

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020717

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-717
IND [REDACTED]

Submission Date:
December 27, '96, -
April 10, '97, -
May 13, '97.
June 16, '97.
July 23, '97 -
Aug. 10, '97 -

PROVIGIL® (Modafinil) (100 mg, 200 mg IR Tablets for Oral Administration)

INDICATION: Narcolepsy

Sponsor: Cephalon Inc., West Chester, PA

Type of submission: NDA (NME),

Reviewer: Rae Yuan, Ph.D.

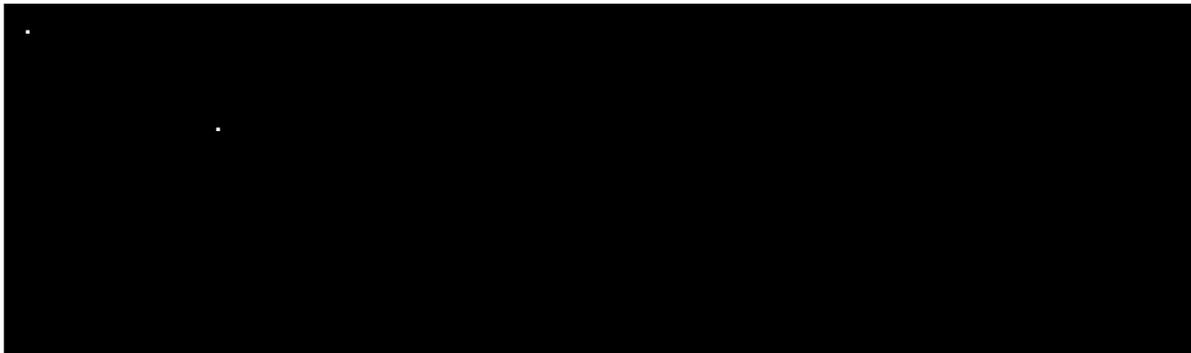
SYNOPSIS:

PROVIGIL® (Modafinil), chemically 2-[(diphenylmethyl)sulfinyl]acetamide (MW=273, pKa=10.4), is claimed to be a centrally acting wakefulness-promoting compound that is developed for the treatment of narcolepsy. The sponsor is seeking for approval on 100 mg and 200 mg uncoated immediate release tablets for oral administration. According to the labeling by the sponsor, modafinil will be administered at an initial dose of 200 mg/day, and may be increased to a maximum of 400 mg/day. Because it is believed that all the metabolites of modafinil are pharmacologically inactive, the focus of this NDA is on the parent drug.

RECOMMENDATIONS:

This NDA is acceptable to the OCPB, provided that the sponsor incorporates OCPB PK labeling in COMMENT 8 and adopts the dissolution specification in COMMENT 9.

Please convey the following COMMENTS to the clinical division and to the sponsor.



modafinil acid is 40% of $AUC_{0-\infty}$ of parent drug, and C_{max} is 50% of the parent drug. In renal impairment patients, these percentages increased to 340% and 160%, respectively (based on single dose study). Had the renal impairment study been conducted in multiple dosing regimen, modafinil acid accumulation could be even higher. Therefore, the toxicity of modafinil acid needs to be studied.

3. The sponsor has conducted a drug-drug interaction study between clomipramine and modafinil, and concluded no interaction between the two drugs. However, the study design, in the reviewer's opinion, was inadequate in the study to draw such a conclusion. A case report submitted as a supplement indicated that PK interaction between modafinil and clomipramine is possible. Furthermore, an in vitro study conducted by the sponsor demonstrated that modafinil competitively inhibits CYP2C19, which may be involved in clomipramine metabolism.
4. Modafinil was able to induce certain CYP enzymes, as demonstrated in an in vitro study. In vivo, modafinil was found to induce self-metabolizing enzyme to result in lowered plasma concentration following chronic dosing (>6 weeks). It was also demonstrated that modafinil induces enzymes metabolizing antipyrine. Furthermore, a case report submitted as supplement indicated that modafinil may induce CYP3A4 in cyclosporine metabolism.

COMMENTS TO THE SPONSOR:

5. The sponsor is encouraged to provide information regarding the interconversion of enantiomers in the future.

6. For the drug-drug interaction study between clomipramine and modafinil, the study design is inadequate. [REDACTED]

7. Clinical information on modafinil interaction with CYP3A and CYP2C19 enzyme substrates (especially narrow therapeutic drugs as CYP2C19 substrates), as those indicated by in vitro studies, should be submitted.

8. The sponsor is requested to incorporate 'OCPB pharmacokinetic labeling' as outlined in the Labeling section (pg. xiv).

9. Based upon data provided by the sponsor, OCPB is setting the following methodology and specification for all strengths of modafinil tablets (100 mg and 200 mg):

Apparatus:	USP 2 (paddle)
Speed:	[REDACTED]
Medium:	900 ml of 0.1N HCl
Temperature:	37 °C
Specification:	Not less than [REDACTED] in [REDACTED] minutes.

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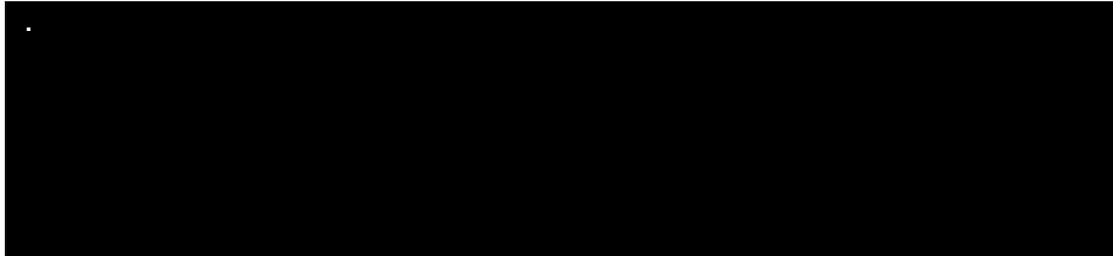
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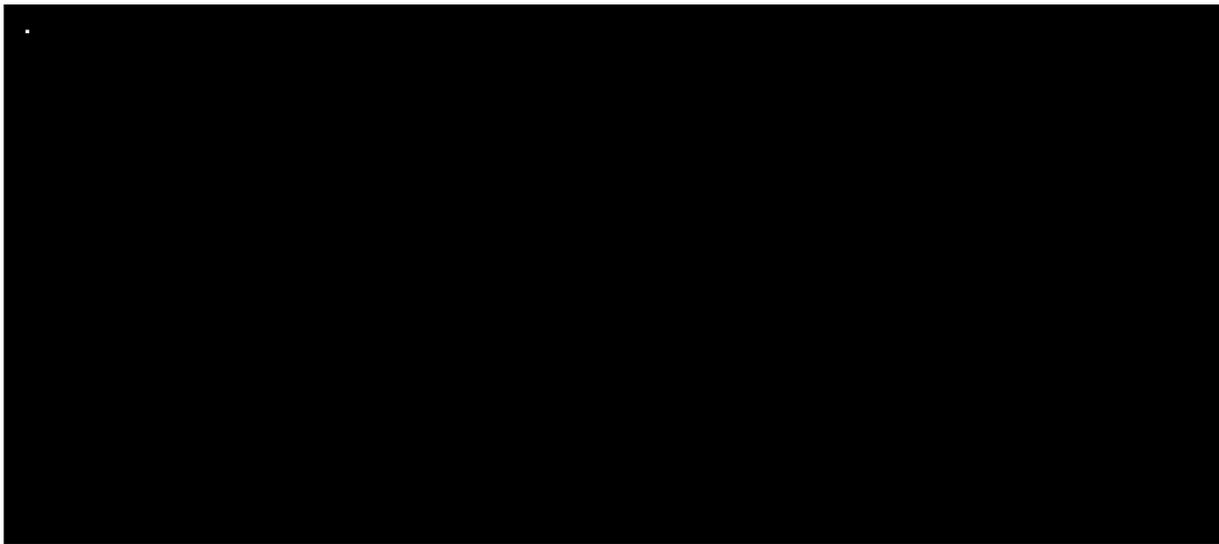
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6. DP-95-005: A Validation of an Internal Standard Assay for Simultaneous Determination of Modafinil and Its Acid and Sulfone Metabolites in Human Plasma Utilizing [REDACTED] and [REDACTED]

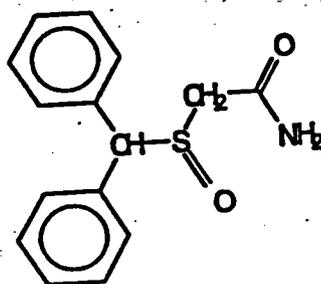
7. C1538b/105/BE/UK: Open, Randomized, 2-Way Crossover Study to Compare the Bioavailability of a Single Oral dose of 200 mg Modafinil (Formulation A) with 200 mg Modafinil (Formulation B) in 20 Healthy Male Volunteers

APPEARS THIS WAY ON ORIGINAL

SUMMARY OF STUDIES

Background:

In the last 40 years, there has not been a novel compound approved for the treatment of narcolepsy. The current therapeutic agents for this disease are methylphenidate, *d*-amphetamine and pemoline, all of whose efficacy assessments were based on uncontrolled case studies, and all of which are considered CNS stimulants acting through dopaminergic/noradrenergic mechanisms. Here, the sponsor proposed MODAFINIL, chemically, 2-[(diphenylmethyl)sulfinyl]acetamide, as a centrally acting wakefulness-promoting agent for the treatment of narcolepsy. Modafinil is currently available in France (as Modiodal), and approval is pending in most European countries. The sponsor seeks approval of 100 mg and 200 mg IR uncoated tablets for the therapeutic use of 200 mg/day as an initial dose and 200-400 mg/day as maintenance dose in adults.



Modafinil

Pharmacokinetics of modafinil and its enantiomers:

Modafinil is a racemic mixture, with its enantiomers showing different kinetics. In the range of 200-600 mg/day once daily, time-independent and dose-independent pharmacokinetics were observed for both modafinil and its enantiomers. PK profile of Modafinil is similar to that of *l*-(-)-modafinil. Apparent C_{∞} (trough) of modafinil and *l*-(-)-modafinil, both of which were much higher than that of *d*-(+)-modafinil (by >10 times) were reached after 3-4 days of dosing. Steady state of *d*-(+)-modafinil was reached within 24 hrs after dosing. Elimination of *d*-(+)-modafinil is 3 times as fast as that of *l*-(-)-modafinil (Cl=102 ml/min and $t_{1/2}$ =4hr vs. Cl=34 ml/min and $t_{1/2}$ =15hr, respectively). The enantiomers have similar volume of distribution (~40 L).

Absorption:

Absorption of modafinil tablets is rapid, with peak plasma concentration of ~5 µg/ml or ~10 µg/ml being achieved at ~2 hours following daily single dose of 200 or 400 mg/day, respectively. The relative bioavailability of modafinil tablet is ~100%, compared to a micronized aqueous suspended solution.

Distribution:

The volume of distribution (V/F) of modafinil is 0.8-0.9 L/kg, larger than the volume of total body water (0.6 L/kg), which suggests a high degree of tissue binding for modafinil. In human plasma, modafinil is moderately bound to plasma protein (~60%, mainly to the albumin).

Metabolism:

In vivo metabolism: The metabolism of modafinil has been investigated in 6 healthy volunteers who received a single oral dose of side-chain labeled ¹⁴C-modafinil (200 mg). Approximately 80% and ~1% of the total dose were recovered in 11-day period in urine and feces, respectively. Unchanged modafinil accounted for 5% of the total radioactivity recovered in urine. Six inactive metabolites were isolated and identified in urine (See the attached page). Modafinil acid, the deamination product from the parent drug, is the major metabolite identified in urine (accounts for ~ 40%). The other metabolites, presumably produced *via* oxidation, aromatic ring hydroxylation, reduction or glucuronidation mechanism, were all minor metabolites. In plasma samples collected up to 192 hr, modafinil, modafinil acid and modafinil sulfone were detected. Modafinil and modafinil acid account for 40 and 20% of the total radioactivity (in terms of AUC_{0-inf}), respectively. Modafinil sulfone accounts for less than 10%. Elimination half life of total radioactivity (3 days) is much longer than that of modafinil (10 hr) or modafinil acid (6 hr).

In vitro metabolism: Human liver microsomal studies revealed that (1) the major renally excreted metabolite, modafinil acid, was not produced from CYP catalysis; (2) the minor metabolite in human, modafinil sulfone, was produced *via* CYP3A catalysis; (3) modafinil inhibits CYP2C19 activity.

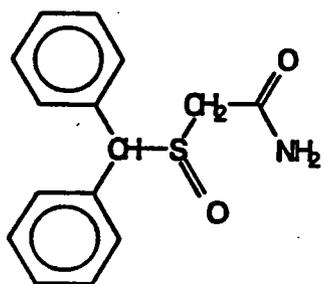
In humans, modafinil at dose higher than 400 mg showed enzyme induction on self metabolism after chronic dosing. The possibility of chronic administration of modafinil to induce certain metabolic enzymes was also demonstrated in isolated hepatocytes that had been incubated with supratherapeutic concentrations of modafinil (100 to 1000 μM) for over 72 hrs.

Elimination:

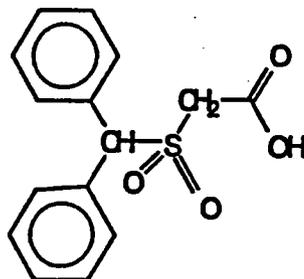
The major route of elimination for modafinil is metabolism (>90%). Renal excretion accounts for the rest (<10%) of the total drug. The mean total plasma clearance of modafinil is ~0.6 ml/min/kg. The mean plasma effective half-life of modafinil following multiple dosing is ~15 hr. Urine alkalization has no effect on the elimination of modafinil.

Food Effect:

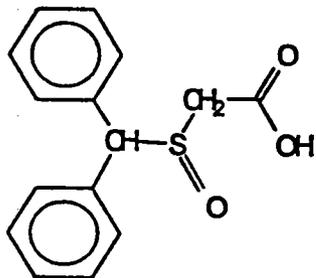
Figure 6.2-20. Modafinil and Modafinil Metabolites Identified by LC/MS/MS Techniques In Urine from Human Subjects Administered a Single Oral Dose of [¹⁴C]-Modafinil



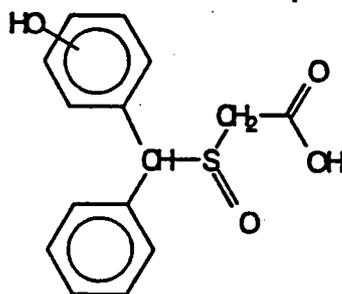
Modafinil



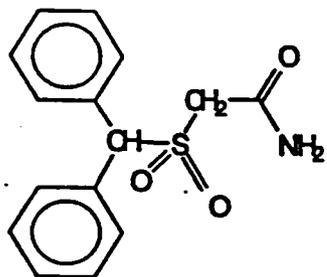
Modafinil Acid Sulfone



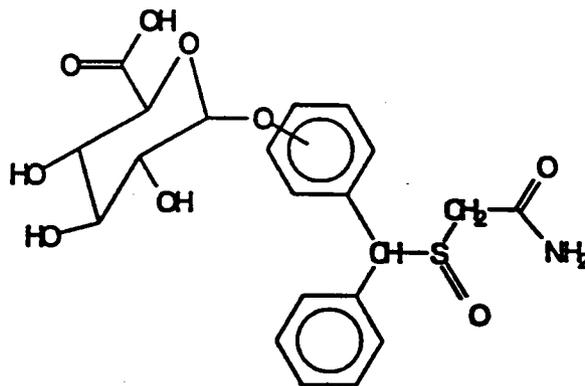
Modafinil Acid



Ring-Hydroxylated
Modafinil Acid



Modafinil Sulfone



Glucuronide Conjugate of
Ring-Hydroxylated Modafinil

Food intake did not show any effect on the bioavailability of modafinil, or the pharmacokinetics of the two enantiomers. Therefore, modafinil can be administered without consideration to food.

Gender Study:

In young healthy volunteers, a slight gender difference in metabolite modafinil acid excretion was demonstrated, but is of little clinical significance. In the pivotal study on patients with narcolepsy (n>30), no gender difference on plasma concentration of modafinil was observed.

Age Study:

In a single dose study, 12 elderly male subjects showed slightly lower clearance of modafinil (by 20%), compared to the young male volunteers (n=12). But all the other pharmacokinetic parameters were comparable between the two groups. In a study of 12 elderly patients with narcolepsy (n=12, 6M & 6F), the plasma concentrations at steady state were comparable to those in the young subjects. No study on elderly female subjects were conducted. But overall, the age effect on modafinil pharmacokinetics did not seem to be prominent.

Hepatic Impaired Subjects:

This was an open trial on PK of multiple dosing of modafinil (2 x 100 mg for 8 days) on 9 subjects (6 men and 3 women) with severe liver cirrhosis. Six healthy male subjects (from another multiple dosing study), who received the same dose and regimen of modafinil as the hepatically impaired patients, served as controls. On Day 1 and Day 8, a single dose of 200 mg of modafinil was given in the morning, but from Day 2 to Day 7, the drug was given as one tablet in the morning and one at noon. PK parameters are altered in severely hepatic impairment patients: $t_{1/2}$ was doubled (from 13.6 hr to 27.7 hr), total volume of distribution was decreased (from ~80 L to ~60 L), and C_{max} at steady state was doubled (from 3.7 $\mu\text{g/ml}$ to 7.9 $\mu\text{g/ml}$). Despite the change of PK parameters, the hepatic insufficient patients had a good tolerance to the drug. A reduction by one-half in the dosage of modafinil is suggested in the patients with severe liver disease. No study was conducted on mild and moderate liver impairment patients.

Impaired Renal Subjects:

This study was a single 200 mg dose, non-randomized, open label study conducted in 10 male subjects with severe chronic renal failure (mean $CL_{cr}=16.6 \pm 2.2$ ml/min. All patients had a history of renal disorder, 4 had hypertension, 1 had glaucoma and 1 of dyspepsia.). Twelve healthy male volunteers from another study served as controls for this group of renal impaired patients. Severe chronic renal failure did not significantly influence the PK of modafinil, compared to the PK in normal volunteers. The inactive metabolite, modafinil acid, accumulated considerably in renal patients ($AUC_{0-\infty}$ increased by >8 fold and $T_{1/2}$ increased by >2 fold). But the clinical implication

of toxicity from modafinil acid, upon chronic administration of modafinil, was not known. The sponsor claimed that dose adjustment in this population was not necessary.

Drug-Drug Interactions:

(a) *In Vivo*:

Modafinil and Clomipramine

This is a single-center, 3-way double-blind crossover study involving 18 healthy male volunteers. Six subjects received one single dose of clomipramine at 50 mg on Day 1 and 200 mg modafinil (2 x 100 mg tablets) once daily from Day 1 to Day 3. Six subjects received the same dose of clomipramine alone on Day 1 and 2 placebo tablets for modafinil for 3 days. The other group of 6 subjects received 1 placebo capsule for clomipramine on Day 1 and modafinil (2 x 100 mg tablets) once daily from Day 1 to Day 3. There was a 2-week washout period between each treatment phase ($t_{1/2}$ of clomipramine > 24 hr). Plasma samples were collected for modafinil upto 108 hrs and clomipramine upto 72 hrs, which is, in this reviewer's opinion, too short to cover the elimination phase. Though it appears that there is no drug interaction between clomipramine and modafinil, in the reviewer's opinion, the poor study design and the large variation on clomipramine plasma concentration may contribute to failure in detecting any potential interaction.

Recently, a case report on a 60 year old female taking long term treatment of 100 mg clomipramine showed drug interaction with 200 mg modafinil. Suffering from cataplexy, she was put on 100 mg clomipramine with steady state concentration of clomipramine and its active metabolite desmethyl clomipramine of 129 and 208 ng/ml respectively. Under 200 mg modafinil, the blood level of clomipramine and desmethyl clomipramine increased to 158 and 238 ng/ml, respectively, although the dose of clomipramine was decreased to 75 mg. Under 400 mg modafinil, the blood level of clomipramine and desmethyl clomipramine increased to 210 and 449 ng/ml, respectively, causing the discontinuity of clomipramine administration.

Modafinil and Methylphenidate

This is an open 3x3 Latin square, randomized, cross-over study in 21 healthy male volunteers (3 groups of 7 subjects). All the drugs were given as single doses. In one treatment group, methylphenidate (immediate release) at a dose of 4 x 10 mg and modafinil at a dose of 2 x 100 mg were given to the subjects concomitantly. In other treatment groups, modafinil (2 x 100 mg) or methylphenidate (4 x 10 mg) was given alone, separately. The results show that the coadministration of these two medications did not change the PK of either agent, except that methylphenidate administration caused a small increase (~1 hr) on modafinil T_{max} , which may result in a delay in modafinil oral absorption.

(b) *In Vitro*:

In vitro studies were conducted in human liver microsomes to investigate the possible inhibitory effect on CYP enzymes by modafinil at concentrations 5 to 250 μ M, covering the range of therapeutic concentrations. Different substrates with specific

reaction to CYP enzymes were employed at concentrations equal to their $K_m/2$, K_m and $4 K_m$ in the incubation. The results show that modafinil has little or no capacity to inhibit the major CYP enzymes, with the exception of CYP2C19. Modafinil competitively inhibits CYP2C19 with K_i of $39 \mu M$, the concentration can be achieved after multiple dosing of 400 mg of the drug. This indicates that drugs whose rates of elimination depend on CYP2C19, especially ones that have narrow therapeutic index, would have a great potential to interact with modafinil to result in significant clinical consequences.

An *in vitro* study using freshly isolated human livers was conducted to investigate the induction potential of chronic dosing of modafinil on various CYP enzymes. Although there is a large variation of enzyme activities among untreated and treated human hepatocytes, increased activities of CYP1A and CYP3A by incubating modafinil for 72 hours with these hepatocytes were observed at its pharmacologically relevant concentrations ($10-100 \mu M$). A case of drug-drug interaction between modafinil and cyclosporine was reported on a 43 year old female organ transplant patient. After one month administration of 200 mg/day modafinil, cyclosporine blood level was decreased by 50%. The interaction was postulated due to the increased metabolism of cyclosporine, since the bioavailability of the drug was not changed.

Bioequivalence Study:

A single-center, open, randomized, 4×4 Latin Square cross-over study was conducted to compare the bioequivalence of the to-be-marketed tablets at 2×100 mg and 1×200 mg strengths to the 2×100 mg tablets used in clinical trials. Comparison of C_{max} , AUC_{0-inf} , and AUC_{0-4} on log transformed scale demonstrated the bioequivalence of TBM tablets and the one used in clinical trial.

Dissolution:

pH-solubility profile of modafinil showed that dissolution of modafinil was not different in [redacted] media [redacted]. Hydrochloric acid at 0.1 N was chosen by the sponsor to be the dissolution medium. Dissolution testing was performed using USP-II at [redacted] at $37^\circ C$. One hundred and 200 mg modafinil tablets were dissolved in 900 ml dissolution media. Biobatches representing various strengths of modafinil indicated that [redacted] of the drug is released in [redacted].

Dissolution method and specification:

Apparatus:	USP 2 (paddle)
Speed:	[redacted]
Medium:	900 ml of 0.1N HCl
Temperature:	$37^\circ C$
Specification:	Not less than [redacted] in [redacted]

Assay:

Quantitation of modafinil, its enantiomers and metabolites in human biological samples were conducted by [REDACTED] followed by [REDACTED] on reverse column with [REDACTED]. Validation for each assay method was performed and found to be acceptable for its specificity, sensitivity, accuracy, precision and stability.

Formulation:

Modafinil Drug Substance

Lactose [REDACTED]

Corn Starch [REDACTED]

Magnesium Silicate [REDACTED]

Povidone [REDACTED]

Croscarmellose Sodium [REDACTED]

Magnesium Stearate [REDACTED]

OCPB Briefing: Nov. 18, 1997

Attendees: Drs. Lesko, Fisher, Heimann, Balian, Al-Habet, Huang, Mehta, Chen, Lazor Blaschke, Katz, Rappoport, Hepp, Tammara, Baweja, Yuan.

Primary Reviewer: Rae Yuan, Ph.D. [REDACTED] 11/19/97

Team Leader: Ray Baweja, Ph.D. [REDACTED] 11/19/97

Date of Signature: 11/19/97

Office of Clinical Pharmacology and Biopharmaceutics/ Division I

CC list: NDA 20-717 (NME): HFD-120; HFD-860 (Yuan, Baweja, Malinowski); CDR (Barbara Murphy)

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OCPB PK LABELING

Pharmacokinetics of modafinil:

DRAFT LABELING



Absorption:

., DRAFT LABELING



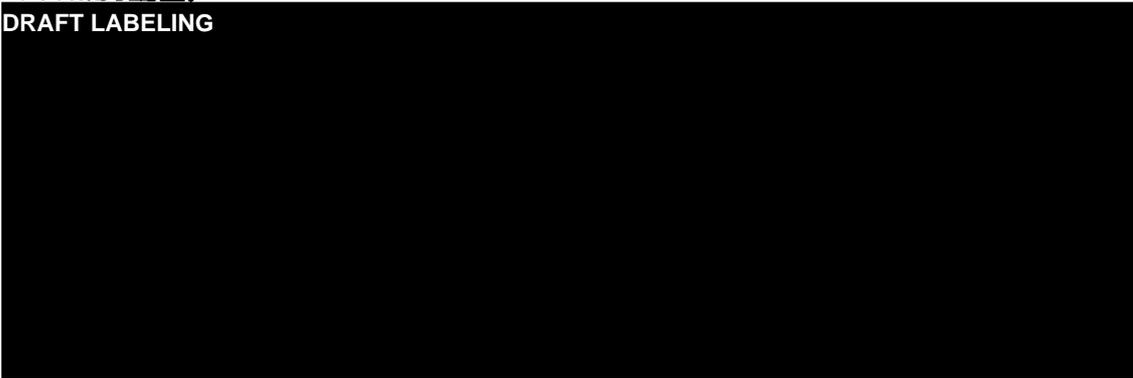
Distribution:

DRAFT LABELING



Metabolism:

DRAFT LABELING



Elimination:

DRAFT LABELING



Special Populations:

Gender Effect:

DRAFT LABELING



Age Effects:

DRAFT LABELING

Race Effect:

DRAFT LABELING

Renal Impairment:

DRAFT LABELING

Hepatic Impairment:

DRAFT LABELING

PRECAUTIONS:

Precaution/Drug Interactions:

DRAFT LABELING

DRAFT LABELING



Precaution/Patients with Severe Renal Disease:

DRAFT LABELING



Precaution/Patients with Severe Hepatic Disease:

DRAFT LABELING



Dosage and Administration:

DRAFT LABELING



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APPENDIX A. REVIEWED INDIVIDUAL STUDY

In Vivo Metabolism

1. Mass Balance study: A Mass Balance and Metabolism Study of ^{14}C -Modafinil (100 uCi) Following the Single Dose Administration of a 200 Mg Oral Suspension (C1538a/111/PK/US)

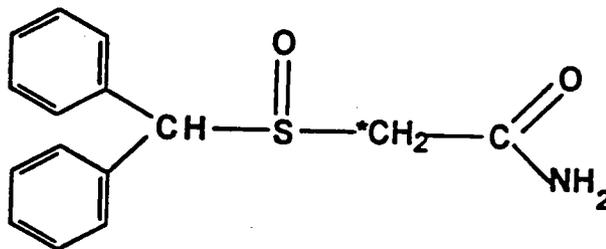
Objectives:

To determine the excretion and metabolism of Modafinil using mass balance methodology.

Study Design and Sampling:

It was an open-label, single-dose study to determine the excretion and metabolism of modafinil after a single oral dose of 200 mg ^{14}C -Modafinil (100 uCi) in 6 healthy male volunteers. ^{14}C was labeled on the β -position on modafinil. Radioactivity recovery and concentrations of modafinil and two metabolites, modafinil acid and modafinil sulfone, were assessed in plasma, urine and feces.

Figure 1. The Chemical Structure of ^{14}C -Modafinil



“*” indicates the position of radiolabeled carbon.

The dosage regimen and sampling schedule of the study were as following:

Subjects received a single oral dose of one 30 mL oral suspension containing 200 mg modafinil labeled with 100 μCi of carbon- 14 followed by three 30 mL rinses of the dispensing container and ingested for a total of 120 mL distilled water.

Preparation of dosing solution:

60.88 mg of ^{14}C -Modafinil and 1272.9 mg of Micronized Modafinil mixed with 200 mL of [redacted] oral suspension. 30 mL each was placed into a separate glass bottle for each participant.

- 1: [redacted] oral suspending vehicle; diluent for final dosing solution; [redacted]

2: ^{14}C -Modafinil 10.95 $\mu\text{Ci}/\text{mg}$, 2.8 mCi/mmol ,
1000 $\mu\text{Ci}/\text{vial}$; [REDACTED]

3: Micronized Modafinil
Cephalon, Inc.
Lot No. 95C001
Expiration date February, 1996

Thirty (30 mL) milliliters of blood were collected at predose and at 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 36, 48, 72, 96, 120, 144, 168, and 192 hours following the dose.

Urine samples were collected during the following intervals: predose, 0-4, 4-9, 9-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, and 168-192 hours postdose. Collections continued in 24 hour intervals, as needed for determination of release criteria. Samples were stored in a freezer set at -20°C until analyzed for radioactivity.

(for 9 days)
Fecal samples were collected predose and on a per sample basis. If more than one sample was produced during a 24 hour interval, the samples were not pooled together. Collections were continued in 24 hour intervals as needed for determination of release criteria. Samples were stored frozen in a freezer set at -20°C until analyzed for radioactivity.

Results (Attachment 1) and Conclusions:

$t_{1/2}$ of Modafinil was 10 hrs, but the $t_{1/2}$ of radioactivity was 3 days, suggesting that one or more than one metabolite of modafinil was/were eliminated at a much slower rate than the parent drug. Eighty percent of the radioactivity was excreted in the urine and < 2% in feces. But the renal clearance of unchanged modafinil accounted for only 6% of total dose, indicating that renal excretion was not a major pathway for modafinil elimination. Of the two detected metabolites, namely, modafinil acid and modafinil sulfone, modafinil acid was the major metabolite (40% of total dose) excreted in urine. Modafinil sulfone existed at low level in the blood and is undetectable in urine or in feces. Assuming that modafinil is stable in human blood, higher levels of parent drug and metabolites were found to be in plasma than to be bound to RBC. The distribution ratio of $C_{\text{RBC}}/C_{\text{p}}$ (=Total RBC radioactivity/Total plasma radioactivity) differs in *in vitro* (0.80) and in *in vivo* (0.39).

Comments:

1. Further analysis on ratio of AUC ($AUC_{\text{modafinil}}/AUC_{\text{total radioactivity}}$, $AUC_{\text{modafinil acid}}/AUC_{\text{total radioactivity}}$, and $AUC_{\text{modafinil sulfone}}/AUC_{\text{total radioactivity}}$) confirmed that ~30% of total drug was not identified in the blood.
2. The difference on radioactivity distribution *in vivo* and *in vitro* was not explained.
3. The formation clearance of modafinil acid is smaller than its disposition clearance and $t_{1/2}$ of modafinil acid is smaller than that of modafinil, indicating modafinil acid is the formation rate limited metabolite.

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Table 4. Mean (\pm SD, n=6) Pharmacokinetic Parameters and Distribution Ratios (*In vitro* and *In vivo*) (C_{RBC}/C_P) of RBC and Plasma Total Radioactivity

In vitro: Spiking Predose Whole Blood Samples with Specific Concentrations (1 and 5 μ g/mL) of 14 C-modafinil (specific activity of 10.59 μ Ci/mg).

In vivo: Following Administration of a Single Oral Dose (200 mg) of 14 C-Modafinil Suspension (100 μ Ci) in Healthy Males (range of plasma radioactivity concentration = 0.21-10.0 μ g equiv./mL).

	Plasma		RBC		Distribution Ratios (C_{RBC}/C_P)		
	λ	$t_{1/2}$	λ	$t_{1/2}$	<i>In vitro</i>		<i>In vivo</i>
	hr^{-1}	hr	hr^{-1}	hr	1 μ g/mL	5 μ g/mL	n=68
Mean	0.0119	67.5	0.0520	14.1	0.78	0.80	0.39
SD	0.0059	23.5	0.0126	3.5	0.03	0.03	0.05

Table 5. Excretion of Radioactivity, Modafinil, Modafinil Acid and Modafinil Sulfone (Expressed as % Modafinil Dose Excreted) Following Administration of a Single Oral Dose (200 mg) of 14 C-Modafinil Suspension (100 μ Ci) in Healthy Males

	% Dose Excreted up to 11 days post dose (mean \pm SD, n=6)		
	Urine	Feces	Total
Modafinil ^a	4.8 \pm 1.9	ND ^b	4.8 \pm 1.9
Modafinil Acid ^a	38.7 \pm 11.7	ND	38.7 \pm 11.7
Modafinil Sulfone ^a	0.0 \pm 0.0	ND	0.0 \pm 0.0
Unknown Metabolites	36.1	ND	37.1
Radioactivity	79.6 \pm 5.9	1.0 \pm 0.3	80.6

^a Quantified by an [redacted] method.

^b ND-Fecal samples were not assayed for modafinil and its metabolites.

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Table 2. Mean (\pm SD, n=6) Pharmacokinetic Parameters of Modafinil Following Administration of a Single Oral Dose (200 mg) of 14 C-Modafinil Suspension (100 μ Ci) in Healthy Males

Subject	C _{max} μ g/mL	T _{max} hr	t _{1/2} hr	AUC _{0-∞} μ g \cdot hr/mL	CL/F mL/min	V/F L	CL _{renal} mL/min
Mean	5.12	0.9	10.0	55.5	65.3	54.7	3.74
SD	1.29	0.6	2.2	16.4	21.4	12.8	0.66

Table 3. Mean (\pm SD, n=6) Pharmacokinetic Parameters of Modafinil Acid Following Administration of a Single Oral Dose (200 mg) of 14 C-Modafinil Suspension (100 μ Ci) in Healthy Males

Subject	C _{max} μ g/mL	T _{max} hr	t _{1/2} hr	AUC _{0-∞} μ g \cdot hr/mL	f _m	CL _m mL/min	CL _(m) mL/min
Mean	2.53	2.0	5.78	27.5	0.39	24.8	47.8
SD	0.35	0.9	0.91	5.3	0.12	11.7	16.9

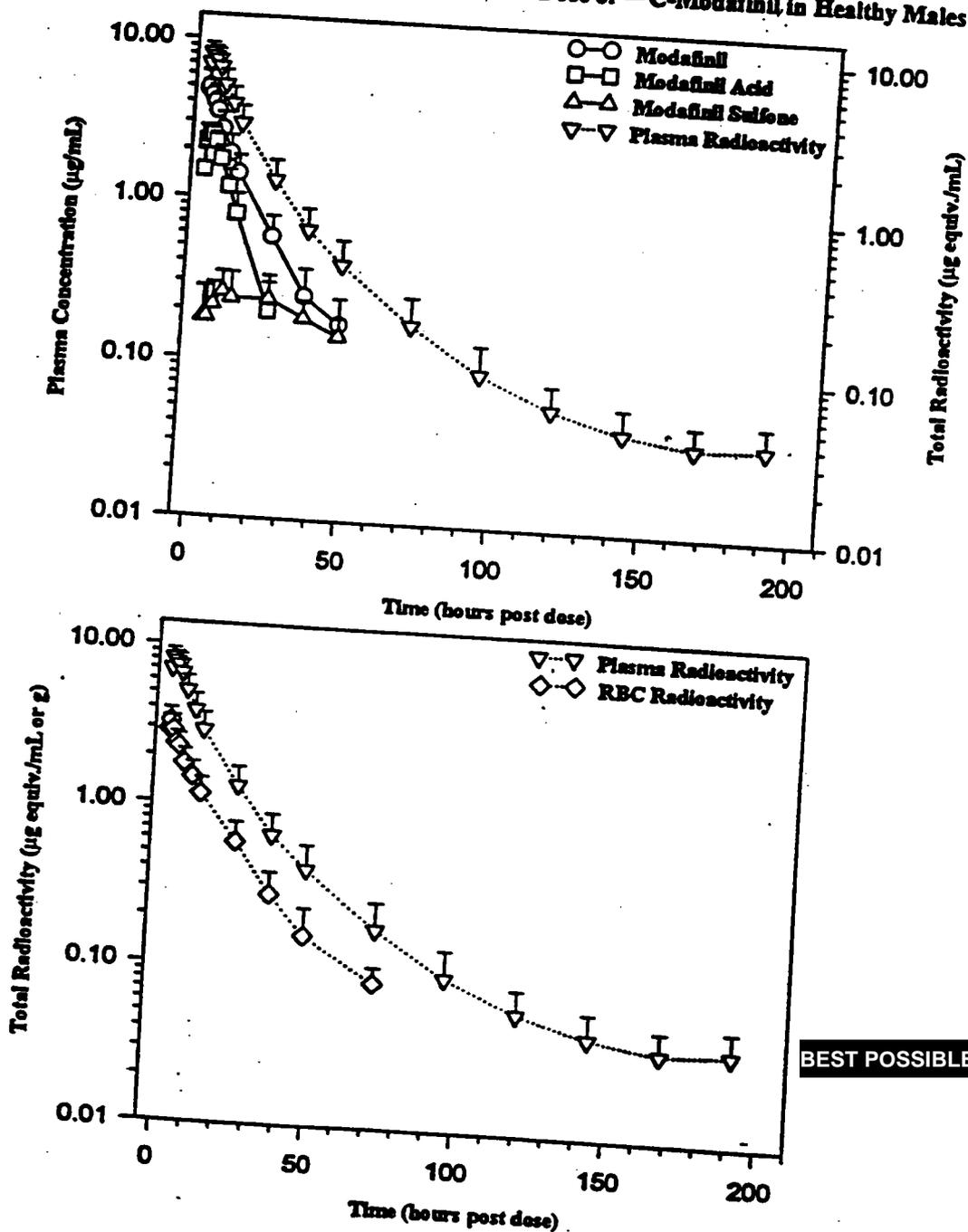
formation clearance of m.A.
↓
disposition clearance of m.A.

$$Cl_m = f_m \cdot Cl_{(parent)}, \quad f_m = \frac{\text{amt of m.A. found}}{\text{Total Dose of m.}}$$

$$Cl_{(m)} = Cl_m - \frac{AUC_{0-\infty} (parent)}{AUC_{0-\infty} (metabolite)} = \frac{\text{amt of m.A.}}{AUC_{0-\infty} m.A.}$$

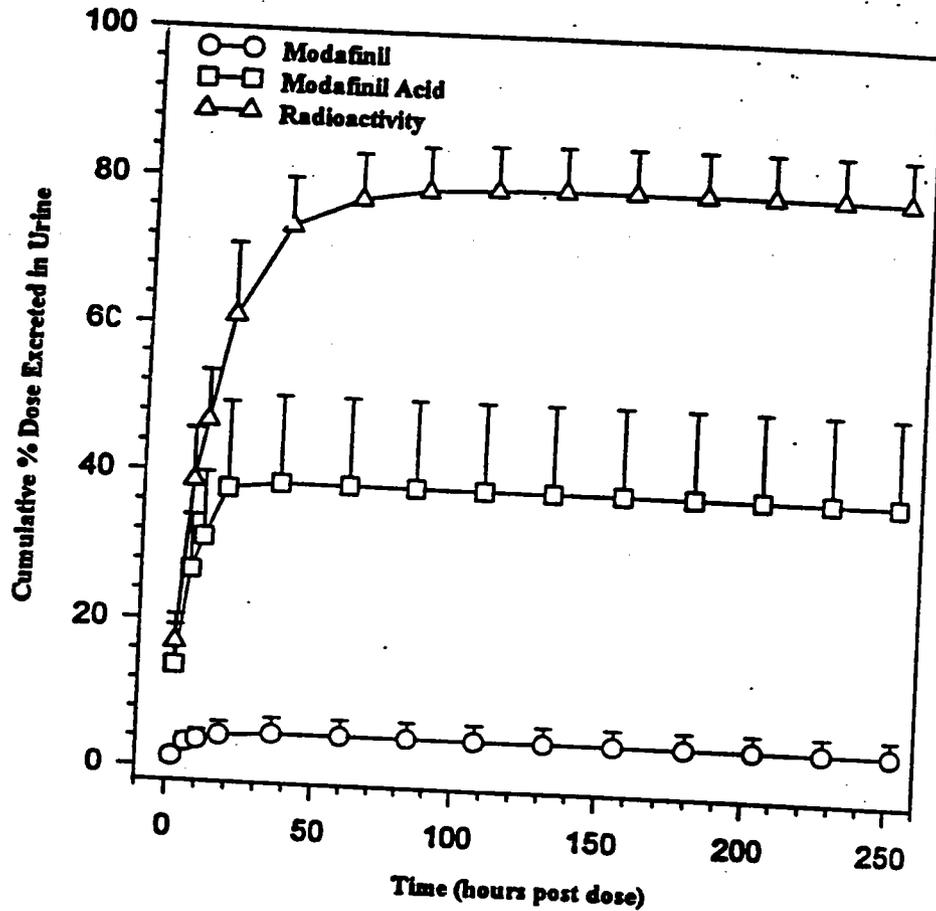
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Figure 2. Semi-logarithmic Plot of Mean (+SD) Modafinil, Modafinil Acid and Modafinil Sulfone Plasma Concentrations ($\mu\text{g/mL}$) and Total RBC and Plasma Radioactivity ($\mu\text{g modafinil equiv./mL or g}$) versus Time Following Administration of a Single Oral Dose of ^{14}C -Modafinil in Healthy Males



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Figure 3. Cumulative Urinary Excretion of Radioactivity, Modafinil and Modafinil Acid (Expressed as mean (+SD) percent modafinil dose excreted) versus Time Following Administration of a Single Oral Dose (200 mg) of 14 C-Modafinil in Healthy Males



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Total Radioactivity, Modafinil, Modafinil Acid, and Modafinil Sulfone in Plasma

Subj. 1

Time	Total Rad Mod	Mod. Acid	Mod. Sulf	AUC (T.R)	% of MO	% of M.A.	% of M.S.	Total %
0	0							
0.5	4.95							
1	6.52							
2	6.32							
3	5.69							
4	5.08							
6	3.62							
9	2.59							
12	1.95							
24	0.81							
36	0.37							
48	0.21							
72	0.08							
96	0.04							
120	0.03							
144	0.02							
168	0.02							
192	0.02							
			AUC0-inf		Ratio (M) AUC _{(m or ma or ms)/AUC_(TR)}	Ratio (MA)	Ratio (MS)	
					43%	24%	1.0%	

Subj. 2

Time	Total Rad Mod	Mod. Acid	Mod. Sulf	AUC (T.R)	% of MO	% of M.A.	% of M.S.	Total %
0								
0.5								
1								
2								
3								
4								
6								
9								
12								
24								
36								
48								
72								
96								
120								
144								
168								
192								
			AUC0-inf		Ratio (M) AUC _{(m or ma or ms)/AUC_(TR)}	Ratio (MA)	Ratio (MS)	
					52%	22%	8.0%	

Subj. 3

Time	Total Rad Mod	Mod. Acid	Mod. Sulf	AUC (T.R)	% of MO	% of M.A.	% of M.S.	Total %
0								
0.5								
1								
2								
3								
4								
6								
9								
12								
24								
36								
48								
72								
96								
120								
144								
168								
192								
			AUC0-inf		Ratio (M) AUC _{(m or ma or ms)/AUC_(TR)}	Ratio (MA)	Ratio (MS)	
					39%	23%	5.0%	

Subj. 4

Time	Total Rad	Mod	Mod. Acid	Mod. Sulf	AUC (T.R)	% of MO	% of M.A.	% of M.S.	Total %
0									
0.5									
1									
2									
3									
4									
6									
9									
12									
24									
36									
48									
72									
96									
120									
144									
168									
192									

Ratio (M) Ratio (MA) Ratio (MS)
 $AUC_{(m \text{ or } ma \text{ or } ms)} / AUC_{(TR)}$
 45% 21% 7.0%

AUC0-inf

Subj. 5

Time	Total Rad	Mod	Mod. Acid	Mod. Sulf	AUC (T.R)	% of MO	% of M.A.	% of M.S.	Total %
0									
0.5									
1									
2									
3									
4									
6									
9									
12									
24									
36									
48									
72									
96									
120									
144									
168									
192									

Ratio (M) Ratio (MA) Ratio (MS)
 $AUC_{(m \text{ or } ma \text{ or } ms)} / AUC_{(TR)}$
 42% 20% 9.8%

AUC0-inf

Subj. 6

Time	Total Rad	Mod	Mod. Acid	Mod. Sulf	AUC (T.R)	% of MO	% of M.A.	% of M.S.	Total %
0									
0.5									
1									
2									
3									
4									
6									
9									
12									
24									
36									
48									
72									
96									
120									
144									
168									
192									

Ratio (M) Ratio (MA) Ratio (MS)
 $AUC_{(m \text{ or } ma \text{ or } ms)} / AUC_{(TR)}$
 43% 23% 5.5%

AUC0-inf

2. Identification and Profiles of Modafinil and Modafinil Metabolites in Urine from Human Subjects Administered a Single Oral Dose of [¹⁴C] Modafinil (DM-96-029)

Objectives:

To identify and quantify the metabolites of modafinil in urine following a single oral administration of 200 mg dose containing 100 μ Ci of 2-[¹⁴C]-Modafinil.

Study Design and Sampling:

The study had an open-label, non-randomized, single dose and single phase design.

6 young male healthy
Subjects received a single oral dose of 30 mL of dosing suspension containing 200 mg modafinil labeled with 100 μ Ci of carbon-14. Ingestion of the dosing solution was followed by ingestion of three 30-mL rinses of the dosing container.

A complete description of the samples taken for analysis is presented in the *Analytical Assays* Pharmacokinetic Report for the study (DP-95-031); since the purpose of this report is to present the metabolite identification in urine, only the urine sample collection is presented here. Total urinary output was collected from 0-4, 4-9, 9-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216, 216-240, and 240-264 hours post-dose. A pre-dose urine sample was also collected to serve as blank matrix. Samples were stored frozen at approximately -20°C until analyzed. Total radioactivity in these samples was determined, and the samples were submitted for separation and identification of modafinil and its metabolites. The results of the total radioactivity determinations are presented in *Analytical Assays* Pharmacokinetic Report DP-95-031.

Results (attachment 2) and Conclusions:

Six metabolites were identified in the urine of all subjects receiving 200 mg modafinil. In the first 4 hours, modafinil acid is the predominant metabolite, accounting for 75% of the total radioactivity and modafinil made up for ~8%. The other metabolites were detected at low levels or barely detectable in [REDACTED] system. From 12 to 24 hr post-dose, the metabolic profile did not change, but modafinil acid levels were reduced and the other metabolites levels, such as modafinil acid sulfone and the two glucuronides, were increased, presumably through secondary metabolism. The parent drug level remained the same as in the first 4 hr.

Comments:

The profile of metabolites in urine samples collected after 24 hr were not reported. But in the previous study (C1538a/111/PK/US), it was demonstrated that modafinil and modafinil acid were mostly below the detection limit after 24 hr, and the accumulative total radioactivity change was less than 10% during 24-240 hr period. The typical patients data were attached in the result portion.

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ATTACHMENT A - 3

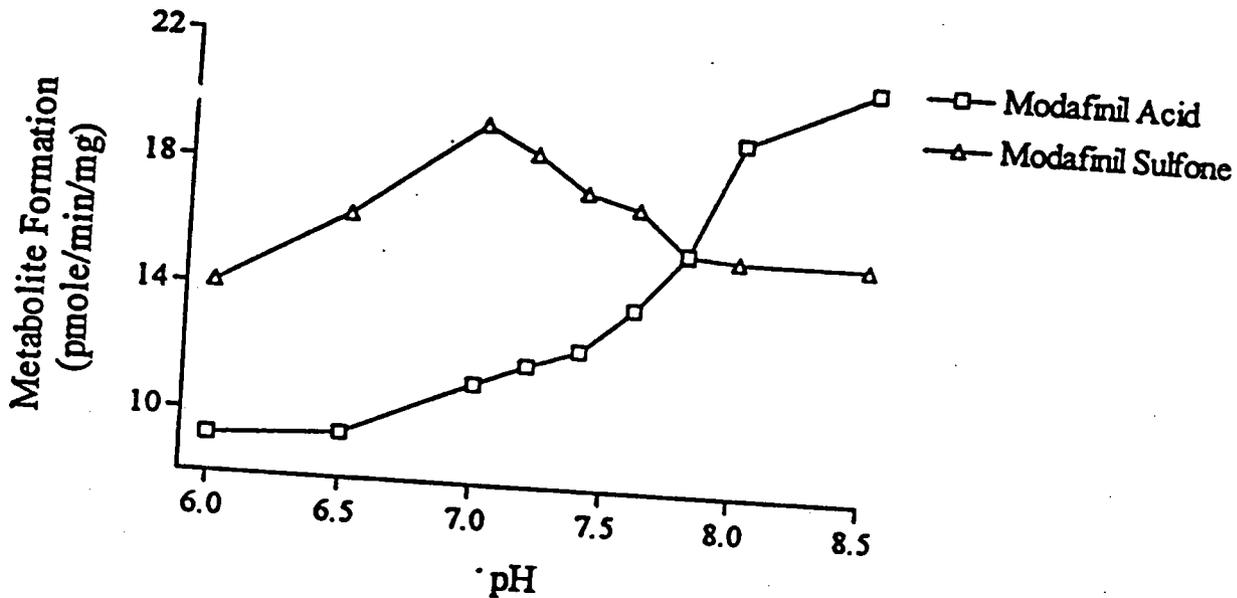


Figure 2. Effect of pH on the biotransformation of modafinil to modafinil acid and modafinil sulfone in pooled human liver microsomes. Each data point represents the average of two determinations in a single experiment.

Incubation Condition: 1 mg/ml protein
2 mg/ml β -NADPH
200 μ M Modafinil
200 mM $\text{KH}_2\text{PO}_4 / \text{K}_2\text{HPO}_4$ Buffer
37° C,

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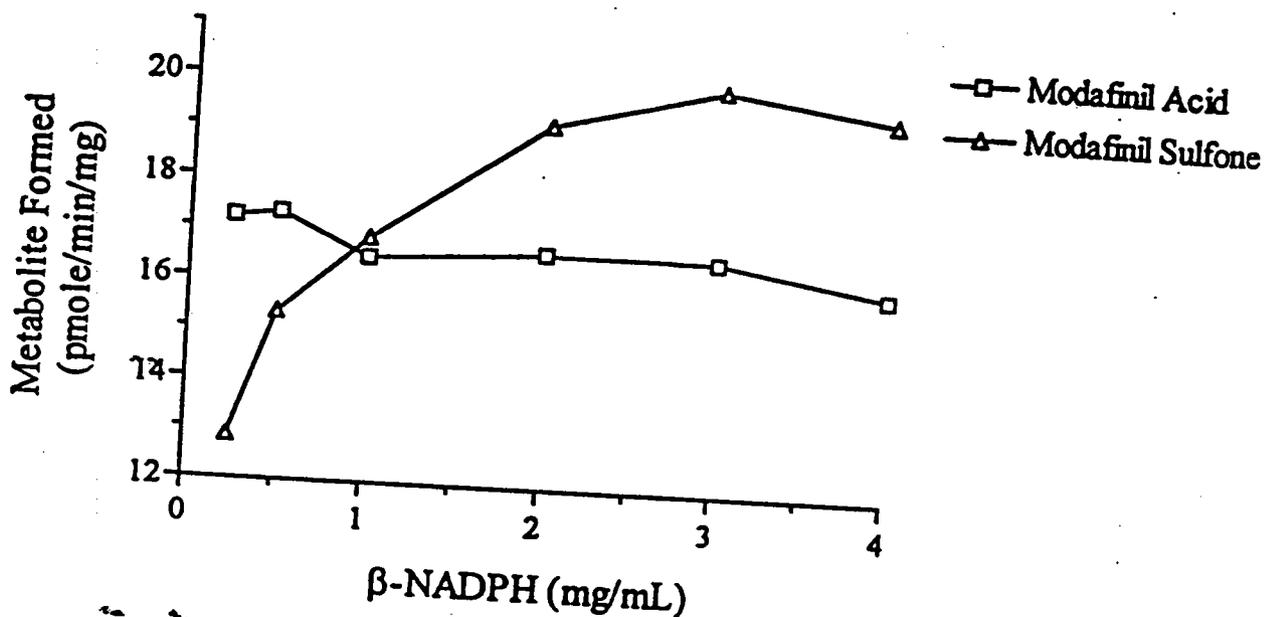


Figure 3. Effect of β -NADPH on the biotransformation of modafinil to modafinil acid and modafinil sulfone in pooled human liver microsomes. Each data point represents the average of two determinations in a single experiment.

Incubation Condition: $n=10$
1 mg/ml protein
200 μ M modafinil,
200 mM $\text{KH}_2\text{PO}_4/\text{K}_2\text{HPO}_4$ Buffer
PH 7.4
37°C
60 min

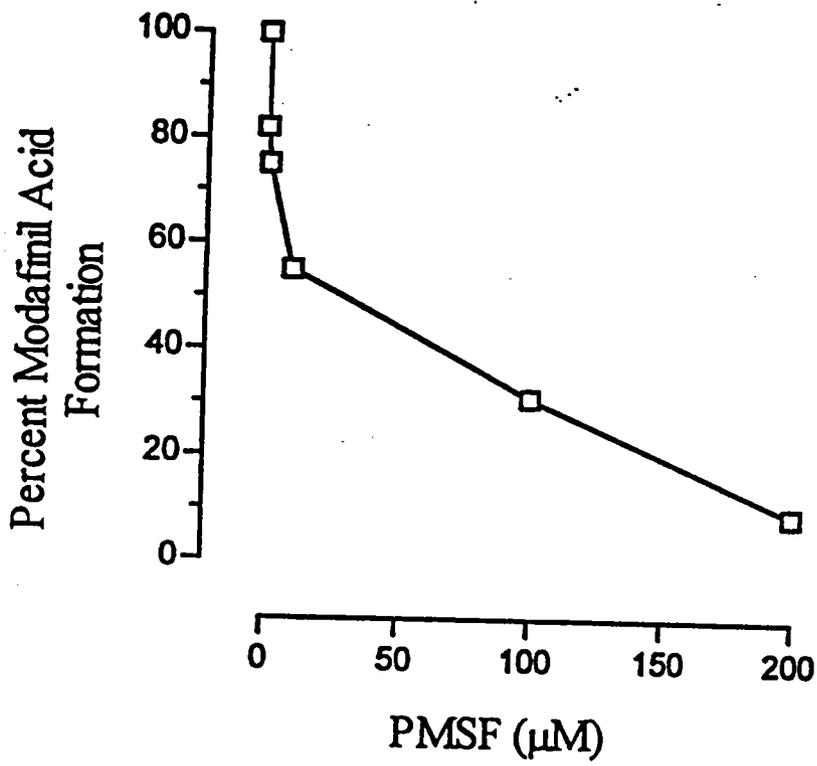


Figure 4. Effect of phenylmethylsulfonylfluoride (PMSF) on the biotransformation of modafinil to modafinil acid in human liver microsomes. Each data point represents the average of two determinations in a single experiment.

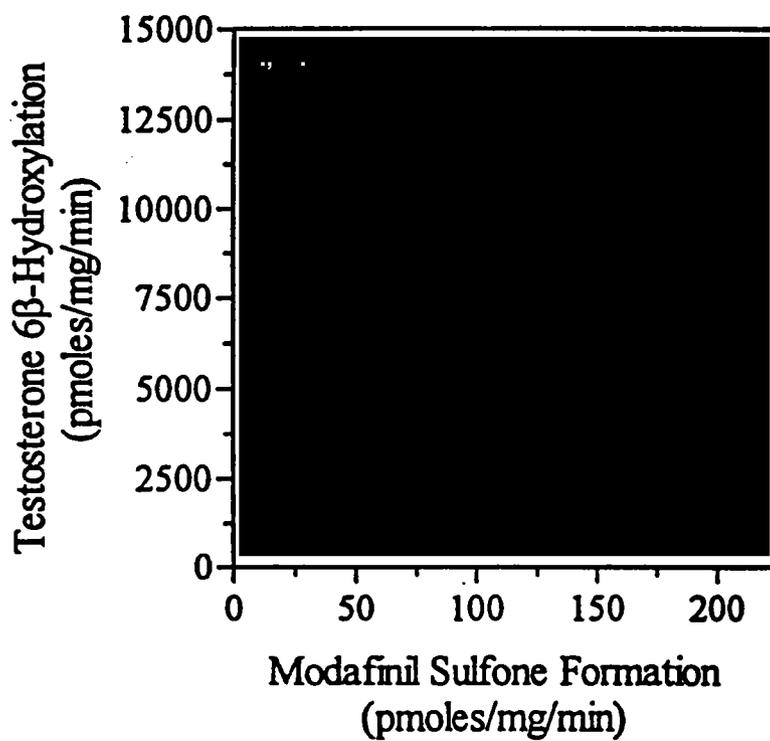


Figure 6. Correlation between the rate of modafinil sulfone formation and testosterone 6β-hydroxylase activity in ten individual human liver microsomes.

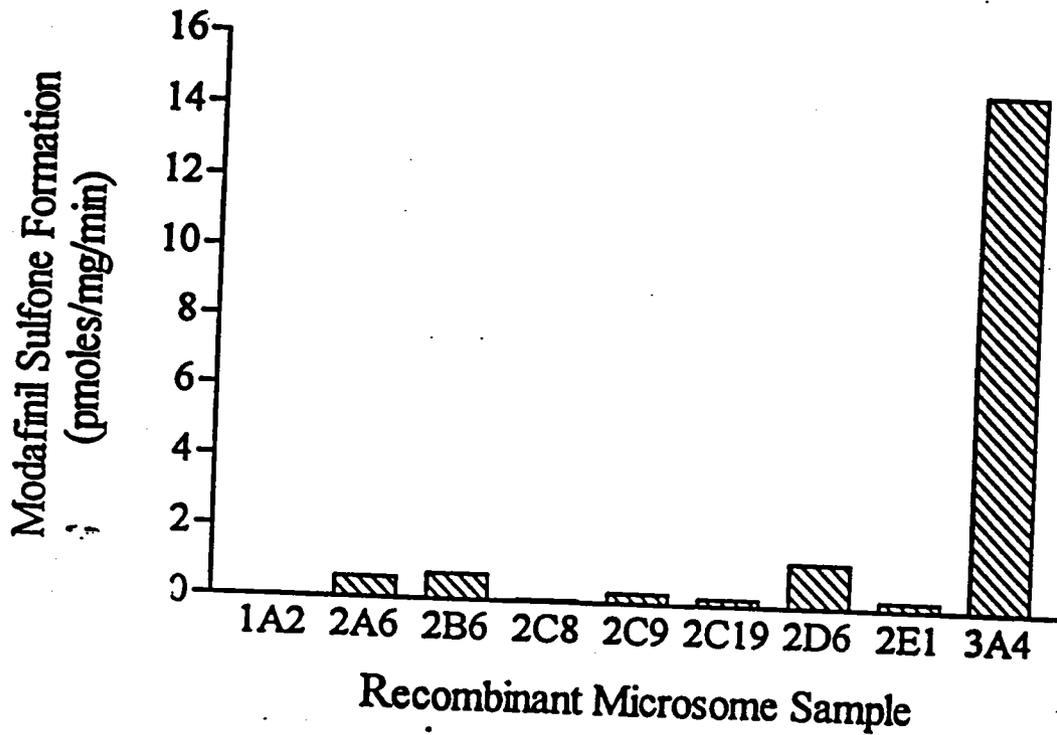


Figure 7. Rates of modafinil sulfone formation in microsomes from β -lymphoblastoid cells expressing individual cytochrome P450 isoforms. Each data point represents the average of two determinations in a single experiment.

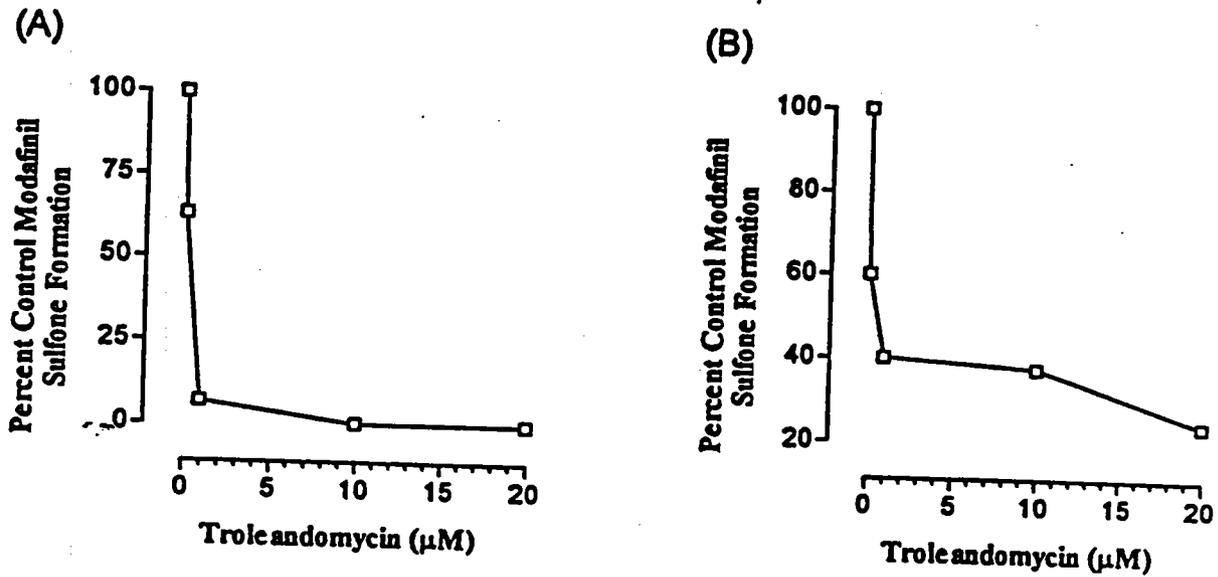


Figure 8. Effect of troleandomycin on the biotransformation of modafinil to modafinil sulfone in (A) pooled human liver microsomes, and (B) recombinant microsomes expressing human CYP3A4. Each data point represents the average of two determinations.

pre-incubation : 10-15 min

Incubation : 1 μg/ml protein
200 μM modafinil
37°C
60 min

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ATTACHMENT A-4
Linearity of the kinetics of MODAFINIL - 1

TABLE I: Inter-individual coefficients of variation of pharmacokinetic parameters of MODAFINIL and of its metabolite for the dose of 50 mg

Parameter	Mean	σ	C.V.
C_{max}	0.67	0.02	0.03
AUC _{ex}	9.53	3.96	0.42
V _d _{beta}	59.37	20.50	0.35
Cl	6.01	2.48	0.41
t _{1/2}	8.38	5.52	0.66
C_{max} metabolite	0.59	0.12	0.20
AUC _{0-12h} metabolite	8.30	2.42	0.34

TABLE II: Inter-individual coefficients of variation of pharmacokinetic parameters of MODAFINIL and of its metabolite for the dose of 100 mg

Parameter	Mean	σ	C.V.
C_{max}	1.48	0.12	0.08
AUC _{ex}	21.67	4.82	0.22
V _d _{beta}	62.77	5.42	0.09
Cl	4.77	0.94	0.20
t _{1/2}	9.30	1.24	0.13
C_{max} metabolite	0.96	0.10	0.10
AUC _{0-12h} metabolite	13.64	1.98	0.15

$\sigma = \text{std. dev.}$

TABLE III: Inter-individual coefficients of variation of pharmacokinetic parameters of MODAFINIL and of its metabolite for the dose of 200 mg

Parameter	Mean	σ	C.V.
C_{max}	2.59	0.22	0.08
AUC _{ex}	41.52	7.58	0.18
V _d _{beta}	61.71	9.74	0.16
Cl	4.93	0.86	0.17
t _{1/2}	8.72	0.78	0.09
C_{max} metabolite	2.08	0.56	0.27
AUC _{0-12h} metabolite	27.47	8.16	0.30

TABLE IV: Inter-individual coefficients of variation of pharmacokinetic parameters of MODAFINIL and of its metabolite for the dose of 400 mg

Parameter	Mean	σ	C.V.
C_{max}	4.27	0.64	0.15
AUC _{ex}	85.14	13.50	0.16
V _d _{beta}	75.17	17.46	0.23
Cl	4.79	0.74	0.15
t _{1/2}	11.06	2.82	0.26
C_{max} metabolite	2.88	0.08	0.03
AUC _{0-12h} metabolite	40.18	5.08	0.13

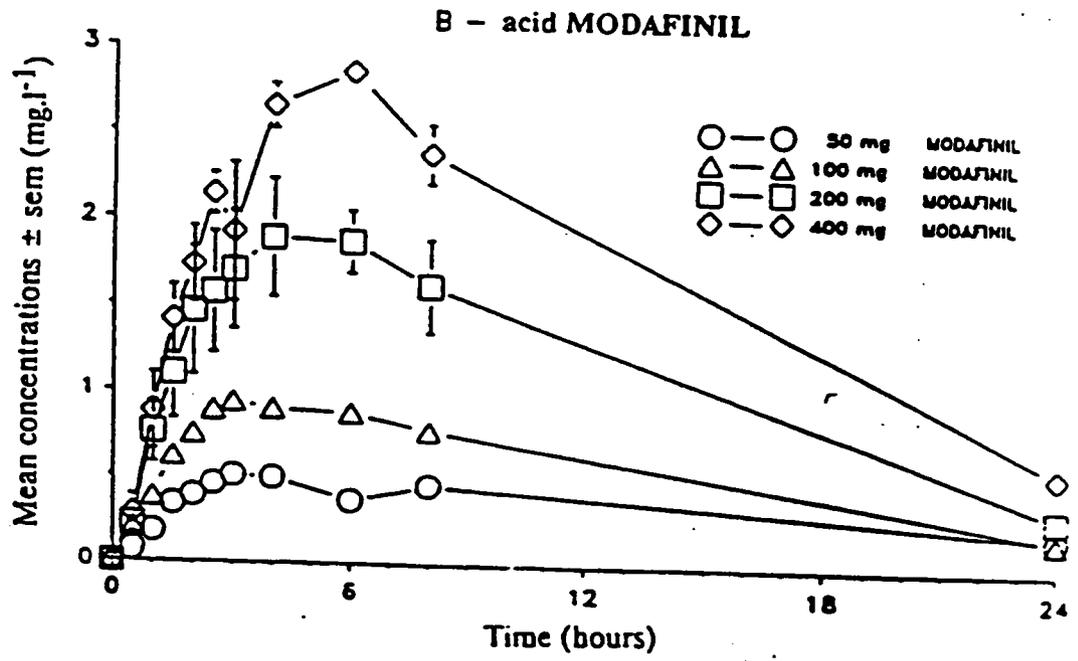
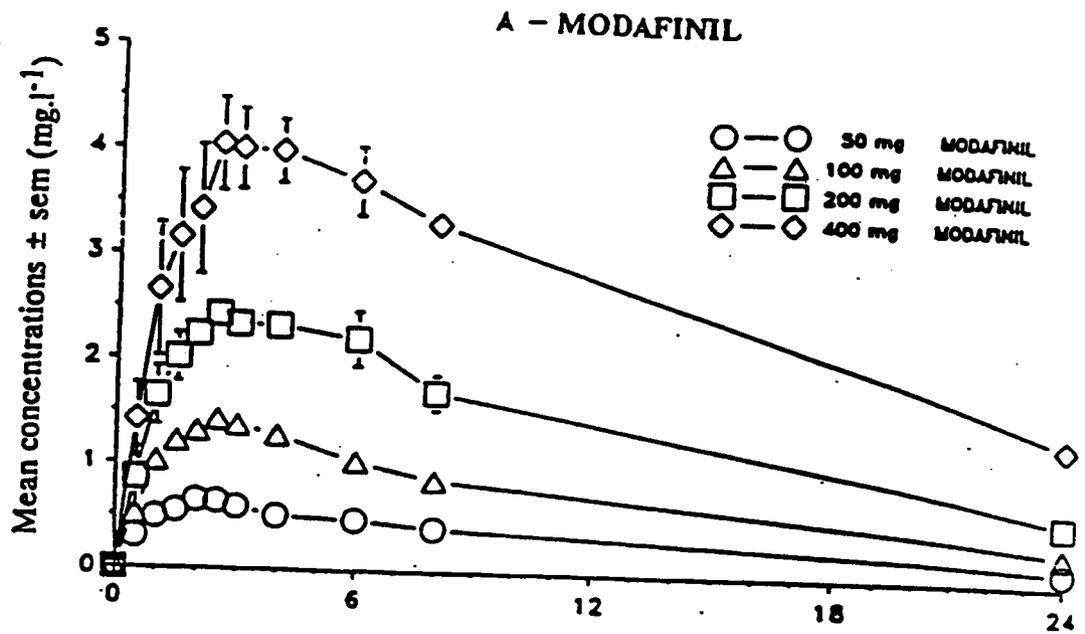
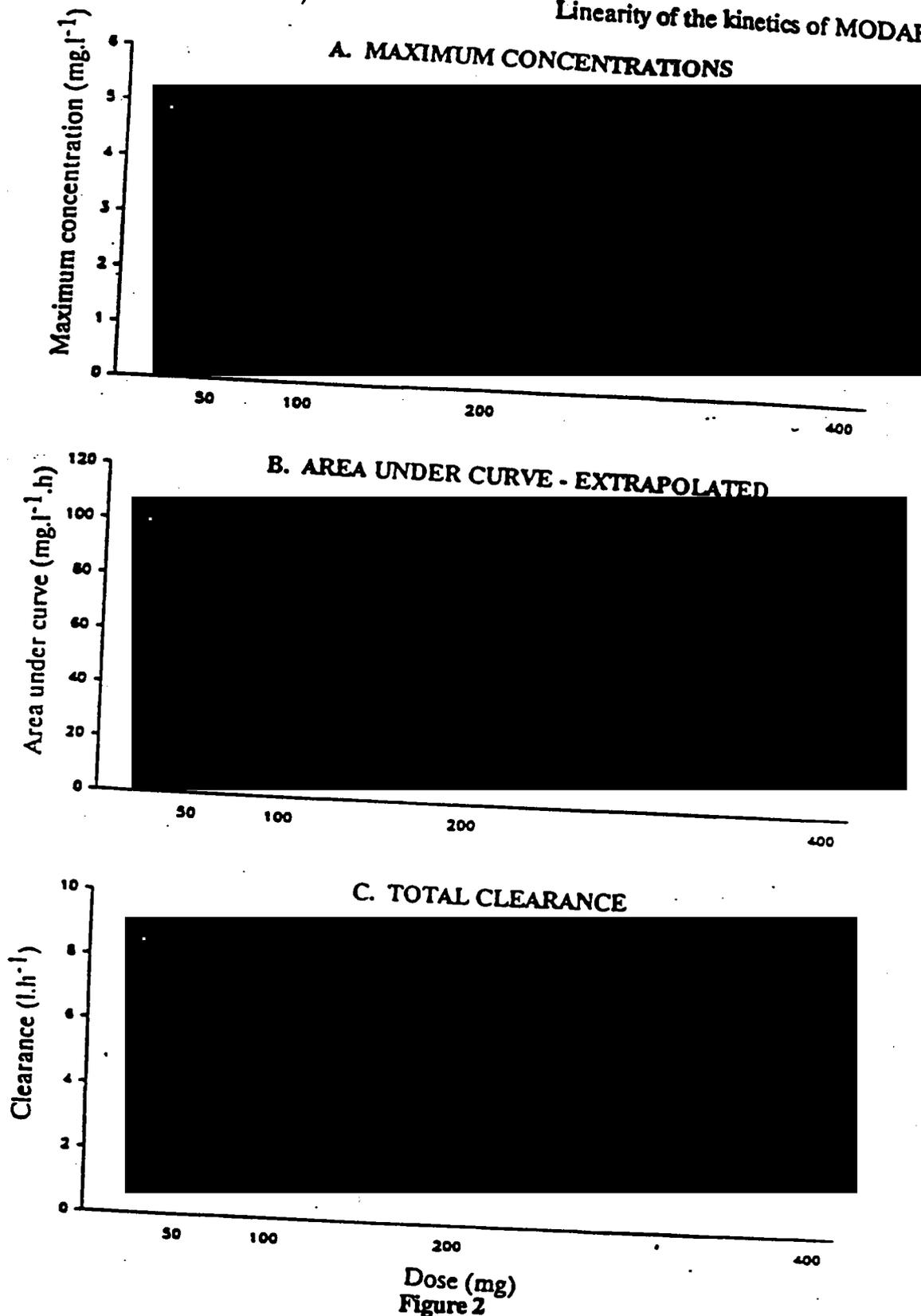


Figure 1
 Plasma concentrations of MODAFINIL (A) and of its metabolite, acid MODAFINIL (B) after oral administration of MODAFINIL in man

Modafinil

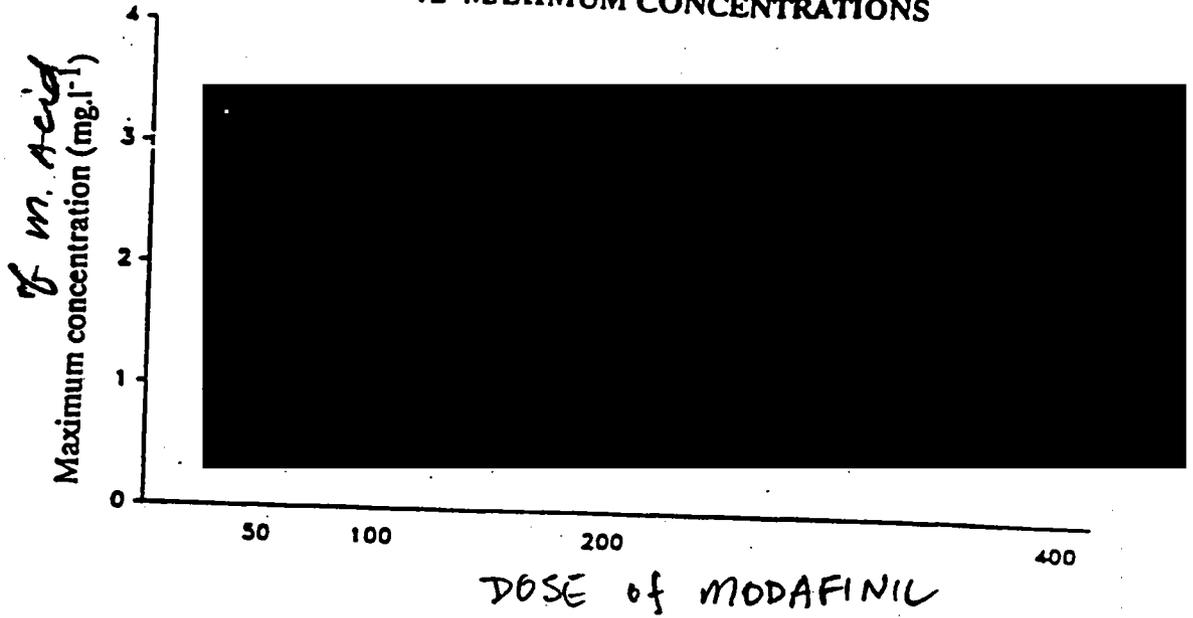
Linearity of the kinetics of MODAFINIL



Correlation of C_{max} MODAFINIL (A), AUCT_{ex} MODAFINIL (B) and total clearances of MODAFINIL (C) with doses of MODAFINIL administered orally in man. Results for each subject are illustrated by the same symbol.

modafinil acid

A. MAXIMUM CONCENTRATIONS



B. AREA UNDER CURVE - EXTRAPOLATED

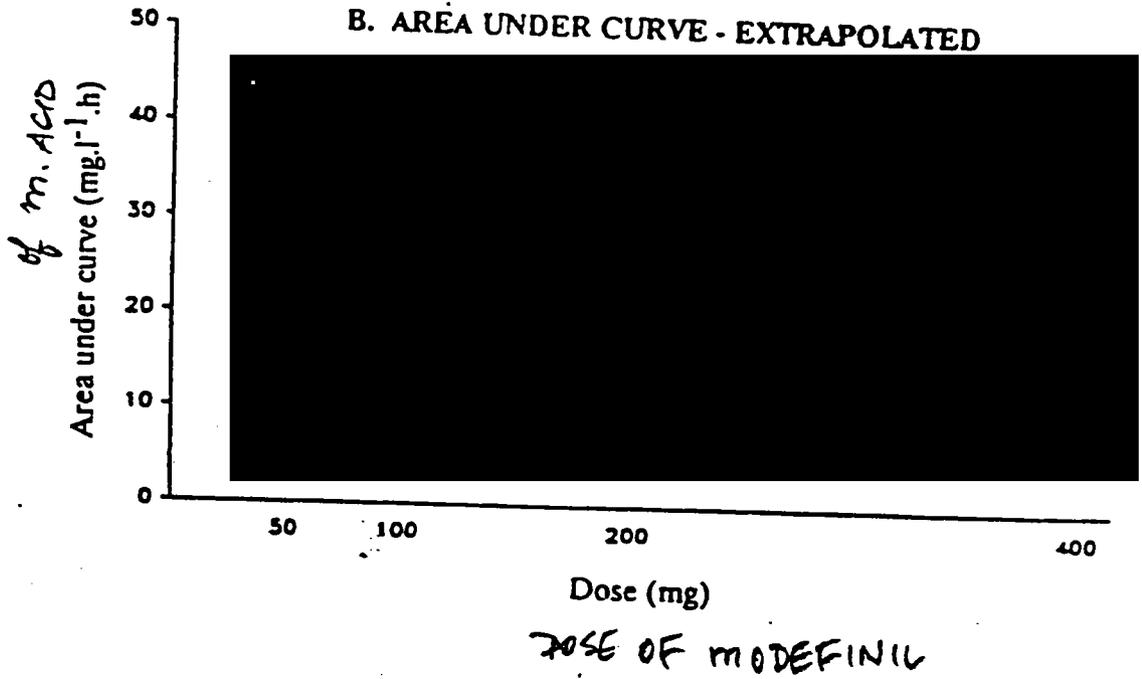


Figure 3

Correlation of C_{max} acid MODAFINIL (A) and of AUC_{0-12h} acid MODAFINIL (B) with doses of MODAFINIL administered orally in man. Results of any one subject are illustrated by the same symbol.

Linearity of the kinetics of MODAFINIL

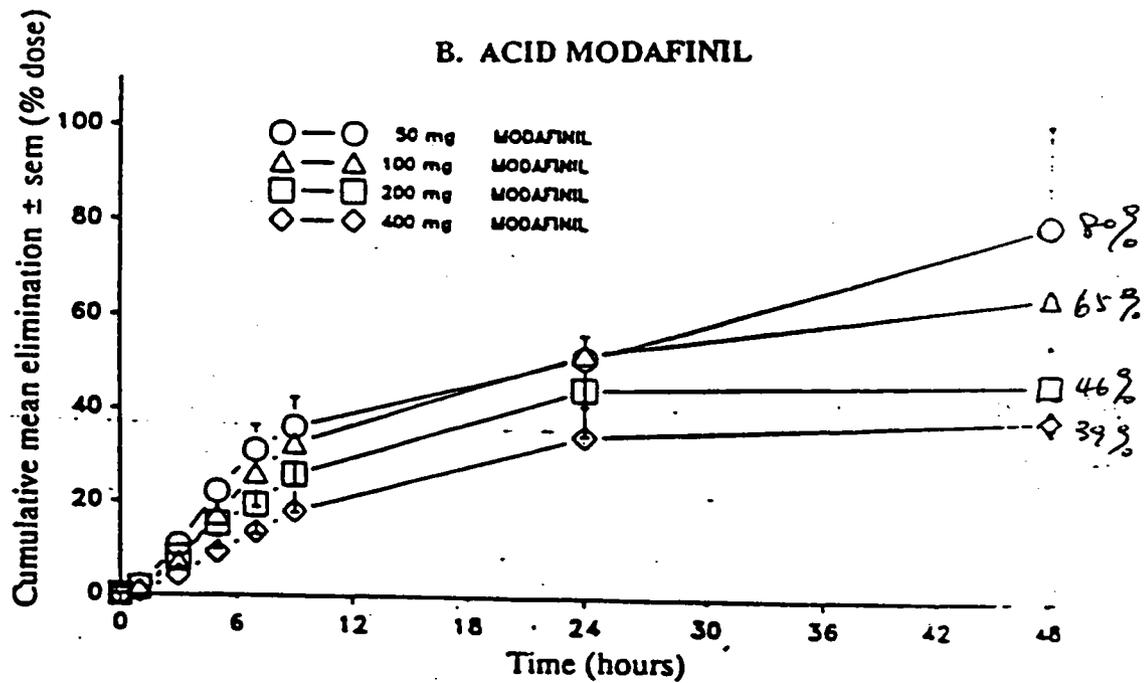
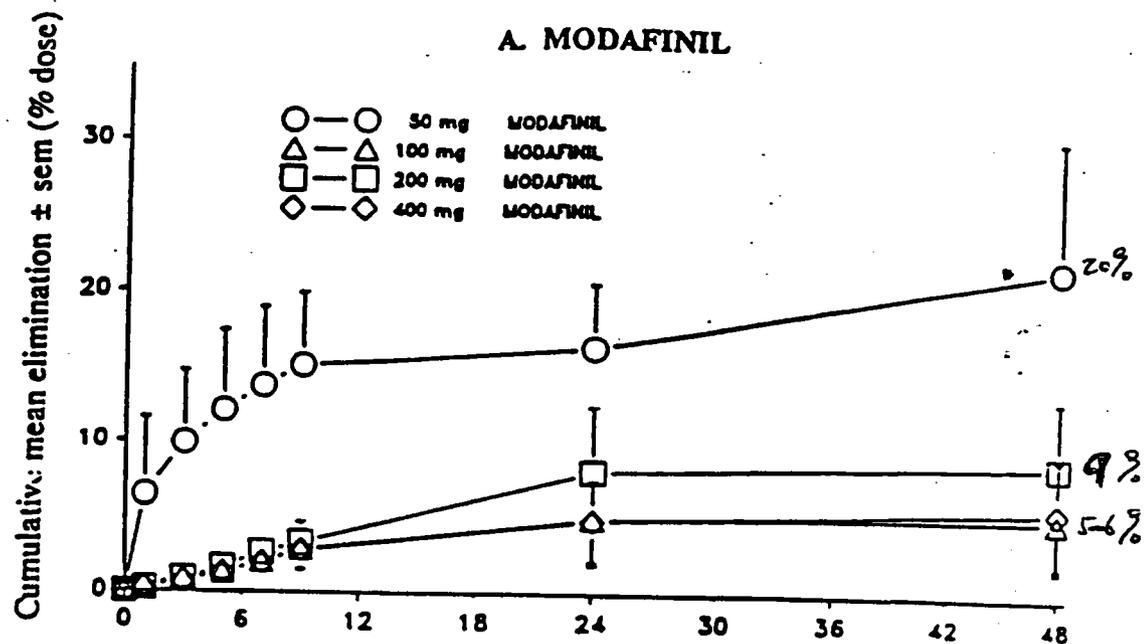


Figure 4

Cumulative urinary elimination of MODAFINIL (A) and of acid MODAFINIL (B) following oral administration of MODAFINIL in man