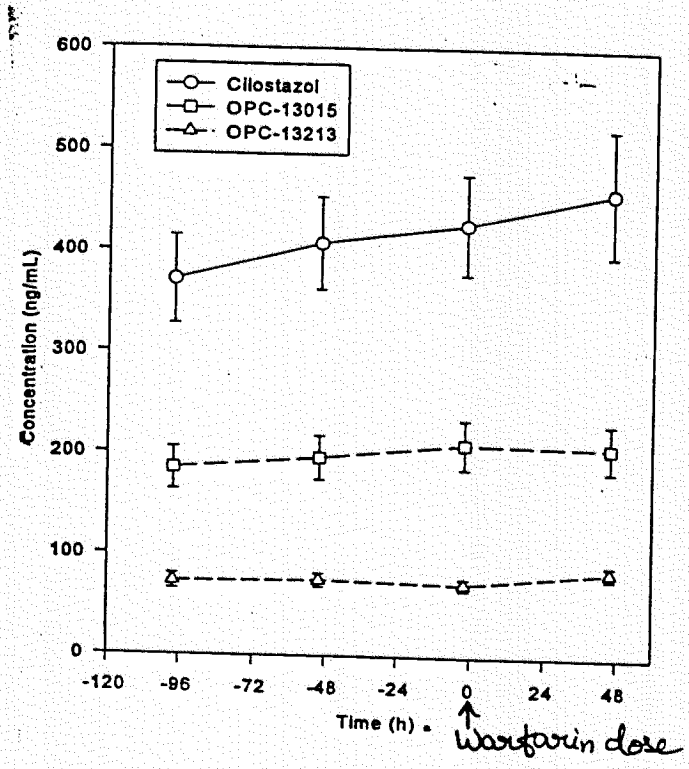
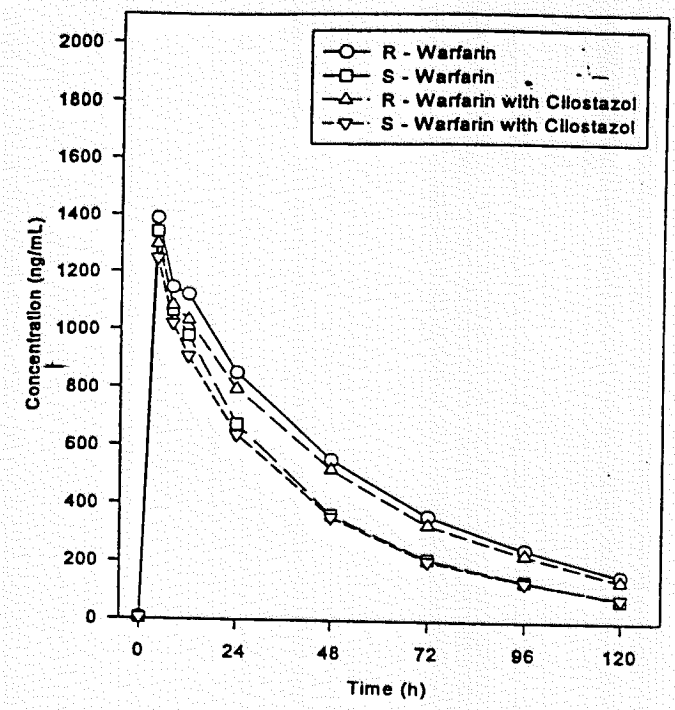
Table below provides a summary of the main pharmacokinetic parameters (mean ± SD) for S(-) warfarin given with or without cilostazol.

Parameters	With Cilostazol	With Placebo	Geometric mean ratio	90% C.I.
Tmax, hrs	4.3 ± 1.0	4.0 ± 0.0		
Cmax, ng/ml	1272 ± 273	1346 ± 246	0.937	0.88 - 1.00
$t_{1/2}$, hrs	31.9 ± 9.6	31.4 ± 8.8	1.008	0.92 - 1.11
AUC_{0-t}, ng-hr/ml	46333 ± 13932	48020 ± 14136	0.963	0.93 - 0.99
$AUC_{0-\infty}$, ng-hr/ml	51373 ± 19474	52967 ± 18589	0.964	0.92 - 1.01
Cl/F, ml/hr/kg	3.42 ± 1.12	3.30 ± 1.09	1.039	0.99 - 1.09
Vz/F, ml/kg	146 ± 24	189 ± 26	1.046	0.99 - 1.10

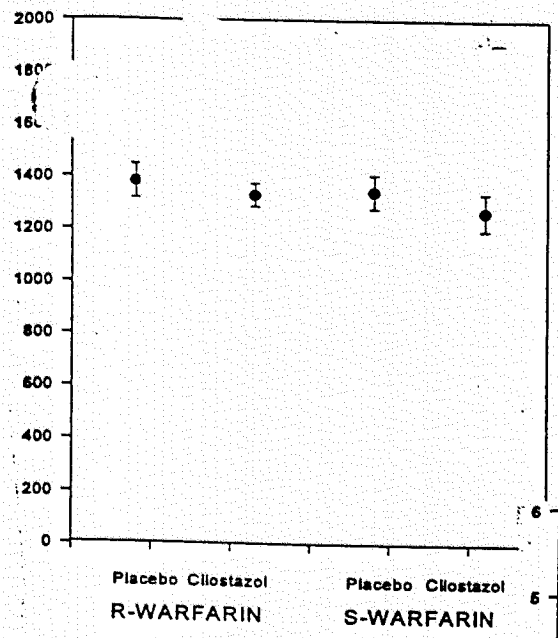
Plot of mean trough concentration profiles for cilostazol and its major metabolites are given in the figure below.

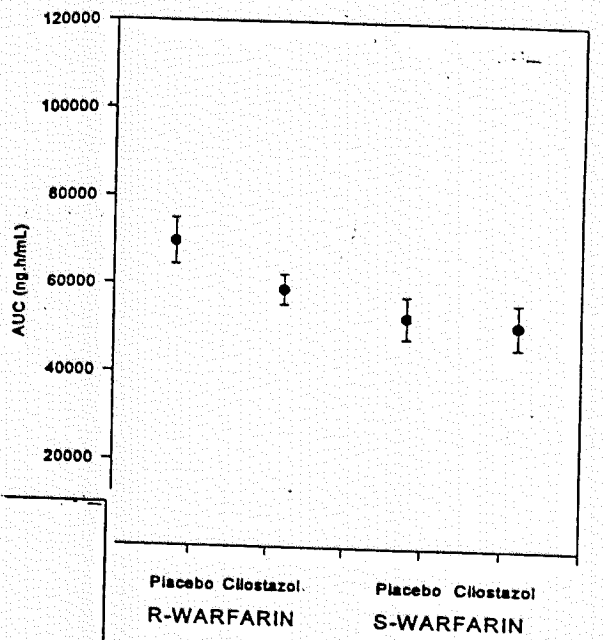


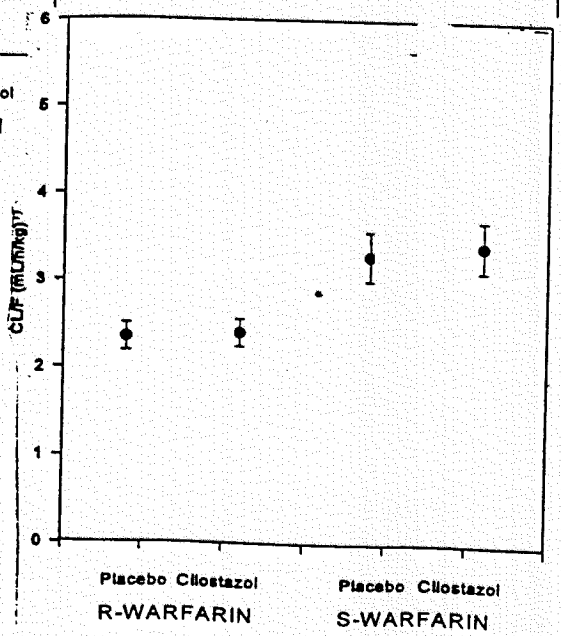
Plots of mean concentration profiles for R(+) and S(-) warfarin given with or without cilostazol are given in the figure below.



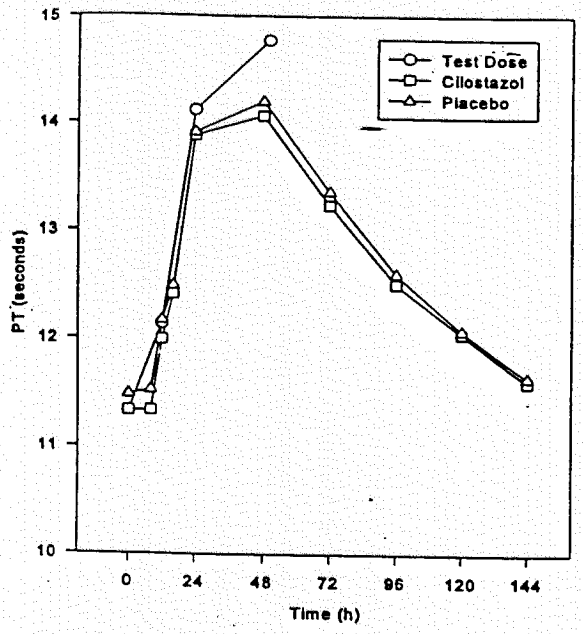
The following 3 figures show the effect of coadministration of cilostazol on Cmax, AUC and Cl/F of R and S-warfarin.

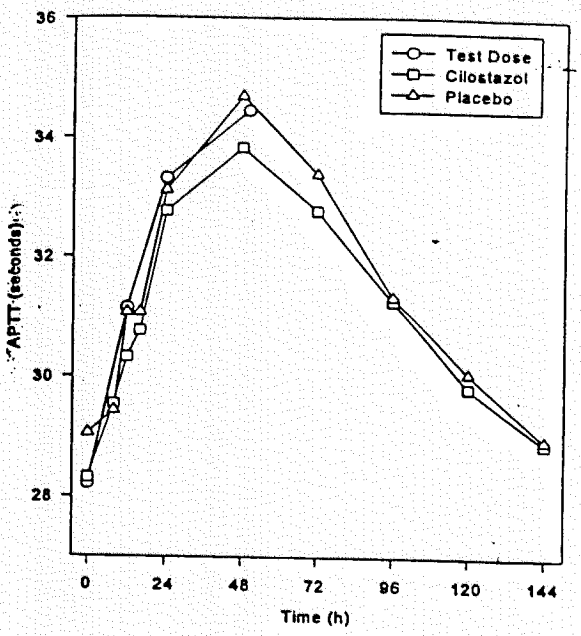






Mean prothrombin time and activated partial thromboplastin time profiles following warfarin administration with or without cilostazol are shown in the following figures:





A summary of protein binding interaction study to evaluate the ability of omeprazole and warfarin to displace protein bound cilostazol (500 ng/ml) was provided. The results indicate that warfarin in the concentrations of 2 and 10 μg/ml displaced cilostazol ($p<0.01$), whereas omeprazole showed concentration-dependent displacement of protein bound cilostazol. Cilostazol and its metabolites also cause significant displacement of warfarin from its protein binding sites with warfarin free fraction changing from (see details under protein binding interaction study report).

Conclusions:

Compared to warfarin alone, coadministration of single dose warfarin with twice daily administration of 100 mg of cilostazol did not alter the R and S-warfarin pharmacokinetics and the pharmacodynamics such as PT, aPTT and Ivy bleeding times.

Comments:

1. While there is no significant interaction between multiple dose of cilostazol and single dose of warfarin, caution may be needed since the drug interaction has not been evaluated with multiple doses of warfarin. Further, from the in vitro study, it was found that the free fraction of warfarin is increased (due to protein binding interaction). This also indicates a need for caution during coadministration of warfarin and cilostazol although the free fractions were not measured in the in vivo study. However, this recommendation is only necessary if data from clinical trials in those patients who are on concomitant cilostazol and warfarin justify this caution.
2. The first plasma sample was collected 4 hours post-dosing in this study. Therefore, the effect of cilostazol on Cmax of warfarin may not have been adequately characterized in this study.

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STUDY 21-95-202: (DRUG INTERACTION STUDY WITH ERYTHROMYCIN)

PHARMACOKINETIC AND SAFETY EVALUATION OF THE POTENTIAL DRUG INTERACTION OF CILOSTAZOL AND ERYTHROMYCIN

Reference: Volumes 92 to 95
Investigator:
Study Location:
Objective:

1. To compare the oral single dose pharmacokinetics of cilostazol and its metabolites when administered alone, and following pretreatment with multiple doses of erythromycin.
2. To measure the catalytic activity of CYP3A4 in vivo following multiple-dose erythromycin administration (by erythromycin breath test).

Study design:

This is an open label fixed sequence single-center, multiple dose erythromycin and single dose cilostazol study in 16 healthy male volunteers of age 18 to 45 years. On day 1, subjects received a single intravenous injection of 3 μCi of ^{14}C-methylerythromycin, followed by the collection of exhaled breath samples at intervals for 60 minutes. The participants received a single dose of 100 mg cilostazol on day 1 (60 minutes after giving i.v. erythromycin for erythromycin breath test) followed by multiple dose administration of erythromycin 500 mg q8 hours on days 8 to 20. On day 15, the i.v. 14C-methylerythromycin and cilostazol 100 mg single dose was repeated as originally administered on day 1. On cilostazol dosing days, food was withheld until 4 hours after dosing. On erythromycin dosing days (8 - 14 and 16 - 20), the morning dose immediately followed breakfast and the afternoon and evening doses followed light snacks.

Plasma and urine samples for the assay of cilostazol and its metabolites were collected on day 1 and day 15.

Batch #s: Cilostazol 100 mg tablet: batch # 4K79PA1
Erythromycin 500 mg (Ery-Tab) tablet: batch# 08193AF22
Erythromycin breath test: 3 μCi of C-14 N-methyl erythromycin in 3 ml of 0.9% NaCl for injection, USP, given i.v., lot # 2469-290

Blood samples were drawn for determination of plasma concentration of cilostazol and its major metabolites (OPC-13015 and OPC-13213) at 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours after cilostazol dosing on days 1 and 15. Urine samples were collected at 0 - 12, 12 - 24, 24 - 36, 36 - 48, 48 - 72 and 72 - 96 hours after cilostazol dosing. Trough blood samples were drawn for determination of erythromycin plasma concentrations on days 13 to 17.

Analysis of plasma and urine samples for cilostazol and its metabolites was carried out using a

Erythromycin in plasma was determined by an

Protein binding of cilostazol in plasma samples was determined by , of the radioactivity of C-14 cilostazol.

Pharmacokinetic parameters were determined by non-compartmental methods. These parameters with and without erythromycin were compared by the sponsor using a paired t-test.

Erythromycin breath test data were utilized to calculate the % of erythromycin dose metabolized in one hour (calculated from C-14 exhaled).

Results:
ASSAY PERFORMANCE:

Plasma samples:

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:

Erythromycin:
Method used:
Range:
Linearity: Linear within the range.
QC samples:
Precision:
Accuracy:

Specificity:

Urine samples:

CILOSTAZOL:
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:

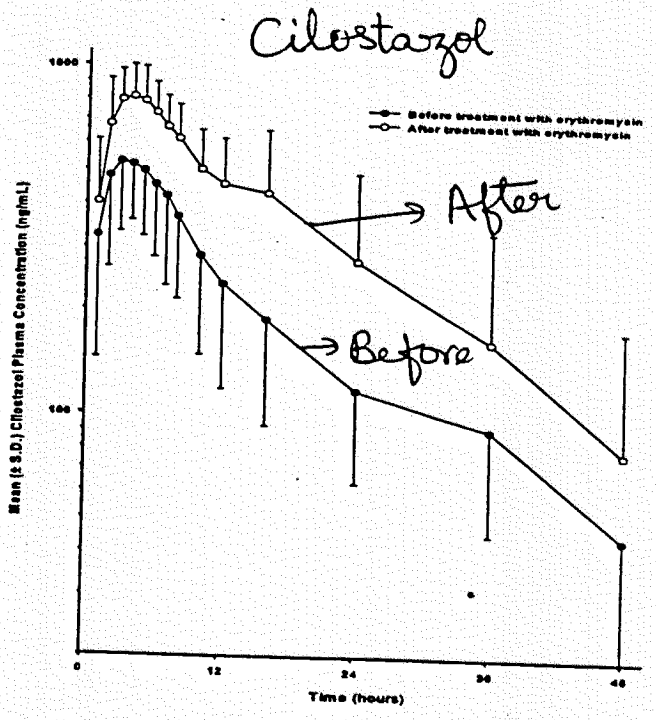
Specificity:

Assays were found to be acceptable.

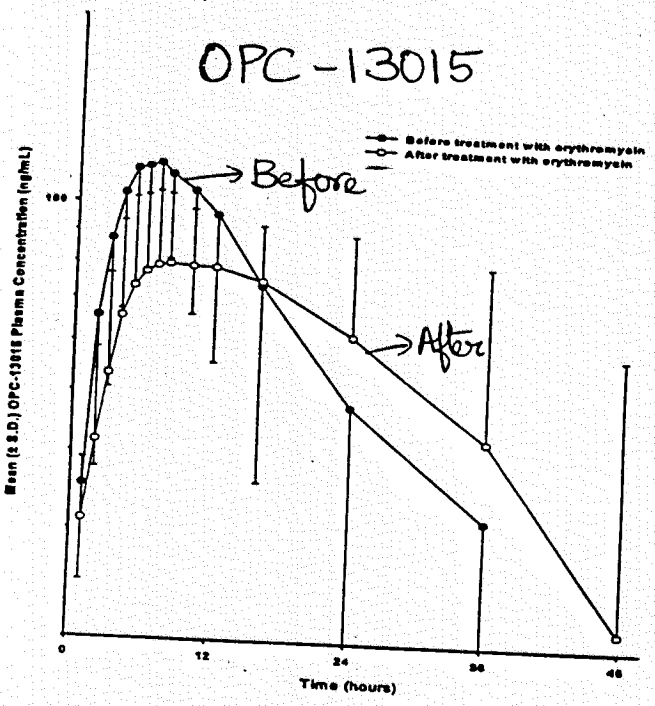
Table below provides a summary of the main pharmacokinetic parameters for cilostazol and its major metabolites given before and after erythromycin.

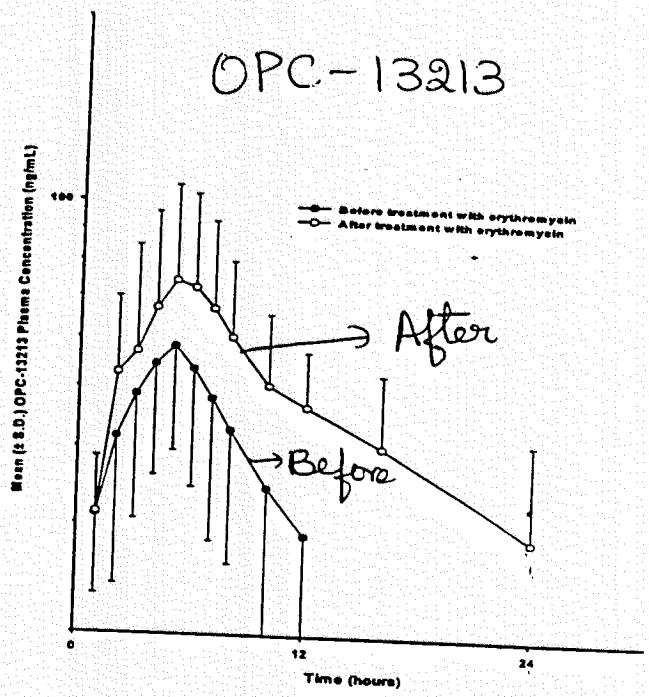
	CILOSTAZOL		OPC-13015		OPC-13213	
	Before	After	Before	After	Before	After
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD
t_{max} (hr)	4 ±2	5 ±3	7 ±3	13 ±9	5 ±2	6 ±3
C_{max} (ng/mL)	621 ±172	886 ±198	129 ±39	95 ±28	61 ±20	78 ±30
t½ (hr)	21 ± 12	14 ± 4	-	-	-	-
AUC_T (hr·ng/mL)	8917 ± 3252	16770 ± 9475	2667 ±1546	2828 ±2165	584 ± 273	1280 ± 484
AUC (hr·ng/mL)	10529 ±3816	18148 ±9836	-	-	-	-
Cl/F (L/hr)	10.7 ± 3.7	6.4 ± 1.9	-	-	-	-
fu (%)	3.0 ± 0.2	3.4 ± 0.3	-			-
fe (%)	22.2 ± 5.3	33.3 ± 5.4	-	-	-	-
Clr (L/hr)	2.5 ± 0.7	2.1 ± 0.7	-	-	-	-

Plot of mean concentration profiles for cilostazol before and after erythromycin treatment are given in the figure below.

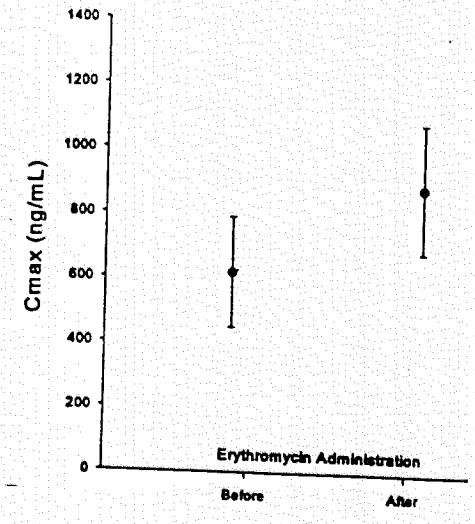


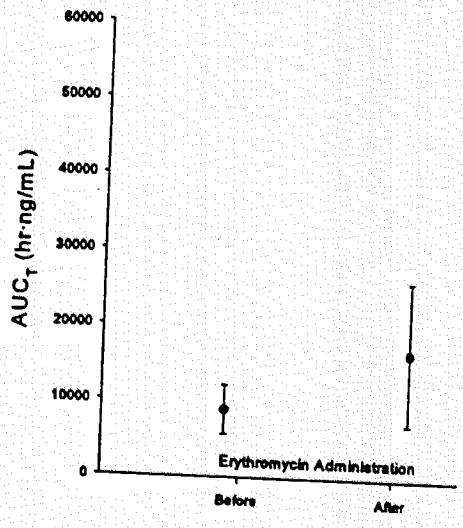
Plots of mean concentration profiles for OPC-13015 and OPC-13213 after administration of cilostazol before and after erythromycin treatment are given in the figures below.

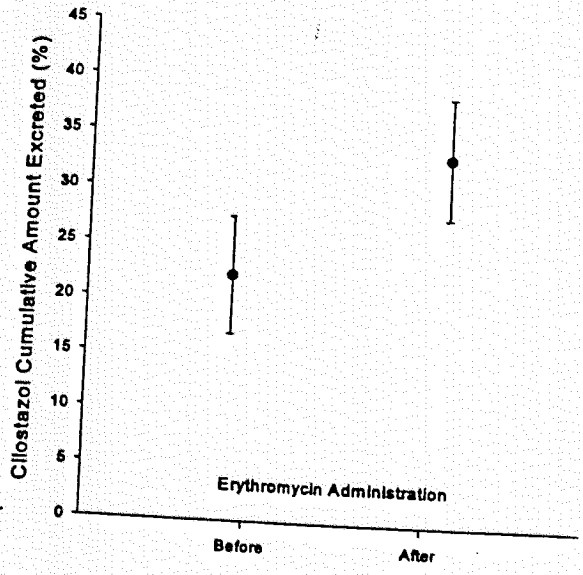




The following 3 figures show the effect of coadministration of erythromycin on Cmax, AUC_T and urinary excretion of parent cilostazol.







Trough erythromycin plasma concentrations were highly variable in this study.

Erythromycin breath test data was utilized to calculate the percentage of erythromycin dose metabolized in one hour. The mean ± SD values for % of erythromycin dose metabolized (by CYP3A4) per hour, before and after treatment with erythromycin (500 mg q8 hours) were 1.7 ± 0.4 and 1.1 ± 0.3 %/hour. This indicates that the % of erythromycin dose metabolized by CYP3A4 in one hour decreased significantly by approximately 30% on concomitant administration of erythromycin.

Conclusions:

Coadministration of 500 mg erythromycin q8 hours with single 100 mg cilostazol resulted in a statistically significant increase in Cmax by 47% and AUC by 74% of cilostazol. % of cilostazol dose excreted in urine after erythromycin coadministration increased significantly by about 50%. The Cmax of OPC-13015 decreased by 24% (significant difference) and AUC_T increased by 8% (not statistically significant). Cmax and AUC_T of OPC-13213 increased significantly by 29% and 141% respectively.

Comments:

1. Results of this study indicate that coadministration of potent CYP3A4 inhibitors like ketoconazole with cilostazol can result in significant drug interactions. Careful monitoring and dosing adjustment might be necessary in patients taking CYP3A4 inhibitors concomitantly with cilostazol.
2. The effect of cilostazol on erythromycin pharmacokinetics has not been evaluated in this study.
3. This study, which evaluated the effect of multiple dose erythromycin on single dose cilostazol, may not reflect the magnitude of interaction that is likely to occur clinically where both drugs may be administered concomitantly as multiple doses.
4. Due to the presence of a secondary peak in cilostazol plasma profile and because the secondary peak was observed at different time points during the 2 treatments, the estimate of terminal half-life in this study may not be accurate.
5. In this study, the % excreted as unchanged cilostazol in urine is about 20% when cilostazol was administered alone (without erythromycin). This is inconsistent with data obtained from mass balance study where no unchanged drug was found in urine.

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STUDY 21-95-203: (DRUG INTERACTION STUDY WITH QUINIDINE)

INFLUENCE OF QUINIDINE SULFATE ON THE PHARMACOKINETICS OF CILOSTAZOL AND ITS ACTIVE METABOLITES IN HEALTHY SUBJECTS

Reference: Volumes 96 to 100
Investigator:
Study Location:
Objective:

To evaluate the effect of quinidine sulfate, an inhibitor of CYP2D6, on the single oral dose pharmacokinetics of cilostazol and its active metabolites in healthy subjects who were previously phenotyped as "extensive" or "poor" metabolizers.

Study design:

This is an open label, randomized sequence single-center, two-period crossover study to evaluate the effect of quinidine sulfate (two 200 mg doses) on single dose pharmacokinetics of cilostazol (100 mg) in 22 healthy male and female volunteers (14 males and 8 females) of age 18 to 45 years. Prior to being entered into the study, the subjects were screened for eligibility and phenotyped using dextromethorphan as "extensive" or "poor" metabolizers. At the clinic, subjects were assigned to one of the two treatment groups, A and B (details in table below). Study drug was administered over the next two days, study days 0 and 1. A 21 day washout period was included between the two dosing periods. A day prior to dosing of cilostazol, metoprolol was administered as a positive control to determine the extent of inhibition of CYP2D6 by quinidine. The ratio of hydroxymetoprolol to metoprolol in 8 hour pooled urine was expected to be much lower following quinidine than without quinidine. All the doses were administered with 240 ml of water.

Study Design

Treatment	Dosing Period I		Washout Period	Dosing Period II	
	Day 0	Day 1	-21 Days-	Day 0	Day 1
A	Water[a]/Met[b]	Water/Clz[c]		Quin[d]/Met	Quin/Clz
B	Quin/Met	Quin/Clz		Water/Met	Water/Clz

[a]240 mL of room temperature water.
[b]25 mg metoprolol dose.
[c]100 mg cilostazol dose.
[d]200 mg quinidine dose.

Plasma samples for the assay of quinidine and cilostazol and its metabolites were collected on day 1 of dosing in each treatment period.
Batch #s: Cilostazol 100 mg tablet: batch # 4K79PA1
Quinidine sulfate 200 mg tablets . batch # C5D0399
Benylin pediatric cough suppressant syrup,

Metoprolol tartrate 25 mg, Geigy: batch # 1KT0100

Blood samples were drawn for determination of plasma concentration of quinidine and cilostazol and its major metabolites (OPC-13015 and OPC-13213) at 0, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96 and 120 hours after cilostazol dosing on days 1 of each treatment period. Urine samples were collected on day 0 of each treatment period at baseline and at -24 to -16 hours prior to cilostazol dosing for measurement of metoprolol and its metabolite concentrations. Urine samples were collected for determination of cilostazol and its metabolite concentrations on day 1 at 0 - 12, 12 - 24, 24 - 36, 36 - 48, 48 - 72 and 72 - 96 hours after cilostazol dosing.

Analysis of plasma and urine samples for cilostazol and its metabolites was carried out using a

Protein binding of cilostazol in plasma samples was determined by of the radioactivity of C-14 cilostazol. Plasma samples were analyzed for quinidine by Urine samples were analyzed for metoprolol and hydroxymetoprolol by an

Pharmacokinetic parameters were determined by methods. Descriptive statistics were calculated for PK parameters. The log of the ratio of the concentration of 4-hydroxymetoprolol to that of metoprolol was analyzed with an ANOVA for a two-period crossover design. For cilostazol and its major metabolites, the PK parameters were analyzed using ANOVA for a two-period crossover design which includes, sequence, subjects within sequence, treatment and period as factors. 90% confidence intervals are then calculated.

Results:
ASSAY PERFORMANCE:

Plasma samples:

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:

Urinary cilostazol and its metabolites:
Method used
Range:
Linearity: Linear within the range;
QC samples:

Accuracy:

Specificity:

Metoprolol and 4-hydroxymetoprolol in urine:

Method used:
Range:
Linearity: Linear within the range,
QC samples:
Precision:

Accuracy:

Specificity:

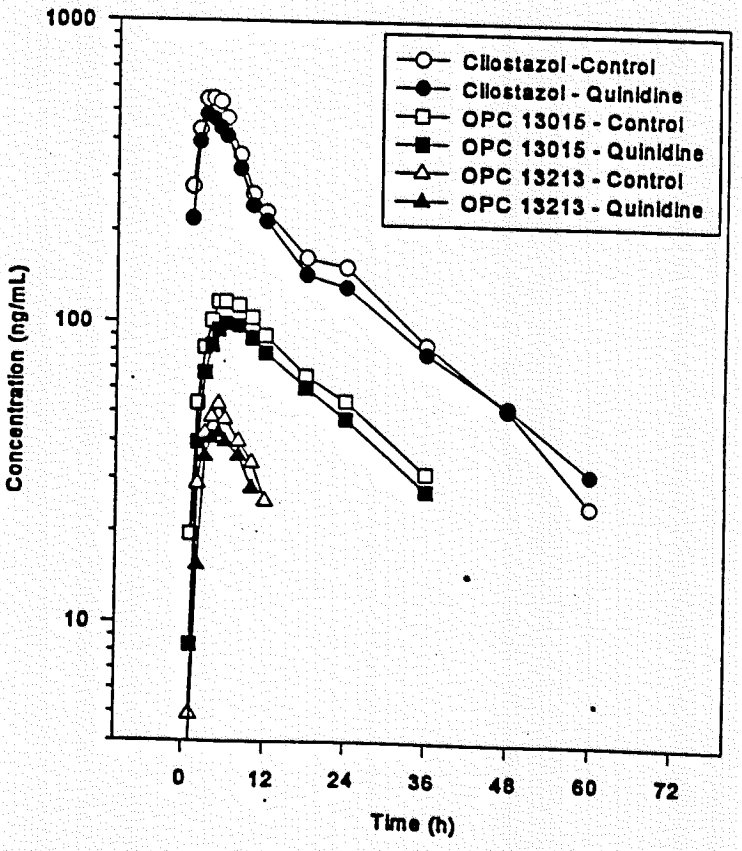
Assays were found to be acceptable.

21 subjects were phenotyped as extensive metabolizers and one subject as poor metabolizer.

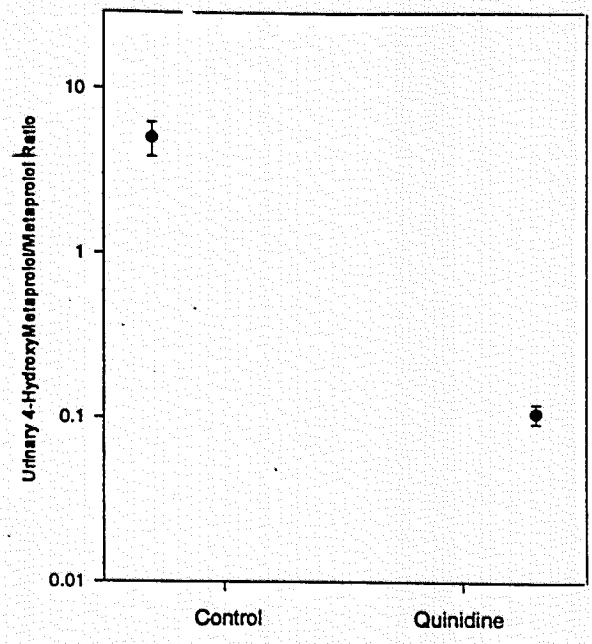
Table below provides a summary of the main pharmacokinetic parameters for cilostazol and its major metabolites given before and after quinidine (mean ± SD).

Parameter	Cilostazol		OPC-13015		OPC-13213	
	with quinidine	without quinidine	with quinidine	without quinidine	with quinidine	without quinidine
Tmax, hrs	3.6 ± 1.4	3.6 ± 1.2	7.9 ± 3.0	7.2 ± 2.6	5.1 ± 1.3	5.2 ± 1.5
Cmax, ng/ml	520.4 ± 96.8	612.2 ± 192.3	104.2 ± 20.4	128.1 ± 39.6	47.2 ± 16.1	55.3 ± 17.4
t1/2, hrs	19.8 ± 9.9	16.9 ± 10.5	34.6 ± 20.3	24.6 ± 13.7	-	-
AUCT, ng.hr/ml	8570 ± 3123	9434 ± 3820	2459 ± 1263	2757 ± 1408	465 ± 237	593 ± 277
AUC, ng.hr/ml	9974 ± 3383	10249 ± 3884	4368 ± 1659	4012 ± 1541	-	-
Cl/F, ml/hr/kg	151.6 ± 63.4	149.6 ± 59.1	367.4 ± 169.5	402.8 ± 214.8	-	-
Vz/F, ml/kg	4136 ± 2403	3493 ± 2238	16795 ± 169.5	12804 ± 6653	-	-

Plot of mean concentration profiles for cilostazol, OPC-13015 and OPC-13213 before and after quinidine treatment are given in the figure below.



Ratio of urinary hydroxymetoprolol to metoprolol following oral administration of metoprolol without and with 200 mg quinidine sulfate is shown in the figure below.



Administration of metoprolol with quinidine caused a statistically significant decrease in urinary 4-hydroxymetoprolol/metoprolol ratio compared to metoprolol alone (47-fold decrease) which indicates that quinidine effectively inhibits CYP2D6 mediated metabolism of metoprolol.

The following table shows the geometric mean ratio (using parameter without quinidine as reference) and 90% confidence interval on Cmax and AUC_T of cilostazol and its active metabolites.

Moiety	Geometric mean ratio of Cmax	90% confidence interval	Geometric mean ratio of AUC_T	90% confidence interval
Cilostazol	0.86 0.85 (unbound)	0.77 - 0.95 0.74 - 0.97 (unbound)	0.89 0.88 (unbound)	0.82 - 0.96 0.80 - 0.97 (unbound)
OPC-13015	0.83	0.75 - 0.91	0.88	0.80 - 0.97
OPC-13213	0.82	0.73 - 0.92	0.70 0.87 (amt in urine)	0.59 - 0.84 0.80 - 0.97 (amt in urine)

Conclusions:

Coadministration of quinidine (a CYP2D6 inhibitor) with cilostazol does not inhibit the metabolism of cilostazol significantly, indicating no significant drug-drug interaction. A small decrease in Cmax and AUC of cilostazol and its metabolites was observed. This could be attributed to possible effects on absorption of cilostazol.