Duration of Occupancy of Opiate Receptors by Naltrexone

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To determine the duration of blockade of mu-opiate receptors by naltrexone, we measured the binding of [^{11}C]carfentanil in the brain of five normal volunteers with a positron radiation detection system before and 1, 48, 72, 120, and 168 hr after naltrexone administration. The half-time of blockade by naltrexone in the brain ranged from 72 to 108 hr which is greater than the fast plasma clearance components (4–12 hr) of naltrexone or its metabolite, beta-naltrexol, but corresponds well to the half-time of the terminal phase of plasma naltrexone clearance (96 hr). These results are consistent with the duration of the pharmacologic effects of naltrexone in response to heroin administration and indicate that 50 mg/day of oral naltrexone results in plasma levels in excess of that needed to saturate opiate receptors. This is the first example of the use of a simple dual-detector system with positron-emitting radioactive drugs to provide information regarding the duration of action of the drug on its specific receptor site. The plasma clearance half-time of a drug may not give an accurate reflection of the duration of action of the drug on a specific neuroreceptor site. Direct measurement of drug effects on recognition sites greatly extend current studies of pharmacokinetics.

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Naltrexone is an orally administered opiate receptor antagonist used in the treatment of opioid dependence (*1,2*). The drug has a longer duration of action than naloxone, which is used to treat acute overdosage of opiates. The apparent plasma half-time of naltrexone is ~4 hr, while that of its major active metabolite, beta-naltrexol is 12 hr after oral dose (*3*). Using a recently developed simple dual detector system for measuring the rate of accumulation of the radioactive narcotic, carbon-11 (^{11}C) carfentanil (*4*), we have assessed the degree of duration of occupancy of mu- opiate receptors in the brain of normal human volunteers after a single oral dose of naltrexone.

METHODS

Nine healthy volunteers (seven men and two women), without evidence of medical or psychological disorders on the basis of examination and taking no medications, were studied after giving written informed consent. They were injected with 200 to 400 μCi (0.1 to 0.6 μg) of [^{11}C]carfentanil (*5*) in a control study, and/or 1, 48, 72, 120, and 168 hr after the oral administration of 50 mg of naltrexone. Three of them were also studied after intravenous injection of 1 mg/kg body weight of naloxone (Table 1). At each time, the rate of accumulation of the [^{11}C]carfentanil in the brain was measured for 60 min after injection of the radiotracer by means of a dual-probe positron radiation detection system described previously (*4*). The detectors were positioned to include within the field-of-view the caudate nucleus, thalamus and cerebral cortex, based on landmarks obtained from a lateral skull x-ray (*6*). Corrections were made for random coincidences, system deadtime and radioactive decay of ^{11}C (*4*). The time-activity curves were normalized by being multiplied by subject's body weight and divided by injected dose of the tracer to compare each study.

From the normalized time-activity curves, three parameters were derived as follows.

1. The "slope index" was defined as the slope of the normalized time/activity curves between 5 and 15 min after injection, calculated by linear regression analysis.
2. The "clearance half-time" was defined as the time taken for the activity to decrease to half of the peak activity.
3. The "percentage blockade" was defined as follows. The normalized activity within the brain averaged for the period between 40 and 60 min after injection of [^{11}C]carfentanil was

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TABLE 1
Summary of Subjects Participating in the Current Study

Subject no.	Sex	Age (yr)	Control	Naltrexone (50 mg p.o.) 1 hr	48 hr	72 hr	120 hr	168 hr	Naloxone (1 mg/kg i.v.) 5 min
1*	M	31	+						+
2*	M	25	+						+
38*	F	18	+	+					
39	F	39	+	+	+	+	+		
41*	M	22	+	+					
42	M	44	+	+	+		+	+	
43	M	36	+	+	+		+	+	+
44	M	29	+	+		+	+	+	
45	M	29	+	+		+	+	+	

* The subject's data were not used for the analysis of percentage blockade of opiate receptors by naltrexone because of inadequate studies.

called "mean normalized activity." In the control studies, this represented the binding of the tracer to opiate receptors in the unblocked state. After administration of naloxone, which blocks at least 90% of the receptors (*7*), the mean normalized activity represented primarily the nonspecific binding of the tracer. At each of the times after administration of naltexone, the measured mean normalized activity was compared to that in the unblocked and naloxone-blocked state. In this way, the "percentage blockade" by naltrexone was determined at the various times after administration.

RESULTS

Table 2 summarizes the results of all studies. The six normalized time-activity curves from the control studies and the five different times after oral naltrexone are shown in Figure 1. The curves are indistinguishable for the first 5 min after injection, reflecting delivery of the tracer to the brain. In the control studies, the half-time of clearance from peak values averaged 55 min. The

TABLE 2
Summary of Three Parameters

Time after oral naltrexone	Slope index (5–15 min)	T-½ (min)	Percentage blockade by naltrexone
1 hr (N = 7)	−1.40 ± 0.18	18 ± 1.7	
48 hr (N = 3)	−1.20 ± 0.13	24 ± 2.1	91 ± 6.4
72 hr (N = 3)	−0.87 ± 0.31	33 ± 6.7	80 ± 6.3
120 hr (N = 5)	−0.64 ± 0.15	47 ± 5.3	46 ± 7.4
168 hr (N = 4)	−0.51 ± 0.15	53 ± 6.8	30 ± 13.8
Control (N = 8)	−0.55±0.11	55 ± 5.1	
Naloxone (N = 3)	−1.20±0.15	17 ± 2.5	

The studies were done before and 1, 48, 72, 120, and 168 hr after oral administration of 50 mg of naltrexone, and 5 min after intravenous injection of 1 mg/kg of naloxone. The values are expressed as mean and 1 s.e.m.

The slope index is the slope of the normalized time-activity curve between 5 and 15 min after injection of [^{11}C]carfentanil, determined by linear regression analysis.

T-½: The clearance half-time (minutes) is the time taken for the activity to decrease the half of the peak value after injection of [^{11}C] carfentanil.

The percentage blockade by naltrexone was obtained from the following equation:

$$\text{Percentage blockade by naltrexone} = \frac{T - B}{T - NS} \times 100$$

where T is the mean normalized activity in the control study, NS is that at 1 hr after administration of naltrexone, and B is that at 48, 72, 120, or 168 hr after administration of naltrexone.

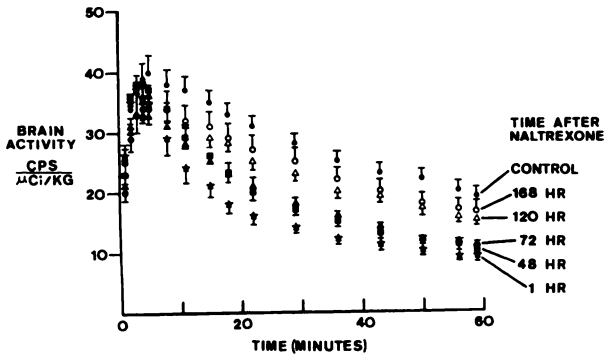

FIGURE 1
The normalized time-activity curves in control studies and 1, 48, 72, 120, and 168 hr after oral administration of 50 mg of naltrexone. Each point shows mean and 1 s.e.m. The activity was normalized to the injected dose and subject's body weight.

lowest curve was obtained 1 hr after the oral dose of naltrexone and was taken to represent maximum blockade by naltrexone. The curves obtained in seven studies when the tracer was injected 1 hr after oral naltrexone were not significantly different from the curves obtained in three studies after intravenous injection of naloxone. The results are illustrated in Figure 2. The slope index and the clearance half-time also showed no significant difference between the studies one hour after oral naltrexone in seven subjects and those 5 min after intravenous injection of naloxone in three subjects (unpaired t-test) (Table 2).

The normalized time-activity curves in the studies performed 48, 72, 120, and 168 hr after administration of 50 mg of oral naltrexone fell between the control and maximally-blocked state (Figure 1).

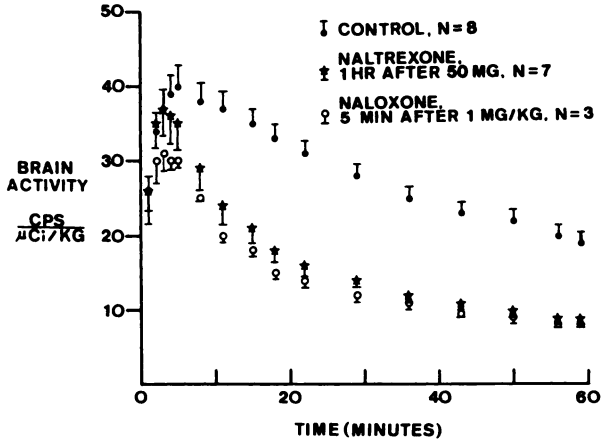

FIGURE 2
The normalized time-activity curves in control studies, at 1 hr after administration of naltrexone and 5 min after injection of naloxone. Each point shows mean and 1 s.e.m. The similarity between the curve at 1 hr after the naltrexone dose and that at 5 min after the naloxone dose is readily noticed.

Semilogarithmic graphs of the slope index and the clearance half-time at various times after administration of naltrexone are shown in Figure 3. The slope index decreases linearly with time, while the clearance half-time increased linearly. Monoexponential regression analysis yielded the equations and correlation coefficients shown in Figure 3.

The half-time for the return of the slope index to the unblocked state averaged 108 hr; the half-time of return of the clearance half-time to the unblocked state averaged 102 hr.

The percentage blockade by naltrexone at 48, 72, 120, and 168 hr after administration of naltrexone in the five subjects were 91, 80, 46, and 30%, respectively, as shown in Table 2. A semilogarithmic graph of the percentage blockade is shown in Figure 4. The percentage blockade by the single oral dose of naltrexone decreased monoexponentially with an average half-time of 72 hr.

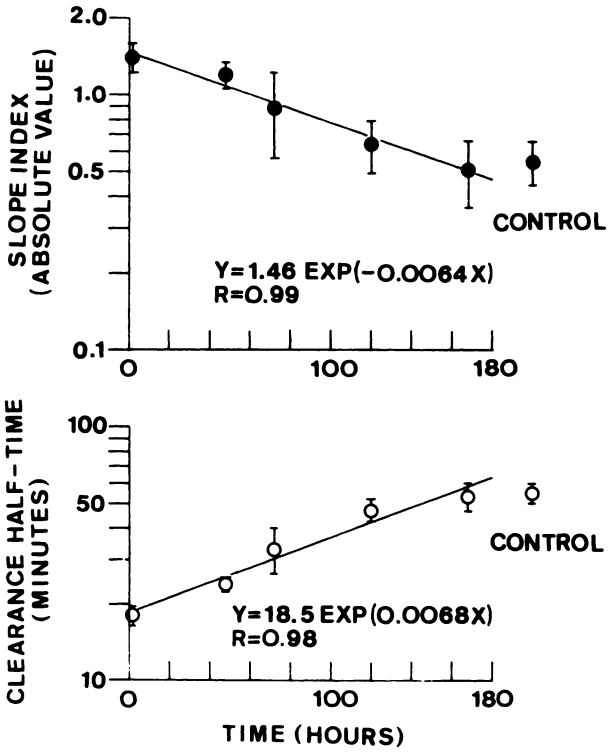

FIGURE 3
Semilogarithmic plots of the slope index (top) and the clearance half-time (bottom) as function of time at 1, 48, 72, 120, and 168 hr after administration of naltrexone. The values in control studies were put outside the coordinates as a reference. Each point shows mean and 1 s.e.m. The regresssion analysis shown both for the slope index and the clearance half-time had a good monoexponential correlation to the time after administration of naltrexone with correlation coefficients of 0.99 and 0.98, respectively. The half-times for return to the unblocked state in the slope index and the clearance half-time were 108 and 102 hr, respectively.

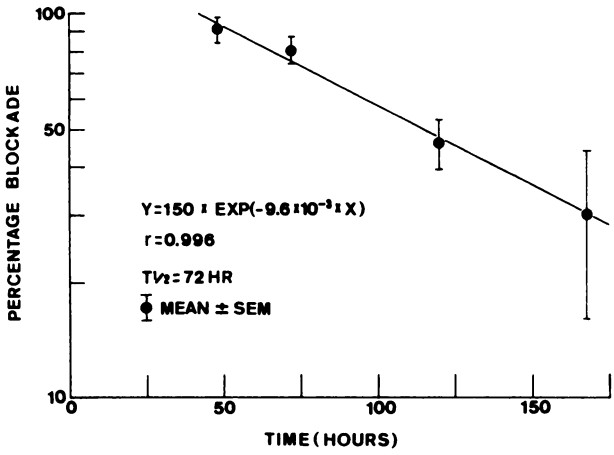

FIGURE 4
Semilogarithmic plot of the percentage blockade of opiate receptors by naltrexone as function of time at 48, 72, 120, and 168 hr after administration of naltrexone. Each point shows mean and 1 s.e.m. With regression analysis, naltrexone bound to opiate receptors was eliminated monoexponentially with a correlation coefficient of 0.996 and an average half-time of 72 hr.

DISCUSSION

Based upon three methods for quantifying changes in mu-opiate receptor occupancy, we estimated the effective half-time for return to baseline opiate receptor occupancy after 50 mg of oral naltrexone to be 72 to 108 hr. This half-time is much longer than the first or second component of the plasma clearance for naltrexone and its major active metabolite, betanaltrexol, which range from 1 to 10 hr, and from 8 to 19 hr, respectively (*3,8–10*). The study illustrates how misleading plasma clearance half-times can be in estimating the duration of action of a drug on a receptor site. Such information is helpful in establishing the effective dose of a drug and the frequency with which it is administered. The information obtained can help decrease side effects of drugs by making it possible to tailor the administered dose to its effect on the site of action.

Verebey et al. (*8*) reported that in addition to the two initial components of naltrexone clearance, there is a third phase with an estimated plasma clearance half-time of 96 hr. Verebey found that inhibition of the physiologic and subjective effects of heroin in human volunteers persists for 72 hr after 100 mg of oral naltrexone, and concluded that 2.4 ng/ml of plasma naltrexone was high enough to completely antagonize the effects of 25 mg of heroin 48 hr after 100 mg of oral naltrexone.

The duration of receptor occupancy by naltrexone measured with [^{11}C]carfentanil was similar to the duration of the pharmacologic effects of naltrexone measured by a heroin challenge, and correlated well with the long half-time of the terminal phase of the plasma clearance of naltrexone (96 hr). These results indicate that 50 mg of oral naltrexone results in plasma levels of naltrexone and beta-naltrexol far greater than that needed to totally occupy opiate receptors. The half-time of the third plasma component (96 hr) which was observed after plasma levels had fallen to 2.4 ng/ml, corresponds to the half-time for reappearance of unoccupied opiate receptors (72 to 108 hr). Doses lower than the recommended 50 mg/day of oral naltrexone should result in complete occupancy of opiate receptors, and perhaps be associated with fewer side effects.

The method used in the present study illustrates that for the solution of some problems, it is not necessary to use a PET scanner. Some problems such as the effect of naltrexone on opiate receptors can be assessed with this simple approach. The study illustrates that for many purposes, imaging is not required to solve biomedical problems using positron-emitting tracers. The new device is ideally suited to measure the effects of drugs on brain chemistry in living human beings (*11, 12*). The cost and administered radioactive tracer dose is much less than that required in PET scanning. Because of the reduced amount of tracer that need be injected, the radiation to the patient is correspondingly low, and multiple studies in the same person can be performed.

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