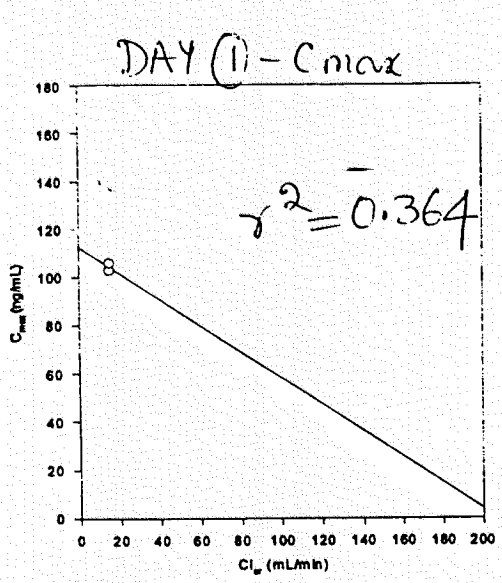
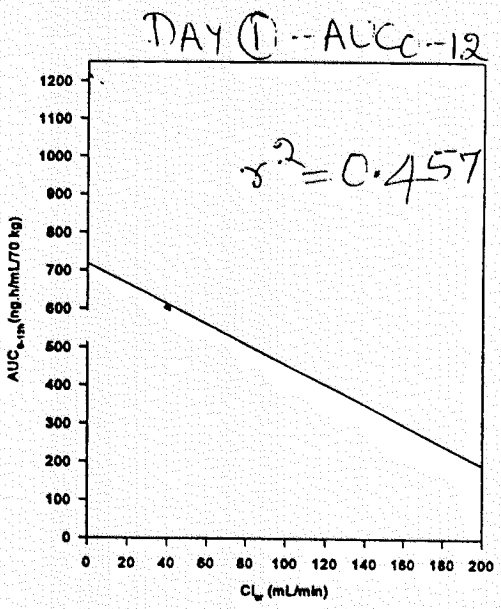
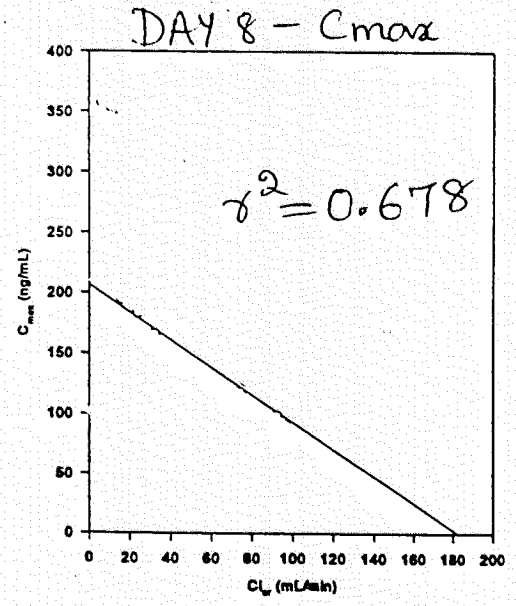
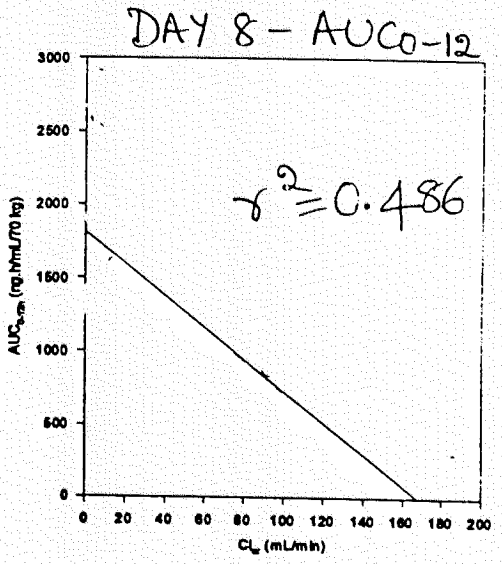
Plots of the relationship between PK parameters of OPC-13213 vs. creatinine clearance are shown in the following 4 figures:









PK of cilostazol was similar in patients with renal impairment and normal subjects (except for free fraction of cilostazol in plasma). The free fraction was significantly higher in the severe renal disease group compared to the normal group (4.39% vs. 3.47%, a 27% increase) or mild disease groups (4.39% vs. 3.55%, a 24% increase). Although not statistically significant, the cilostazol Cmax and AUC are lower in severe renal disease group on day 8 by 29% and 39%. Unbound cilostazol clearance ($Cl/F_{unbound}$) is 59% higher in the severe renal disease group as compared to the normal group. Since unchanged cilostazol is not excreted in urine, renal

impairment does not have any impact by itself except possibly by alteration of protein binding or hepatic metabolism. No correlation between cilostazol PK and creatinine clearance was observed.

PK of OPC-13015 was similar in patients with renal impairment and normal subjects (except for AUC0-12). AUC was significantly larger in the normal and mild groups compared to the severe impairment group. On day 8, OPC-13015 Cmax and AUC0-12 were 41% and 47% lower in severe renal disease group as compared to the normal renal function group. Since unchanged OPC-13015 is not primarily excreted in urine, renal impairment does not have any impact by itself except possibly by alteration of protein binding or hepatic metabolism. A poor correlation between cilostazol PK and creatinine clearance was observed.

A significant increase in OPC-13213 Cmax and AUC at steady state was observed with a change of +173% and +209% in subjects with severe renal impairment compared to normal subjects. The renal clearance differed significantly between the renal function groups with decreased renal clearance as the degree of renal insufficiency increased. A reasonably good correlation between the PK of OPC-13213 and creatinine clearance was observed. This is expected since the primary metabolite excreted in urine is OPC-13213.

Evaluation of relative contribution of cilostazol and its active metabolites can be made in subjects with various degrees of renal impairment based on PK in these patients, the relative pharmacological activity of the 3 moieties and the fraction unbound in plasma. OPC-13015 is 3 - 4 fold more potent than cilostazol, whereas OPC-13213 is 30 - 50% as potent as cilostazol. OPC-13213 is substantially unbound (%fu = 34%) compared to cilostazol and OPC-13015 (%fu = 3% and 4% respectively). This evaluation is provided in the following table. This information should be interpreted with due caution, since the information is based on in vitro data obtained from different studies (not necessarily from the patients in this study).

Evaluation of the Relative Contribution of Cilostazol, OPC-13015 and OPC-13213 to the In Vivo Pharmacologic Effects of Oral Cilostazol for Subjects with Varying Degrees of Renal Impairment

Degree of Renal Failure	Parameter	Inhibition of platelet aggregation			
		Cilostazol	OPC-13015	OPC-13213	Total
Normal	Free Fraction+	0.0258	0.0363	0.339	
	Normalized Activity* for Cmax	23.4	20.9	9.0	53.3
	Normalized Activity* for AUC_{0-12h}	171	190	68.7	429
Mild	Normalized Activity* for Cmax	20.7	17.2	10.8	48.6
	Normalized Activity* for AUC_{0-12h}	135	167	84.6	387
Moderate	Normalized Activity* for Cmax	21.9	17.2	18.9	57.9
	Normalized Activity* for AUC_{0-12h}	161	162	168	491
Severe	Normalized Activity* for Cmax	16.6	12.5	24.5	53.6
	Normalized Activity* for AUC_{0-12h}	104	99.3	213	415

+Protein binding is not from patients but from the only study which evaluated all three analytes (Report 1182PB)

Normalized activity = (pharmacokinetic parameter value)(free fraction)*(relative potency), Relative potency for inhibition of platelet aggregation for cilostazol/OPC-13015/OPC-13213 = 1/3.5/0.33

Conclusion: Renal impairment has a small effect on cilostazol and OPC-13015 pharmacokinetics. However, a significant increase in OPC-13213 plasma concentrations was observed in patients with renal impairment. Based on relative exposure of cilostazol and its metabolites and based on their relative potency, dosage adjustment in patients with renal impairment is not necessary. However, caution should be exercised when administering cilostazol to patients with renal impairment especially since the relative potency based on safety for each moiety is not well known.

Comments:

1. Effect of dialysis on the pharmacokinetics of cilostazol and its metabolites has not been evaluated in this study.

STUDY 21-94-304: (STUDY IN HEPATICALLY IMPAIRED PATIENTS):

STUDY TO EVALUATE THE PHARMACOKINETICS OF 100 MG CILOSTAZOL (OPC-13013) AFTER SINGLE ORAL DOSE ADMINISTRATION IN VOLUNTEERS WITH IMPAIRED LIVER FUNCTION COMPARED WITH HEALTHY CONTROLS

Volumes: 77 to 79
Study ID: 21-94-304
Investigators:
Clinical Site:
Objective:

To compare the pharmacokinetics and safety of cilostazol and its major metabolites in subjects with impaired liver function and healthy controls.

Drug Dosage Forms:
Cilostazol 2 x 50 mg tablets, batch # 4K77PB1

Study Design:

This study was an open-label, parallel, nonrandomized, single dose pharmacokinetic study in 12 male subjects of age 25 to 75 years, with impaired and compensated liver function (10 mild and 2 moderately impaired) compared to 12 healthy controls who were matched for gender, age and height.

The stabilized hepatically impaired subjects were selected based on a liver biopsy (histologically confirmed hepatic impairment) or by clinical criteria (e.g. pathological findings in ultrasonic examination of epigastric region, oesophageal varices, splenomegaly, cutaneous manifestation, and lab parameters like SGPT, SGOT, γ-GT, bilirubin, AP, albumin, Quick's test, PTT etc.), a Child-Pugh score between 5 to 10 and impaired hepatic metabolic function as defined by an aminopyrine breath test result of less than 0.6 scale units (% of dose) within the past year.

Grading of severity of liver disease in accordance with **Child-Pugh classification**

Measurement	Numerical score for increasing abnormality		
	1	2	3
Ascitis	None	Mild	Severe
Encephalopathy	None	Slight to moderate	Moderate to severe
Bilirubin (mg/dl)	<2	2 - 3	>3
Albumin (g/dl)	>3.5		<2.8
Prothrombin time, Quick (%)	>70		<40

Addition of above scores for five criteria gives the risk grade by which a subject was classified. Classes A (mild), B (moderate) and C (severe) were defined by the ranges respectively for the sum of scores.

All eligible subjects received a single oral dose of 100 mg cilostazol which was administered together with 240 ml of non-carbonated mineral water. Subjects remained in a fasted condition for 12 hours before and 2 hours after administration of cilostazol.

Blood samples were collected for determination of cilostazol and its metabolite concentrations at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120 and 144 hours post-dosing. Urine was collected post-dosing at 0-24, 24-48, 48-96 and 96-144 hours after drug administration. Plasma and urine samples were analyzed using validated analytical methods. Plasma protein binding was determined using ultrafiltration technique.

Pharmacokinetic parameters of cilostazol, OPC-13015 and OPC-13213 were estimated by non-compartmental methods. All PK parameters including % excreted in urine were compared statistically between the two groups (normal and hepatically impaired) using analysis of variance after logarithmic pre-transformation. The group ratios, in subjects with impaired liver function vs. healthy subjects, were determined along with 90% confidence intervals.

Results:

ASSAY PERFORMANCE (plasma assays): Assay conducted at

1. For plasma cilostazol, OPC-13213 and OPC-13015:
Method used:
Range:
Linearity: Linear within the range.
QC sample levels:

Accuracy:

Precision:

Specificity:

2. For urine cilostazol and its metabolites:
Method used:
Range:
Linearity: Linear within the range,

QC sample levels:

Accuracy:

Precision:

Specificity:

Assays for cilostazol and its metabolites were found to be acceptable.

The 12 subjects with hepatic impairment that were enrolled in the study were classified as mild impairment (n = 10) and moderate impairment (n = 2).

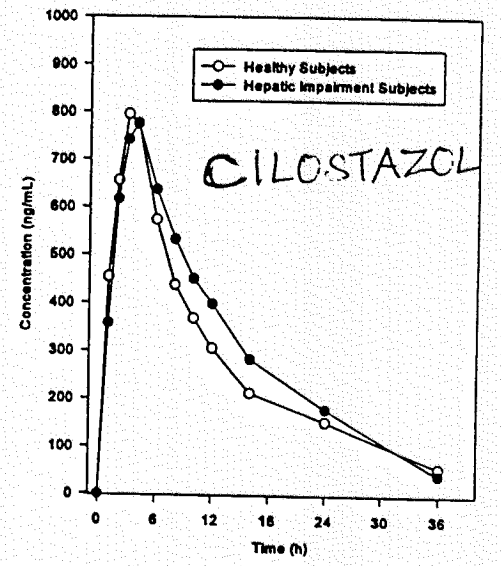
The pharmacokinetic parameters of cilostazol and its major metabolites in plasma for each group of subjects are summarized in the table below.

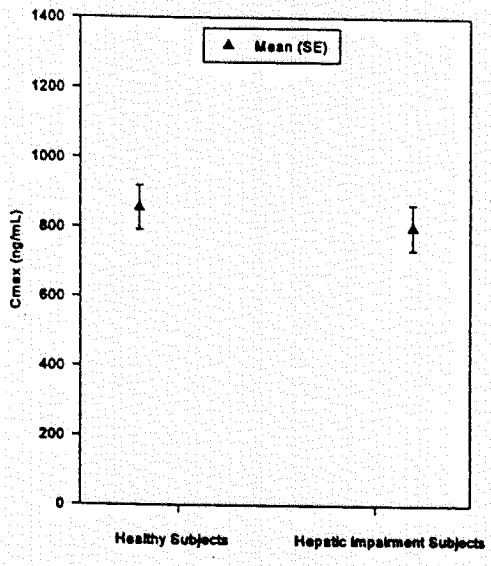
Summary of Pharmacokinetic Parameters of Cilostazol and Its Main Metabolites

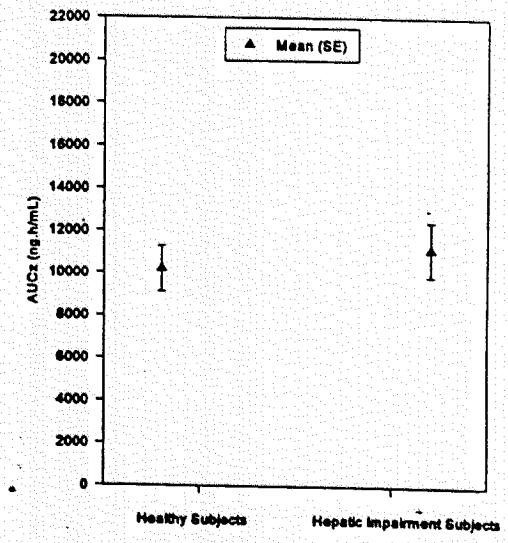
Parameter (units)	Hepatic Impairment Mean (SD) (N=12)	Healthy Subjects Mean (SD) (N=12)	% Ratio of Geometric Means (90% C.I.)
Cilostazol			
C_{max} (ng/ml)	800.5 (226.8)	856.0 (220.7)	92.5(75.9,112.7)
t_{max} (h)	3.5 (2.0-6.0)*	3.5 (2.0-6.0)*	not calculated
$t_{1/2}$ (h)	7.64 (2.06)&	10.92 (5.47)	74.4 (56.3,98.3)
AUC_z (ng·h/ml)	11180 (4458)	10206 (3746)	107.9 (78.5,148.3)
$AUC_{0\text{-infinity}}$ (ng·h/ml)	11835 (4687)&	11492 (3497)&	98.7 (72.3,134.7)
CL/f (ml/min)	175.4 (112.9)&	161.4 (61.5)&	101.3 (74.3,138.2)
CL_z/f (ml/min)	3258.8 (2031.8)&	3375.0 (1402.7)&	91.4 (66.9,124.8)
V_z/f (l)	106.0 (44.3)&	132.9 (54.2)&	79.8 (58.9,108.0)
$V_{z,ss}$/f (l)	1981.2 (828.6)&	2774.3 (1142.5)&	72.0 (52.8,98.0)
OPC-13213			
C_{max} (ng/mL)	60.3 (23.3)	72.5 (26.2)	82.3 (63.2,107.3)
t_{max} (h)	4.0 (3.0-12.0)*	4.0 (3.0-6.0)*	not calculated
AUC_z(ng.h/mL)	841 (812)	742 (319)	87.2 (52.9,143.6)
OPC-13015			
C_{max} (ng/ml)	156.5 (39.6)	141.4 (38.4)	110.8 (89.6,137.0)
$t_{max\ (h)}$	8.0 (4.0-24.0)*	7.0 (4.0-12.0)*	not calculated
$t_{1/2}$ (h)	12.48 (2.76) n = 8	13.12 (6.30) n = 10	104.9 (71.5,154.1)
AUC_z (ng.h/mL)	3635 (1363)	2880 (1319)	128.6 (87.3,189.6)
$AUC_{0\text{-infinity}}$ (ng.h/mL)	4488 (1048) n = 7	3816 (1626) n = 7	125.3 (88.2,178.1)

* median (range).
& n=11

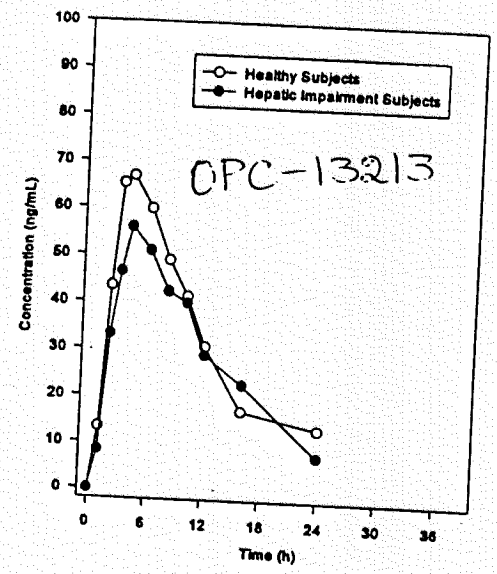
Following figures show the mean plasma concentration-time profiles, Cmax and AUC of cilostazol in healthy subjects and patients with hepatic impairment.

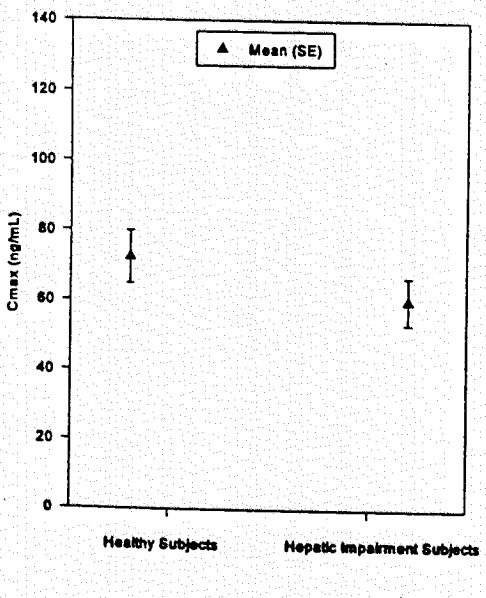


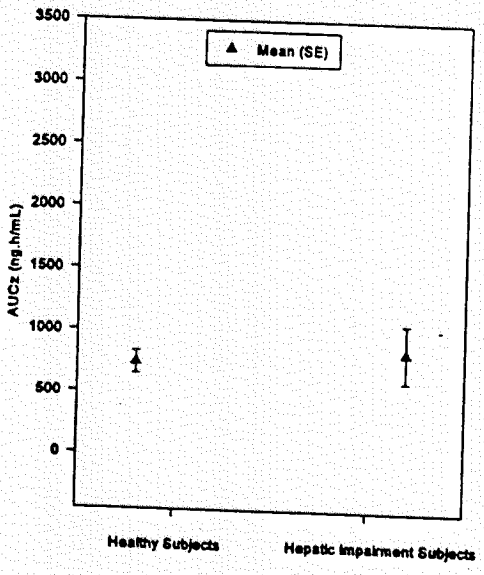




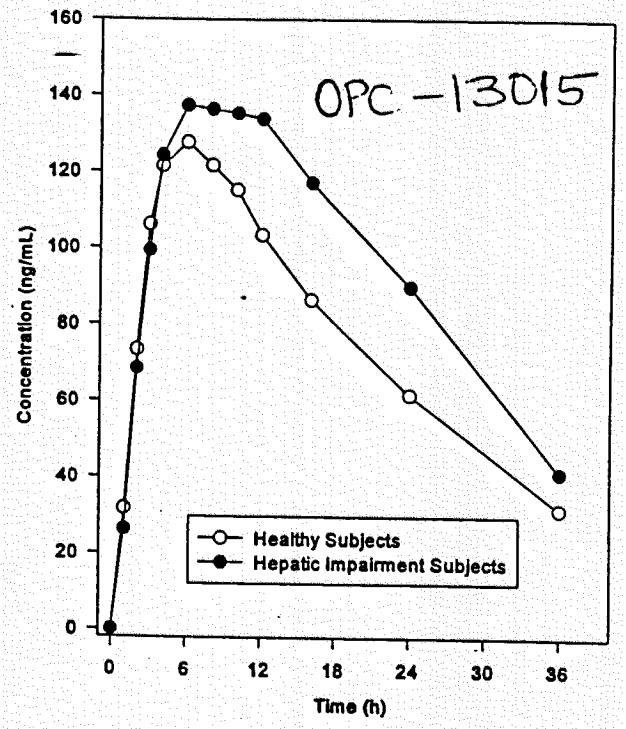
Following figures show the mean plasma concentration-time profiles, Cmax and AUC of OPC-13213 in healthy subjects and patients with hepatic impairment.

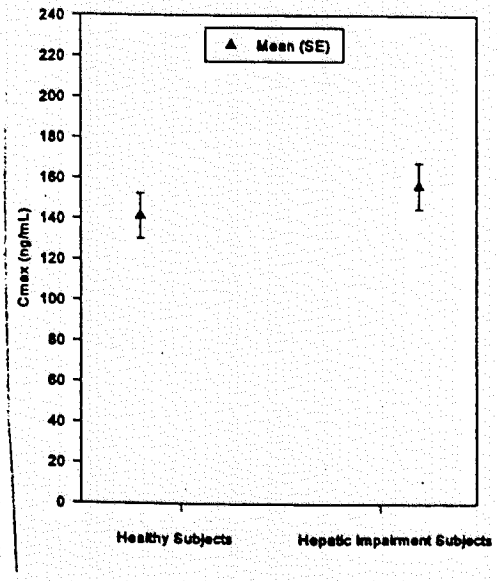


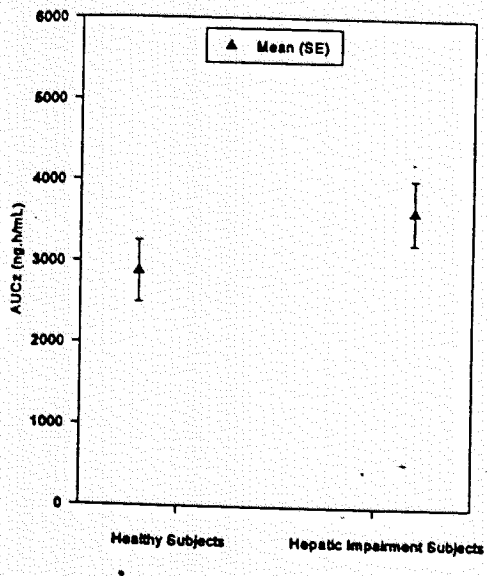




Following figures show the mean plasma concentration-time profiles, Cmax and AUC of OPC-13015 in healthy subjects and patients with hepatic impairment.







URINARY EXCRETION: Concentrations of cilostazol and its metabolites OPC-13211 and OPC-13015 were below quantifiable limits in urine samples. Results for % excretion (%Ae) are summarized in the table below:

Table 6-4: Summary of Mean Cumulative Urinary Excretion of Metabolites Indicated as Percent of the Dose Excretion (%Ae)

Metabolite	Hepatic Impairment Mean (SD) (N=12)	Healthy Subjects Mean (SD) (N=12)	% Ratio of Geometric Means (90% C.I.)
OPC-13213	11.5 (5.04)	17.7 (5.31)	61.2 (46.1,81.2)
OPC-13217	1.33 (0.58)	2.64 (0.84)	47.9 (35.3,64.9)
OPC-13269	3.30 (1.25)	4.33 (0.88)	71.3 (54.8,92.7)
OPC-13326	1.16 (0.66)	1.47 (0.62)	73.8 (49.8,109.1)
OPC-13366	0.99 (0.45)	1.25 (0.32)	73.3 (54.9,97.8)

% protein binding of cilostazol was similar in both treatment groups, with a mean of 94.6% (range 93.8 to 95.3%) in subjects with impaired liver function and 95.2% in healthy subjects.

Conclusion: Results indicate that there is no clinically significant effect of mild hepatic impairment on the pharmacokinetics of cilostazol and its major metabolites. Hence, a dose adjustment in these patients is not necessary. However, only patients with mild impairment have been studied adequately. The patients with moderate and severe hepatic impairment have not been studied. Further, accumulation after multiple dosing in this population has not been studied. In addition, higher concentrations of OPC-13015 were observed in patients with mild hepatic impairment. Hence, patients should be carefully monitored when cilostazol is administered to patients with severe hepatic impairment.

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STUDY 21-93-202: AGE AND GENDER EFFECT

AN OPEN LABEL, MULTIPLE DOSE STUDY OF THE EFFECTS OF AGE AND GENDER ON THE SAFETY AND PHARMACOKINETICS OF CILOSTAZOL

Reference: Volumes 71 to 76
Investigator:
Study Location:

Objective: To determine the effects of age and gender on the safety and pharmacokinetics of cilostazol in male and female subjects after both single and multiple dosing of cilostazol.
Study design:

This study was an open label, multiple dose study in at least 42 male and female volunteers (of age 50 years and older) to determine the safety and pharmacokinetics of 100 mg bid cilostazol administered for 7 days (single dose on day 1 and 8 and multiple dose on days 2 to 7). Subjects were classified into three groups based on their age (50 - 59, 60- 69 and ≥70 years with 7 males and 7 females per group). All the dosing occurred in a fasted state administered with 240 ml water.

Cilostazol 100 mg tablets, lot # 4A933PA1

Blood samples for cilostazol and its metabolites analysis were drawn on day 1 at 0 (pre-dose), 1, 2, 3, 4, 5, 6, 8, 12 and 16 hours after cilostazol dosing. On days 2 to 7, pre-dose plasma samples were collected. On day 6, samples were also collected at 2, 4, 6 and 8 hours after dosing. On day 8, plasma samples were collected at 0, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120 and 144 hours after dosing. Additional blood samples were collected at specific times for determination of cilostazol protein binding. ADP, collagen, epinephrine and arachidonic acid induced platelet aggregation has also been measured on day 0 and four hours after dosing on day 1 and day 8. PK parameters for cilostazol and its major metabolites were determined by noncompartmental methods. Both log-transformed and untransformed data were analyzed by a two-way ANOVA with a model that included age and gender groups and their interaction. Gender was also compared within each age group.

Results:

ASSAY PERFORMANCE: Assay conducted

CILOSTAZOL (OPC-13013):
Method used:
Range:
Linearity: Linear within the range,
QC samples:
Precision:
Accuracy:

Specificity:

OPC-13015:
Method used:
Range:
Linearity: Linear within the range.
QC samples:
Precision:
Accuracy:

Specificity:

OPC-13213:
Method used:
Range:
Linearity: Linear within the range.
QC samples:
Precision:
Accuracy:

Specificity:

Assays were found to be acceptable.

Mean pharmacokinetic parameters for cilostazol, OPC-13015 and OPC-13213 following administration of single and multiple doses of cilostazol are shown in the following tables.

Summary of Pharmacokinetic Parameters for Study Day 1 CILOSTAZOL

Pharmacokinetic Parameter	Gender	Age Group (years old) 50 - 59 Mean (S.D.)	60 - 69 Mean (S.D.)	≥ 70 Mean (S.D.)	p-values Age	Gender	Age/Gender
Day 1							
C_{max} (ng/mL)	male	603.85 (215.47)	794.64 (378.27)	654.08 (157.63)			
	female	829.22 (204.94)	718.19 (234.10)	856.85 (343.24)			
Gender within Age		0.0605	0.7714	0.2277	0.9272	0.1130	0.3008
T_{max} (hours)	male	2 (1)	4 (2)	3 (2)			
	female	3 (2)	3 (1)	4 (1)			
Gender within Age		0.5170	0.8421	0.6392	0.4073	0.3508	-
Half-life (hours)	male	15.7 (6.2)	12.5 (1.6)	21.7 (10.8)			
	female	14.5 (1.4)	14.4 (0.9)	21.7 (10.1)			
Gender within Age		0.9104	0.6559	0.8394	0.2114	0.7366	0.9141
AUC_{12} (ng*hr/mL)	male	5023.2 (1768.0)	6802.8 (3362.1)	5417.7 (1150.4)			
	female	6600.7 (1396.6)	5212.1 (1271.8)	6343.9 (2048.5)			
Gender within Age		0.0806	0.2890	0.4528	0.9833	0.4247	0.1401
AUC (ng*hr/mL)	male	14250.2 (6833.9)	17419.3 (8253.7)	16259.8 (7481.7)			
	female	17041.5 (5079.0)	9364.6 (5240.1)	17177.6 (3916.0)			
Gender within Age		0.5140	0.1425	0.7211	0.5083	0.7027	0.2620
Cl/F/kg (mL/min/Kg)	male	1.54 (0.34)	1.51 (0.94)	1.77 (1.03)			
	female	1.69 (0.74)	2.73 (1.21)	1.66 (0.29)			
Gender within Age		0.9149	0.1170	0.8934	0.7768	0.2641	0.4426
Vd/F/kg (L/kg)	male	1.95 (0.19)	1.68 (1.17)	2.63 (0.49)			
	female	2.13 (0.93)	3.37 (1.31)	2.98 (0.90)			
Gender within Age		0.9792	0.0274	0.7236	0.3040	0.1040	0.1861

Summary of Pharmacokinetic Parameters for Study Day 8

Pharmacokinetic Parameter	Gender	Age Group (years old) 50 - 59 Mean (S.D.)	60 - 69 Mean (S.D.)	≥ 70 Mean (S.D.)	p-values Age	Gender	Age/Gender
Day 8							
C_{max} (ng/mL)	male	1058.96 (438.75)	1156.19 (508.01)	1228.70 (473.24)			
	female	1497.33 (266.38)	1210.80 (543.75)	1224.29 (348.07)			
Gender within Age		0.0543	0.8248	0.9344	0.7272	0.1882	0.3271
T_{max} (hours)	male	2 (1)	3 (2)	2 (2)			
	female	2 (1)	1 (1)	3 (2)			
Gender within Age		0.2135	0.0337	0.3907	0.4712	0.2019	-
C_{trough} (ng/mL)	male	460.37 (208.43)	656.64 (450.89)	533.68 (303.07)			
	female	665.25 (303.30)	528.90 (323.28)	541.08 (218.51)			
Gender within Age		0.2510	0.6523	0.7996	0.9700	0.5785	0.5222
half-life (hours)	male	12.9 (7.3)	23.6 (13.4)	12.0 (1.6)			
	female	15.7 (2.3)	25.5 (8.3)	ND			
Gender within Age		0.4221	0.6876	-	0.2526	0.4130	0.8299
AUC (ng*hr/mL) (up to ∞)	male	15564.7 (7753.0)	22496.9 (9861.1)	17668.6 (7766.6)			
	female	24567.2 (10644.9)	20284.0 (12322.5)	20222.8 (6590.6)			
Gender within Age		0.0708	0.4540	0.5001	0.9412	0.3099	0.1938
AUC_{12} (ng*hr/mL)	male	8920.1 (4250.4)	10538.2 (5794.2)	9522.9 (3947.6)			
	female	11793.3 (3649.7)	9316.9 (4731.2)	10062.6 (3308.8)			
Gender within Age		0.1829	0.6928	0.7557	0.8605	0.4653	0.4647
Cl/F/kg (mL/min/Kg)	male	2.52 (0.76)	2.48 (1.23)	2.71 (0.91)			
	female	2.63 (1.09)	3.15 (1.50)	3.25 (1.40)			
Gender within Age		0.9897	0.3041	0.4909	0.7066	0.3200	0.7632
Vd/F/kg (L/kg)	male	3.24 (2.29)	5.23 (3.98)	2.32 (0.94)			
	female	4.53 (1.60)	8.69 (1.58)	ND			
Gender within Age		0.3289	0.2335	-	0.2811	0.1350	0.7584
C_{avg} (ng/mL)	male	743.34 (354.20)	878.18 (482.85)	793.58 (328.97)			
	female	982.78 (304.15)	776.41 (394.26)	838.55 (275.73)			
Gender within Age		0.1829	0.6928	0.7556	0.8605	0.4653	0.4647
Effective t½ (hours)	male	10.4 (4.7)	9.0 (2.9)	9.6 (5.1)			
	female	10.5 (6.6)	9.5 (4.3)	8.6 (3.8)			
Gender within Age		0.9534	0.9613	0.9059	0.8807	0.9440	0.9931
AUC_{0-12h} Day 8/AUC_{0-12h} Day 1	male	1.84 (0.48)	1.56 (0.42)	1.75 (0.54)			
	female	1.86 (0.74)	1.72 (0.49)	1.63 (0.41)			
Gender within Age		0.9114	0.5371	0.6905	0.6437	0.9419	0.7576
C_{max} Day 8/C_{max} Day 1	male	1.80 (0.41)	1.53 (0.46)	1.90 (0.54)			
	female	1.98 (0.88)	1.90 (0.76)	1.59 (0.65)			
Gender within Age		0.8269	0.3441	0.2634	0.7326	0.9596	0.3345

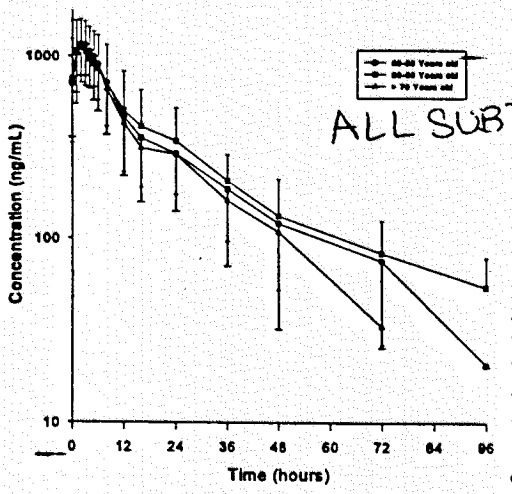
Summary of Pharmacokinetic Parameters for OPC-13015 on Study Days 1, 6 and 8

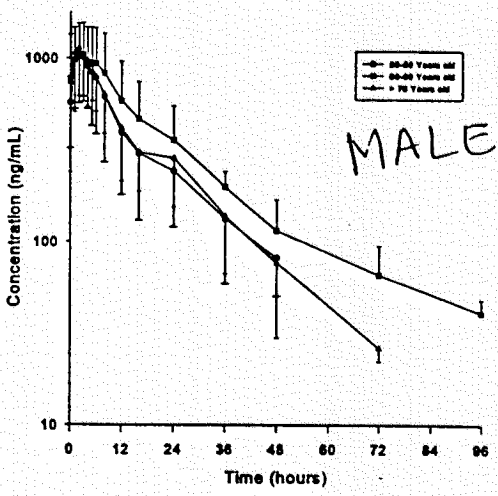
Pharmacokinetic Parameter	Gender	Age Group (yeans old) 50 - 59 Mean (S.D.)	60 - 69 Mean (S.D.)	≥ 70 Mean (S.D.)
Day 1				
C_{max} (ng/mL)	male	112.28 (28.06)	148.91 (55.49)	140.90 (36.08)
	female	174.03 (39.96)	170.30 (44.91)	202.00 (87.10)
T_{max} (hours)	male	7 (2)	9 (4)	7 (3)
	female	8 (3)	6 (3)	7 (3)
half-life (hours)	male	22.2 (10.1)	16.3 (11.7)	30.2 (20.0)
	female	41.3 (41.0)	NA	15.6 (5.9)
AUC_{12h} (ng*hr/mL)	male	1051.5 (294.6)	1302.8 (466.1)	1317.1 (328.6)
	female	1522.9 (471.2)	1376.1 (289.4)	1771.3 (754.8)
Day 6				
C_{max} (ng/mL)	male	312.16 (147.15)	414.75 (236.50)	343.22 (95.38)
	female	495.85 (148.60)	454.36 (208.84)	499.96 (126.91)
T_{max} (hours)	male	3 (2)	3 (2)	2 (0)
	female	2 (1)	3 (1)	3 (2)
AUC_{12h} (ng*hr/mL)	male	3108.4 (1724.8)	4343.2 (2825.0)	3383.3 (969.3)
	female	5171.6 (1797.0)	4520.3 (2279.0)	4987.3 (1436.3)
Day 8				
C_{max} (ng/mL)	male	293.63 (129.56)	417.75 (241.82)	365.95 (98.05)
	female	486.22 (132.82)	432.25 (189.93)	455.52 (141.53)
T_{max} (hours)	male	2 (1)	3 (2)	3 (1)
	female	3 (1)	3 (1)	4 (2)
half-life (hours)	male	13.8 (4.8)	19.0 (7.4)	15.3 (3.2)
	female	15.5 (3.3)	18.4 (9.3)	21.6 (10.6)
AUC_{12h} (ng*hr/mL)	male	3010.3 (1534.0)	4425.5 (2754.8)	3714.8 (1027.7)
	female	4771.7 (1378.5)	4264.0 (2110.8)	4617.5 (1598.5)
AUC_{∞}/AUC_{0-12h} Day 1	male	2.97 (0.77)	3.32 (1.47)	2.92 (0.80)
	female	3.49 (1.84)	3.07 (1.49)	2.74 (0.81)

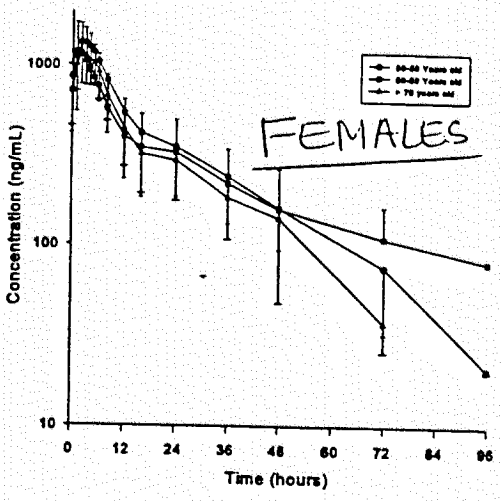
Summary of Pharmacokinetic Parameters for OPC-13213 on Study Days 1, 6, and 8

Pharmacokinetic Parameter	Gender	Age Group (years old) 50 - 59 Mean (S.D.)	60 - 69 Mean (S.D.)	≥ 70 Mean (S.D.)
Day 1				
C_{max} (ng/mL)	male	46.59 (13.59)	57.88 (10.50)	49.40 (5.28)
	female	66.12 (26.41)	71.89 (27.77)	75.53 (26.06)
T_{max} (hours)	male	4 (1)	5 (2)	5 (2)
	female	4 (2)	4 (1)	5 (1)
half-life (hours)	male	14.5 (7.4)	19.2 (7.9)	26.0 (25.8)
	female	NA	23.7 (NA)	8.3 (5.8)
AUC_{12h} (ng*hr/mL)	male	375.2 (151.2)	493.7 (76.6)	441.6 (36.9)
	female	501.4 (188.7)	550.2 (147.4)	605.1 (161.9)
Day 6				
C_{max} (ng/mL)	male	117.22 (21.69)	120.98 (25.49)	107.69 (40.30)
	female	147.50 (64.99)	146.82 (15.29)	180.78 (45.46)
T_{max} (hours)	male	3 (2)	3 (2)	3 (2)
	female	2 (1)	2 (1)	3 (2)
AUC_{12h} (ng*hr/mL)	male	1015.3 (214.3)	1160.1 (314.3)	1021.3 (404.7)
	female	1322.1 (661.9)	1346.9 (158.4)	1611.2 (393.3)
Day 8				
C_{max} (ng/mL)	male	108.61 (30.42)	115.28 (16.84)	116.22 (38.59)
	female	146.18 (52.48)	130.61 (22.26)	137.70 (20.78)
T_{max} (hours)	male	3 (1)	3 (2)	2 (2)
	female	3 (2)	2 (1)	3 (2)
half-life (hours)	male	10.6 (6.0)	20.6 (7.5)	16.8 (2.5)
	female	21.3 (2.4)	19.9 (8.1)	30.9 (16.3)
AUC_{12h} (ng*hr/mL)	male	977.2 (296.1)	1110.1 (232.9)	1034.3 (326.8)
	female	1178.1 (517.3)	1158.5 (235.4)	1270.4 (191.0)
AUC_{∞}/AUC_{0-12h} Day 1	male	3.12 (1.82)	2.31 (0.60)	2.32 (0.57)
	female	2.65 (1.41)	2.21 (0.64)	2.20 (0.50)

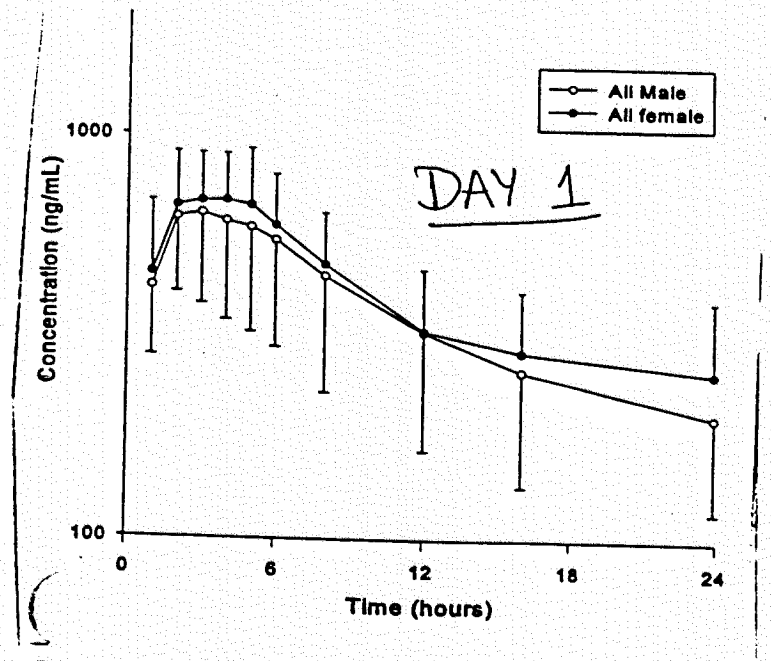
Mean plasma concentration-time curves for cilostazol in males and females after multiple cilostazol dosing to study the effect of age are shown in the following three figures.

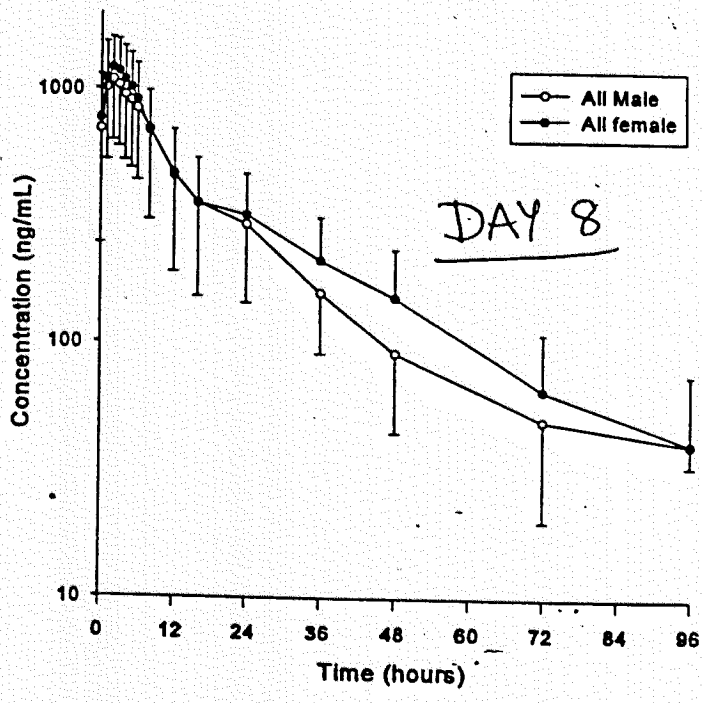




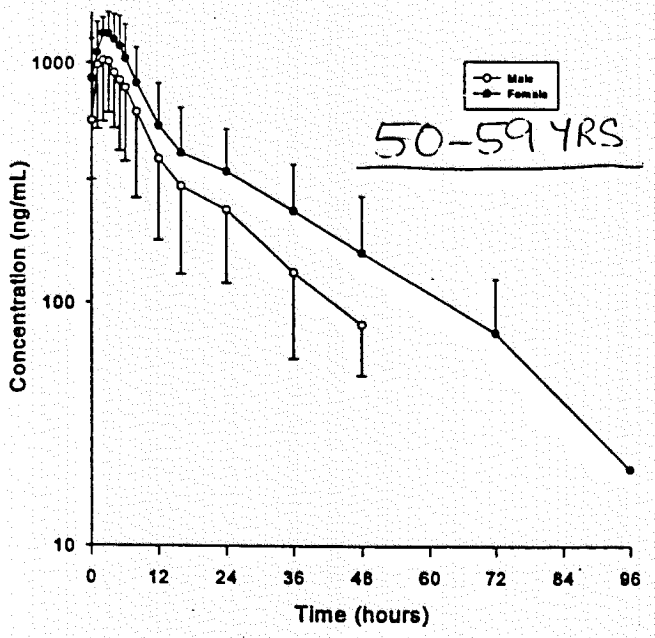


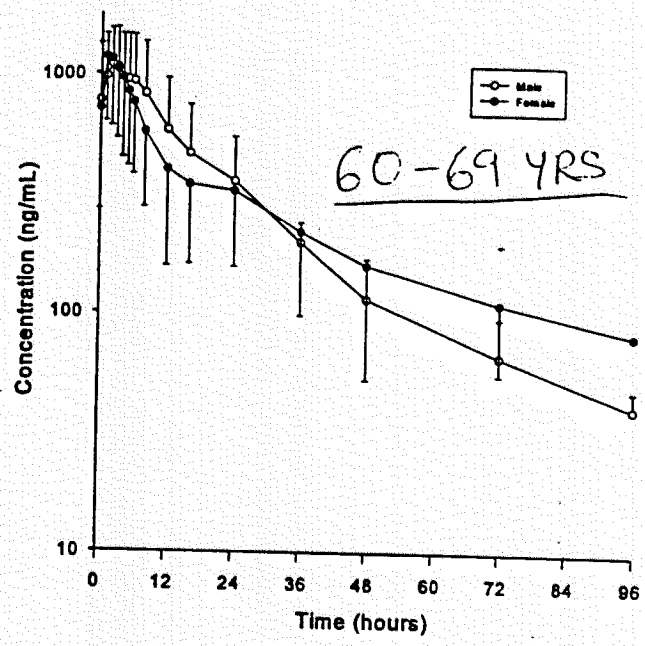
Mean plasma concentration-time curves for cilostazol in males and females on day 1 and day 8 are shown in the following two figures. A 1.7 fold accumulation in cilostazol concentrations was observed upon multiple dosing.

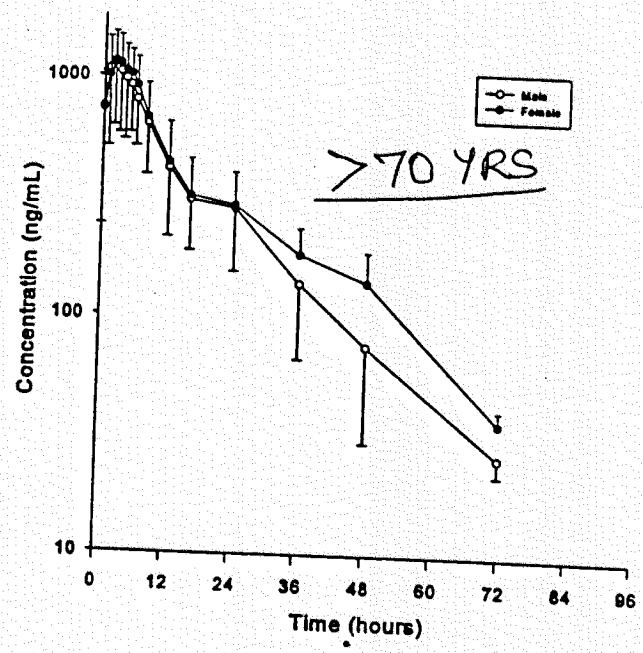




Mean (± SD) cilostazol plasma concentration time curves for male and female subjects by age group on day 8 are shown in the following 3 figures.

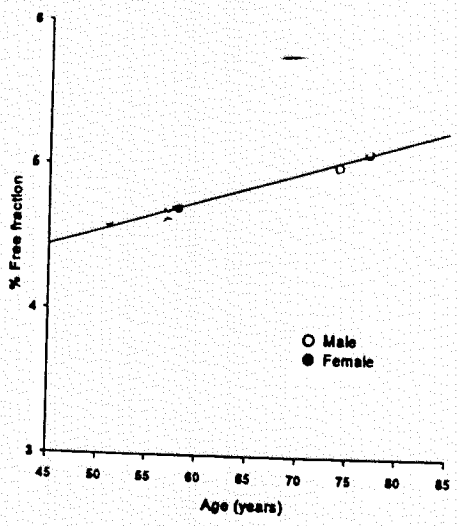


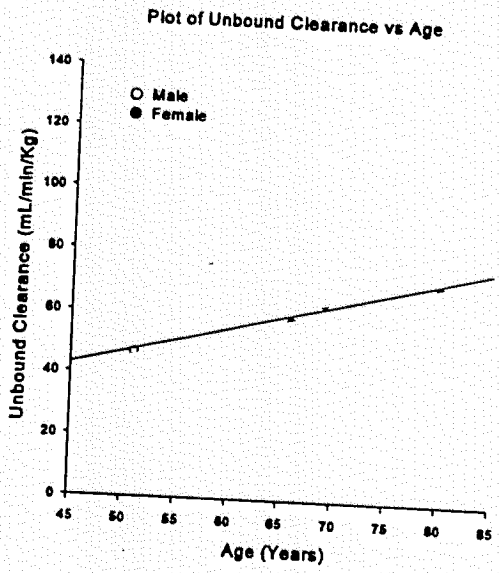




Plasma cilostazol profiles in several subjects showed secondary peaks occurring approximately 20 - 25 hours after dose administration.

The following two figures show the free fraction and unbound clearance vs. age. There is a significant difference in free fraction between different age groups and gender.





The greatest inhibition of platelet aggregation was seen following inducement with arachidonic acid. % aggregation was inhibited by 48.1% in males and 44.7% in females on day 1. The % inhibition in platelet aggregation was enhanced on day 8 with a value of 66.1% in males and 78.6% in females. Inhibition of ADP-induced platelet aggregation was low.

Conclusions: No significant differences were found in the pharmacokinetics of cilostazol and its metabolites between males and females. No age effect was also found. However, a trend towards higher plasma concentrations in females was observed. A higher ADP and arachidonic acid induced platelet aggregation was found in females than males. Also, the percentage of females who reported drug-related treatment-emergent adverse events were higher than the % in males. While there is a trend, the differences are not significant, therefore no dosage adjustment may be necessary.