APPENDIX B

Naltrexone: Disposition, metabolism, and effects after acute and chronic dosing

The disposition of naltrexone during acute and chronic administration of 100-mg oral dose was studied in 4 subjects. Following an acute dose the mean ($\bar{X}$) peak naltrexone plasma level was 43.6 ± 29.9 ng/ml at 1 hr and for the major biotransformation product, β-naltrexol, was 87.2 ± 25.0 ng/ml at 2 hr. Twenty-four hours after the dose the X levels of naltrexone and β-naltrexol declined to 2.1 ± 0.47 and 17.6 ± 5.0 ng/ml, respectively. Following chronic administration the $\bar{X}$ peak plasma levels of naltrexone and β-naltrexol rose to 46.4 ± 18.5 and 158.4 ± 89.9 ng/ml at 1 hr, but by 24 hr both compounds declined to levels of the same order as in the acute state at 24 hr. Plasma levels of naltrexone and β-naltrexol measured 24 hr after the daily doses of naltrexone throughout the study indicated that steady-state equilibrium was rapidly attained and that there was no accumulation of naltrexone and beta naltrexol in the plasma after chronic treatment on 100 mg oral doses. Biexponential kinetics were observed for naltrexone and β-naltrexol in the first 24 hr. The half-life of naltrexone and β-naltrexol decreased slightly from the acute to the chronic study from 10.3 ± 3.3 to 9.7 ± 1.1 hr and from 12.7 ± 2.6 to 11.4 ± 2.0 hr. The plasma levels of naltrexone declined slowly from 24 through 72 hr from 2.4 to 1.7 ng/ml, with an apparent half-life of 96 hr. The renal clearance data indicate that naltrexone is partially reabsorbed while beta naltrexol is actively secreted by the kidney. During acute and chronic naltrexone administration the mean fecal excretion was 2.1% and 3.6%, while urinary excretion was 38% and 70% of the dose in a 24-hr period. Opiate antagonism to 25 mg heroin challenges was nearly complete through 48 hr after naltrexone. At 72 hr the objective responses reappeared to a greater extent than the subjective ones. Correlation coefficient (r) between naltrexone plasma levels and opiate antagonism was 0.91 and between individual half-life of naltrexone and opiate antagonism it was 0.99.

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Naltrexone (N-cyclopropylmethylnoroxymorphone), a potent narcotic antagonist, is an experimental drug proposed for the treatment of opiate dependence. It was synthetized in 1965 by Blumberg, Pachter, and Matossian.[3] Animal

Table I. *Clinical study protocol for drug administration, sample collection, heroin challenges, and pupillary photography*

Subject	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*
C. L.	PL H*	PL	PL H†	PL	NT t½ UF F24	NT	NT	NT	NT H‡	NT	NT	NT	PL	NT H§	NT
				P	P	B	B	B	B	B	B	B	B		B
E. M.	PL H*	PL	PL	PL H†	NT t½ UF F24	NT	NT	NT	NT	NT	NT	NT	NT	NT H‡	NT
			P		P	B	B	B	B	B	B		B		B
B. P.	PL H*	PL	PL H†	PL	NT t½ UF F24	NT	NT	NT	NT H‡	NT	NT	NT	NT	PL	NT H§
				P	P	B	B	B	B	B	B	B	B		
R. J.	PL H*	PL	PL H†	PL	NT t½ UF F24	NT	NT	NT	NT H‡	NT	NT	NT	NT	PL	NT H§
				P	P	B	B	B	B	B	B	B	B		

PL, Placebo dose of naltrexone; NT, 100 mg oral dose of naltrexone; H (15, 25 mg), heroin challenge, 15 mg, 25 mg intravenously, H (24, 48, 72 hr), heroin challenge of 25 mg intravenously; 24, 48, and 72 hr after the last naltrexone dose (when NT is noted on the same day the dose was given after the challenge); B, blood sample 24 hr after naltrexone: t½, serial blood samples in a 24-hr period for biological half-life determination; P, pupillary photography; UF, fractional urine collection 0-4, 4-8, 8-12, and 12-24 hr; U(24), 24-hr urine collection, F(24), 24-hr fecal collection.

*15 mg.

†25 mg.

‡24 hr.

§48 hr.

studies indicated that naltrexone had undetectable or minimal agonistic effects and its relative opiate antagonistic potency was 40 times that of nalorphine and 2 to 3 times that of naloxone.[2, 17] In man, naltrexone was 17 times as potent as naloxone in precipitating acute abstinence.[20] The time-course of narcotic blockade in rats was 3 times as long as that achieved by naloxone.[1] A slow-release preparation of zinc-tennate-naltrexone complex in mice maintained about 40% opiate blockade for 21 days, whereas a similar dose of naltrexone HCl lasted only 1 day.[12] Martin and Sandquist reported 21 to 29 days antagonistic activity of naltrexone suspended in small particles of a polylactide plastic given intramuscularly to dogs.[22]

The pharmacology and narcotic antagonistic activity of naltrexone in man were studied by Martin, Jasinsky, and Mansky,[21] Resnick and associates,[24] and Volavka and associates.[31] These investigators found that the greater potency (smaller oral doses) and longer duration of action of naltrexone present a definite therapeutic advantage over naloxone. No withdrawal symptoms were observed after the abrupt discontinuation of 200-mg daily doses given for 3 to 8 wk.[24]

A comparative urinary excretion study of naltrexone in man and animals was reported by Dayton and Inturrisi.[9] Cone[5] isolated and identified β-naltrexol, the major urinary excretion product of naltrexone in man. The chemistry of β-naltrexol was investigated in detail by Cone, Gorodetzky, and Yeh,[6] Chattargie and colleagues,[4] and Malspeis and colleagues.[19] The quantitative aspects of human urinary disposition of naltrexone was studied by Cone, Gorodetzky, and Yeh[7] and Verebey, Mulé, and Jukofsky,[28] both reporting that the major urinary excretion product was β-naltrexol and that

16	17	18	19	20	21	22	23	24	25	26	27
NT	NT	NT U (24) F (24)	NT U (24) F (24)	NT U (24)	NT t½ UF	PL	PL	H (72 hr)			
	B	B	B	B	P	B					
PL	NT H§	NT	NT U (24) F (24)	NT U (24) F (24)	NT U (24)	NT	NT	NT t½ UF	PL	PL	H (72 hr)
B		B	B		B		B	P	B		
NT	NT	NT U (24) F (24)	NT U (24) F (24)	NT U (24)	NT	NT t½ UF	PL	PL	H (72 hr)		
B	B	B	B		B	P	B				
NT	NT	NT U (24) F (24)	NT U (24) F (24)	NT U (24)	NT	NT t½ UF	PL	PL	H (72 hr)		
B	B		B	B	B	P	B				

a small quantity of unchanged drug, mainly in the conjugated form, was also present in the urine.

The relative narcotic antagonistic potency of β-naltrexol to naltrexone was reported to be 1:53 in the rat by Fujimoto and associates.[11] Naltrexone was 12 times as potent as β-naltrexol in the chronic spinal dog.[7] Recently, Verebey and co-workers[26] reported the isolation and identification of another human urinary metabolite of naltrexone, 2-hydroxy-3-methoxynaltrexol, which represents approximately 10% of the urinary excretion products of naltrexone. Determination of naltrexone and β-naltrexol in human plasma after therapeutic doses was only recently accomplished.[27] Using this method, the total disposition of naltrexone in conjunction with its pharmacological activity was evaluated and the results reported in this communication.

Methods

Subjects. Four male post-addict paid volunteers from the New York State Office of Drug Abuse Services were the subjects in the study. The subjects were admitted to a closed metabolic ward located at Manhattan State Hospital. The physical characteristics and drug history of subjects were: (1) average age, 28 yr (24 to 36); (2) average weight, 159 pounds (135 to 180); (3) average duration of heroin use, 11 yr (6 to 16). The subjects were all heavy cigarette smokers and occasional cocaine users. Some, but not all, of the subjects occasionally used marijuana, LSD, and barbiturates. At the beginning of the study all subjects stated that they were free of drugs for an average of 3 mo (2 to 6). After admission, the subjects were kept in the metabolic ward for 1 wk to assure a drug-free state. Prior to the study, each subject received a thorough physical examination and clinical blood chemistry survey; control urine and blood samples were collected. The urine samples were screened for all common drugs of abuse.[23]

Drug administration and protocol schedule. All subjects received initial and subsequently daily oral doses of 100 mg naltrexone. The dosage schedule, metabolic sample collections, and time of heroin challenges are presented in Table 1. The techniques used in this study to measure pupil size and to calculate plasma half-lifes have been reported.[29] Heroin in aqueous solution was injected intravenously

Table II. *Plasma levels of naltrexone (NT) and beta-naltrexol (β-OL) (ng/ml) in acute and chronic treatment after 100 mg doses of naltrexone*

Subject	Drug	Type of treatment	Hours					
			1	2	4	8	12	24
C. L.	NT	Acute	58.7	47.1	32.4	11.2	4.7	1.5
		Chronic	55.5	42.9	21.4	10.8	7.3	3.5
	β-OL	Acute	129.7	110.8	69.3	40.5	34.8	18.1
		Chronic	143.3	114.7	103.4	79.6	56.7	34.2
E. M.	NT	Acute	64.2	50.3	20.7	7.6	5.0	2.6
		Chronic	53.7	28.8	18.0	9.5	4.9	2.2
	β-OL	Acute	80.8	98.7	49.3	37.5	25.2	11.7
		Chronic	288.0	204.0	163.8	67.1	54.0	21.4
B. P.	NT	Acute	11.2	15.2	8.9	5.3	3.3	2.3
		Chronic	18.7	21.9	15.1	9.1	6.0	3.1
	β-OL	Acute	39.1	52.6	85.1	33.6	28.9	16.7
		Chronic	119.3	131.1	68.4	56.6	44.0	22.4
R. J.	NT	Acute	40.3	32.0	18.6	8.0	4.3	2.0
		Chronic	57.6	32.9	20.8	10.3	7.0	3.1
	β-OL	Acute	81.0	86.7	72.5	57.6	44.0	23.8
		Chronic	83.0	96.0	68.8	53.0	38.6	18.6

over a period of 3 min. Two such injections (15 and 25 mg) were given before the naltrexone treatment. All subsequent heroin injections were of 25 mg.

Sample collections. Following an acute oral dose of 100 mg naltrexone, 20 ml of blood was collected in tubes containing sodium oxalate at times 1, 2, 4, 8, 12, and 24 hr after naltrexone for the determination of the acute half-life (t½). The same blood collection schedule was used during the maintenance phase of the study for the determination of the chronic t½. The samples were centrifuged, the plasma obtained and frozen at −16° C until analyzed. Single blood samples were collected throughout the study, 24 hr after each dose of naltrexone, to evaluate build-up and stabilization plasma levels of drug and metabolite during continued naltrexone administration. A single blood sample was collected just prior to heroin challenges to determine the narcotic antagonist blood levels at that time. Twenty-four hour urine specimens were collected on 3 successive days and feces samples on 2 successive days during the chronic phase of the study. Fractional urine samples of 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hr were collected along with the acute and chronic t½ blood samples, to allow determination of renal clearance values and cumulative urinary excretion patterns. The volumes of urine samples and weights of feces were recorded and the samples frozen at −16° C until analyzed.

Analytical methods. The methods used in this study have been reported.[27, 28] An aliquot of plasma and internal standard (naloxone) were mixed and extracted into chloroform at pH 8.5.[27] After a series of purification steps, the residue resulting from the evaporation of the last organic phase was derivatized with pentafluropropionic anhydride (PFPA). The PFPA derivatives of naltrexone, β-naltrexol, and naloxone were analyzed on a Hewlett-Packard Model 5830A instrument, equipped with a ^{63}Ni linear electron capture detector. The column was packed with 3% OV-22 and the operating column oven temperature was 215° C. For urine and feces determinations of naltrexone and metabolites a modified method was used.[28] Bis(trimethylsilyl)-trifluoracetamide (BSTFA) derivatives of the weak organic bases were

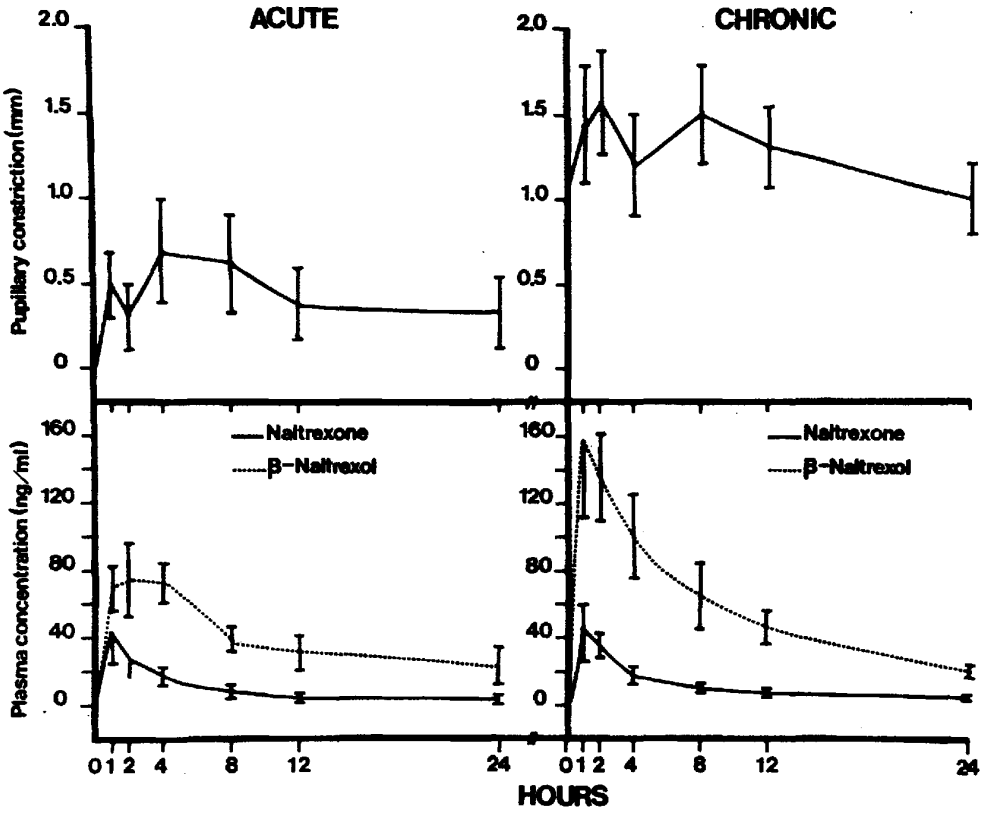

Fig. 1. The time-course of naltrexone and β-naltrexol plasma levels and the corresponding pupillary effects after a single 100-mg dose (acute) and following multiple 100-mg doses of naltrexone (chronic). Each point on the graph represents the mean ± SD (n = 4).

prepared and anlyzed using a hydrogen flame ionization detector. The column was packed with 3% OV-17 and the operating column oven temperature was 270° C. Feces samples were weighed and homogenized (1:10 w/v) in 0.1 N HCl with a Waring blender, and small aliquots were extracted, derivatized, and analyzed.[28]

Objective responses. Respiration rate was measured by a strain-gauge and recorded on a polygraph. Respiratory depression was determined by calculating the difference between the respiratory rate just prior to a heroin challenge and the rate 10 min after heroin administration. Pupillography was performed prior to a heroin challenge and 5 min after heroin administration. Pupillary miosis is expressed as the difference in millimeters between the pre- and post-challenge pupil sizes. Total objective responses were determined by summing the respiratory and pupillary responses.

the ARCI (Addiction Research Center Inventory) was used. Table VIII presents a list of questions: (1) absolute heroin effects were investigated by 10 true or false questions, representing commonly reported opiate symptoms elicited by intravenous heroin; (2) the relative heroin effects were examined by a comparative test relating to past heroin experiences, referred to as "opiate high"; (3) "liking" is a separate entity from "highs" and symptoms and is strongly influenced by the circumstances under which the drug is taken. It represents a state of euphoria, rated on a scale of 0 to 4 (none to best); (4) the observers not knowing what was administered, placebo or drug, also rated the subjects' state of euphoria during and after challenges on a scale of 0 to 5; (5) the economics of heroin appears to provide a numerical subjective measure. The test is based on the subject's estimate of the street value in dollars

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