

**EST-CE QUE LE MODAFINIL AUGMENTE LE NIVEAU SANGUIN D'ANTI-DÉPRESSEURS TRICYCLIQUES LORS D'UN TRAITEMENT ASSOCIÉ ?
DOES MODAFINIL INCREASE THE BLOOD LEVEL OF TRICYCLIC
ANTIDEPRESSIVE COMEDICATION ? AND WITHOUT LORAZEPAM
MEDICATION**

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Modafinil is a psychostimulant compound that is scientifically known for about 10 years, but is just now becoming available for routine treatment in many countries. It is reported to be a central alpha 1 adrenergic agonist and seems to have some affinity to the dopamine uptake carrier site (E.Mignot et al., 1994 Sleep 17(5):436-437), while in therapeutic dosages there are no peripheral sympathomimetic effects. Sleep attacks and drowsiness are significantly reduced in narcoleptic and hypersomnic patients treated with 200 to 500 mg modafinil daily (H.Bastuji and M.Jouvet, 1988 Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 12:695-700). In contrast to most other comparable drugs no tolerance or dependence were reported so far. Since the compound does not have a sufficient effect on cataplexy in narcoleptic patients, it is often combined with tricyclic antidepressive medication especially clomipramine (CL) or imipramine. The knowledge of possible pharmacokinetic interactions with tricyclic substances is therefore of high therapeutic relevance. A 60 year old female patient suffering from narcolepsy since her adolescence had been under ambulatory treatment in our hospital for about 4 years. The daytime sleepiness and the automatic behavior were interfering badly with her professional life as a nurse. For the last 25 years most of the available psychostimulant drugs had been tried without sufficient success. She was comedicated with 100 mg of clomipramine because of cataplexy. The CL / DMCL (Desmethyloclopramine) blood levels were 129/208 ng/ml under steady state conditions. Finally she could be included in a clinical study with modafinil, which at that time was not yet approved in Germany for routine treatment. Under 200 mg modafinil the blood levels of CL and DMCL increased to 158/238 ng/ml although the dosage of clomipramine was lowered by 25% to 75 mg. With 400 mg the blood levels went up to 210/449 ng/ml and because of the marked increase in the liver enzymes, most likely due to the high drug concentrations, we had to discontinue the clomipramine medication. After three weeks without clomipramine the DMCL level was still 63 ng/ml, while the liver enzymes had returned to normal. Because of the still restricted availability of modafinil we were not able yet to further examine the effect in other patients and with other comedications. Until further results are available we recommend a close monitoring of patients under simultaneous treatment with modafinil and tricyclic substances.

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Table I - Clomipramine (CL) and desmethylclomipramine (DCL) concentrations in a patient treated with modafinil.

Date	Dose CL	Dose modafinil	Concentrations (ng/mL)		Ratio CL/DCL
			CL	DCL	
03/01/96	100	0	129	208	0.62
02/05/96	75	200	158	238	0.66
06/08/96	75	400	210	449	0.47
27/08/96	0	400	0	63	
13/09/96	25	400	32	79	0.41

CL = t_{1/2} = 20 hr

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CL = t_{1/2} = 96 hr

(CL) → DCL

patient gradually decreased in hydroxylation

CL → DCL

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15. An Open, 3x3 Latin Square, Randomized, Cross-over Study to Investigate the Pharmacokinetics of Modafinil And Methylphenidate When Given Alone and in Combination in Healthy Male Volunteers (C1538a/109/PK/UK)

Objectives:

To study the interaction of Modafinil and methylphenidate on their single dose pharmacokinetics.

Introduction:

Narcolepsy is generally treated with a central nervous system stimulant (e.g. amphetamine, methylphenidate, or pemoline) to reduce excessive daytime sleepiness and an antidepressant (e.g. clomipramine) to control cataplexy and other REM-sleep related symptoms. Ritalin® (methylphenidate hydrochloride) currently is the only FDA-approved drug for narcolepsy. Although it is unlikely that both methylphenidate and modafinil would be given at the same time, it is quite possible that patients on one treatment could be changed over to the other, which makes it necessary to study the interaction of these two agents.

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Study Design

This was an open 3 x 3 Latin square, randomized, cross-over study involving 21 healthy male volunteers, performed in 3 groups of 7 volunteers. Only non-smokers and/or ex-smokers for at least 6 months were screened; similarly, volunteers were only allowed to be moderate alcohol drinkers (i.e. a maximum of 21 units per week). The three treatment schedules were:

- Treatment A: Methylphenidate (immediate release) 4 x 10 mg and modafinil 2 x 100 mg. Both given concomitantly as a single dose on Day 1.
- Treatment B: Modafinil 2 x 100 mg as a single dose on Day 1.
- Treatment C: Methylphenidate (immediate release) 4 x 10 mg as a single dose on Day 1.

Volunteers were randomized to one of the following sequence order of treatment schedules:
With a 7-day wash out period between treatment.

Treatment A→Treatment B→Treatment C

Treatment B→Treatment C→Treatment A

Treatment C→Treatment A→Treatment B

**ANALYTICAL AND
PHARMACOKINETIC
METHODS**

Blood samples (10 mL) were collected into lithium heparin monovette tubes pre-dose (0 hr) and at the following times post-dose: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 18 hours for *d*- and *l*-threo-methylphenidate analysis; and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours for analysis of modafinil and its acid and sulfone metabolites. Plasma was separated and frozen at -20°C until assayed for modafinil and metabolites by a validated high performance liquid chromatographic (HPLC) method and *d*- and *l*-methylphenidate by a validated [REDACTED] method with [REDACTED] detection.

Results (Attachment 15) and Conclusions:

The statistical analyses resulted in no difference ($p > 0.05$) in dosing sequence or dosing periods for any of the PK parameters and plasma concentrations. Modafinil and methylphenidate coadministration did not alter the extent of oral absorption or disposition of either agent. However, methylphenidate caused a small increase in t_{max} for Modafinil (from 1.9 hr to 2.9 hr), which indicated that coadministration of methylphenidate and modafinil may cause a delay in the oral absorption of modafinil.

Comments:

Since it is unlikely that both of these two narcolepsy drugs would be given at the same time and the study aims to investigate on those patients switching from one agent to the other, the study should be designed in such a way to study the effects of multiple dosing of modafinil or methylphenidate on PK of the other drug. Moreover, it was known from the previous study (C1538a/301/NA/US) that multiple dosing of modafinil at certain concentration might result in an induction on its own metabolism. If methylphenidate shares the same metabolic enzyme system with Modafinil, only multiple dosing study can demonstrate the potential interaction between these two agents.

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Table I. Mean (SD) Pharmacokinetic Parameters for Modafinil (Mod) and Modafinil Acid (Mac) After Single Dose Oral Administration of 200 mg Modafinil Alone or Combined with 40 mg Methylphenidate in Healthy Male Volunteers.

Compound	Treatment	n	C _{max} µg/mL	t _{max} hr	t _{1/2} hr	AUC(0-∞) µg·hr/mL	CL/F mL/min	V/F L
Mod	Alone	21	4.10 (0.77)	1.9 (0.8)	12.2 (2.7)	56.9 (14.4)	62.0 (14.6)	63.5 (12.2)
	Combined	21	3.71 (0.75)	2.9 (1.4)*	12.3 (2.3)	57.1 (13.3)	61.3 (13.6)	63.5 (10.3)
MAc	Alone	21	1.91 (0.48)	2.8 (0.9)	6.31 (1.61)	22.6 (5.0)	—	—
	Combined	21	1.90 (0.47)	3.6 (1.3)*	6.24 (1.25)	22.9 (4.8)	—	—

* Statistically significant difference between treatments (p<0.05) using a nonparametric Wilcoxon test.

Table II. Mean (SD) Pharmacokinetic Parameters for *d*- and *l*-Methylphenidate (Meth) After Single Dose Oral Administration of 40 mg Methylphenidate Alone or Combined with 200 mg Modafinil in Healthy Male Volunteers.

Compound	Treatment	n	C _{max} ng/mL	t _{max} hr	t _{1/2} hr	AUC(0-∞) ng·hr/mL	CL/F mL/min	V/F L
<i>d</i> -Meth	Alone	21	17.8 (3.9)	1.7 (0.7)	2.78 (0.38)	93.6 (32.4)	3990 (1390)	924 (230)
	Combined	21	17.8 (5.0)	1.6 (0.6)	2.67 (0.49)	92.7 (32.0)	4020 (1350)	895 (248)
<i>l</i> -Meth	Alone	5*	0.821 (0.557)	0.6 (0.2)	1.09 (0.19)	1.51 (1.03)	384000 (343000)	34000 (28700)**
	Combined	5*	1.00 (0.72)	0.7 (0.4)	1.15 (0.20)	1.95 (1.23)	284000 (237000)	25400 (17500)

* Pharmacokinetics could only be evaluated in five subjects crossed-over to each treatment.

** Statistically significant difference between treatments (p<0.05) using an ANOVA.

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Table III. Mean (SD) Plasma Modafinil (Mod), Modafinil Acid (MAc) and Modafinil Sulfone (MSul) Concentration ($\mu\text{g/mL}$) Vs. Time (hr) After Single Dose Oral Administration of 200 mg Modafinil Alone or Combined with 40 mg Methylphenidate in Healthy Male Volunteers.

Conc.	Treatment	0	0.5	1	2	3	4	6	8	12	24	36	48
Mod	Alone	BLQ —	1.82 (1.27)	2.97 (1.37)	3.67 (0.69)	3.51 (0.78)	3.07 (0.53)	2.44** (0.49)	2.10 (0.45)	1.50 (0.34)	0.74 (0.22)	0.37 (0.15)	0.20 (0.15)
	Combined	BLQ —	1.62 (1.04)	2.40 (1.09)	3.06 (1.14)	3.19 (0.67)	3.24 (0.48)	2.61 (0.45)	2.16 (0.41)	1.55 (0.34)	0.74 (0.24)	0.39 (0.16)	0.22 (0.13)
MAc	Alone	BLQ —	0.38 (0.40)	1.01 (0.56)	1.65 (0.49)	1.83** (0.46)	1.74 (0.42)	1.48** (0.36)	1.20 (0.27)	0.75 (0.21)	0.18 (0.10)	BLQ —	BLQ —
	Combined	BLQ —	0.32 (0.25)	0.88 (0.37)	1.43 (0.64)	1.61 (0.45)	1.75 (0.40)	1.58 (0.35)	1.24 (0.30)	0.79 (0.23)	0.18 (0.10)	BLQ —	BLQ —
MSul	Alone	BLQ —	BLQ —	BLQ —	BLQ —	BLQ —	BLQ —	0.13 (0.09)	0.16 (0.09)	0.21 (0.08)	0.24 (0.10)	0.19 (0.12)	0.14 (0.13)
	Combined	BLQ —	BLQ —	BLQ —	BLQ —	BLQ —	BLQ —	0.11 (0.09)	0.14 (0.09)	0.19 (0.10)	0.23 (0.09)	0.20 (0.12)	0.15 (0.13)

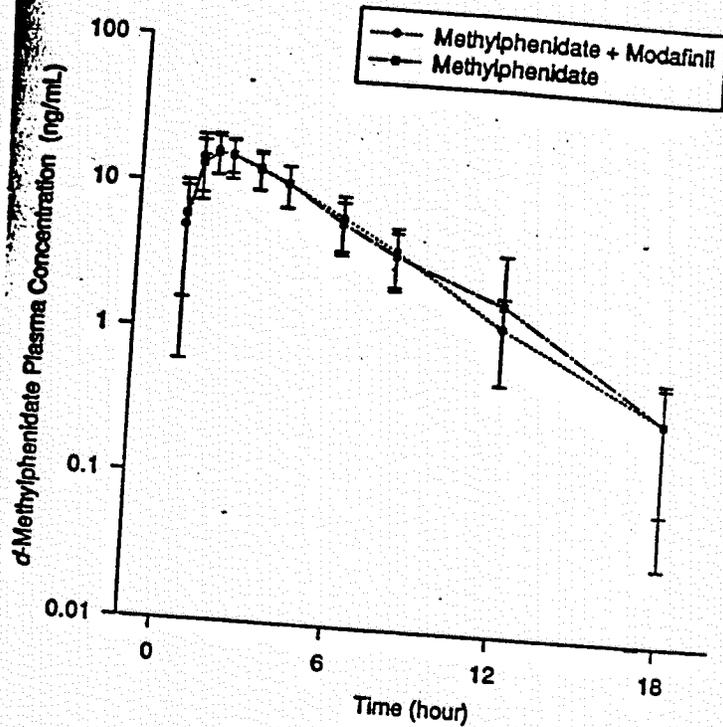
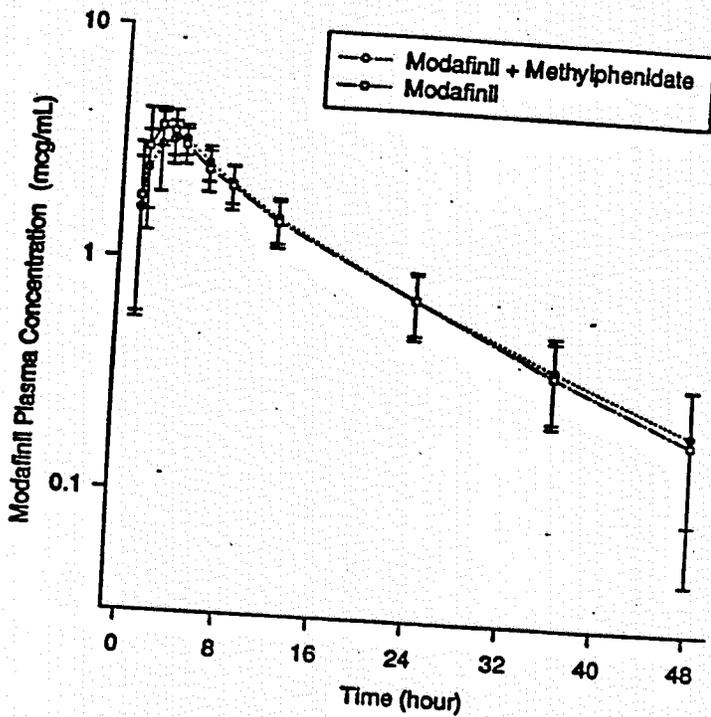
* n = 21 subjects for each treatment; BLQ (<0.1 $\mu\text{g/mL}$) values treated as zero for mean calculations.
 ** statistically significant difference between treatments ($p < 0.05$) using an ANOVA.

Table IV. Mean (SD) Plasma *d*- and *l*-Methylphenidate (Meth) Concentration (ng/mL) Vs. Time (hr) After Single Dose Oral Administration of 40 mg Methylphenidate Alone or Combined with 200 mg Modafinil in Healthy Male Volunteers.

Conc.	Treatment	0	0.5	1	1.5	2	3	4	6	8	12	18
<i>d</i> -Meth	Alone	BLQ —	6.01 (4.40)	13.6 (6.0)	16.2 (4.7)	15.8 (4.0)	12.8 (3.6)	10.5 (3.4)	5.88** (2.32)	3.72** (1.59)	1.88 (2.23)	0.341 (0.261)
	Combined	BLQ —	5.05 (4.44)	15.0 (6.4)	16.7 (5.3)	15.5 (4.7)	13.2 (3.9)	10.5 (3.3)	6.42 (2.63)	4.00 (1.74)	1.31 (0.78)	0.340 (0.306)
<i>l</i> -Meth	Alone	BLQ —	0.236 (0.408)	0.192 (0.280)	0.150 (0.214)	0.111** (0.164)	BLQ —	BLQ —	BLQ —	BLQ —	BLQ —	BLQ —
	Combined	BLQ —	0.286 (0.525)	0.247 (0.309)	0.182 (0.271)	0.156 (0.212)	BLQ —	BLQ —	BLQ —	BLQ —	BLQ —	BLQ —

* n = 21 subjects for each treatment; BLQ (<0.1 ng/mL) values treated as zero for mean calculations.
 ** statistically significant difference between treatments ($p < 0.05$) using an ANOVA.

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1. Semilogarithmic plot of mean (SD) modafinil plasma concentration
 2. In twenty-one healthy male volunteers following a single oral dose of
 modafinil alone or combined with 40 mg methylphenidate.
 (Protocol C1538a/109/PK/UK)

Figure-4: Semilogarithmic plot of mean (SD) d-methylphenidate plas
 concentration vs. time in twenty-one healthy male volunteers following
 single oral dose of 40 mg methylphenidate alone or combined with 20
 mg modafinil. (Protocol C1538a/109/PK/UK)

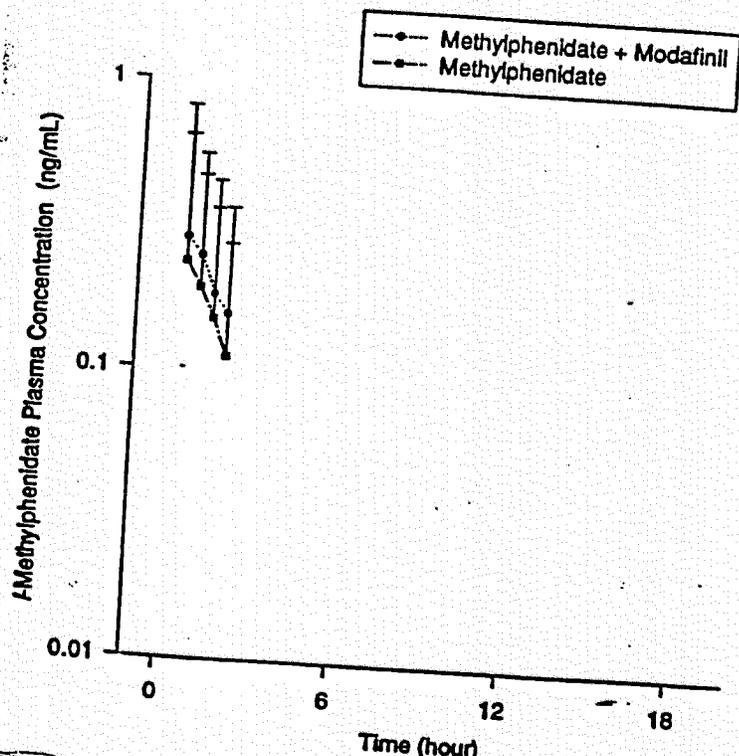


Figure-5: Semilogarithmic plot of mean (SD) l-methylphenidate plasma
 concentration vs. time in twenty-one healthy male volunteers following a
 single oral dose of 40 mg methylphenidate alone or combined with 200
 mg modafinil. (Protocol C1538a/109/PK/UK)

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16. Evaluation of a New Chemical Entity, Modafinil as an Inhibitor of Human P450 Enzymes (DM-96-051 (XT052396))

Objectives:

To evaluate the ability of modafinil to reversibly inhibit the major P450 enzymes in human liver microsomes (namely CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11), with the aim of detecting any potential for modafinil to inhibit other drug metabolism in vivo.

Methodology:

Microsomes from 7 individual donors were collected. The pooled microsomes were separated into 2 batches. Each batch was characterized for CYP subfamily activities by standard marker substrates. Marker substrates were employed at concentrations equal to their $K_m/2$, K_m and $4K_m$ in the simultaneous incubation with and without modafinil. The concentrations of Modafinil in the incubation ranged from 5 to 250 μM , covering its therapeutic concentration ($\sim 40 \mu M$, calculated from $C_{max}=12 \mu g/ml$ at steady state of 400 mg daily dose).

<u>P450 Enzyme</u>	<u>Positive Control</u>	<u>Concentration Studied</u>
CYP1A2	α -Naphthoflavone	1.0 μM
CYP2A6	Nicotine	200 μM
CYP2B6	Orphenadrine	500 μM
CYP2C9	Sulfaphenazole	10 μM
CYP2C19	Hexobarbital	200 μM
CYP2D6	Quinidine	10 μM
CYP2E1	4-Methylpyrazole	1 μM
CYP3A4/5	Ketoconazole	0.5 μM
CYP4A9/11	No competitive inhibitor is available for this enzyme	

For each P450 enzyme, a positive control (known competitive inhibitor) was included.

Results (Attachment 16) and Conclusions:

The results of this study suggest that modafinil has little or no capacity to function as a reversible inhibitor of the major P450 enzymes expressed in human liver microsomes, with the exception of CYP2C19. The K_i value for the competitive inhibition of human CYP2C19 by modafinil was equal to 39 μM . The plasma levels of modafinil in humans after a 400 mg dose (p.o.) have been reported to be as high as 40 μM . Therefore, fractional inhibition, i , of modafinil for inhibition of CYP2C19 is sufficiently close to unity (0.50) to deserve special attention. The possibility exists that modafinil may competitively inhibit the metabolism of those drugs that are metabolized by CYP2C19. In this regard, modafinil would be expected to inhibit the metabolism of those drugs that are substrates for CYP2C19, which include omeprazole, lansoprazole, hexobarbital, mephobarbital, propranolol, citalopram, diphenylhydantoin (dilantin), imipramine, mephentoin, pentamidine, proguanil and diazepam. The clinical and toxicological consequences of such inhibition will be relevant only if the rate of elimination of these drugs is determined by CYP2C19. Furthermore, most of these drugs have a high therapeutic index and are well tolerated even in individuals who are genetically deficient in CYP2C19. However, drugs with a narrow therapeutic index, such as diazepam, may be an exception to this general rule, hence, the combined use of modafinil and diazepam may result in clinically significant interactions.

In another study (Submitted as IND [REDACTED]), the sponsor evaluated modafinil as a mechanism-based (reversible and irreversible) inhibitor of various CYP enzymes. The study condition was the same as the one mentioned above, except that modafinil was preincubated with the microsomes prior to the addition of marker substrates. The result showed that modafinil or a monooxygenase-dependent metabolite of modafinil has no capacity to inhibit these CYP enzymes in a mechanism-based manner.

Comments:

The reversible competitively inhibition action of modafinil on CYP2C19 seen in vitro indicated a drug-drug interaction in vivo. As sponsor mentioned in the conclusion, for drugs with narrow therapeutic window, the interaction could be clinically significant. A clinical study to investigate the interaction between modafinil and one of the CYP2C19-metabolized narrow therapeutic drug is encouraged.

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17. An In Vivo Study of Modafinil Using Primary Human Hepatocyte Cultures: Induction of Hepatic Drug Metabolism Activities and Biotransformation (DM-96-042)

Objectives:

To investigate the effect of modafinil on major CYP enzymes in cultured human hepatocytes obtained from three donors.

Methodology:

Modafinil at concentrations of 10 μ M, 100 μ M and 1 mM were used in the incubation with human hepatocytes for 72 hours. Classic inducers of each examined CYP enzyme were used in the same batch of cells as positive controls for modafinil. The rate of metabolism for each marker substrate of the enzyme was recorded to determine the enzyme activities.

Results (Attachment 17) and Conclusions:

The results showed that there were large variations of CYP activity among three liver microsomes, among the nontreated freshly isolated hepatocytes, among the nontreated hepatocytes at 72 hours, and among the response to both the classic inducers and modafinil. Nevertheless, modafinil showed slight induction on CYP3A activity and inhibition on CYP2C19 in the cultured cells.

Comments:

It is a good attempt to study the induction potential of modafinil in vitro, using human hepatocyte. However, the inconsistency and big variation of enzymatic activities and responses to the prototypical inducers and modafinil limited the use of this cell culture model to predict *in vivo* interaction.

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The effects of reference compounds on drug metabolizing enzyme activities is summarized in Table 6.2-93.

Table 6.2-91. Drug Metabolizing Enzyme Activities in Microsomes Prepared from the Human Livers

Substrate (Reaction)	Microsome Enzyme Activities					
	Donor Included in the Study			Other Donors ^a		
	H94	H97	H100	Min./Max.	Average	n
Ethoxyresorufin (O-deethylation) ^b	143	18	61	4-240	70	23
Phenacetin (deethylation) ^c	2.7	1	1.9	0.1-4	1.3	24
Pentoxyresorufin (O-dealkylation) ^b	0.3	0.5	0.9	0.03-1.2	0.4	23
Mephenytoin (hydroxylation) ^b	60	200	190	<5-200	40	23
Dextrometorphan (demethylation) ^c	0.4	0.2	0.2	0.02-0.5	0.15	27
p-nitrophenol (hydroxylation) ^c	2.3	2	4.6	0.5-8	2.8	21
Nifedipine (oxidation) ^c	6.3	1.8	6	0.1-10	3.5	29
Lauric acid (hydroxylation) ^c	1.8	1.8	1.6	0.1-2	0.7	18

^a Values obtained in the laboratory with other human donors (min = minimum; max. = maximum; n = number of donors).

^b Values are expressed as picomole of metabolite formed/min/mg microsomal protein.

^c Values are expressed as nanomole of metabolite formed/min/mg microsomal protein.

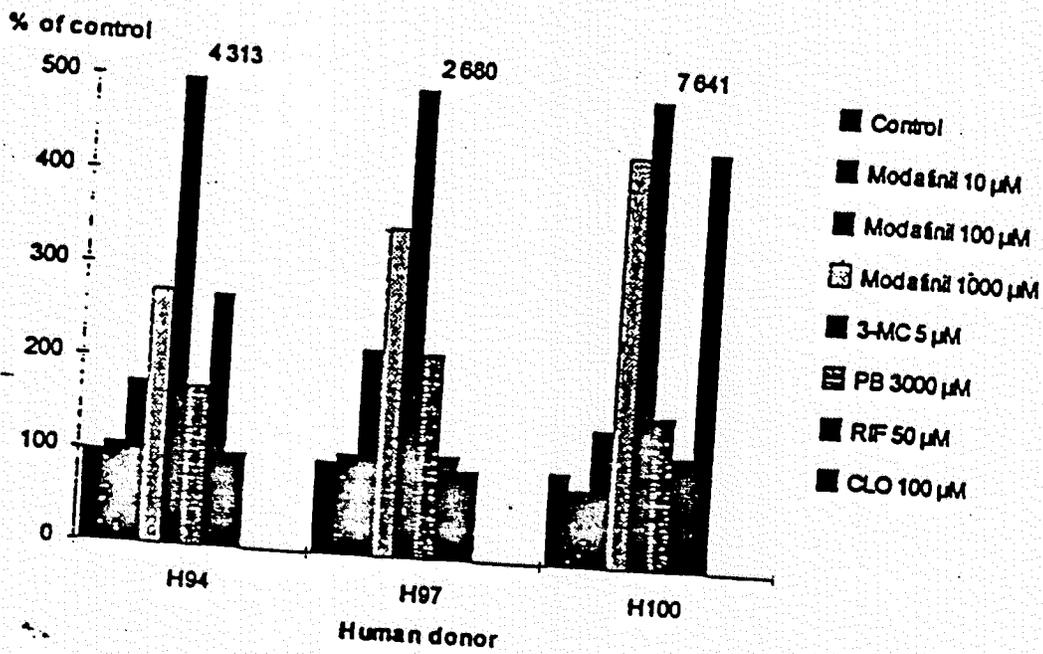
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Table 6.2-92. Drug Metabolizing Enzyme Activities in Hepatocytes Prepared from the Human Livers

Substrate (Reaction)	Hepatocyte Enzyme Activities								
	Donor Included in the Study						Other Donors ^a		
	H94		H97		H100		Min./Max.	Average	n
T0	T72	T0	T72	T0	T72				
Ethoxyresorufin (O-deethylation) ^b	1.9	0.9	0.7	1.4	7.3	0.6	0.2-8	3	19
Phenacetin (deethylation) ^c	1.6	3.4	4.1	3.3	5.4	1.5	0.1-25	4.7	25
Pentoxyresorufin (O-dealkylation) ^b	2.2	1.3	0.3	0.8	1.7	2.0	0.1-5	0.7	19
Mephenytoin (hydroxylation) ^c	0.3	0.4	1	0.7	0.6	0.4	0.1-2	0.7	6
Dextrometorphan (demethylation) ^c	0.6	1.3	0.6	0.5	0.3	0.3	0.1-2	0.5	6
Nifedipine (oxidation) ^c	5.8	17	3.4	8	13	3.8	0.5-13	5.3	8
Lauric acid (hydroxylation) ^c	0.9	0.5	1	1.3	1.4	1.2	0.3-2	0.8	7
Paracetamol ^c									
-Glucuroconjugate	1.6	2.6	5.9	5.7	1.5	1.1	0.3-16	4.1	26
-Sulfoconjugate	2.6	3	5.2	4	1.7	1.7	0.1-14	3.6	27
GST ^d	0.17	0.15	0.03	0.04	0.08	0.06	0.05-0.5	0.2	14
Procainamide (N-acetyl Transferase) ^c	2	4.1	1.1	1.5	0.8	1.4	0.1-7	1.1	32

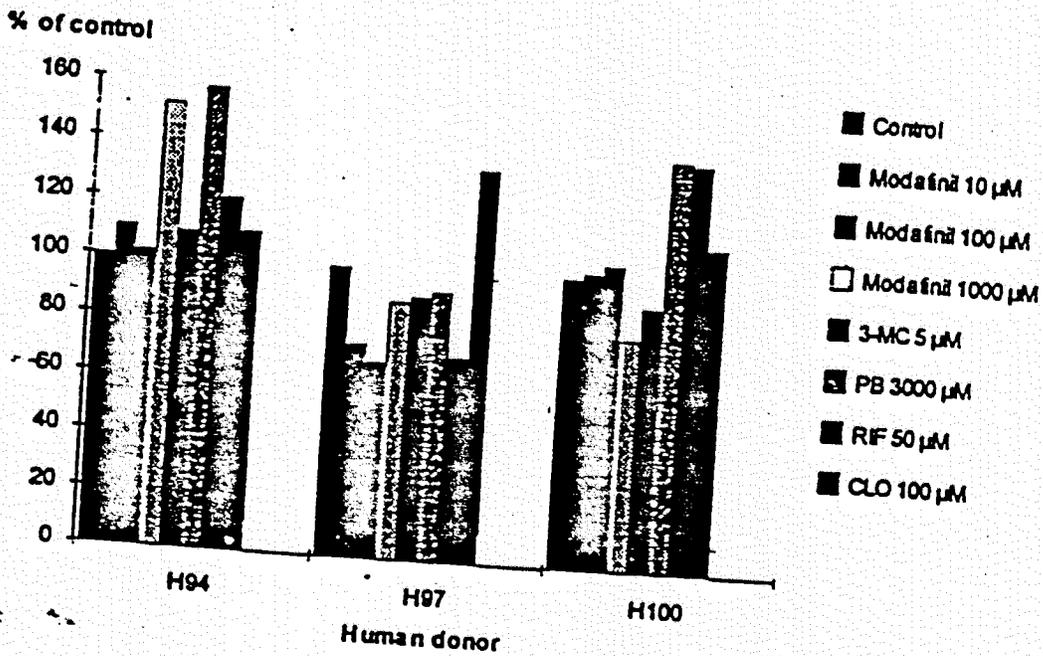
^a Values obtained in the laboratory with other human donors (min. = minimum; max. = maximum; n = number of donors). Activity measurement was done 16-48 hours seeding.
^b Values are expressed as picomole of metabolite formed/min/mg cellular protein.
^c Values are expressed as nanomole of metabolite formed/min/mg cellular protein.
^d Values are expressed as U/mg cellular protein.

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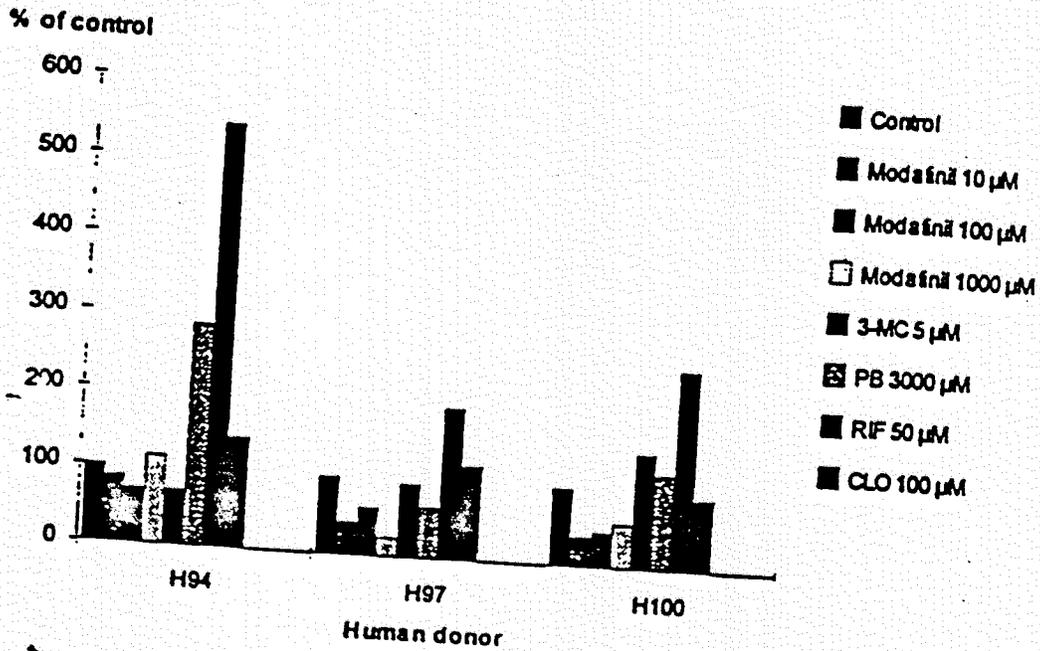
3-MC : 3-methylcholanthrene
PB : phenobarbital
RIF : rifampicin
CLO : clofibrinic acid

8.4 - Ethoxyresorufin O-deethylase activity, supported by CYP 1A, in human hepatocyte cultures, after a 72 hour incubation period in the presence of modafinil (Modiodal®) and of reference inducers



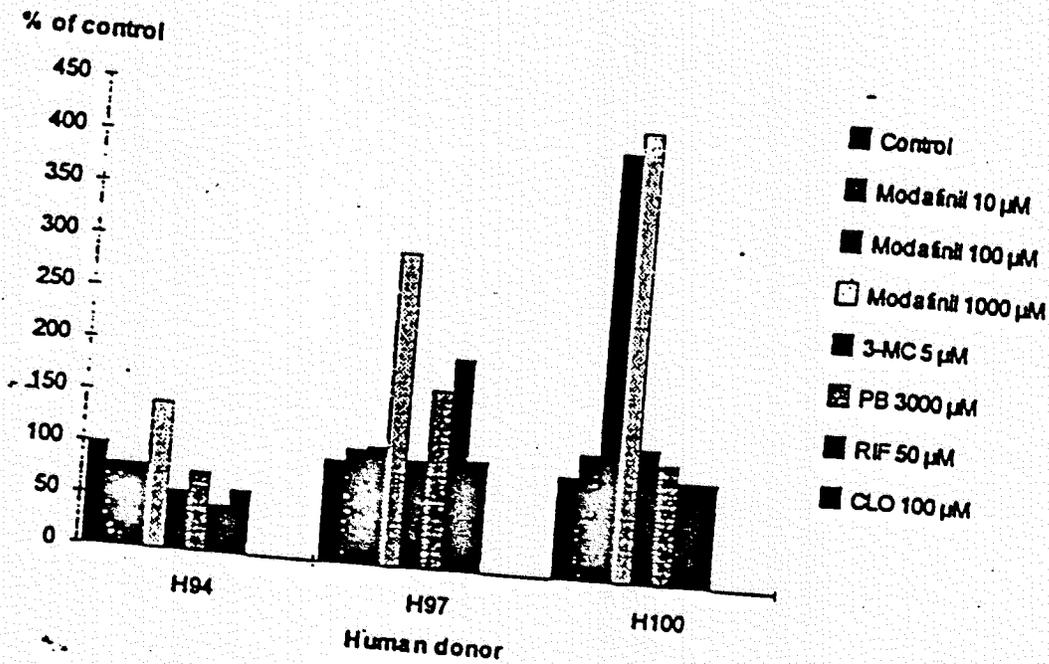
3-MC : 3-methylcholanthrene
PB : phenobarbital
RIF : rifampicin
CLO : clofibrac acid

8.5 - Pentoxoresorufin O-dealkylase activity, supported by CYP 2B, in human hepatocyte cultures, after a 72 hour incubation period in the presence of modafinil (Modiodal®) and of reference inducers



3-MC : 3-methylcholanthrene
PB : phenobarbital
RIF : rifampicin
CLO : clofibrac acid

8.6 - Mephenytoin hydroxylase activity, supported by CYP 2C, in human hepatocyte cultures, after a 72 hour incubation period in the presence of modafinil (Modiodal®) and of reference inducers



3-MC : 3-methylcholanthrene
PB : phenobarbital
RIF : rifampicin
CLO : clofibrate

8.7 - Dextrometorphan demethylase activity, supported by CYP 2D6, in human hepatocyte cultures, after a 72 hour incubation period in the presence of modafinil (Modiodal®) and of reference inducers