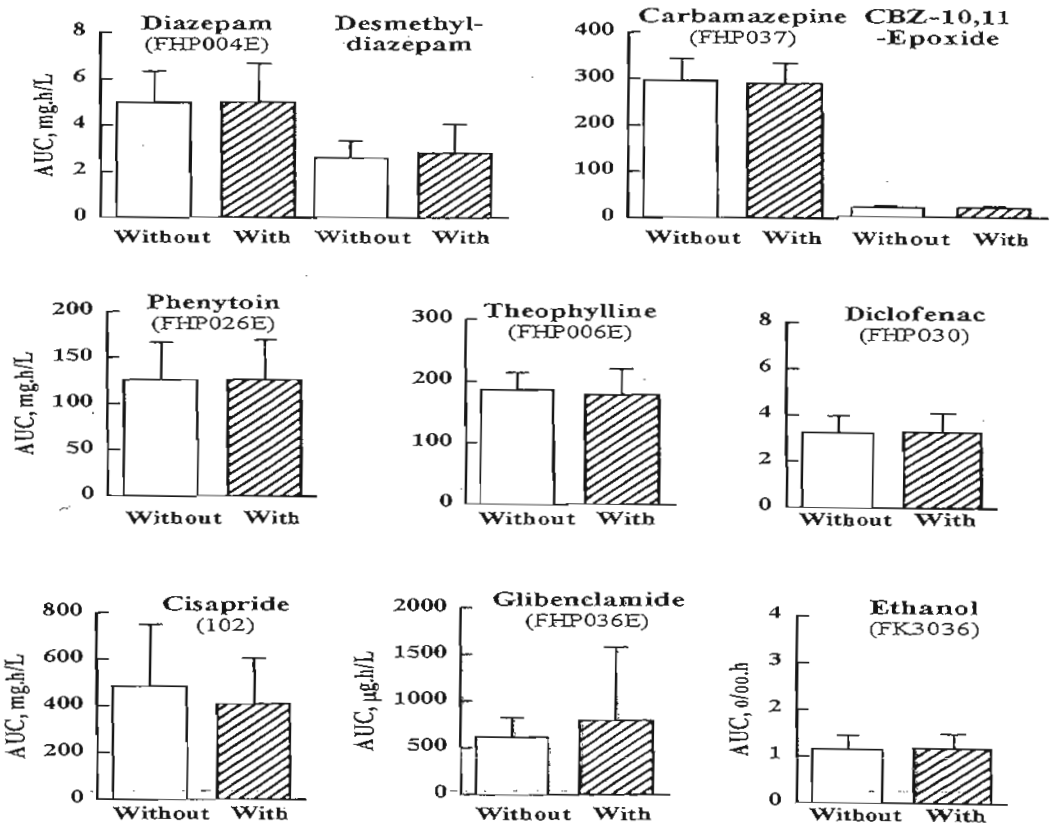
PANTOPRAZOLE IS METABOLIZED MAINLY BY CYP2C19 AND TO MINOR EXTENTS BY CYPS 3A4, 2D6 AND 2C9. IN *IN VIVO* DRUG-DRUG INTERACTION STUDIES WITH CYP2C19 SUBSTRATES (DIAZEPAM [ALSO A CYP3A4 SUBSTRATE] AND PHENYTOIN [ALSO A CYP3A4 INDUCER]), NIFEDIPINE (A CYP3A4 SUBSTRATE), METOPROLOL (A CYP2D6 SUBSTRATE), DICLOFENAC (A CYP2C9 SUBSTRATE) AND THEOPHYLLINE (A CYP1A2 SUBSTRATE) IN HEALTHY SUBJECTS, THE PHARMACOKINETICS OF PANTOPRAZOLE WERE NOT SIGNIFICANTLY ALTERED. IT IS, THEREFORE, EXPECTED THAT OTHER DRUGS METABOLIZED BY CYPS 2C19, 3A4, 2D6, 2C9 AND 1A2 WOULD NOT SIGNIFICANTLY AFFECT THE PHARMACOKINETICS OF PANTOPRAZOLE.

Figure 7. Pantoprazole Exposure (Mean ± SD) With or Without Coadministration of Other Drugs (Protocol Number)



***IN VIVO* STUDIES ALSO SUGGEST THAT PANTOPRAZOLE DOES NOT SIGNIFICANTLY AFFECT THE KINETICS OF OTHER DRUGS (CISAPRIDE, THEOPHYLLINE, DIAZEPAM [AND ITS ACTIVE METABOLITE, DESMETHYLDIAZEPAM], PHENYTOIN, WARFARIN, METOPROLOL, NIFEDIPINE, CARBAMAZEPINE AND ORAL CONTRACEPTIVES) METABOLIZED BY CYPS 2C19, 3A4, 2C9, 2D6 AND 1A2. THEREFORE, IT IS EXPECTED THAT PANTOPRAZOLE WOULD NOT SIGNIFICANTLY AFFECT THE PHARMACOKINETICS OF OTHER DRUGS METABOLIZED BY THESE ISOZYMES. DOSAGE ADJUSTMENT OF SUCH DRUGS IS NOT NECESSARY WHEN THEY ARE CO-ADMINISTERED WITH PANTOPRAZOLE. IN OTHER *IN VIVO* STUDIES, DIGOXIN, ETHANOL, GLYBURIDE, ANTIPYRINE, AND CAFFEINE HAD NO CLINICALLY RELEVANT INTERACTIONS WITH PANTOPRAZOLE.**

Figure 8. Coadministered Drug Exposure (Mean ± SD) With or Without Pantoprazole Administration (Protocol Number)



PANTOPRAZOLE DRUG INTERACTION STUDIES

Conclusion: No Pharmacokinetic or Pharmacodynamic Interactions Observed

Drug Tested	Major Cytochrome P450
Theophylline	1A2
Caffeine	1A2
Nifedipine	3A4
Clarithromycin	3A4
Midazolam	3A4
Oral Contraceptive	3A4
Antipyrine	3A4
Warfarin	2C9
Phenytoin	2C9
Carbamazepine	2C9
Diclofenac	2C9
Phenprocoumon	2C9
Diazepam	2C19
Metoprolol	2D5
Ethanol	2E1
Glyburide	Unknown
Metronidazole	Unknown
Digoxin	None
Amoxicillin	None
Antacid	None

CONCLUSION

MOST NDAs REQUIRE AN EXTENSIVE CLINICAL PHARMACOLOGY PROGRAM FOR APPROVAL. WHILE THERE IS A LARGE SET OF DATA TO REFERENCE, A CLEAR SUMMARY WITH IMPORTANT AND RELEVANT DATA IS NECESSARY TO HIGHLIGHT KEY PRESCRIBING INFORMATION.

Back-Up Slides

Highlights

Concise, one-half page summary of information in FPI

- Limitations Statement
- Product Names and Date of Initial US Approval
- Boxed Warning
- Recent Major Changes
- Indications and Usage
- Dosage & Administration
- Dosage Forms & Strengths
- Contraindications
- Warnings & Precautions
- Adverse Reactions (listing of most common ARs)
- Drug Interactions
- Use in Specific Populations
- Patient Counseling Information Statement

Drug Interaction Information

- Details in section 7: *Drug Interactions*
- Other sections briefly discuss interactions and cross-reference details
- Dose adjustments in section 2: *Dosage and Administration*
- Study details in section 12: *Clinical Pharmacology*

Where do I find Dose Adjustment Information?

- Section 2 (DOSAGE AND ADMINISTRATION)

  Recommended dose regimen and dose adjustments for the drug.

- Section 7 (DRUG INTERACTIONS)

  May include instructions for dose adjustments for concomitant medications.

Mean and Individual Concentration – Time Profile on Day 4 Following Daily Administration of 40 mg of Pantoprazole