13. **Evaluations of The Pharmacokinetics of Modafinil and Its Metabolites in Severe Chronic Renal Failure ([redacted]-P1595)**

The aim of the study was:

a) To evaluate the effect of severe chronic renal failure on the pharmacokinetic profile of modafinil, administered orally, and its main metabolite;

b) To assess the safety and incidence of adverse effects with modafinil in this patient group.

2.2. STUDY DESIGN

mean clcr = 16.58 ± 2.23 ml/min

This was a non-randomised open label study conducted in 10 male subjects with severe chronic renal failure who were not receiving any type of dialysis. Subjects received a single 200mg dose of oral modafinil at 8 am after an overnight fast. Blood and urine samples were taken before dosing and at intervals over 96 hours to assess levels of modafinil and its main metabolite, modafinil acid. The pharmacokinetic parameters Cmax, Tmax, $AUC_{(0\text{-}t\,obs)}$, $AUC_{(0\text{-}inf)}$, T½, $AE_{(0\text{-}96h)}$ and Cl_R were assessed.

Approximately 7ml of blood was taken at the following times for the analysis of plasma levels of modafinil and its metabolite:

0h (taken before dosing), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 15, 24, 36, 48, 72 and 96h after dosing.

The blood was placed in a lithium heparin tube, centrifuged at 2000g for 10 minutes and the plasma separated into a plain tube and stored at -18°C pending collection by the sponsor.

ii) Urine Samples

Urine was collected over the following intervals after dosing:

0 - 6, 6 - 12, 12 - 24, 24 - 36, 36 - 48, 48 - 72 and 72 - 96h.

The total volume collected in each interval was measured and a 20ml aliquot withdrawn and stored at -18°C pending collection by the sponsor.

Results (Attachment 13) and Conclusions:

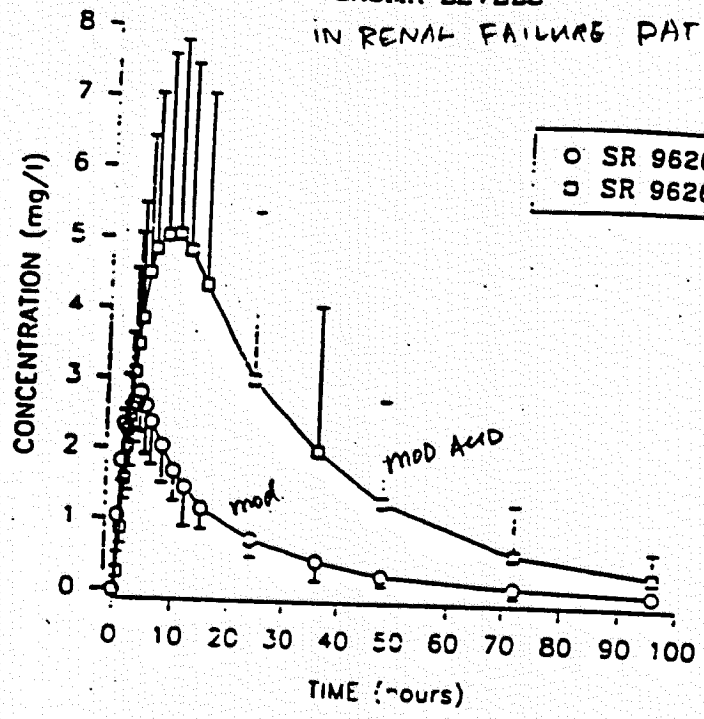
Following a single dose of modafinil, severe renal failure did not influence the PK of modafinil. A slight reduction in renal clearance (f_e=3% in renal patients and 5% in healthy volunteers), and C_{max} (3.33 mg/l in renal patients and 4.01 mg/l in healthy volunteers) would not have any impact on the plasma concentration of modafinil. However, PK parameters of the acid metabolite changed markedly in renal patients. Renal clearance of modafinil acid was greatly reduced, resulting in the elevated plasma concentrations (to ≈2 fold) and AUC0-∞ (to ≈9 fold) , increased T_{max} (by 5 hr), and

prolonged $t_{1/2}$ (to >3 fold). Nevertheless, subjects with renal failure exhibited no adverse effect in this study, indicating that these subjects had a good tolerance of modafinil and modafinil acid.

Comments:

1. At single dose of 200 mg, only 25% of the modafinil dose was excreted in urine as modafinil acid in the renal patients, compared to ~45% in healthy subjects. This indicated that kidney was the major organ for elimination of modafinil acid.
2. From the increased AUC, t1/2 and Cmax, it is clear that modafinil acid was accumulated longer and more in renal patients in this single dose study. Had the study been designed as multiple dose, the accumulation of modafinil acid would be even more, if not equal to, that in single dose in renal patients. Since modafinil is to be administered chronically, it is important to know the clinical outcome of chronic accumulation of modafinil acid.

PLASMA LEVELS
IN RENAL FAILURE PATIENTS ATTACHMENT A-13



URINARY EXCRETION IN RENAL FAILURE PATIENTS

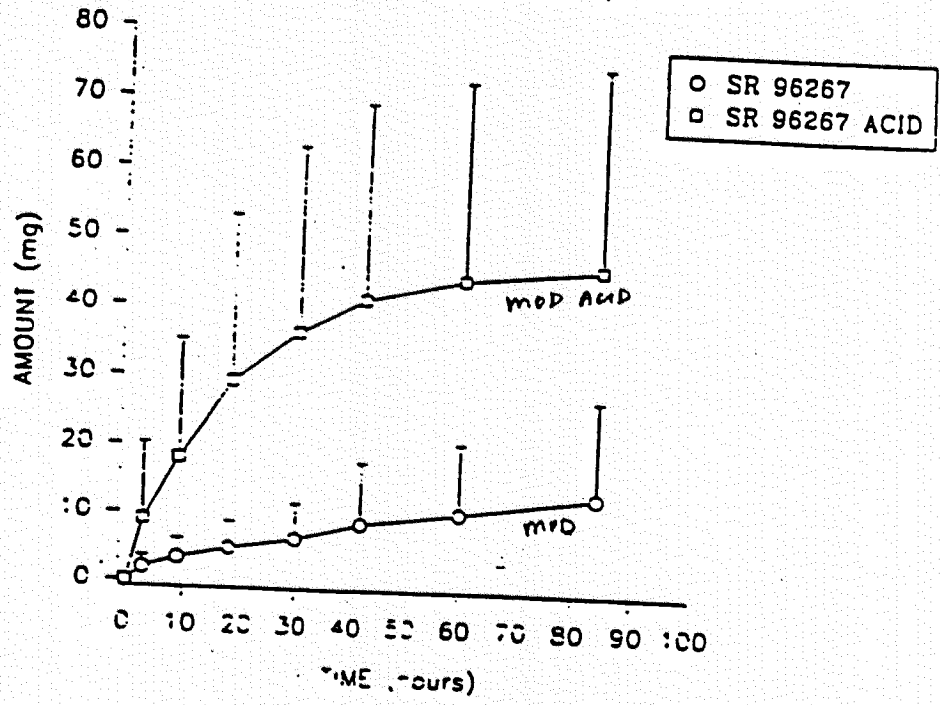


Figure 13: Time related changes in mean (± SD) plasma concentrations and cumulative urinary excretion of modafinil and modafinil acid

SAFETY RESULTS

Exposure

10 subjects with severe chronic renal failure received a single dose of oral modafinil 200mg.

Clinical Tolerability

a) Blood Pressure and Heart Rate

Individual supine BPs taken at baseline and 24h post-dose are given in Listing 6; individual heart rates can be found in Listing 7. Mean values (standard deviation) are shown in Table (5.5.2)1. Blood pressure and pulse data taken at 0, 2, 4, 8, 24, 48, and 96h post-dose is given in Listing 15. No abnormalities were found. The data are presented as means and standard deviations in Table (5.5.2)1.

Table (5.5.2)1. Mean Heart Rate and Blood Pressure at Baseline and 0 - 96h Post-Dose

Time after dosing	Mean (standard deviation) [n = 10]		
	Heart Rate (b/min)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Baseline	69.4 (16.08)	149.7 (11.39)	85.6 (6.85)
0h	70.4 (11.11)	150.2 (11.33)	87.0 (5.27)
2h	71.5 (11.21)	148.6 (10.92)	86.2 (6.29)
4h	72.1 (11.97)	150.4 (10.57)	85.2 (4.64)
8h	70.2 (9.68)	149.2 (9.94)	85.8 (6.36)
24h	74.3 (12.75)	151.6 (11.03)	86.2 (6.29)
48h	71.2 (9.62)	147.5 (11.19)	84.8 (7.38)
96h	70.2 (10.52)	147.4 (10.71)	83.8 (4.76)

(taken from Tables 2 and

No obvious trends were observed.

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b) ECG Results

All subjects were found to be in sinus rhythm at baseline and 24 hours post-dose as shown in Listing 7. An abnormality reported in subject 4 at both assessments was described as left ventricular hypertrophy and strain due to hypertension which was thought to be associated with chronic renal failure.

c) Adverse Events

No adverse events were recorded in this study.

5.5.3. Laboratory Safety Test Results

a) Haematology

Trends in the numbers of subjects experiencing haematological laboratory parameters that fell outside the normal range before and during the study are summarised below:

Table (5.5.3)1. Summary of Baseline to 24h Post-Dose Trends in Abnormal Haematological Parameters

Parameter	Baseline → 24h Post-Dose					
	Low → Low	Normal → Low	Normal → Normal	Normal → High	High → Normal	High → High
Haemoglobin	9 (90%)	-	1 (10%)	-	-	-
Haematocrit	9 (90%)	-	1 (10%)	-	-	-
Mean Cell Volume	-	-	7 (70%)	-	1 (10%)	2 (20%)
Red Cell Count	9 (90%)	-	1 (10%)	-	-	-
Mean Cell Haemoglobin	-	-	7 (70%)	-	-	3 (30%)
Mean Cell Haemoglobin Concentration	-	1 (10%)	9 (90%)	-	-	-
Lymphocytes	2 (20%)	2 (20%)	6 (60%)	-	-	-
Monocytes	1 (10%)	-	9 (90%)	-	-	-
Granulocytes	-	-	9 (90%)	1 (10%)	-	-
Platelets	-	-	9 (90%)	-	1 (10%)	-
Prothrombin Time	-	-	9 (90%)	-	1 (10%)	-

Haemoglobin levels, the haematocrit and the red cell count were below normal in 9 of 10 subjects at baseline and during the study period, whereas the mean cell volume and mean cell haemoglobin remained high in 2 and 3 subjects, respectively. None of the out-of-range values was of clinical significance.

b) Biochemistry

Baseline to 24h post-dose trends in biochemical laboratory parameters that fell outside the normal range are summarised below:

Table (5.5.3)2. Summary of Baseline to 24h Post-Dose Trends in Abnormal Biochemical Parameters

Parameter	Baseline → 24h Post-Dose					
	Low → Low	Normal → Low	Normal → Normal	Normal → High	High → Normal	High → High
Alkaline Phosphatase	-	-	8 (80%)	1 (10%)	-	1 (10%)
Urea	-	-	-	-	-	10 (100%)
Uric Acid	-	-	8 (80%)	1 (10%)	-	1 (10%)
Creatinine	-	-	-	-	-	10 (100%)
Cholesterol			2 (20%)	1 (10%)		7 (70%)
Phosphate	-	-	5 (50%)	-	2 (20%)	3 (30%)
Potassium	-	1 (10%)	8 (80%)	1 (10%)	-	-
Bicarbonate	5 (50%)	2 (20%)	3 (30%)	-	-	-

Using fasting reference range of 3.4 - 5.2 mmol/l

Although fasting glucose samples were not taken, the glucose levels given in Listing 9 show that samples from 9 of the 10 subjects fell within the normal fasting glucose range (3.6 - 5.6 mmol/l). Glucose levels of 6.1 and 6.0 mmol/l were recorded at baseline and 24h post-dose, respectively, in 1 subject.

Urea and creatinine levels were markedly higher than the upper normal value in all subjects, reflecting their chronic renal failure. Bicarbonate levels were low in 50% of the subjects and fell from normal levels to below normal in 2 subjects.

None of the changes in laboratory parameters were attributable to modafinil.

c) Urinalysis : No glucose was recorded in any of the urine samples. Microscopy result consistent with renal failure

Table 6.2-79. Mean (±SD) Pharmacokinetic Parameters of Modafinil and Modafinil Acid After a 200 mg Oral Dose of Modafinil in Chronic Renal Impaired Patients and Healthy Subjects*

		Subjects with Chronic Renal Failure		Healthy Subjects*	
Parameter		Modafinil	Modafinil Acid	Modafinil	Modafinil Acid
C_{max} (mg/L)	Mean	3.33	5.36	4.01	1.95
	SD	0.45	2.49	0.90	0.35
T_{max} (hr)	Mean	2.55	7.25	2.05	2.75
	SD	1.38	2.72	0.46	0.66
$t_{1/2}$ (h)	Mean	22.18[a] 14.21[b]	19.25	11.69	5.69
	SD	21.43[a] 4.17[b]	9.75	2.18	1.13
AUC_{0-t} (mg•hr/L)	Mean	53.75	175.7	NA	NA
	SD	17.13	133.26	NA	NA
$AUC_{0-\infty}$ (mg•hr/L)	Mean	55.49	188.39	51.83	21.03
	SD	17.43	148.74	12.58	4.66
CL_{renal} (mg/L)	Mean	0.103	0.216[c]	NA	NA
	SD	0.031	0.200[c]	NA	NA
Ae (0-96 hr) (mg)	Mean	13.38[d] 6.80[c]	46.15[e]	9.02	82.62
	SD	14.07[d] 2.09[c]	28.94[e]	1.12	10.64

[a] n=7
[b] n=6
[c] n=8
[d] n=10
[e] n=9
NA = Not Applicable.
* Data obtained from a previous study Lafon P1589 (MOD-022). N=12

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14. A Double-Blind Placebo-Controlled 3 Way Crossover Study to Investigate the Kinetics and Acute Tolerability of Modafinil and Clomipramine Alone and in Combination in Healthy Male Volunteers (C1538a/107/PK/UK)

Objectives:

To study the kinetic interaction between modafinil and clomipramine.

Introduction:

Narcolepsy is generally treated with a central nervous system stimulant, such as modafinil, to reduce excessive daytime sleepiness and an antidepressant to control cataplexy and other REM sleep-related symptoms. The obvious need to coadminister modafinil and antidepressant makes it necessary to conduct PK drug interaction between modafinil and a representative tricyclic antidepressant, such as clomipramine.

Clomipramine is well absorbed orally. It is metabolized by CYP2D6 to its active metabolite desmethyl clomipramine. Both the parent drug and the metabolite are eliminated slowly ($t_{1/2}$>24 hr).

Study Design and Sampling:

The study was a single-center, 3-way double-blind crossover study involving 18 healthy male volunteers. The protocol of the study was as following:

After fasting, the subjects were dosed with the following treatment schedule:

Treatment A: Clomipramine (1 x 50 mg capsule) - Day 1
Modafinil (2 x 100 mg tablets) once daily - Days 1 to 3

Treatment B: Clomipramine (1 x 50 mg capsule) - Day 1
2 x placebo tablets once daily - Days 1 to 3

Treatment C: 1 x placebo capsule - Day 1
Modafinil (2 x 100 mg tablets) once daily - Days 1 to 3

D1: Single dose of clomipramine/placebo given at the same time as the modafinil/placebo

There was a two-week washout period between each treatment phase. For modafinil, blood samples were collected immediately prior to the Day 1 modafinil dose (time zero) and at 1, 2, 3, 4, 6, 12, and 24 hours following administration of the Day 1 modafinil dose, and at 60, 72, 84, 96 and 108 hours after dosing of the Day 3 modafinil dose using the Treatment Schedules A and C. Sampling time for clomipramine is 72 hr **The prepared plasma samples were stored in a -20°C freezer and frozen in dry ice during shipment, and were stored at -80 to -90°C awaiting analysis.**

Results (Attachment 14) and Conclusions:

It appeared that co-administration of clomipramine did not affect the PK of modafinil or its metabolites in humans. Modafinil did not affect the PK of clomipramine or desmethyl clomipramine, either. Further, since the metabolism of clomipramine is known to utilize CYP2D6, lacking of PK interaction in this study seems to indicate that 3 days dosing of modafinil had no effect on CYP2D6.

Comments:

1. This study design is inadequate. First, the single dose design of clomipramine in the study does not reflect the "real situation" where the multiple dosing of this antidepressant is usually administered to the patients. The single dose design could mask the potential drug-drug interaction if the interactant from clomipramine is the metabolites, rather the parent drug. Secondly, the relatively low dose of clomipramine in the study (50 mg), besides single dosing, might "hide" the interaction that would be reached at high doses.
2. The sampling time for clomipramine, 72 hrs, is too short to cover the elimination phase of the drug, which may result in wrong estimation of $AUC_{0-\infty}$ on clomipramine.
3. The sampling time for desmethyl clomipramine, whose reported t1/2 is 96 hr, is too short in this study to draw meaningful conclusions on its t/12, AUC0-∞ in this study. Therefore, the conclusions for desmethyl clomipramine can only based on Cmax and AUC_{0-t}.
4. Variation on plasma concentrations and AUC_{0-t} for both clomipramine and its active metabolites were big.

ATTACHMENT A-14

~~Table 1~~. Pharmacokinetic Parameters of Modafinil after Dosing with Treatment A and Treatment C in Healthy Males

Treatment A: Clomipramine (50 mg single dose) and Modafinil (200 mg once daily dose for 3 days (τ=24hr))
Treatment C: Placebo (single dose) and Modafinil (200 mg once daily dose for 3 days (τ=24hr))

	C_{max}	T_{max}	λ [a]	$t_{1/2}$ [a]	$AUC_{0-\tau}$	$AUC_{0-\infty}$	CL/F	V/F
	µg/mL	hr	hr^{-1}	hr	µg•hr/mL	µg•hr/mL	mL/min	L
Treatment A	4.3±0.8	2.2±0.9	0.0537±0.0100	13.5±3.3	42.4±6.8	55.3±10.6	62.2±11.0	71.1±13.9
Treatment C	4.4±0.9	1.7±0.7	0.0547±0.0103	13.1±2.6	41.6±6.0	54.2±10.2	63.6±12.0	70.5±10.2

[a] The terminal rate constant, λ, the half-life, $t_{1/2}$, was determined from Day 3 data and used to determine $AUC_{0-\infty}$, CL/F and V/F following administration of Day 1 dose.

~~Table 2~~. Pharmacokinetic Parameters of Modafinil Acid after Dosing with Treatment A and Treatment C in Healthy Males

	C_{max}	T_{max}	λ	$t_{1/2}$	$AUC_{0-\tau}$	$AUC_{0-\infty}$
	µg/mL	hr	hr^{-1}	hr	µg•hr/mL	µg•hr/mL
Treatment A	2.3±0.4	3.2±0.9	0.126±0.018	5.6±0.7	23.9±5.6	25.5±5.9
Treatment C	2.4±0.5	3.2±0.8	0.118±0.023	6.1±1.5	23.6±4.5	25.7±5.4

~~Table 3~~. Pharmacokinetic Parameters of Modafinil Sulfone after Dosing with Treatment A and Treatment C in Healthy Males

	λ	$t_{1/2}$
	hr^{-1}	hr
Treatment A	0.0258±0.0119	33.1±17.1
Treatment C	0.0261±0.0092	30.9±13.9

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Figure 1. Mean (±SD) Semi-logarithmic Plasma Level versus Time Plots of Modafinil after Dosing with Treatment A and Treatment C in Healthy Males

Treatment A: Clomipramine (50 mg single dose) and Modafinil (200 mg once daily doses for 3 days (τ=24hr))
Treatment C: Placebo (single dose) and Modafinil (200 mg once daily doses for 3 days (τ=24hr))

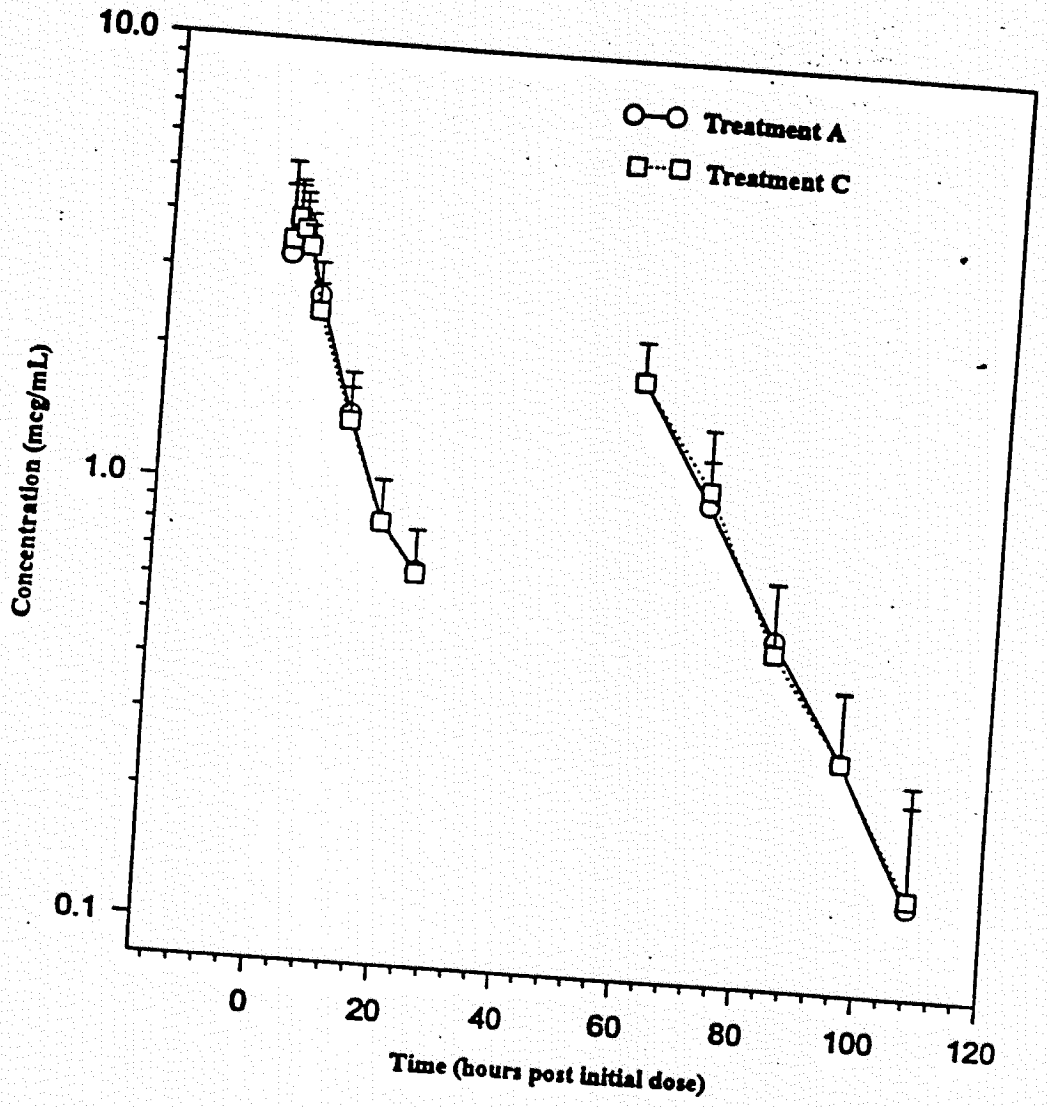

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Figure 2. Mean (±SD) Semi-logarithmic Plasma Level versus Time Plots of Modafinil Acid after Dosing with Treatment A and Treatment C in Healthy Males

Treatment A: Clomipramine (50 mg single dose) and Modafinil (200 mg once daily doses for 3 days (τ=24hr))

Treatment C: Placebo (single dose) and Modafinil (200 mg once daily doses for 3 days (τ=24hr))

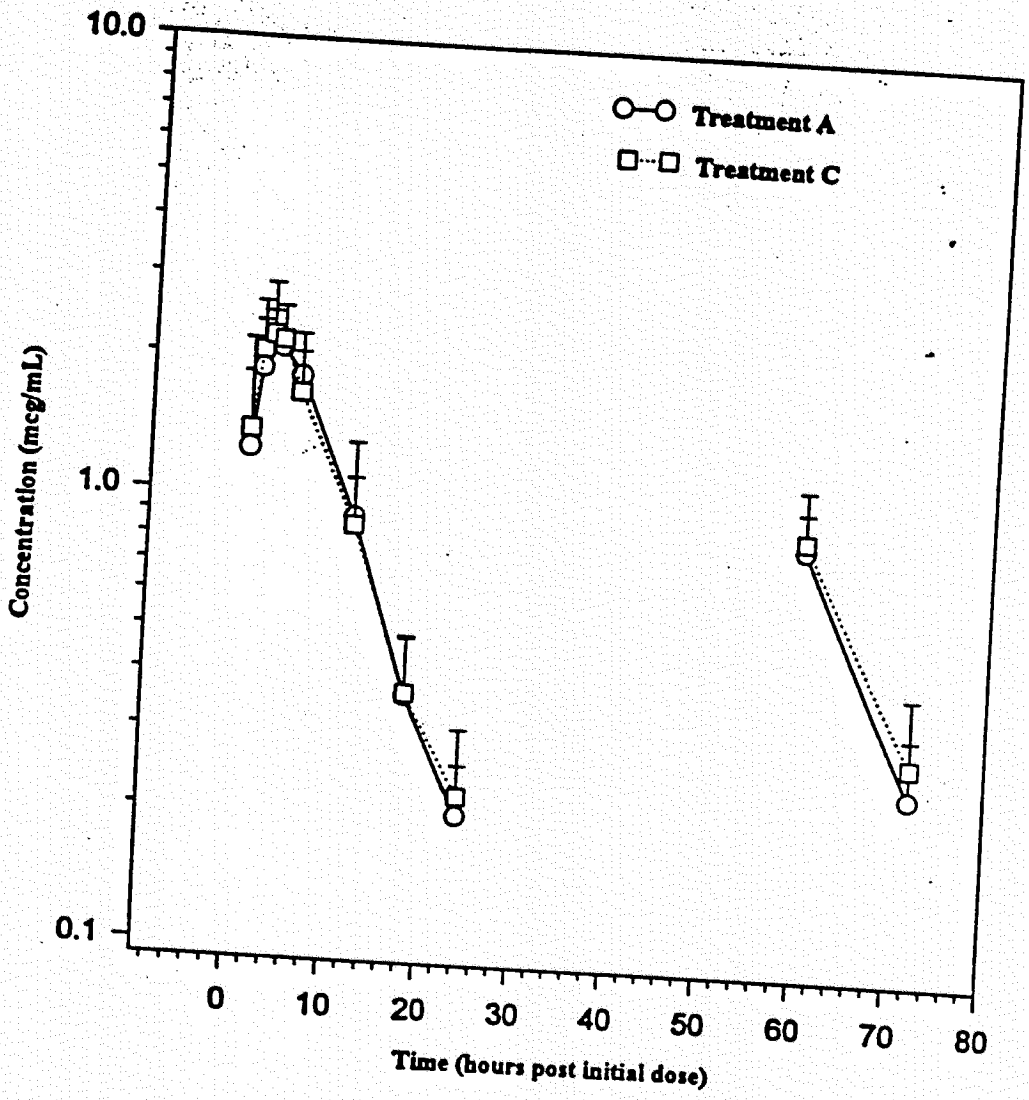

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Figure 3. Mean (±SD) Semi-logarithmic Plasma Level versus Time Plots of Modafinil Sulfone after Dosing with Treatment A and Treatment C in Healthy Males

Treatment A: Clomipramine (50 mg single dose) and Modafinil (200 mg once daily doses for 3 days (τ=24hr))

Treatment C: Placebo (single dose) and Modafinil (200 mg once daily doses for 3 days (τ=24hr))

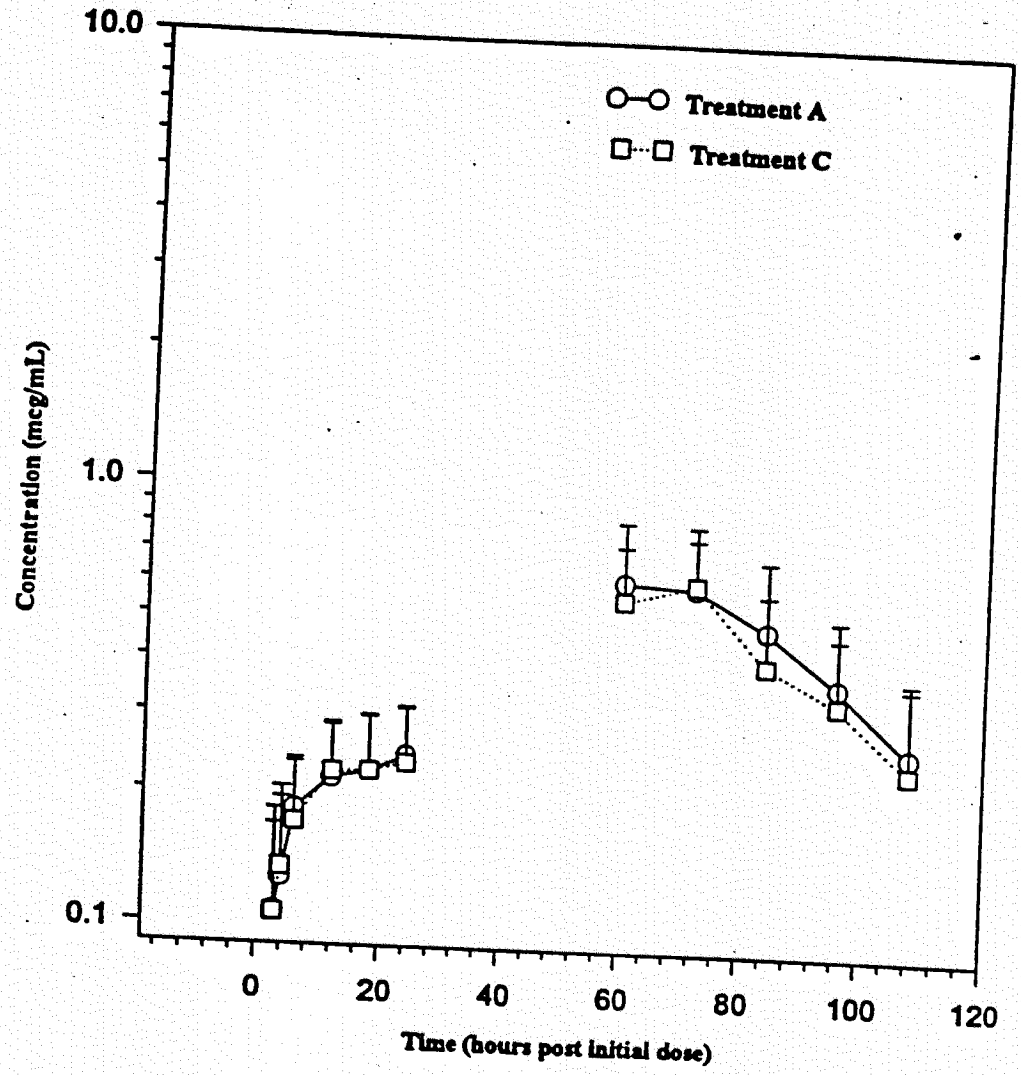

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Table 6.2-53. Mean (±SD) Pharmacokinetic Parameters of Clomipramine Following Administration of Clomipramine (50 mg) with Either Modafinil or Placebo in Healthy Subjects

	Treatment A	Treatment B
C_{max} (µg/L)	44.1 (15.2)	39.0 (11.3)
T_{max} (hr)	3 (2-6)*	3 (2-4)*
AUC_{0-t} (µg •hr/L)	486 (216)	431 (247)
$AUC_{0-\infty}$ (µg •hr/L)	663 (364)	601 (353)
$t_{1/2}$ (hr)	19 (19)	20 (20)

* median range.
Treatment A: Clomipramine (50 mg, Day 1) and Modafinil (200 mg, Days 1 to 3).
Treatment B: Placebo and Clomipramine (50 mg, Day 1).

Table 6.2-54. Mean (±SD) Pharmacokinetic Parameters of Desmethyl Clomipramine Following Administration of Clomipramine (50 mg) with Either Modafinil or Placebo in Healthy Subjects

	Treatment A	Treatment B
C_{max} (µg/L)	8.2 (3.1)	11.6 (4.6)
T_{max} (hr)	12 (2-36)*	6 (3-36)*
AUC_{0-t} (µg •hr/L)	332 (200)	413 (273)
$AUC_{0-\infty}$ (µg •hr/L)	6190 (12999)	1128 (1141)
$t_{1/2}$ (hr)	483 (1018)	88 (102)

* median range
Treatment A: Clomipramine (50 mg, Day 1) and Modafinil (200 mg, Days 1 to 3).
Treatment B: Placebo and Clomipramine (50 mg, Day 1).

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Plasma Clomipramine Concentration-time data ($\mu g \cdot L^{-1}$) for Treatment A

Subject	1	2	3	4	5	6	13	14	15	16	MEAN	SD	CV %	MIN	MAX
Time (h)															
0															
1															
2															
3															
4															
6															
10															
14															
18															
24															
36															
48															
72															

[redacted]

Plasma Clomipramine Concentration-time data ($\mu g.L^{-1}$) for Treatment B

Subject	1	2	3	4	5	6	13	14	15	16	MEAN	SD	CV %	MIN	MAX
Time (h)															
0															
1															
2															
3															
4															
6															
10															
14															
18															
24															
36															
48															
72															