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BRIEF COMMUNICATION

Clonidine Partially Blocks the Physiologic Effects but not the Subjective Effects Produced by Smoking Marijuana in Male Human Subjects

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CONE, E J , P WELCH AND W R LANGE *Clonidine partially blocks the physiologic effects but not the subjective effects produced by smoking marijuana in male human subjects* PHARMACOL BIOCHEM BEHAV **29**(3) 649–652, 1988 —Clonidine, an α_2-agonist, was studied in three male human subjects in a multi-dose pilot study in combination with smoking marijuana cigarettes Marijuana alone caused increases in responses on subjective effect questionnaires and increased heart rate Pretreatment with single oral doses of clonidine three hours prior to marijuana induced no changes in subjective effects prior to smoking marijuana and did not diminish the subjective effects produced by marijuana Clonidine did substantially reduce but did not abolish the marijuana-induced rise in heart rate Based on these preliminary data from three subjects, it is concluded that clonidine does not have therapeutic value in the clinical management of active marijuana abuse

Clonidine Physiologic effects Subjective effects Marijuana Human studies, males

CLONIDINE, an α-agonist, has become an accepted pharmacologic adjunct in the management of opioid withdrawal [3, 13, 19, 22], even though this is not an approved indication The reason for clonidine's effectiveness is not clear, however it is reported that heroin and other opioids increase the density and sensitivity of certain α_2-adrenoceptors in human addicts [9]. Clonidine could potentially attenuate withdrawal by interaction at these receptors, rather than through any interaction with the mu opiate receptor Clonidine also has been employed as an adjunct in treating other types of dependence, including alcohol [1,15], tobacco [10], and sedative hypnotic drugs [12] Its effectiveness in attenuating the withdrawal symptoms of benzodiazepine dependence has been inconsistent [11, 17, 21]

The potential efficacy of clonidine as an adjunct in the management of marijuana abuse has not been investigated When marijuana is smoked, tetrahydrocannabinol (THC), the major psychoactive component, is rapidly absorbed producing a variety of effects, most notable being development of a pleasant "high" or euphoria and tachycardia [18] These effects generally peak immediately after cessation of smoking Other common effects of smoking marijuana include short-term memory loss, psychomotor performance impairment, conjunctival reddening, and slight changes in body temperature [16]

Recent studies on the acute effects of smoking marijuana by male human subjects detected changes in the circulating levels of cortisol and luteinizing hormone accompanying the behavioral effects [5] Although the mechanism of action of marijuana's influence on the endocrine system is unknown, evidence suggests that some of the behavioral effects of THC are mediated through stimulation of pituitary adrenocortical hormone (ACTH) secretion [6] A physiological blockade of marijuana's effects through an adrenergic mechanism is a possibility which has not been explored Clonidine has been shown to inhibit ACTH secretion in the dog [8], and human [14] and could potentially ameliorate the reinforcing effects of THC by the inhibition of the hypothalamic-pituitary-adrenal axis This study was undertaken to determine if clonidine suppresses subjective and physiologic effects of marijuana smoking If so, clonidine might have potential use in the chemotherapeutic intervention of marijuana abuse

METHOD

An ascending series of doses of clonidine and marijuana

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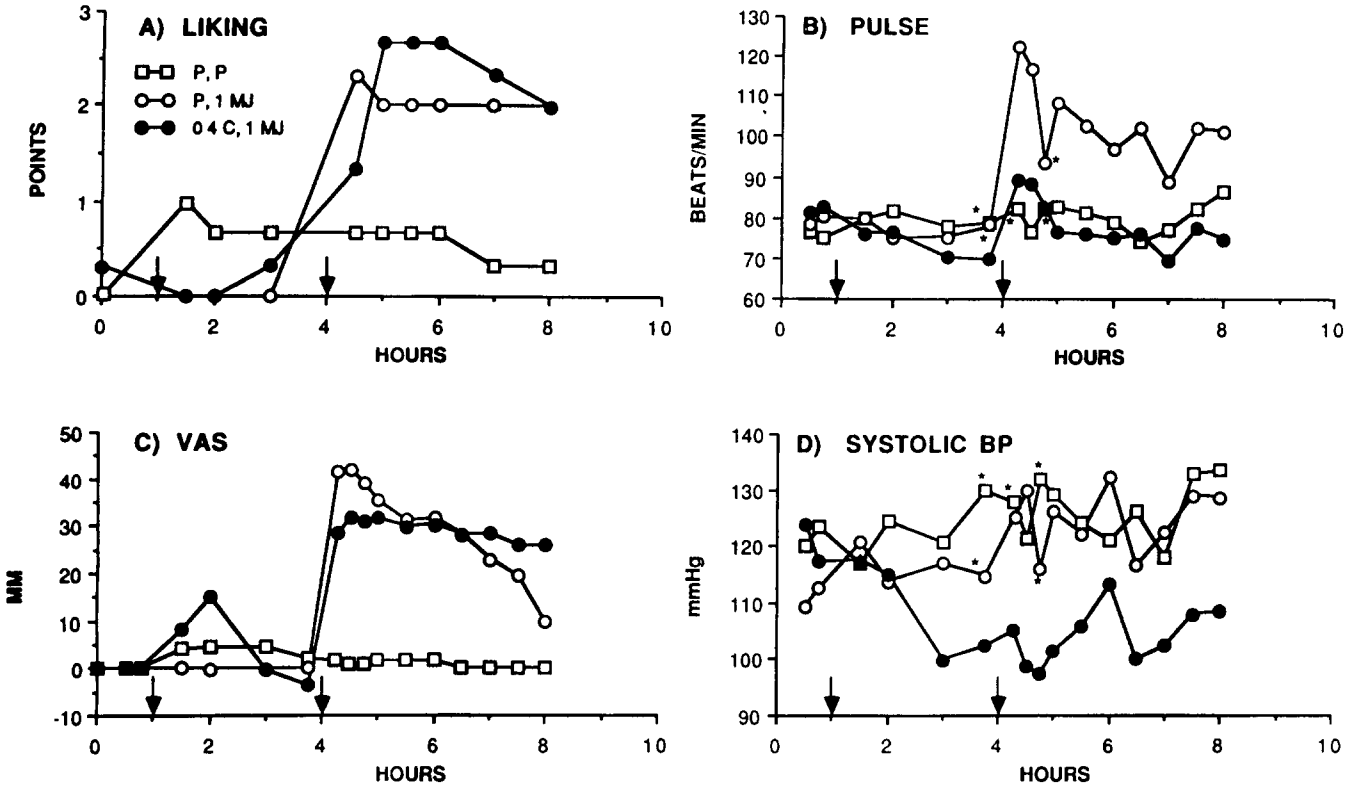

FIG 1 Mean subjective and physiologic effects of subjects (N=3) during test sessions with clonidine (C) or placebo (P) pretreatment at 1 0 hour (first arrow) and smoking marijuana cigarettes (MJ) or placebo cigarettes (P) at 4 0 hours (second arrow) *Indicates mean of two subjects at that time point

were administered to three healthy male volunteers after obtaining informed consent The subjects were free of acute and chronic disease as determined by medical history, physical examination, laboratory evaluation, and psychometric testing All reported use of marijuana on a daily basis for more than 10 years

The subjects were blinded to test conditions On each day the participant consumed two oral tablet preparations containing clonidine and/or placebo and smoked two investigational cigarettes [marijuana (MJ) cigarettes contained 1 3% THC, placebo (P) cigarettes contained 0% THC] under the following progressive regiment.

Day	Clonidine (mg)	Cigarettes
1	0 0	2 P
2	0 0	1 P, 1 MJ
3	0 1	1 P, 1 MJ
4	0 2	1 P, 1 MJ
5	0 4	1 P, 1 MJ
6	0 4	2 MJ

Each subject fasted from midnight to 3 00 p m. of the study day. Subjective measures were made at the following times 8 00 a m , 9·30 a m., 10 00 a m , 11 00 a m , 12 30 p m , 1.00 p m., 1 30 p m , 2 00 p m , 3.00 p m , and 4 00 p m Physiologic measures were made at similar times Two clonidine/placebo tablets were administered orally at 9 00 a m and two marijuana/placebo cigarettes were smoked at 12 00 noon The clonidine tables (Boehringer Ingelheim Ltd) were matched with placebo tablets and the cigarettes were research marijuana cigarettes (NIDA Research Technology Branch)

Study parameters which were measured were identical to those previously collected for human subjects smoking marijuana [5] and included electrocardiographic monitoring, vital signs (heart rate, blood pressure, respiration measurements), and subjective effects (single dose questionnaire, Addiction Research Center Inventory (ARCI) subscales, Single Dose Questionnaire and Visual Analog Scale) For each measure, area under the curve (AUC) calculations were made for the test period immediately following clonidine or placebo (1 5–3 hr) and for the test period following marijuana (4 5–7 hr)

RESULTS

Subjective Measures

Subjective measures for the 3 subjects were relatively unchanged during the 1 5–3 0 hour period following clonidine prior to smoking marijuana as indicated by the $AUC_{1\,5-3}$ measures in Table 1 After marijuana, elevations occurred in measures on Feel Drug, Liking, Sensations, Mar 15 and VAS on these scales (see Table 1, $AUC_{4\,5-7}$) Equivalent increases on these scales occurred with both placebo and clonidine (0 1–0.4 mg) pretreatment Increases in subjective response measures occurred immediately after smok-

TABLE 1

AREA UNDER THE CURVE MEASURES FOR EFFECTS FROM SMOKING MARIJUANA WITH PLACEBO AND CLONIDINE PRETREATMENT

Effect	Time† (HR)	Dose Condition* P,P	P, 1MJ	0 1C, 1MJ	0 2C, 1MJ	0 4C, 1MJ	0 4C, 2MJ
Feel Drug	1 5–3	0 83 (0 44)	0 (0)	0 50 (0 5)	0 67 (0 08)	0 58 (0 08)	0 83 (0 22)
	4 5–7	0 92 (0 58)	3 22 (0 17)	3 5 (0)	3 42 (0 08)	3 33 (0 17)	3 08 (0 22)
Liking	1 5–3	1 08 (0 42)	0 (0)	1 08 (1 08)	0 50 (0 29)	0 17 (0 17)	0 17 (0 17)
	4 5–7	1 83 (1 01)	7 08 (2 11)	7 42 (3 33)	7 17 (3 30)	8 33 (2 35)	8 83 (2 62)
Sensations	1 5–3	2 25 (0 63)	1 33 (0 73)	2 00 (1 04)	2 92 (0 82)	3 00 (1 18)	3 50 (1 13)
	4 5–7	3 00 (1 30)	8 67 (2 67)	9 00 (1 76)	11 83 (2 54)	12 25 (2 24)	14 16 (2 51)
Mar 15	1 5–3	4 00 (1 94)	2 25 (1 15)	3 33 (1 88)	2 08 (0 79)	6 67 (3 67)	4 58 (1 58)
	4 5–7	7 17 (4 19)	16 41 (4 95)	24 91(14 25)	22 58(10 86)	25 83(12 89)	20 00 (7 89)
PCAG	1 5–3	6 58 (2 17)	6 25 (1 81)	7 25 (2 13)	7 08 (2 31)	7 25 (2 41)	6 42 (1 12)
	4 5–7	12 33 (4 13)	11 25 (3 13)	14 08 (4 23)	17 58 (5 78)	14 91 (5 39)	17 16 (3 34)
LSD	1 5–3	3 75 (0 88)	4 08 (0 65)	3 67 (0 93)	4 25 (0 90)	5 17 (1 23)	3 58 (0 65)
	4 5–7	10 00 (1 81)	14 00 (4 25)	13 25 (4 54)	11 91 (3 58)	11 33 (3 18)	10 25 (3 83)
MBG	1 5–3	3 92 (2 02)	2 83 (2 13)	3 50 (2 57)	3 50 (2 78)	4 58 (2 92)	3 75 (2 92)
	4 5–7	8 67 (6 66)	14 91 (7 45)	18 50 (9 27)	18 25 (9 79)	16 50 (9 32)	15 50(10 29)
VAS	1 5–3	9 42 (6 91)	0 (0)	6 33 (6 33)	−1 58 (7 40)	11 66(39 22)	15 70(16 01)
	4 5–7	3 00 (3 00)	108 70(46 83)	98 83(50 79)	63 50(38 14)	109 7 (57 42)	105 20(54 87)
Pulse	1 5–3	120 10 (1 04)	114 00 (1 17)	114 50 (5 53)	115 60 (2 00)	111 70 (5 51)	108 60 (6 84)
	4 5–7	279 10(10 04)	355 00(33 71)	307 80(12 13)	287 60 (6 02)	266 40(12 44)	282 00(22 81)
Systolic BP	1 5–3	182 80 (7 15)	174 10 (5 21)	167 90(15 97)	170 10 (8 97)	165 80 (9 67)	161 40 (5 92)
	4 5–7	439 40(17 51)	439 50(27 80)	396 80(34 04)	384 10(19 27)	368 00(20 91)	347 50(10 59)
Diastolic BP	1 5–3	106 50 (4 04)	96 50 (1 59)	94 41 (7 31)	95 41 (3 71)	95 16 (2 31)	94 66 (7 29)
	4 5–7	253 5 (4 68)	233 00(15 48)	220 90(13 39)	212 70 (4 63)	202 70 (4 75)	192 50 (6 11)
Respiration	1 5–3	28 33 (0 17)	28 50 (0 76)	27 33 (1 48)	27 66 (1 17)	27 83 (1 17)	26 50 (0 29)
	4 5–7	67 00 (0)	70 66 (2 03)	67 5 (0 76)	66 66 (0 67)	64 00 (0 76)	64 83 (1 42)

*Mean area under the curve (AUC) ±S E M measures for three male subjects who received placebo (P) or clonidine pretreatment and smoked one marijuana cigarette (1MJ) or two marijuana cigarettes (2MJ)

†Times after start of test session used for calculation of AUC Clonidine was administered at 9 00 a m and marijuana was administered at 12 00 noon

ing marijuana (Fig 1A and C) and generally remained elevated over the remainder of the test session, i e , 4 hours following marijuana

Physiologic Measures

Following clonidine pretreatment but prior to smoking marijuana, measures of pulse rate, respiration and diastolic blood pressure remained relatively unchanged while systolic blood pressure was diminished by approximately 15 mmHg at the highest dose (0.4 mg) of clonidine (See Table 1 and Fig 1B and D) Following marijuana (0 4 mg clonidine pretreatment), systolic blood pressure remained depressed by approximately 15 mmHg throughout the remainder of the test session. Diastolic blood pressure and respiration were slightly depressed

Following marijuana with placebo pretreatment, pulse rate increased from a control mean±S E M of 78±3 to a maximum rate immediately after smoking of 123±21 Under these conditions, other physiologic measures, i e , respiration, systolic and diastolic blood pressure, remained relatively unchanged When marijuana was preceded by increasing doses of clonidine, graded decrements were observed in pulse rate increases induced by marijuana With a 0.4 mg pretreatment dose of clonidine, pulse rate rose from a mean of 70±3 prior to marijuana to a maximum of 89±10 after smoking marijuana This decrement in pulse rate with clonidine pretreatment also was reflected by a 25% drop in AUC for the period 4.5–7 hr for 1 marijuana cigarette with a 0 4 mg clonidine pretreatment compared to placebo pretreatment When the dose of marijuana was increased to 2 cigarettes (with 0 4 mg clonidine pretreatment), both pulse rate and $AUC_{4\,5-7}$ measures were increased over measures after 1 cigarette (with 0 4 mg clonidine pretreatment).

DISCUSSION

The potential use of clonidine as a pharmacologic adjunct in the clinical management of marijuana abuse was suggested from observations that clonidine suppresses basal levels of ACTH and cortisol in dog [8] and human [14] and tobacco cigarette induced release of ACTH and cortisol in humans

[4] Smoking marijuana cigarettes also produced release of cortisol [5] presumably through release of ACTH If the actions of marijuana were mediated through stimulation of ACTH release, clonidine might serve to block subjective and/or physiologic effects In the present study, clonidine pretreatment failed to block or reduce any of the marijuana induced increases in subjective measures but did serve to partially block the chronotrophic effects of marijuana The characteristic robust increase in heart rate which occurred following smoking marijuana was markedly reduced by pretreatment with a 0 4 mg oral dose of clonidine (Fig 1B), but was not completely abolished By increasing the number of marijuana cigarettes smoked to two, the effect of clonidine pretreatment on heart rate was further reduced

The failure of clonidine to block the subjective effects of marijuana suggests either that clonidine is ineffective at blocking the release of ACTH or that those effects are not primarily mediated through the release of this hormone Recent reports have suggested that the clonidine-induced drop in basal cortisol levels were actually a result of diurnal variation and were not drug induced [7,20] Further controlled studies of the effects of clonidine on ACTH release in humans are needed to resolve this issue

Although there were no indications that clonidine would be useful in direct intervention with subjects actively abusing marijuana, there may be other indications for use of clonidine in combination with marijuana or tetrahydrocannabinol derivatives Clonidine should serve to lower blood pressure and heart rate in hypertensive cancer subjects who are undergoing chemotherapy and are receiving marijuana therapeutically as an antiemetic In addition, clonidine has utility for treatment of mania, anxiety and panic disorders [2], effects which could serve as additional beneficial properties in the potential therapeutic utilization of a clonidine/marijuana combination

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REFERENCES

1 Bjorkquist, S E Clonidine therapy for alcohol withdrawal *Acta Psychiatr Scand* **327:** 114–120, 1986
2 Bond, W S Psychiatric indications for clonidine The neuropharmacologic and clinical basis *J Clin Psychopharmacol* **6:** 81–87, 1986
3 Charney, D S , G R Heninger and H D Kleber The combined use of clonidine and naltrexone as a rapid, safe, and effective treatment of abrupt withdrawal from methadone *Am J Psychiatry* **143:** 831–837, 1986
4 Chiodera, A , L Camellini, G Rossi, M L Maffei, R Volpi and V Coiro Effect of clonidine on ACTH and cortisol release induced by cigarette smoking in man *Horm Metab Res* **16:** 501–502, 1980
5 Cone, E J , R E Johnson, J D Moore and J D Roache Acute effects of smoking marijuana on hormones, subjective effects and performance in male human subjects *Pharmacol Biochem Behav* **24:** 1749–1754, 1986
6 Drew, W G and D E Slagel Delta-9-THC Selective impairment of corticosterone uptake by limbic structures of the rat *Neuropharmacology* **12:** 909–914, 1973
7 Ellis, N F , M H MacGillivray and M L Voorhess Effect of clonidine on plasma cortisol concentrations *Clin Pharmacol Ther* **39:** 660–663, 1986
8 Ganong, W F Neurotransmitters and pituitary function Regulation of ACTH secretion *Fed Proc* **39:** 2923–2930, 1980
9 Garcia-Sevilla, J A , L Ugedo, I Ulibarri and M Gutierrez Heroin increases the density and sensitivity of platelet alpha 2-adrenoceptors in human addicts *Psychopharmacology (Berlin)* **88:** 489–492, 1986
10 Glassman, A H , W L Jackson, B T Walsh, S P Roose and B Rosenfeld Cigarette craving, smoking withdrawal, and clonidine *Science* **226:** 864–866, 1984
11 Goodman, W K , D S Charney, L H Price, S W Woods and G R Heninger Ineffectiveness of clonidine in the treatment of the benzodiazepine withdrawal syndrome Report of three cases *Am J Psychiatry* **143:** 900–903, 1986
12 Hughes, P L and R M Morse Use of clonidine in a mixed-drug detoxification regimen Possibility of masking clinical signs of sedative withdrawal *Mayo Clin Proc* **60:** 47–49, 1985
13 Jasinski, D R , R E Johnson and T R Kocher Clonidine in morphine withdrawal Differential effects on signs and symptoms *Arch Gen Psychiatry* **42:** 1063–1066, 1985
14 Lanes, R , A Herrera, A Palacios and G Moncada Decreased secretion of cortisol and ACTH after oral clonidine administration in normal adults *Metabolism* **32:** 568–570, 1983
15 Manhem, P , L H Nilsson, A L Moberg, J Wadstein and B Hokfelt Alcohol withdrawal Effects of clonidine treatment on sympathetic activity, the renin-aldosterone system, and clinical symptoms *Alcoholism* **9:** 238–243, 1985
16 Miller, L L (Ed) *Marijuana, Effects on Human Behavior* New York Academic Press, 1974
17 Moodley, P and M Lader Management of benzodiazepine dependence *S Afr Med J* **69:** 563–564, 1986
18 Perez-Reyes, M , S D Guiseppi, K H Davis, V H Schindler and C E Cook Comparison of effects of marijuana cigarettes of three different potencies *Clin Pharmacol Ther* **31:** 617–624, 1982
19 Preston, K L and G E Bigelow Pharmacological advances in addiction treatment *Int J Addict* **20:** 845–867, 1985
20 Slover, R H , G J Klingensmith, R W Gotlin and J Radcliffe A comparison of clonidine and standard provocative agents of growth hormone *Am J Dis Child* **138:** 314–317, 1984
21 Vinograder S , A L Reiss and J G Csernansky Clonidine therapy in withdrawal from high-dose alprazolam *Am J Psychiatry* **143:** 1188, 1986
22 Washton, A M and R B Resnick Clonidine in opiate withdrawal Review and appraisal of clinical findings *Pharmacotherapy* **1:** 140–146, 1986