Narcotic Antagonists:

Naltrexone Pharmacochemistry and Sustained-Release Preparations

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Pharmacokinetic Quantitation of Naltrexone Release From Several Sustained-Release Delivery Systems

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A method designed to quantitate in vivo naltrexone release rates from sustained-release systems has been applied to the evaluation of seven different naltrexone delivery systems in the monkey. The method consists of two phases: a single intravenous bolus dose quantitation of each monkey's pharmacokinetic parameters coupled with a delivery system study in which plasma naltrexone levels are measured throughout the time period of sustained-release. In vivo release rates and the total amount released are then calculated. It should be noted that these determinations require the analysis of unchanged naltrexone in plasma as the only experimental measurement. Data from injectable naltrexone pamoate microcapsule delivery systems indicate that 1) when these microcapsules are suspended in an aqueous vehicle, a significant part of the dose is released very rapidly, yielding release rate-time data that parallel a non-sustained-release control; 2) this rapid release for the aqueous vehicle is followed by a slow release phase lasting to about 24 days for the subcutaneous route and to about 45 days for the intramuscular route; and 3) when these microcapsules are suspended in an oily vehicle there is no initial rapid release, substantial release rates are obtained for at least 60 days, and an average of 89% of the dose is calculated to have been released. Data from implantable naltrexone delivery systems show that 1) the Alza system most closely ap-

proximates a zero-order release rate-time profile; 2) the Battelle system provides a rapid initial release followed by a slowly declining release rate; 3) the Dynatech system is characterized by a more rapid initial release rate of 3-8% of the dose per day over the first 3-5 days followed by a rather constant 1-3% per day to about day 36; and 4) essentially complete recovery of the dose was obtained for the Battelle and Dynatech systems.

INTRODUCTION

The rationale for developing sustained-release narcotic antagonist delivery systems for treatment of opiate addiction has recently been reviewed (1,2). One phase of a scheme for evaluating these systems consists of a pharmacokinetic quantitation of drug release rates *in vivo* (2). The methodology that has been developed for quantitating naltrexone release in monkeys is characterized by two phases: 1) calibration of the pharmacokinetics of each individual monkey from plasma level-time data obtained after an intravenous bolus dose of naltrexone, and 2) measurement of plasma levels of unchanged naltrexone over the time period that the sustained-release system yields measurable concentrations. Data from 1) and 2) above permit calculation of an *in vivo* release rate-time profile as well as the total amount of naltrexone released during the study.

The purpose of this report is to summarize the naltrexone release data for those delivery systems that have been evaluated pharmacokinetically in the monkey. In order to obtain an overview it was necessary to average the release rate data obtained from the several monkeys utilized in evaluating each delivery system. Also, data related to the calibration of each monkey's pharmacokinetic parameters has been omitted. Both types of data for individual monkeys will be included in subsequent manuscripts.

EXPERIMENTAL

Delivery Systems

The following seven delivery systems have been evaluated:

I. Naltrexone in a physical blend with 90% (L+)lactic acid-10% glycolic acid copolymer, spherical beads 1.5 mm in diameter, subcutaneous, Dynatech #24086;

II. Naltrexone pamoate-poly(lactic acid) microcapsules suspended in 2% aluminum monostearate-peanut oil and injected intramuscularly, Thies #GL-1-6-76-1;

III. Naltrexone pamoate-poly(lactic acid) microcapsules suspended in a medium consisting of water, 2% Tween 20, 0.02% anti-foam silicone and 1:10,000 phemerol and injected intramuscularly, Thies #GL-1-6-75-1;

IV. Naltrexone pamoate-poly(lactic acid) microcapsules suspended in an aqueous medium of 0.1% Tween 80 in Macrodex (6% dextran 70 in 5% dextrose/water for injection) and injected subcutaneously, Thies #GL-3-9-77-3;

V. Micronized naltrexone pamoate (batch #2M1869-866-16) suspended in 2% aluminum monostearate-peanut oil and injected intramuscularly;

VI. Rods-naltrexone and hydrophobic polymer, Chronomer, Alza, subcutaneous;

VII. Naltrexone 33% in a dipalmitin (75%) - tripalmitin (25%) mixture, shaped into rods and administered subcutaneously (Battelle).

These sustained release systems will be referred to by the numerical designation throughout the text. Additional data concerning these delivery systems has been provided by the developers (2,3). All are intended to be bio- degradable, with systems I, VI and VII designed for subcutaneous implant and systems II, III and IV designed for injection. System V was included as a non-sustained-release control.

Experiments in Monkeys

Each delivery system was administered to 3 or 4 monkeys at a dose of approximately 10 mg/kg. With the exception of delivery system VII, these were self-administrating monkeys and were on a rotating schedule of morphine, methamphetamine and saline self-injection. Effects of the naltrexone delivery system on morphine self-administration were measured as described previously (4) and will be reported separately. Blood samples were obtained, usually from a femoral vein, at periodic intervals up to 60 days after administration of the sustained release system.

At least several days were allowed to elapse after the delivery system either was removed or ceased releasing measurable amounts of naltrexone. Subsequently, a single intravenous bolus dose of naltrexone (3-5 mg/kg) was administered and periodic blood samples were obtained for a sufficient time so that the pertinent pharmacokinetic parameters of naltrexone could be determined from the plasma level-time profile.

DISCUSSION

Injectable Systems

The *in vivo* release rate data for the injectable naltrexone delivery systems are presented in fig. 1. Systems II, III and IV differ mainly in the vehicle used to suspend the microcapsules and in the route of injection. System V is a non-sustained-release control formulation included for comparative purposes. Comparison of the curve for sustained release system II (microcapsules suspended in the oily vehicle and administered intramuscularly) with the curve for the control formulation, system V (*micronized* naltrexone pamoate suspended in the oily vehicle and administered intramuscularly), permits the conclusion that the microcapsule coating is responsible for the pronounced sustained release effect with system II.

Assay for Naltrexone

A sensitive and specific assay for naltrexone concentrations in plasma has been described previously (5,6,7). The pharmacokinetic calculation of *in vivo* release rates is dependent on an assay that is specific for unchanged naltrexone and this specificity has been demonstrated with respect to the known metabolites of naltrexone (7).

Calculation of Release Rates

Release rates were calculated according to the Loo-Riegelman method (8). Either a two- or a three-compartment, open pharmacokinetic model was used to fit the plasma level-time data for the intravenous bolus dose of naltrexone in each monkey (9). The three-compartment model was utilized when needed to obtain a good overall fit to the data. The pharmacokinetic parameters for naltrexone, obtained from the intravenous bolus dose, were then utilized to calculate naltrexone release rates from the plasma naltrexone level-time data obtained in the delivery system study (8). The total amount released over the entire time period was subsequently determined according to an equation presented previously (10).

RESULTS

The data for naltrexone concentration in plasma as a function of time after administration are summarized in table 1 for each of the seven delivery systems tested. Levels of about 0.25-0.5 ng/ml are needed to block morphine self-administration in these monkeys (11). Since this range is also the approximate sensitivity limit of

TABLE 1. Naltrexone Concentration in Plasma During the Time Period in Which the Monkey was Administered a Naltrexone Sustained Release Delivery System

Time (day)	Mean Concentration of Naltrexone in Plasma (ng/ml)[a]						
	I	II	III[b]	IV	V	VI	VII[b]
0.125	—	—	—	—	—	—	5.55(1.31)
0.25	—	—	—	—	—	—	5.19(0.41)
0.29	4.11(0.87)	—	—	23.95(6.31)	—	4.57(2.54)	—
0.33	—	0.79(0.10)	13.87(5.39)	—	99.7(41.4)[b]	—	—
0.5	—	—	—	—	—	—	5.07(2.50)
1	4.69(4.90)	0.58(0.12)	4.40(2.03)	14.04(6.02)	44.55(13.66)	2.41(0.77)	3.19(1.03)
2	—	0.44(0.07)	—	—	10.63(7.97)	—	2.55(0.65)
3	8.08(5.36)	0.99(0.19)	1.12(0.21)	7.90(2.65)	3.12(2.46)	2.31(0.78)	—
4	—	2.45(0.69)[b,e]	—	—	1.70(1.32)	—	—
5	2.64(0.42)	2.13(0.75)	0.65(0.25)	2.60(1.07)	0.70(0.84)	3.57(2.31)	—
6	—	1.58(0.56)	—	—	—	—	—
7	2.14(0.43)	2.16(0.61)	0.55(0.18)	1.26(0.63)	0.11(0.23)	3.71(1.45)	2.06(0.43)
9	2.50(0.37)	—	0.92(0.26)	1.19(0.30)	[g]	3.84(1.64)	—
11	—	3.02(0.68)	—	—	—	—	—
12	2.07(0.24)	—	1.17(0.32)	0.57(0.04)[c]	[g]	—	—
13	—	—	—	—	—	5.80(4.0)	—
14	2.16(0.19)	2.87(0.51)	—	—	—	—	1.38(0.38)
15	—	—	1.47(0.72)	0.66(0.21)	—	—	—
16	—	—	—	—	—	4.66(1.58)	—
18	—	1.93(0.46)	—	—	—	—	—
19	1.96(0.10)	—	1.52(0.70)	—	—	—	—
20	—	—	—	0.56(0.38)	—	2.25(1.98)	—
21	—	2.24(0.71)	—	—	—	—	1.46(0.36)
22	—	—	1.23(0.50)	0.35(0.40)	—	—	—

23	1.88(0.096)	—	—	—	—	0.36(0.30)	—
25	—	1.72(0.56)	—	—	—	—	—
26	—	—	1.01(0.27)	0.28(0.33)	—	—	—
28	—	1.40(0.45)	—	—	—	—	0.80(0.18)
29	1.33(0.085)	—	0.83(0.28)	0.13(0.27)	—	—	—
30	—	—	—	—	—	0.06(0.1)[b]	—
32	—	1.37(0.26)	—	—	—	—	—
33	—	—	0.84(0.68)	0.14(0.28)	—	—	—
35	—	—	—	—	—	—	0.79(0.45)
36	0.48[d,f]	—	0.65(0.46)	0.13(0.27)	—	—	—
37	—	—	—	—	—	0.21(0.24)	—
40	—	—	0.56(0.38)	[g]	—	—	—
41	—	0.82(0.20)[b,f]	—	—	—	—	—
42	—	—	—	—	—	—	0.08(0.14)
43	1.39(0.028)[c,f]	—	0.23(0.23)	[g]	—	—	—
47	—	0.58(0.21)[c,f]	0.20(0.18)	[g]	—	—	—
50	[g]	—	0.36(0.35)	[g]	—	—	—
54	—	—	0.11(0.18)	—	—	—	—
56	—	0.60(0.21)[b,f]	—	—	—	—	—
57	—	—	—	[g]	—	—	—
64	—	0.64(0.39)	—	—	—	—	—

[a]Mean of 4 animals unless indicated otherwise. Standard deviation in parenthesis. Delivery systems are identified in the text and in Table 3.

[b]Mean of 3 animals.

[c]Mean of 2 animals.

[d]Only one value available.

[e]Sample(s) lost due to breakage.

[f]Sample(s) omitted due to apparent assay interference. Values of the omitted samples were at least 5-fold greater than corresponding values in other animals.

[g]Below detectable limits.

the assay, "measurable" levels can be considered to be "effective" levels in these monkeys. The corresponding average naltrexone release rates for the seven systems are shown in table 2 and in figures 1 and 2. Table 3 contains data summarizing the results of a comparison of the dose administered with the calculated amount of naltrexone released and, when available, the amount of naltrexone recovered from the delivery system after removal from the monkey.

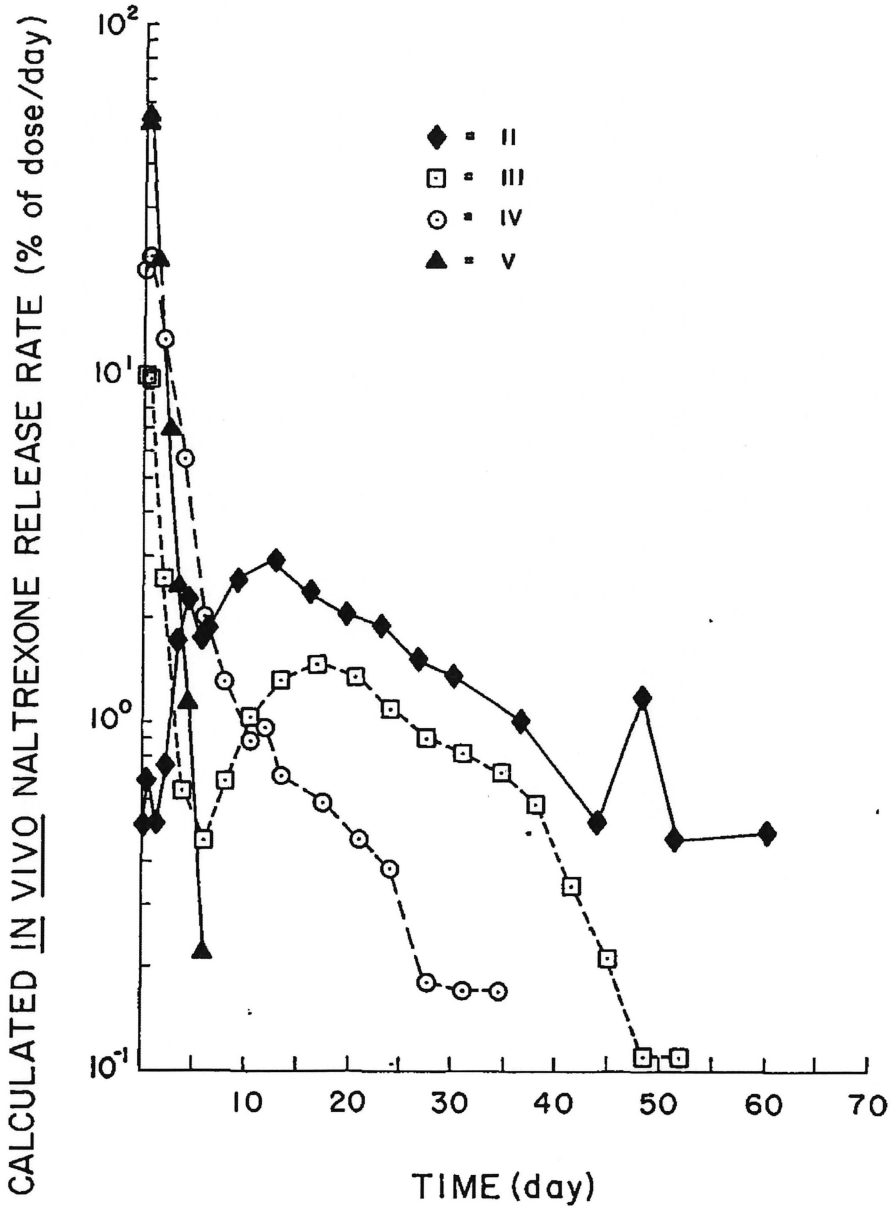

FIGURE 1. Semilog plot of naltrexone *in vivo* release rate as a function of time for injectable sustained release delivery systems II, III, IV and V. Delivery systems are identified in the text and in table 3. Closed symbols represent an oil vehicle and open symbols an aqueous vehicle.

The influence of the vehicle used to suspend the microcapsules on release of naltrexone can also be observed in fig. 1. A comparison of system III (microcapsules suspended in an aqueous vehicle and administered intramuscularly) with system II suggests that the influence of the vehicle occurs mainly over the first 15 days after administration. Subsequently, the release rate declines in approximately parallel exponential fashion for the two systems. During the first 4-6 days after administration, system III has a release rate-time profile that parallels the exponential decline of release rate for the non-sustained-release control. This rapid and extensive decline in release rate (note the logarithmic y-axis in fig. 1) suggests that a very significant fraction of the naltrexone in delivery system III was available for rapid release. A similar early rapid release can also be observed for system IV (microcapsules suspended in an aqueous vehicle and administered subcutaneously). A comparison of aqueous microcapsule suspension systems III and IV (fig. 1) suggests that the intramuscular route (III) yielded much higher release rates than the subcutaneous (IV) from 10-50 days after administration. Delivery system IV provides the smallest degree of sustained release of any of these microencapsulated naltrexone pamoate systems. On the other hand, system II provides a significant release rate for a period of 60 days. Although the release was not zero order, the rates were within a fairly narrow range (fig. 1). In addition, it appears that the oil vehicle "protects" the naltrexone pamoate microcapsules from whatever causes the rapid initial burst of release with the aqueous vehicle.

The calculated total extent of naltrexone release from each delivery system is compared with the dose administered in table 3. Systems III and IV yielded an incomplete recovery of the administered dose whereas the average recovery for system II was 89% of the dose. The microcapsule delivery systems (II, III and IV) were characterized by a high degree of variability in the extent of recovery of the administered dose (table 3). Part of the reason for the greater variability observed for the microcapsule systems, compared to the other delivery systems, may be the difficulty in administering an accurate dose of the microcapsule suspension (especially for the aqueous systems). Alternatively, the release of naltrexone may be more variable with these delivery systems. Unfortunately, the nature of these microcapsule delivery systems precluded the possibility of removing the microcapsules remaining at the end of the sustained release study. Therefore, the unabsorbed naltrexone could not be assayed directly.

TABLE 2. Mean Calculated Release Rates as a Function of Time After Administration for the Various Naltrexone Delivery Systems[a]

I[b]		II		III[b]		IV		V[b,e]		VI		VII[b]	
Time (day)	%/day	Time (day)	%/day	Time (day)	%/day	Time (day)	%/day	Time (day)	%/day	Time (day)	%/day	Time (day)	%/day
0.15	2.71(0.90)	0.16	0.50(0.17)	0.16	9.84(4.64)	0.15	19.6(7.82)	0.16	51.9(14.8)	0.15	2.51(1.31)	0.06	5.17(1.11)
0.64	5.28(4.43)	0.66	0.68(0.21)	0.66	9.70(4.44)	0.64	21.5(9.19)	0.66	54.5(3.16)	0.64	2.77(1.12)	0.19	5.54(0.72)
2.0	7.14(1.03)	1.5	0.51(0.19)	2.0	2.58(1.02)	2.0	12.4(4.06)	1.5	21.2(10.6)	2.0	1.93(0.54)	0.37	5.13(1.97)
4.0	5.24(2.36)	2.5	0.75(0.26)	4.0	0.64(0.23)	4.0	5.68(2.13)	2.5	6.86(5.70)	4.0	2.39(1.06)	0.75	3.92(1.44)
6.0	2.25(0.40)	3.5	1.68(0.46)[b]	6.0	0.46(0.22)	6.0	2.01(0.45)	3.5	2.50(1.63)	6.0	2.91(1.26)	1.5	2.82(0.95)
8.0	2.22(0.64)	4.5	2.24(0.39)[b]	8.0	0.68(0.13)	8.0	1.31(0.27)	4.5	1.14(0.99)	8.0	3.04(1.07)	4.5	2.28(0.25)
10.5	2.24(0.50)	5.5	1.74(0.43)	10.5	1.03(0.13)	10.5	0.88(0.02)[c]	6.0	0.22(0.38	11.0	4.06(1.60)	10.5	1.69(0.32)
13.0	2.16(0.48)	6.5	1.84(0.58)	13.5	1.31(0.48)	12.0	0.96(0.08)[c]			14.5	4.36(2.28)	17.5	1.41(0.29)
16.5	2.07(0.39)	9.0	2.56(0.83)	17.0	1.47(0.65)	13.5	0.70(0.11)[c]			18.0	2.78(1.39)	24.5	1.11(0.26)
21.0	1.89(0.21)	12.5	2.89(0.89)	20.5	1.34(0.55)	17.5	0.59(0.41)			21.5	0.92(0.90)	31.5	0.78(0.29)
26.0	1.58(0.22)	16.0	2.33(0.65)	24.0	1.09(0.37)	21.0	0.46(0.53)			26.5	0.13(0.15)	38.5	0.09(0.16)
32.5	1.09[d]	19.5	2.04(0.69)	27.5	0.90(0.32)	24.0	0.38(0.45)			33.5	0.08(0.14)[b]		
36.0	1.24[d]	23.0	1.91(0.64)	31.0	0.81(0.47)	27.5	0.18(0.36)						
		26.5	1.51(0.52)	34.5	0.72(0.52)	31.0	0.17(0.34)						
		30.0	1.35(0.43)	38.0	0.58(0.38)	34.5	0.17(0.34)						
		36.5	1.01(0.27)	41.5	0.34(0.32)								
		44.0	0.52(0.08)[c]	45.0	0.21(0.19)								
		48.0	1.18(0.39)[c]	48.5	0.11(0.20)								
		51.5	0.46(0.11)[c]	52.0	0.11(0.19)								
		60.0	0.48(0.15)[b]										

[a]Mean of 4 animals unless indicated otherwise. Standard deviation in parenthesis. Delivery systems are identified in text and in Table 3.

[b]Mean of 3 animals.

[c]Mean of 2 animals.

[d]Only one value available.

[e]One monkey was omitted from the data analysis because one early sample had an unusually high naltrexone concentration that resulted in an erroneously high recovery value.

TABLE 3. Comparison of the Naltrexone Dose Administered in Sustained Release Form with the Amount of Naltrexone Accounted for Experimentally in the Monkey

Delivery system[a]	Mean amount naltrexone administered (mg)	Mean calculated amount naltrexone released (mg)	Mean assayed amount remaining in delivery system (mg)	Percent of administered dose accounted for[b]
I	42.1[c]	38.9[c]	0.0023[c]	92(91–94)[c]
II	35.3	31.6	—	89(58–116)
III	36.3	18.3	—	53(30–74)[d]
IV	26.2	19.5	—	76(48–91)
V	37.8	32.4	—	86(78–100)[e]
VI	44.0	30.0	—	68(56–87)
VII	30.7	16.4	16.4[f]	107(92–120)[d]

[a]Delivery system identification: I = naltrexone in a physical blend with 90% (L+) lactic acid-10% glycolic acid copolymer, spherical beads 1.5 mm in diameter, subcutaneous, Dynatech #24086; II = naltrexone pamoate-poly(lactic acid) microcapsules suspended in 2% aluminum monostearate-peanut oil and injected intramuscularly, Thies #GL-1-6-76-1; III = naltrexone pamoate-poly(lactic acid) microcapsules suspended in a medium consisting of water, 2% Tween 20, 0.02% anti-foam silicone and 1:10,000 phemerol and injected intramuscularly (Thies #GL-1-6-75-1); IV = naltrexone pamoate-poly(lactic acid) microcapsules suspended in an aqueous medium of 0.1% Tween 80 in Macrodex (6% dextran 70 in 5% dextrose/water for injection) and injected subcutaneously (Thies #GL-3-9-77-3); V = micronized naltrexone pamoate (batch #2M-1869-866-16) suspended in 2% aluminum monostearate-peanut oil and injected intramuscularly; VI = rods containing naltrexone supplied by Alza and administered subcutaneously; VII = naltrexone 33% in a dipalmitin (75%)-tripalmitin (25%) mixture shaped in rods and administered subcutaneously (Battelle).

[b]Mean of 4 animals, unless stated otherwise. Range in parenthesis.

[c]Mean of 2 values. One animal became ill during the study and another had a sufficient number of plasma samples with assay interference that a quantitation of total amount released could not be made.

[d]Mean of 3 animals.

[e]Mean of 3 animals. One animal omitted because of a 163% recovery due to one high data point and an insufficient number of other data points to obtain an accurate estimate of the amount released.

[f]The rods removed from each monkey were weighed, dissolved in chloroform, and assayed spectrophotometrically for naltrexone at 282 nm.

Subcutaneous Implants

The release rate-time profiles for the subcutaneous implant delivery systems are shown in fig. 2. System I (Dynatech) is characterized by a more rapid release over the first 6 days followed by a very constant rate of naltrexone release throughout the remainder of the study. System VI (Alza) yielded a release rate-time profile

that was closer to being constant over the entire release period than any of the other systems. However, this system also was the shortest of the three in terms of duration. Delivery system VII (Battelle) is characterized by a rapid initial rate of release followed by a slowly declining rate from day 2 to about day 38. Overall, system I provides the longest duration of meaningful release rates of naltrexone. The "initial burst" of release with this delivery system is larger than that observed with the other two implantable systems (fig. 2) but much smaller than that for the aqueous injectable systems (compare fig. 2 with fig. 1, noting the logarithmic ordinate in fig. 1).

The possibility of removal of the implanted delivery systems at termination of the sustained release study permits a more rigorous "mass balance" comparison of naltrexone dose with the sum of the calculated amount released plus the amount remaining in the delivery system. Such a comparison was carried out with systems I and VII (table 3). Assay of the removed delivery system for naltrexone content yielded negligible amounts in system I. However, about

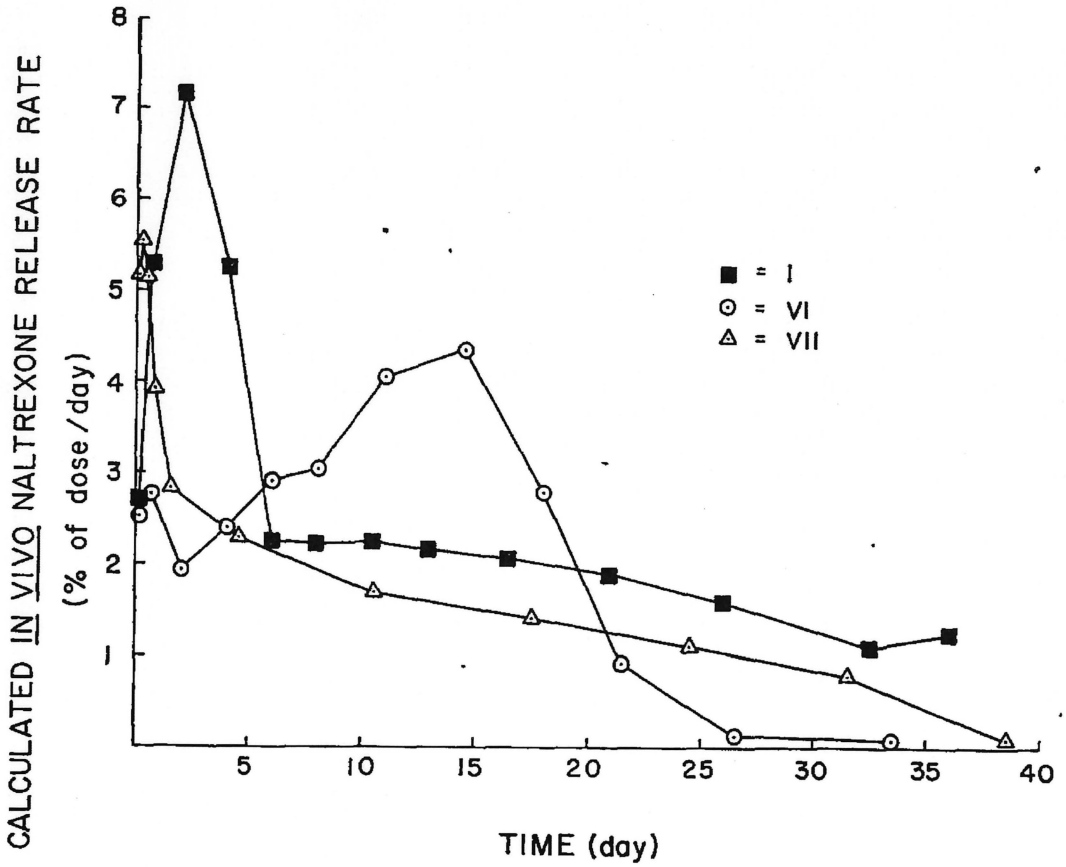

FIGURE 2. Linear plot of naltrexone *in vivo* release rate as a function of time for implantable sustained release delivery systems I, VI and VII. Delivery systems are identified in the text and in table 3.

half the dose remained in system VII at termination of the study. Data from both of these delivery systems provided an essentially complete accounting of the fate of the administered dose, as summarized in table 3. In system VI the device could not be removed at the end of the study and the lower recovery with this system may be due to unreleased drug. The variability in recovery between replicate monkeys was less with the three implantable naltrexone delivery systems than with the injectable microcapsule systems (table 3). This may be due to more accurate administration of the intended dose as well as to the ability to remove the system and assay for unreleased naltrexone.

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