EFFECTS OF LONG-TERM TREATMENT WITH NALTREXONE ON HEPATIC ENZYME ACTIVITY

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SUMMARY

The influence of naltrexone on liver function in heroin addicts was studied, with respect to the metabolizing function by using the antipyrine clearance and to cellular damage by monitoring plasma levels of hepatic enzymes. The clearance of antipyrine was not affected by naltrexone treatment, and, during the study period, the use and withdrawal of benzodiazepines and alcohol did not change this parameter; moreover, there was no relationship between changes in plasma hepatic enzymes and antipyrine half-life. Mean plasma levels of hepatic enzymes did not show significant modification in the course of treatment with naltrexone.

KEY WORDS

naltrexone; antipyrine; hepatic enzymes

INTRODUCTION

Naltrexone (*N*-cyclopropyl-methyl-noroxymorphone) is a derivative of oxymorphone synthesised in 1963, active after oral administration with relatively pure long-acting opioid receptor antagonist activity, mainly on μ-receptors, and less active on κ-opioid receptors (1/20 with respect to μ) and δ-receptors ($<1/20$ with respect to μ) /1/. In opioid-dependent humans oral naltrexone precipitates an acute abstinence syndrome and in this respect is 17 times more potent than naloxone /1/. The use of naltrexone in addiction treatment prevents or helps to eliminate opioid-seeking behaviour; oral administration of 100 mg is able to block at 24 hours 90% of euphorizing and pleasant symptoms of 25 mg i.v. heroin challenge, its activity decreasing over 72 hours /2/.

Naltrexone is rapidly absorbed after oral administration, reaching peak plasma concentration after one hour, with bioavailability from 20% to 60%, probably depending on relevant hepatic first-pass effect /3-4/. Plasma protein binding ranges between 21% and 25%, animal studies demonstrating rapid and extensive distribution. There are no data on the tissue distribution of naltrexone in man. The apparent volume of distribution in man is 16.1 l/kg after a 100 mg single dose and 14.2 l/kg after long-term dosing /5/.

Naltrexone is extensively metabolized in the liver and the major metabolite is 6-β-naltrexol, an active compound playing a role in the therapeutic effect. Following oral administration of 2 doses of naltrexone of 200 mg to 4 subjects, the relative percentages in plasma for naltrexone and 6-β-naltrexol at both 16 and 24 hours after administration were 3.4% for naltrexone and 73.5% for 6-β-naltrexol /6/.

Other metabolites, less important and almost inactive, are 2-hydroxy-3-methoxy-6-β-naltrexol, 2-hydroxy-3-O-methyl-naltrexone and glucuronide compounds (see Fig. 1).

After oral administration plasma half-life ranges between 1.1 /7/ to 10.3 hours /3/, and 2.7 hours after intravenous administration /4/. The route of administration seems to affect half-life: the same study reported values of 8.9 hours for oral and 2.7 hours for i.v. administration, suggesting that differences in enterohepatic recycling could account for the variance in half-lives reported /1,4,6/.

Oral long-term treatment does not affect the plasma half-life of naltrexone and its metabolites, and plasma concentrations of

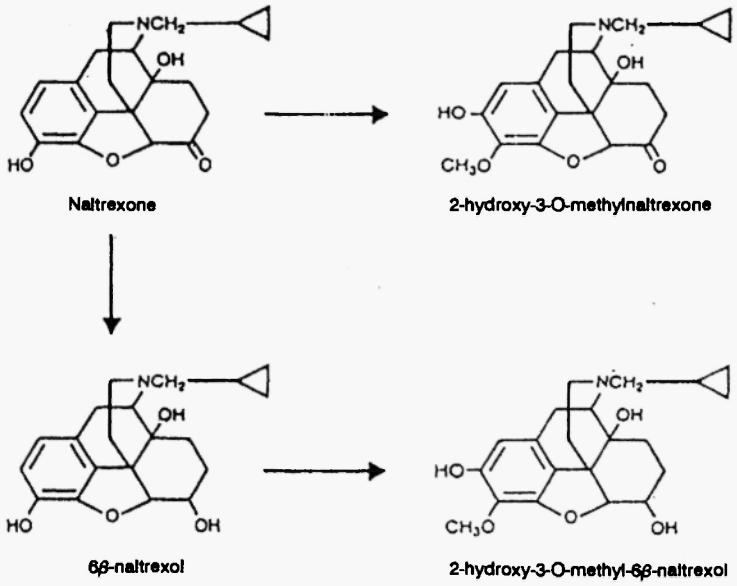

Fig. 1: Naltrexone and its metabolites

6-β-naltrexol are doubled, reducing slowly over 24 hours; in steady-state, the plasma concentration of 6-β-naltrexol is about 10-fold higher than naltrexone, and in this condition the major therapeutic activity depends on this metabolite /3/.

Naltrexone metabolism involves different pathways including both microsomial and non-microsomial enzymes /4/. In mice, during chronic treatment, naltrexone itself inhibits monooxygenase enzymes, while in man, where the parent drug is rapidly and extensively metabolized to 6-β-naltrexol, there should not be any direct inhibition by naltrexone of these enzymes /5-8/.

Naltrexone, as stated above, is a long-acting drug used in long-term treatment for patients who are poly-drug abusers and smokers, who often have a history of hepatitis, and this drug could interact on biotransformation of xenobiotics as food or legal and illicit drugs, leading to unpredictable reactions. A number of authors have studied the safety of naltrexone in long-term

treatment, and some of them described plasma increase in aspartate aminotransferase (AST) and other hepatic enzymes during chronic treatment in heroin addicts /9,10/ and obese patients /11/. Other studies have produced conflicting data on the ability of naltrexone to elevate hepatic enzymes, because it is difficult to determine the individual effects of this drug on the addicts' plasma levels of hepatic enzymes because of the concomitant use of legal or illicit drugs /12-14/. Therefore, it should be useful to monitor the levels of plasma AST and other hepatic enzymes, because this parameter is stated to be a marker in evaluating liver function with respect to antipyrine clearance in patients suffering from chronic hepatitis /15,16/.

The aim of this study was to evaluate in addicts the effects of long-term treatment of naltrexone on plasma half-life of antipyrine and at the same time to measure the plasma concentration of hepatic enzymes /14-17/.

MATERIALS AND METHODS

Subjects

The subjects of the study were 19 addicts, aged 20-29 (mean 24.8 ± 1.8 years), without concomitant actual viral hepatitis or other acute illness, who decided of their own free will to begin a detoxification program including long-term treatment with naltrexone and periodic control of hepatic enzymes and antipyrine test (see Table 1). Before the naltrexone therapy, patients were submitted to a test with 0.4-0.8 mg of naloxone i.v., and when the naloxone test was negative, patients were treated with increasing doses of naltrexone (10 mg by mouth on the first day, and on the following days 20, 30, 40, 50, 100 mg). The subsequent schedules were: Monday and Wednesday 100 mg and Friday 150 mg of naltrexone p.o. The antipyrine test was performed before starting naltrexone therapy (i.e., during the detoxification period) and after one and four months.

The antipyrine test was also carried out on 12 healthy volunteers (5 female and 7 male, aged 21-31, mean 25 ± 3.9). The protocol was submitted to and approved by the Faculty of Medicine Ethics Committee.

In Table 1, the main characteristics of the subjects are listed: sex, age, length of addiction, drugs used during heroin withdrawal,

the habit of hashish and tobacco smoking, and the use of alcohol and benzodiazepines. Six patients (GM, CG, GA, SP, MG, MR) abused alcohol (> 350 g/week) before starting the protocol, and 2 cases (GM and CG) continued alcohol abuse during the therapy. Eleven patients reported previous acute hepatitis.

TABLE 1

Characteristics of the subjects included in this study

Initials	Sex	Weight kg	Use of BZD	Alcohol	Hashish	Tobacco*	Viral hepat.	Drug used for withdrawal	Drug-free days**
B.I.	M	56	-	-	+	15	+	Self-reduction	20
F.P.	M	68	-	-	+	30	+	Self-reduction	30
B.R.	M	64	-	-	+	20	+	Self-reduction	30
G.M.	M	64	1M	4M	-	20	+	Methadone	25
F.D.	M	65	3M	-	+	40	-	Methadone	2
C.G.	M	64	1M	4M	+	20	+	Methadone	32
P.D.	M	70	-	-	+	40	+	Self-reduction	20
B.A.	F	47	-	-	+	20	+	Self-reduction	10
T.M.	M	120	1M	-	+	15	+	Methadone	20
F.A.	M	71	1M	-	+	40	-	Self-reduction	20
G.A.	M	71	1M	+	+	30	+	Self-reduction	20
S.P.	M	60	-	+	-	25	-	Self-reduction	10
C.G.R.	M	58	-	-	-	30	-	Self-reduction	25
P.G.	M	69	1M	-	+	10	-	Self-reduction	7
V.G.	M	71	-	-	+	20	+	Self-reduction	90
Pa.G.	M	69	-	-	-	20	-	Self-reduction	30
M.G.	F	53	+	+	+	15	-	Methadone	5
C.G.	M	59	-	-	-	20	-	Self-reduction	18
M.R.	F	64	2M	+	+	15	+	Methadone	60

* = Number of cigarettes
** = Drug-free days before starting naltrexone treatment
M = Drugs used before and for # Month(s) during the treatment

Antipyrine test

1000 mg of antipyrine was administered in the morning with 200 ml of water to fasting patients, and 10 ml blood was collected in ampoules containing 100 μl of EDTA 5% at time 0, 1.5, 3, 6, 9, 12, 24, 48 hours; after centrifugation, plasma samples were frozen at -20°C until HPLC analysis. The analyses were performed as described by Shargel with little modification /18/. The antipyrine

half-life was calculated using a one-compartment open model /19/.

RESULTS

The hepatic monooxygenases play an important role in the biotransformation of drugs and their activity is crucial for the formation of active metabolites. It has recently been demonstrated that liver alcohol damage is associated with induction of hepatic monooxygenase /8/. If the liver damage depends at least in part on the activity of cytochrome P-450 isozymes, antipyrine and its metabolites could be used as an *in vivo* parameter of the hepatic oxidative drug-metabolizing enzyme capacity in humans /20,21/.

TABLE 2A

Antipyrine half-life (hours)

Controls	Naltrexone treated patients				
	Patient		T-0	T-30	T-120
12.17	B.I.	(1)	8.88	10.25	14.06
12.4	F.P.	(2)	9.66	6.42	10.6
14.9	B.R.	(3)	18.39	18.63	15.63
15.61	G.M.	(4)	18.83	20.36	17.33
10.81	F.D.	(5)	11.00	12.05	12.07
11.8	C.G.	(6)	9.49	13.96	11.27
16.21	P.D.	(7)	16.88	9.76	12.64
10.1	B.A.	(8)	10.68	12.38	9.98
10.4	T.M.	(9)	15.36	16.93	12.36
11.8	F.A.	(10)	8.49	14.05	10.46
11.9	G.A.	(11)	12.78	11.09	10.41
9.6	S.P.	(12)	11.29	10.32	8.6
	CG.R.	(13)	9.64	9.43	8.40
	P.G.	(14)	12.72	11.74	11.86
	V.G.	(15)	9.24	11.45	10.36
	PA.G.	(16)	12.72	12.15	10.20
	M.G.	(17)	10.53	12.15	11.49
	C.G.	(18)	9.64	9.50	10.04
	M.R.	(19)	13.41	13.05	12.26
Mean 12.30			12.08	12.40	11.58
± SD 2.16			3.19	3.33	2.22

P = ns vs Controls and vs T-0 (t-test)

TABLE 2B

Antipyrine pharmacokinetic parameters in patients and controls

	V_d (l/kg)	$t_{½}$ (h)	Cl (l/h)	AUC (mg/h/l)
Controls	0.75 ± .25	12.30 ± 2.16	2.94 ± .99	383 ± 175
T-0	0.68 ± .11	12.08 ± 3.19	2.79 ± .78	374 ± 178
T-30	0.74 ± .17	12.40 ± 3.33	3.09 ± 1.13	340 ± 142
T-120	0.80 ± .10	11.58 ± 2.22	3.25 ± .79	314 ± 99

Data are expressed as mean ± SD. There are no significant differences between patients treated with naltrexone and controls at any time. (Student's t-test for paired data.)

The antipyrine pharmacokinetics of controls and patients are listed in Tables 2A and B. There were no differences in antipyrine disposition parameters (half-life, V_d, Cl, AUC) of all patients at T-0 time vs controls and vs times T-30 and T-120.

We studied patients also with regard to the daily use of benzodiazepines, looking for a possible induction of microsomial enzymes following the use of these drugs. At the beginning of the treatment the antipyrine half-life in 10 patients not using benzodiazepines was 11.69 ± 3.32 hours, whereas 9 cases taking benzodiazepines daily for more than 3 months showed a plasma clearance of antipyrine of 12.45 ± 3.04 hours. Values of half-life, clearance and V_d are listed in Table 3.

These values do not differ significantly from control values and the antipyrine test seems not to be able to elucidate differences between addicts with respect to the use of benzodiazepines.

Another drug able to interact with antipyrine clearance is alcohol and we compared the plasma clearances of antipyrine in controls and patients drinking more or less than 350 g/week of alcohol (Table 4). The data did not show differences at T-0 values in all groups.

TABLE 3

Antipyrine clearance in patients using benzodiazepines (BZD)

		T-0	T-30	T-120
Users	$t_{½}$	12.4±3.04	13.93±2.97	12.15±2.06
N=9	Cl	2.9±0.79	2.8 ±0.68	3.1 ±0.76
	V_d	0.71±0.11	0.75±0.14	0.82±0.70
Non-users	$t_{½}$	11.69±3.32	11.03±3.16	11.05±2.33
N=10	Cl	21.6±0.71	3.2 ±1.41	3.3 ±0.83
	V_d	0.66±0.12	0.74±0.20	0.77±0.12

p = ns vs T-0 (t-test)

TABLE 4

Antipyrine disposition in patients drinking alcohol (values at T-0 time)

	N	$t_{½}$ ± SD (h)	Cl ± SD (l/h)	$V_{..}$ ± SD (l/kg)
Controls	12	12.3 ± 2.16	2.94 ± 0.99	0.75 ± 0.25
Drinker > 350 g/week	6	12.6 + 3.15	2.80 ± 0.85	0.71 ± 0.13
Non drinker < 350 g/week	13	11.0 + 4.31	2.61 ± 1.01	0.63 ± 0.20

P = ns vs controls (t-test and ANOVA)

A possible drug interaction was the simultaneous use of alcohol and benzodiazepines; patients using BZD alone and BZD with alcohol were compared. Four cases (cases 5, 9, 10, 14) used BZD only and had an antipyrine half-life of 11.89 ± 2.89 hours at T-0, and 13.69 ± 2.38 and 11.68 ± 0.84 at T-30 and T-120, respectively. There were no significant differences between these data. The five patients who used BZD and alcohol (cases 4, 6, 11, 17, 19) had an initial half-life of 13.00 ± 3.62. Three patients stopped using alcohol on starting naltrexone therapy, and their antipyrine half-life

did not differ from controls and versus T-0 values (12.24 ± 1.52, 12.09 ± 0.998, 11.38 ± 0.92, at T-0, T-30 and T-120, respectively.)

The course of plasma hepatic enzymes is shown in Figs. 2 and 3, and there are no significant differences between different time samples. Only one case (F.D.) had augmented values at the beginning of the treatment, and values came back to the normal range during the course of the treatment (AST after one and six months were 100 U/l and 38 U/l and γ-GT 210 U/l and 58 U/l, respectively.

Cross-tabulation of increase of γ-GT with reduction or increase of antipyrine half-life is evaluated in Table 5, and we did not find any significant relationship between length of heroin habit, type of drug consumption, drug-free interval, alcohol abuse, tobacco and hashish habits and previous hepatitis and antipyrine half-life before and after naltrexone therapy.

TABLE 5

Antipyrine half-life and modifications of plasma liver enzymes in patients treated with naltrexone

		γ-GT increased		
		YES	NO	
	YES	2	5	7
$t_{½}$ prolonged	NO	5	7	12
		7	12	19
				McNemar's test = n.s.

		AST increased		
		YES	NO	
	YES	8	4	12
$t_{½}$ reduced	NO	3	4	7
		11	8	19
				McNemar's test = n.s.

There are no significant correlations between the effect "increase of γ-GT or AST" and antipyrine half-life modifications.

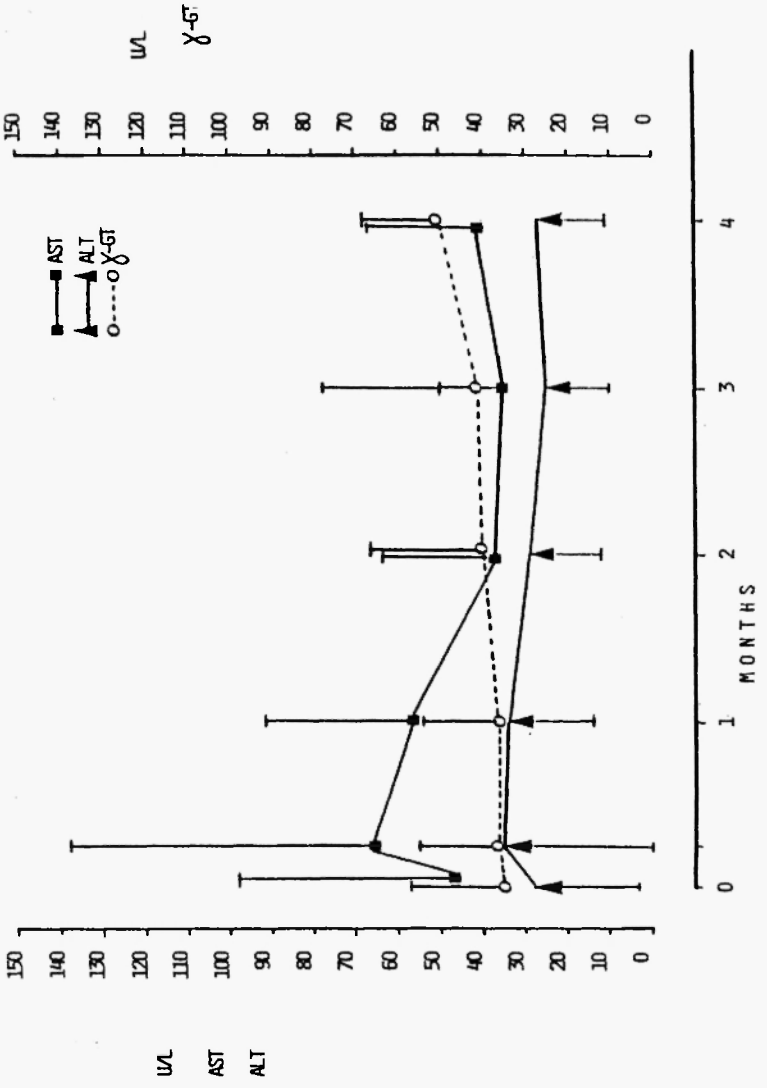

Fig. 2: Time course of plasma hepatic enzymes (AST, ALT and γ-GT) during treatment with naltrexone.

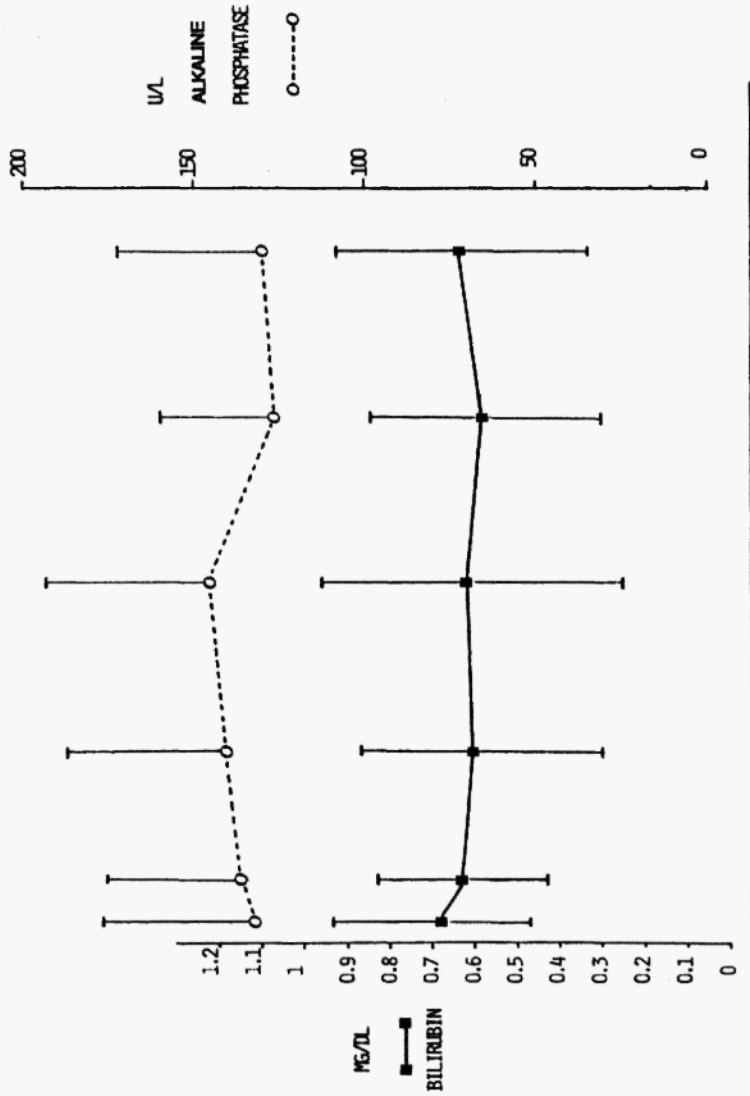

Fig. 3: Time course of plasma bilirubin and alkaline phosphatase during treatment with naltrexone.

Partially in contrast with data by Atkinson in obese patients /11/, who were treated with high doses of naltrexone, our data suggest a good hepatic tolerance in patients who in the past had used drugs and often alcohol in large amounts, and/or with a history of viral hepatitis. The large interindividual variability in our cases is due to a number of causes, and motivations leading our patients to naltrexone treatment were different, depending on both pharmacological and non-pharmacological previous personal experiences.

It is interesting to note that 70% of our cases reduced the use of heroin of their own free will before beginning the naltrexone treatment, indicating a strong motivation for starting the programme.

CONCLUSIONS

Despite our data, chronic treatment with naltrexone seems not to be able to alter hepatic functions either with respect to the common clinical tests or to the hepatic clearance of antipyrine. Moreover there is no direct relationship between changes of antipyrine half-life and the sole use of benzodiazepines or alcohol, nor vs modifications of plasma hepatic enzymes.

These results should be checked in a larger population to minimize the environmental, genetic, pharmacological and habit factors that can significantly influence the metabolic pathways.

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