Intravenous Cocaine Challenges During Naltrexone Maintenance: A Preliminary Study

Thomas Kosten, David G. Silverman, Julia Fleming, Therese A. Kosten, Frank H. Gawin, Margaret Compton, Peter Jatlow, and Robert Byck

In 1976 Byck hypothesized that opioid antagonists would block the euphoric effect of cocaine, and recent clinical observations have suggested lower rates of cocaine abuse by people receiving naltrexone (NTX) than by those receiving methadone (Kosten et al 1989). Although early workers found that both rodents and primates maintained on antagonists showed no attenuation of cocaine self-administration (Killian et al 1978; Carroll et al 1986), more recent studies have found attenuation with NTX administration (Mello et al 1990; DeVry et al 1989; Ramsey and van Ree 1991). Furthermore, Bain and Kornetsky (1987), using rewarding brain stimulation in rodents, showed that the antagonist naloxone can reverse cocaine's potentiation of this stimulation.

An early human study using cocaine administration found a potentiation rather than a reduction of cocaine effect after acute high-dose naloxone (20 mg i.v.; Byck et al 1982), but this situation is clearly different from maintenance blocking with lower doses of NTX. We therefore undertook the current cocaine challenge study during chronic NTX.

From the Substance Abuse Research Center, the Departments of Psychiatry, Pharmacology, and Anesthesiology, Yale University School of Medicine.
Address reprint requests to Thomas R. Kosten, M.D., Substance Abuse Research Center, 27 Sylvan Avenue, New Haven, CT 06519.
Received January 7, 1992; revised April 9, 1992.

Methods

Five male cocaine abusers aged 32 yr (± 1.8) reported 3–15 yr of freebase (n = 3) and intravenous (n = 2) cocaine dependence. They used cocaine 2.6 g/wk (range, 0.2–5.5 g/wk) for 7.5 days/month (range, 3–20 days), alcohol 10 days/month (range, 2–18 days), and reported no other drug abuse. They gave written informed consent and were paid to participate.

Outpatient cocaine challenges were performed in a double-blind, randomized sequence in dosages of 0, 0.125, 0.25, and 0.5 mg/kg. Eight challenges were administered during 6–8 wk with at least 72 hr between consecutive challenges. The first four cocaine challenges began after taking placebo for 10 days, and the second four challenges after taking NTX (50 mg daily) for 10 days. Cocaine use averaged 0.86 g/wk (SD = 0.66) during the challenge weeks, with no use within 72 hr before any laboratory challenge.

Heart rate, ECG and blood pressure were recorded using automated equipment, and four 10-point Visual Analog Scales assessing "high," "quality of the cocaine given," "dollar value of cocaine," and "unpleasant" were collected at baseline, immediately after cocaine infusion, at 5 min after infusion, and for the next 90 min at 15-min intervals (Van Dyke et al 1982). Cocaine plasma levels were assessed by the method of Jatlow and Nadim (1990) at these same times.

0006-3223/92/$05.00

More detailed procedures are available (Kosten et al, in press).

Baseline to peak psychological and physiological response changes and area under the response curve (AUC) were compared across cocaine doses (df = 3,36) and for NTX vs placebo (df = 1,38) using two-way analysis of variance. The AUC to 90 min was calculated using Simpson's rule.

Results

As expected, the high, quality of cocaine, and value of cocaine scales in Table 1 showed substantial increases with increasing cocaine doses both for peak effect (F = 8.4, 10.5, and 9.9, respectively; $p < 0.0003$–0.0001) and AUC (F = 8.5, 9.0, and 5.7, respectively; $p < 0.005$–0.0002). As in Figure 1, the value of cocaine (AUC) ($F = 4.2$; $p < 0.05$) and the peak change in unpleasant ($F = 5.6$; $p < 0.02$) were significantly greater for placebo than NTX. These peaks occurred at 5 min after infusion for value and at 90 min for unpleasant.

As in Table 2, baseline heart rate ($F = 28$; $p < 0.0001$) and peak heart rate change after cocaine administration ($F = 6.6$; $p < 0.02$) were augmented by treatment with NTX. Baseline systolic ($F = 5.3$; $p < 0.05$) and peak systolic ($F = 3.5$; $p < 0.05$), but not diastolic blood pressures, were significantly higher on NTX, with a substantial flattening in the cocaine dose response curve on NTX as compared with placebo. Peak change in heart rate and in systolic (but not diastolic) blood pressure were significantly higher at larger cocaine doses (F = 13, 7.4, 2.0, respectively; $p < 0.0001$, 0.001, ns, respectively). As in Table 3, heart rate (AUC) ($F = 12$; $p < 0.0001$) and systolic blood pressure (AUC) $F = 3.7$; $p < 0.02$) increased with higher cocaine doses, but diastolic pressure did not. Cocaine plasma levels did not differ between placebo and NTX conditions, but peak cocaine plasma levels were higher at higher co-

Table 1. Visual Analog Scale Response to Cocaine Challenge during Naltrexone vs Placebo Maintenance

Scale[b]	Cocaine (mg/kg)	Peak change[a]		Area under the curve[c]	
		Placebo	Naltrexone	Placebo	Naltrexone
High					
	0	0.4 ± 0.9	0 ± 0	6 ± 13	0 ± 0
	0.13	3.8 ± 3.3	2.3 ± 2.9	75 ± 96	34 ± 39
	0.25	6.2 ± 3.6	4.6 ± 3.8	120 ± 45	96 ± 89
	0.50	7.2 ± 3.3	5.6 ± 3.6	252 ± 165	147 ± 130
Quality					
	0	0.2 ± 0.5	0 ± 0	9 ± 20	0 ± 0
	0.13	4.2 ± 3.0	2.0 ± 2.8	93 ± 83	30 ± 37
	0.25	6.6 ± 3.1	4.8 ± 3.3	132 ± 35	117 ± 99
	0.50	6.6 ± 3.0	5.2 ± 3.0	258 ± 176	150 ± 111
Value					
	0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
	0.13	4.8 ± 3.6	1.5 ± 1.9	150 ± 178	19 ± 23
	0.25	6.4 ± 3.3	4.6 ± 3.8	108 ± 47	78 ± 73
	0.50	7.2 ± 3.0	6.0 ± 4.0	207 ± 108	129 ± 115
Unpleasant					
	0	3.6 ± 0.9	3.0 ± 2.0	1170 ± 585	1305 ± 345
	0.13	6.8 ± 2.8	3.0 ± 2.0	1180 ± 225	1164 ± 400
	0.25	6.6 ± 3.3	4.8 ± 1.1	1095 ± 315	1100 ± 405
	0.50	5.4 ± 3.0	4.6 ± 2.2	1290 ± 360	1125 ± 450

[a] n = 5; mean ± SD.
[b] Each scale ranges from 0 to 10.
[c] Area under the curve expressed in minutes to 90 min after infusion.

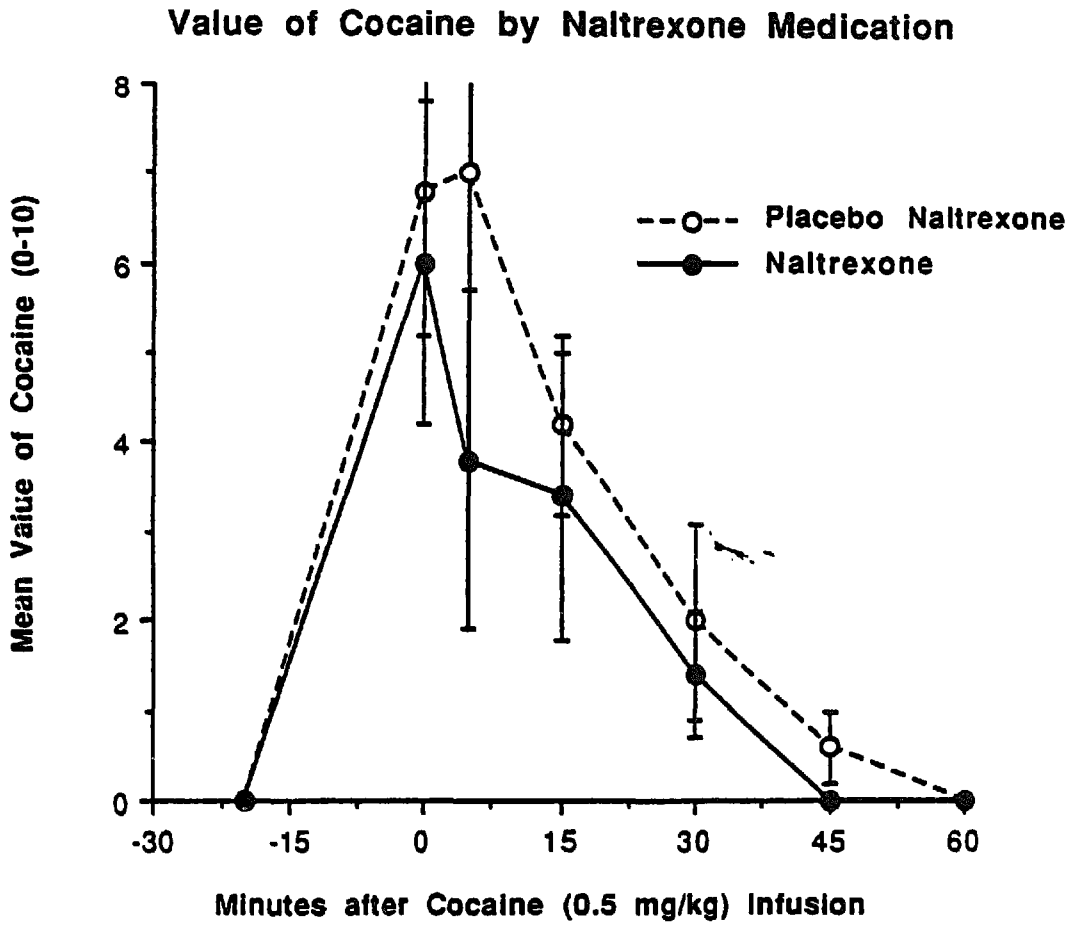

Figure 1. Comparison of the subject (value) effects of cocaine at 0.5 mg/kg during naltrexone (*solid circles*) or placebo (*open circles*) maintenance in 5 subjects; mean ± SE.

caine doses ($F = 43$; $p < 0.0001$), as shown in Table 4.

Discussion

In addition to the expected dose-related effects of cocaine administration, NTX reduced responses to the value of cocaine and unpleasant scales, suggesting that chronic administration of NTX reduced euphoria and the "crash" from cocaine (peak, 90 min). Cardiovascular responses included elevated baseline levels of heart rate and blood pressure during NTX administration, as well as increased responses to cocaine administration while receiving NTX. Although the sequence of NTX and placebo were not counterbalanced, baseline ratings and scores during placebo cocaine challenges were no different between the NTX and placebo NTX conditions, and four subjects, who also had cocaine challenges on desipramine, showed no effect of desipramine on any of these four scales (Kosten et al, in press).

Recent animal data indicating that antagonists attenuate cocaine's effects on rewarding brain stimulation (Bain and Kornetsky 1987), decrease cocaine self-administration (Mello et al 1990; Ramsey and van Ree 1991) and attenuate acquisition of cocaine self-administration (DeVry et al 1989), are consistent with our human results. Increased heart rate is consistent with rodent studies using naloxone in combination with sympathomimetic amines and with human studies using naloxone during mental

Table 2. Physiological Response to Cocaine Challenge During Naltrexone vs Placebo Maintenance[a]

Measure	Cocaine (mg/kg)	Placebo		Naltrexone	
		Baseline	Peak change	Baseline	Peak change
Heart rate (bpm)					
	0	74 ± 6	74 ± 9	84 ± 4	94 ± 8
	0.13	71 ± 6	76 ± 10	81 ± 4	104 ± 11
	0.25	72 ± 7	94 ± 9	81 ± 4	106 ± 18
	0.50	73 ± 5	103 ± 6	84 ± 4	116 ± 12
Blood pressure, systolic (mm Hg)					
	0	117 ± 15	125 ± 17	125 ± 12	137 ± 10
	0.13	117 ± 16	132 ± 22	128 ± 20	155 ± 15
	0.25	113 ± 13	133 ± 18	[illegible] ± 15	153 ± 12
	0.50	114 ± 12	149 ± 17	128 ± 19	150 ± 15
Blood pressure, diastolic (mm Hg)					
	0	67 ± 13	71 ± 9	69 ± 10	74 ± 11
	0.13	67 ± 13	78 ± 13	74 ± 12	88 ± 13
	0.25	63 ± 9	80 ± 17	71 ± 13	84 ± 12
	0.50	66 ± 9	80 ± 10	72 ± 13	79 ± 8

[a] $n = 5$; mean ± SD.

Table 3. Physiological Responses to Cocaine Challenge During Naltrexone vs Placebo Maintenance[a]

Scale	Cocaine (mg/kg)	Area under the curve[b]	
		Placebo	Naltrexone
Heart rate (bpm)			
	0	−186 ± 165	−240 ± 165
	0.13	−59 ± 156	148 ± 430
	0.25	279 ± 142	180 ± 85
	0.50	540 ± 375	474 ± 465
Systolic blood pressure (mmHg)			
	0	69 ± 186	−310 ± 261
	0.13	147 ± 189	375 ± 840
	0.25	386 ± 345	255 ± 270
	0.50	735 ± 405	285 ± 675
Diastolic blood pressure (mmHg)			
	0	−22 ± 203	−95 ± 242
	0.13	71 ± 240	57 ± 118
	0.25	128 ± 176	−2 ± 308
	0.50	249 ± 255	−22 ± 323

[a] $n = 5$; mean ± SD.

[b] Area under the curve in minutes × beats/minute or minutes × mmHg includes 60 min after infusion and measures the change from baseline levels.

Table 4. Peak Cocaine Blood Levels on Naltrexone vs Placebo by Cocaine Challenge Doses (mg/kg)

Cocaine dose	Peak cocaine (ng/ml)		Significance vs placebo[b]
	Naltrexone	Placebo	
0	0	0	—
0.125	85 ± 34	100 + 49	ns
0.25	150 ± 61	159 ± 37	ns
0.50	355 ± 81	364 ± 77	ns
Dose effect signficance	$p < 0.0001$	$p < 0.0001$	

[a] $n = 5$; mean SD.
[b] Placebo vs naltrexone on peak cocaine levels ns = not significant.

stress (Feria et al 1990; Morris et al 1990). Although previous human studies of naloxone found no baseline increase associated with isometric exercise or mental stress, the mental and physical stress associated with our cocaine challenge sessions, including placement of two intravenous lines at baseline may have influenced our baseline measures (Farrell et al 1991; Morris et al 1990).

In summary, as NTX appears to decrease both the positive (value) and negative (unpleasant) effects of cocaine, they many cancel each other out, and NTX may show little net treatment efficacy. Furthermore, the potentiation of cocaine's heart rate effects by NTX may create a safety issue. More successful treatment approaches may employ partial opioid agonists (Kosten et al 1989; Mello et al 1990; Kosten et al 1991).

This work was conducted with Janice Bracken MSN and supported by the National Institute on Drug Abuse grants P50-DA04060 and K02-DA00112 (TRK).

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