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ESTIMATION OF THE SYSTEMIC AVAILABILITY AND OTHER PHARMACOKINETIC PARAMETERS OF NALTREXONE IN MAN AFTER ACUTE AND CHRONIC ORAL ADMINISTRATION

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Abstract

First pass metabolism, metabolic clearance, volume of distribution and steady state plasma levels were estimated in man following acute and chronic 100 mg oral doses of naltrexone. Essentially no statistical difference was observed in these values between the acute and chronic physiologic state. The values for the first pass effect were 79.6 ± 4.6% and 78.0 ± 3.0% for acute and chronic treatment respectively. From our pharmacokinetic data an apparent chronic release rate (ACRR) for a sustained release preparation of naltrexone was calculated as 11.8 µg/kg/hr. In practice a release rate of one half the ACRR should be sufficient to provide continuous antagonism of 25 mg i.v. heroin. In conclusion our data clearly indicate that naltrexone is an effective and safe narcotic antagonist in man.

Introduction

Studies of orally and intravenously administered naloxone to man (Fishman, et al., 1973) and rats (Weinstein, et al., 1973) suggested the existence of a large first pass metabolism after oral administration. More recently, Verebey et al. (1976) reported urinary, fecal, and plasma levels of naltrexone, the N-cyclopropylmethyl congener of naloxone, in man after single and multiple 100 mg oral doses of maltrexone. This study suggests that the pharmacokinetics of naltrexone in man can be explained by a two compartment open model, and that naltrexone was subject to a large first pass metabolism as suspected by Cone et al. (1974). The extent of the first pass effect (1-f) can be estimated by using either the blood flow model of Gibaldi et al. (1971), which assumes virtually complete liver metabolism, or by a more generalized form of the blood flow model (Vaughan, 1975) which includes both renal excretion and hepatic metabolism. We chose the latter method because the investigations of

Verebey et al. (1976) demonstrated that naltrexone does undergo hepatic metabolism and renal excretion. In this communication we report in addition to the first pass metabolism, the metabolic clearance, the volume of distribution and the steady state plasma levels for naltrexone in man after acute and chronic administration.

Methods

The clinical study protocol for naltrexone administration, sample collection, and analytical techniques were as described previously by Verebey et al. (1976). The total area under the plasma level curve (AUC) was estimated using the trapezoidal rule, while that under the terminal portion of the curve was the concentration of the last sampling time (24 hr) divided by the slope of the slow disposition phase (β) (Stramentinoli et al., 1976). The initial plasma concentration was zero at t=0 for the acute (single dose) case, while for chronic treatment, the initial naltrexone concentration at t=0 was taken as the 24 hr concentration after the last daily dose. The percentage first pass metabolism was calculated from the AUC, as was the metabolic clearance and the apparent volume of distribution. The steady state plasma concentration following multiple dosing was also calculated. The method of Greenblatt et al. (1976) was employed in calculating the metabolic clearance and the steady-state plasma concentration.

Results and Discussion

In Table I appears the pharmacokinetic data on naltrexone in man after acute and chronic oral administration of the drug. Essentially, no statistical differences were observed between the acute and chronic physiologic state for first pass metabolism, metabolic clearance or volume distribution. This might be expected since steady state conditions were achieved immediately after the first dose. The large magnitude of the apparent volumes of distribution suggest that the drug is both intracellularly as well as extracellularly distributed.

Inspection of the Verebey et al. (1976) data revealed, among other things, that:

Table 1 Pharmacokinetics of Naltrexone in Man After Acute and Chronic 100 mg Oral Doses[a]

Subject	First Pass Metabolism[b] (1-f) x 100 [%]		Metabolic Clearance[c] 1/hr		Volume of Distribution[d] 1/kg		Steady State Plasma Level[e] µg/l	
	Acute	Chronic	Acute	Chronic	Acute	Chronic		Chronic
E.M. (61.3 kg)	75.7	80.1	74.0	74.2	18.8	14.1		10.1
B.P. (81.8 kg)	85.5	80.9	84.9	76.6	22.0	14.5		8.4
C.L. (69.1 kg)	76.3	74.7	71.0	70.2	10.8	15.0		12.9
R.J. (75.9 kg)	80.7	76.2	78.2	72.4	12.6	13.1		12.0
$\bar{X}$ ± S.D.	79.6±4.6	78.0±3.0	77.0±6.0	73.4±2.7	16.1±5.2	14.2±0.8		10.9±2.0

a Data from Verebey et al., 1976

b Determined by the method of Vaughan, 1975; hepatic blood flow rate = 1.53 l/min.

c Metabolic clearance = f•D/AUC, where f is the systemic availability, D = the administered dose and AUC = area under the curve.

d Volume of Distribution = f•D/AUC β.

e Steady State Plasma Level = AUC_0^T/T, where T = 24 hr.

(1) the biologic half-lives $t_{\frac{1}{2}}$ (β) of naltrexone was 10.3 hr in the acute, and 9.7 hr in the chronic case; (2) a steady state equilibrium was reached immediately after the first dose; and (3) chronic administration of naltrexone does not result in accumulation of the drug in plasma.

The latter two observations are consistent with the low value of 1.2 calculated for the accumulation ratio $R = (1-e^{-\beta t})^{-1}$. Accumulation of drug was not observed probably because the dosing interval was every two half-lives.

The magnitude of the renal clearance of naltrexone (10-110 mg/min) was such that it had a minimal effect on the calculated first pass effect. By omitting the renal clearance term in the Vaughan (1975) model, the equation reduces to the one described by Gibaldi et al., 1971. To illustrate: the mean ± S.D. chronic systemic availability calculated from the Gibaldi et al., 1971 model was 0.216 ± 0.029, while the Vaughan (1975) model yields 0.220 ± 0.030. Neither model was sensitive to F, the fraction of the oral dose absorbed. In the case of naltrexone, F is unity (Verebey et al., 1976). Repeating the calculation using the mean renal clearance of 0.06 l/min and apparent clearance (Dose/AUC) of 6.0 l/min at F=0.5 (50% absorption) yields only a slightly higher first pass effect of 82.5%

Verebey and Mule' (1975) in their review of naltrexone pharmacology, indicated that a slow sustained release preparation of naltrexone could be employed for the long term treatment of opiate addicts. Verebey et al., 1976 reported that in man a 100 mg dose of naltrexone blocks the euphoric effects of 25 mg i.v. heroin for 48-72 hours after the last chronic dose of naltrexone; the time at which the naltrexone plasma level is about 1.3 µg/l. The value of 1.3 µg/l is approximately 1/10 the chronic steady plasma level. A release rate suitable for such a long term sustained vehicle can be readily estimated from data in Table 1. The apparent chronic release rate (ACRR) is the product of the metabolic clearance times the steady state plasma level. By expressing the release rate in terms of the amount of naltrexone (µg) released per kg body weight per hour, the ACRR becomes 78.0 l/hr x 10.9 µg/l ÷ 72 kg (mean body weight). Thus,

$$\text{ACRR} = 11.8 \text{ µg/kg/hr}$$

Therefore, a sustained release preparation of naltrexone with a release rate of one half the ACRR (6 μg/kg/hr) should be sufficient to provide a continuous antagonism to the agonistic effects of a 25 mg i.v. heroin challenge. Harrigan et al., 1977 reported that continuous naltrexone infusion of 1-20 μg/kg/hr produced effective blockade of morphine self-administration in the monkey. Based on their animal study, they proposed a value of 5 μg/kg/hr as an effective release rate of naltrexone for a human drug delivery system.

In conclusion, it appears that orally administered naltrexone undergoes a large first pass metabolism. It is estimated that only one fourth of the administered dose actually reaches the systemic circulation. However, the drug that becomes bioavailable appears to have a long duration of action as reflected in the effective blockade of heroin challenges for more than 48 hours (Verebey et al., 1976). The contribution of the major metabolite beta-naltrexol to the pharmacologic effects of the drug can not all together be excluded since there is evidence of the metabolite's narcotic antagonistic activity in man (Verebey, et al., 1976) and in other species (Fujimoto et al., 1975). From our pharmacokinetic data a release rate of 6 μg/kg/hr is suggested as suitable for a sustained release preparation of naltrexone in man.

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