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HUMAN METABOLITE OF NALTREXONE (N-CYCLOPROPYLMETHYLNOROXYMORPHONE) WITH A NOVEL C-6 ISOMORPHINE CONFIGURATION

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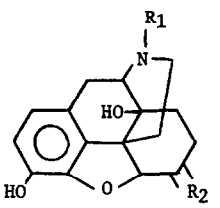
Naltrexone I (1) like naloxone II (2) has been reported to be a potent narcotic antagonist with little or no agonistic effects. Since naltrexone is more potent than naloxone and has a greater duration of action in man (3) and in rodents (4) it was felt that its mode of



I; $R_1 = CH_2$-cyclopropyl, $R_2 = O$

II; $R_1 = CH_2CH{=}CH_2$, $R_2 = O$

III; $R_1 = CH_2$-cyclopropyl, $R_2 = H, OH$

IV; $R_1 = CH_2$-cyclopropyl, $R_2 = OH, H$

metabolism and rate of excretion of metabolites were of interest as possible explanations of these differences. Naloxone has been reported to be metabolized in man by glucuronidate conjugation (5) N-dealkylation (6) and reduction of the C-6 carbonyl to form N-allyl-7,8-dihydro-14-hydroxynormorphine (6). No metabolic data has been reported for naltrexone.

The subjects in this study were healthy, adult, male federal prisoner volunteers; all are former narcotic addicts who were incarcerated at the NIMH Addiction Research Center at the time of the study. Urine from two subjects receiving 50 mg/day of naltrexone orally for approximately six weeks (and free from other drugs) was collected ad lib and every eight hours for two days. Three subjects received a single oral dose of naltrexone, 50 mg, and urine was collected as described above.

Urine samples from the chronic subjects which were richest in metabolite (as monitored by tlc comparison with authentic III) were extracted with chloroform after adjustment of

pH to 9.5 with sodium hydroxide and phosphate buffer. Evaporation of solvent gave ~4 mg of brown residue. Preparative tlc of the zone corresponding to III (elution on silica gel-benzene:diethylamine {4:1} followed by elution on Gelman type SG fiber glass sheets-chloroform saturated with ammonia (5)) gave a substance which was visualized with potassium iodoplatinate spray as a single spot on both systems. Treatment of an ether extract of the substance with dry hydrogen chloride gave a fluffy white precipitate which was washed with ether and dried (~0.2 mg) (7). Silylation of a portion of the metabolite and III with BSTFA (10% TMCS) (8) in acetonitrile (1:1) in a sealed tube at 70°C for one hour followed by injection on gc (3% OV-17 on GCQ, 2 mm x 6 ft. glass, 270°C, f.i.d. 275°C) gave a major peak with uncorrected R_t = 5.10 min. for the metabolite and 5.55 min. for III (9).

Spectral data on the metabolite, I and III are given in the Table. The excitation and emission spectra of the metabolite and III indicate a similar but nonidentical structural relationship. The lack of a carbonyl absorption coupled with the molecular weight of 343 for the metabolite support assignment of structure IV, the C-6 epimer of III.

TABLE

Spectral Characteristics of the Metabolite, I and III

Metabolite	III	I	Type of Analysis
247, 277, 318 417	249, 278, 320 427	-[d]	Fluoresence[a] Excitation (nm) Emission (nm)
3450 -	3450 -	3450(OH) 1730(C=O)	Infrared[b] (cm^{-1})
M^+343(100) M^+-41(43) M^+-55(23)	M^+343(36) M^+-41(16) M^+-55(10)	M^+341(9) M^+-41(37) M^+-55(31)	Mass Spectra[c]

[a] Values represent λ max, uncorrected with quinine sulfate standard. Samples were developed on silica gel (chloroform saturated with ammonia), sprayed with ferri-ferrocyanide reagent (10) and eluted with pH 9 phosphate buffer.

[b] KBr

[c] Molecular ion M^+ (% abundance), 70 eV.

[d] No fluoresence observed under these conditions.

In a study of the C-6 configuration of morphine derivatives Sargent, et al. (11) were able to conclude that 14-hydroxycodeine (prepared by sodium borohydride reduction of 14-hydroxycodeinone) had the C-6 codeine configuration (α-hydroxy) since similar reduction of

codeinone gave a quantitative yield of codeine (12). In addition Weis and Daum (13) reported that borohydride reduction of dihydro-14-hydroxymorphinone gave dihydro-14-hydroxymorphine without any indication of the C-6 epimer. In the present study sodium borohydride reduction of I in methanolic dioxane resulted in a quantitative yield of III confirming the C-6 morphine configuration of III.

In order to confirm the structural assignment of the metabolite as IV its reactivity was compared to that of III in the Oppenauer reaction. Rapoport, et al. (14) reported in a study of dihydro alcohols of morphine origin in the Oppenauer reaction that the cis-alcohol (C-6 α-hydroxy) is more easily oxidized than the trans (C-6 β-hydroxy) and concluded that the effect was likely due to presence of steric hindrance of the α-substituent to the formation of the pseudo-ring in the case of the trans alcohol vs the cis. Oxidation of III and metabolite with aluminum isopropoxide and cyclohexanone in refluxing benzene (3 hr.) gave 20% and 0% yield of I respectively. Under forcing conditions (potassium t-butoxide and benzophenone in refluxing toluene for 3 hr.) III and the metabolite were oxidized to I in yields of 99% and 74%. The conversion of the metabolite to I establishes the link between the C-6 epimers and confirms the structural assignment of the metabolite as IV. The metabolite also was found in the urine of the single dose subjects.

This is the first reported example of metabolic reduction of a morphine related compound to a metabolite with the C-6 isomorphine configuration. Studies are being continued to assess the pharmacological implications of this metabolite.

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7. A sufficient amount of metabolite was not isolated to permit elemental analysis.

8. Bis-(trimethylsilyl)-trifluoroacetamide (10% trimethylchlorosilane) obtained from Regis Chemical Co., Morton Grove, Illinois.

9. The retention times remained unchanged when cochromatographed. Gc analysis of control urine collected prior to drug administration was negative.

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