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Marijuana and Cocaine Interactions in Humans: Cardiovascular Consequences

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FOLTIN, R. W., M. W. FISCHMAN, J. J. PEDROSO AND G. D. PEARLSON. *Marijuana and cocaine interactions in humans: Cardiovascular consequences.* PHARMACOL BIOCHEM BEHAV **28**(4) 459–464, 1987.—Seven adult male volunteers residing on a research ward received intravenous cocaine and smoked marijuana, alone and in combination, during daily experimental sessions. Following the determination of baseline cardiovascular indexes, a one gram marijuana cigarette (0–2.7% Δ^9-THC w/w) was smoked. Cocaine hydrochloride (0–32 mg) was administered intravenously 13 minutes after the start of marijuana smoking. Cocaine alone produced dose-dependent increases in heart rate, while both low and high THC blood levels produced a similar increase in heart rate. Both doses of cocaine increased mean arterial pressure (MAP) similarly, while THC alone produced blood level dependent increases in MAP. Combinations of cocaine and marijuana increased heart rate above levels seen with either drug alone, with increases plateauing at nearly 50 bpm for all dose-blood level combinations. Increases in mean arterial pressure following combinations of cocaine and marijuana were equivalent to those produced by cocaine alone.

Marijuana THC Cannabis Cocaine Heart rate Blood pressure Drug interaction Humans

THE cardiovascular effects of cocaine and marijuana are well documented. Consistent increases in heart rate and blood pressure have been reported following intranasal [12,16], intravenous [4] and inhaled freebase administration [14] of cocaine. On the other hand, only significant increases in heart rate and nonsignificant blood pressure changes have been reported following oral [11], intravenous [15], or smoked [17] marijuana administration.

In contrast to the research on the cardiovascular effects of these drugs when given alone, surprisingly little research has concentrated on the effects of these drugs in combination. Anecdotal reports indicate that it is common for cocaine users to smoke marijuana by itself, as well as in close proximity to cocaine self-administration [1,10]. Given the significant cardiovascular effects of these drugs, it is clear that an analysis of the cardiovascular effects of their concurrent use is warranted. The current experiment provides such an analysis for combinations of intravenous cocaine and smoked marijuana.

METHOD

Subjects

Seven healthy male volunteers, ranging in age from 27 to 38 years and each with a history of both marijuana and intravenous cocaine use, participated. Prior to acceptance each subject was given a drug history interview and physical examination. All of the subjects were admitted to the Clinical Research Unit of The Johns Hopkins Hospital 24 hours before the first test day and remained in the hospital for the duration of the 14-day study. Each subject signed a consent form that described the study, outlined any possible risks, and indicated that cocaine and marijuana, singly and in combination, would be administered, possibly on a daily basis, during the 14-day study. When not participating in experimental sessions subjects were free to engage in non-drug-related recreational activities of their own choice on the ward.

Procedure

Subjects were individually tested in daily, three-hour sessions. Approximately 30 minutes prior to the experimental session two scalp vein IV needles were inserted, one into each arm, and attached to saline solution drip bottles. A 20-gauge Angiocath (Deseret Co., Sandy, UT) was used for drug injection and an 18-gauge Angiocath was used for blood withdrawal. Subjects sat quietly during the first 30 minutes of each session while baseline data were collected. Immediately after this baseline period, subjects were given an active or placebo marijuana cigarette to smoke. Cigarettes were smoked using a signaled paced smoking procedure with instructions presented via the intercom connecting the observation and subject rooms. A 5-second "get ready" period was followed by a 5-second inhalation, a 10-second "hold" and a 10-second exhalation. This sequence was repeated once each minute for 5 minutes. Previous research from this laboratory has shown that this procedure produces reliable drug effects [5,6]. Thirteen minutes after the start of marijuana administration saline or cocaine was injected

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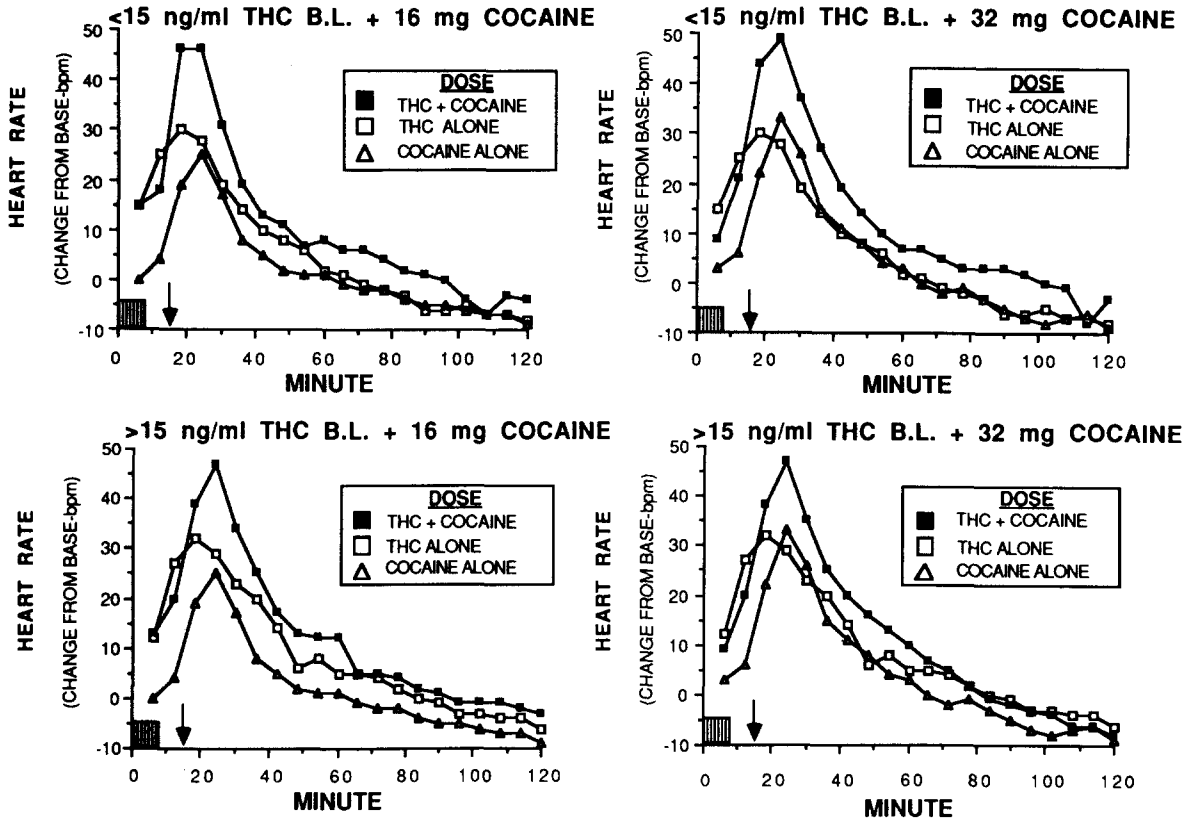

FIG. 1. *Upper Left Panel.* Mean change in heart rate associated with THC blood levels of <15 ng/ml, and 16 mg cocaine, alone and in combination, as a function of time during the session. A marijuana cigarette was smoked from 0 to 5 min as indicated by the striped bar and IV cocaine was given at 13 min as indicated by the arrow. Blood was withdrawn for THC determination at 35 min. *Upper Right Panel.* Mean change in heart rate associated with THC blood levels of <15 ng/ml, and 32 mg cocaine, alone and in combination, as a function of time during the session. *Lower Left Panel.* Mean change in heart rate associated with THC blood levels of >15 ng/ml, and 16 mg cocaine, alone and in combination, as a function of time during the session. *Lower Right Panel.* Mean change in heart rate associated with THC blood levels of >15 ng/ml, and 32 mg cocaine, alone and in combination, as a function of time during the session.

through the intravenous catheter. The order of dose-dose combinations was mixed so that all subjects were tested with low dose cominations prior to testing with high dose cominations. Blood was withdrawn 35 minutes after the start of marijuana smoking for determination of Δ^9-THC levels by radioimmunoassay.

During each session, heart rate was monitored continuously through bipolar chest leads. Blood pressure (diastolic, systolic, and mean arterial) and heart rate were sampled every two minutes via a Dinamap 825XT automated blood pressure monitor (Critikon, Tampa, FL). The subjects were continuously monitored through one-way glass and could communicate with the investigators by intercom.

Drug

Subjects were given a one gram marijuana cigarette supplied by the National Institute on Drug Abuse. Each cigarette had one of the following Δ^9-THC concentrations (w/w): 0%, 1.3%, 1.84% or 2.7%. Intravenous solutions were always injected over 60 seconds and consisted of 1 ml physiological saline (placebo) or 16 or 32 mg cocaine hydrochloride (Mallenkrodt, St. Louis, MO) dissolved in 1 ml saline. Unit doses were prepared by the Pharmacy Manufacturing Department of The Johns Hopkins Hospital.

Data Analysis

Heart rate and blood pressure (systolic, diastolic, and mean arterial), expressed as change from resting baseline, were analyzed during the period of peak drug effects (18–24 minutes after the initiation of marijuana smoking). Area-under-the-curve (AUC, trapezoidal approximation) was also determined for the first 60 minutes following the initiation of marijuana smoking for all four measures. Due to differences in inhalation volume, the paced smoking procedure does not guarantee equivalent THC blood levels among subjects smoking the same THC concentration cigarette. Therefore, the distribution of THC blood levels 35 minutes after the initiation of marijuana smoking was analyzed. Fifteen ng/ml was approximately the median level of this distribution, and this value was used to divide the results into two levels (B.L.$\leq$15 ng/ml, B.L.>15 ng/ml). A third THC blood level was provided by the <5 ng/ml concentration observed on all placebo days. Mean THC blood levels regardless of cocaine dose for the three THC blood level groups were 0.32, 11.0, and 24.2 ng/ml, respectively. Unfortunately, as a consequence of this post hoc distribution, not all subjects had data points in all cells, necessitating the use of a between groups analysis of variance. Each cardiovascular measure was analyzed using a three (cocaine dose) by three (THC blood

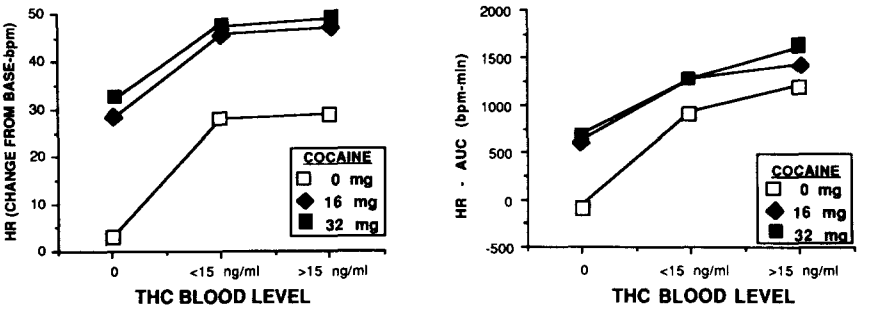

FIG. 2. *Left Panel.* Mean change in peak heart rate (HR) as a function of THC blood level and dose of cocaine. *Right Panel.* Area under the curve for change in heart rate for the first hour after marijuana smoking as a function of THC blood level and dose of cocaine.

TABLE 1

RESULTS OF THE ANALYSIS OF VARIANCE FOR EACH CARDIOVASCULAR MEASURE

	Marijuana		Cocaine	
	F*	*p*	F*	*p*
Heart Rate				
bpm	15.9	0.001	22.6	0.001
AUC	13.1	0.001	4.2	0.02
Systolic Pressure				
mmHg	4.6	0.01	17.9	0.001
AUC	2.6	0.07	44.1	0.001
Diastolic Pressure				
mmHg	10.1	0.001	20.6	0.001
AUC	6.9	0.002	28.1	0.001
Mean Arterial Pressure				
mmHg	9.7	0.002	23.0	0.001
AUC	3.2	0.05	25.5	0.001

*(2,64) degrees of freedom.

level) factorial analysis of variance. Results were considered statistically significant at $p<0.05$.

RESULTS

Table 1 contains the results of the analysis of variance for each cardiovascular measure. Figure 1 presents the mean change in heart rate following active marijuana and cocaine, alone and in combination, as a function of time during the session. Peak increases in heart rate were observed at 12–18 minutes following active marijuana (open square symbols) administration alone, and at 18–24 minutes following administration of both cocaine (open triangle symbols) alone, and combinations of active marijuana and cocaine (closed square symbols). Combinations of active marijuana and cocaine not only increased heart rate to a greater extent than following either drug alone, but also maintained heart rate increases for a longer time than either drug alone.

Figure 2 summarizes the peak heart rate effects data (18–24 minutes) and the area-under-the-curves in Fig. 1. THC alone significantly increased heart rate (left panel) up to 29 beats per minute (bpm), while cocaine alone also significantly increased heart rate up to 32 bpm. When given in combination, heart rate was increased to levels significantly above those seen following independent administration of these two drugs. Increases in heart rate, however, were not dose-dependent, as all four dose-blood level combinations produced similar maximal increases in heart rate in the range of 47–49 bpm. Analysis of the area-under-the-curves (right panel) showed the same pattern with both drugs producing dose-dependent increases in AUC when given alone, and similar, but larger increases when both drugs were given in combination.

Figure 3 presents the mean change in mean arterial pressure (MAP) following active marijuana and cocaine administration, alone and in combination, as a function of time during the session. The increase in MAP following active marijuana alone (open square symbols) remained at approximately the same levels from 6–24 minutes followed by a rapid decline. In contrast, peak increases in MAP following adminstration of cocaine (open triangle symbols) alone, and combinations of active marijuana and cocaine (closed square symbols) were observed at 18–24 minutes followed by a slower decline than following active marijuana alone. Combinations of active marijuana and cocaine increased MAP to the same extent as each dose of cocaine alone.

Figure 4 summarizes the peak MAP effects data (18–24 minutes) and the area-under-the-curves in Fig. 3. THC produced significant blood level dependent increases in

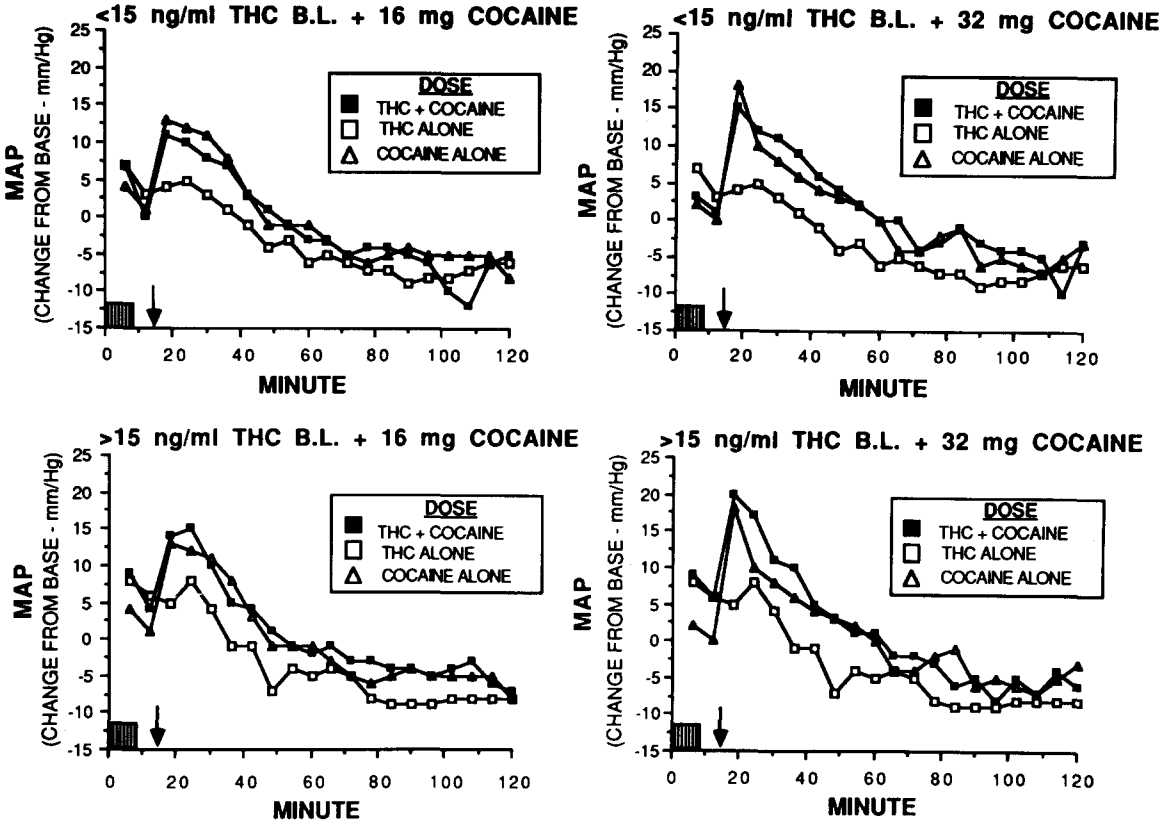

FIG. 3. *Upper Left Panel.* Mean change in mean arterial pressure associated with THC blood levels of <15 ng/ml, and 16 mg cocaine, alone and in combination, as a function of time during the session. A marijuana cigarette was smoked from 0 to 5 min as indicated by the striped bar and IV cocaine was given at 13 min as indicated by the arrow. Blood was withdrawn for THC determination at 35 min. *Upper Right Panel.* Mean change in mean arterial pressure associated with THC blood levels of <15 ng/ml, and 32 mg cocaine, alone and in combination, as a function of time during the session. *Lower Left Panel.* Mean change in mean arterial pressure associated with THC blood levels of >15 ng/ml, and 16 mg cocaine, alone and in combination, as a function of time during the session. *Lower Right Panel.* Mean change in mean arterial pressure associated with THC blood levels of >15 ng/ml, and 32 mg cocaine, alone and in combination, as a function of time during the session.

mean arterial pressure (left panel) of up to 8 mmHg, while only 32 mg of cocaine in combination with the larger THC blood level significantly increased MAP greater than when both drugs were given alone. This increase is due to a sustained peak increase following 32 mg cocaine alone (Fig. 3, lower right panel). A similar pattern is evident for the AUC measure (right panel).

Figure 5 compares the effects of both drugs on systolic pressure. THC produced significant blood level dependent increases in systolic blood pressure (left panel) of up to 8 mmHg, while both doses of cocaine significantly increased systolic pressure by 17 mmHg. Only the highest dose combination increased systolic pressure above that produced by cocaine alone. The pattern of results is similar for the AUC index (right panel) with the exception that THC alone had no significant effect on the AUC measure. Figure 6 presents the effects of both drugs on diastolic blood pressure. Smoking marijuana produced significant blood level dependent increases in diastolic pressure up to 7 mmHg, while both doses of cocaine significantly increased diastolic pressure by 9 mmHg (left panel). When given in combination, only the high dose combination increased diastolic pressure above levels seen with either drug alone. A similar pattern of results is evident for the AUC measure (right panel).

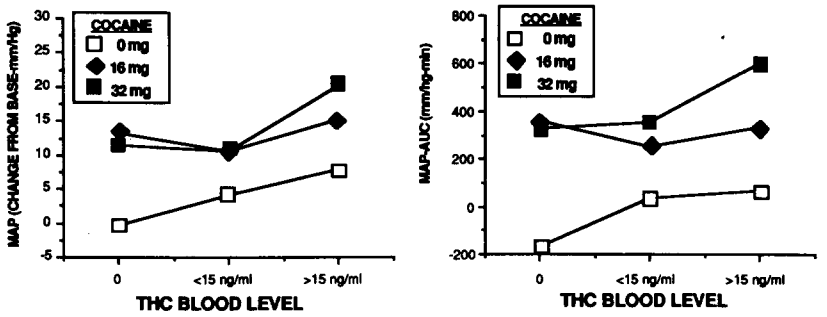

FIG. 4. *Left Panel.* Mean change in peak mean arterial pressure (MAP) as a function of THC blood level and dose of cocaine. *Right Panel.* Area under the curve for change in mean arterial pressure for the first hour after marijuana smoking as a function of THC blood level and dose of cocaine.

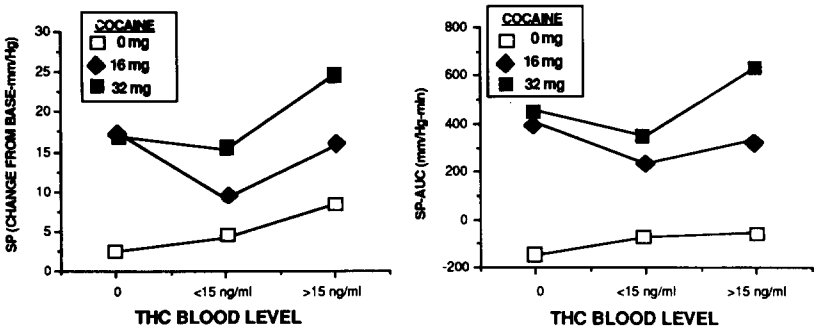

FIG. 5. *Left Panel.* Mean change in peak systolic pressure (SP) as a function of THC blood level and dose of cocaine. *Right Panel.* Area under the curve for change in systolic pressure for the first hour after marijuana smoking as a function of THC blood level and dose of cocaine.

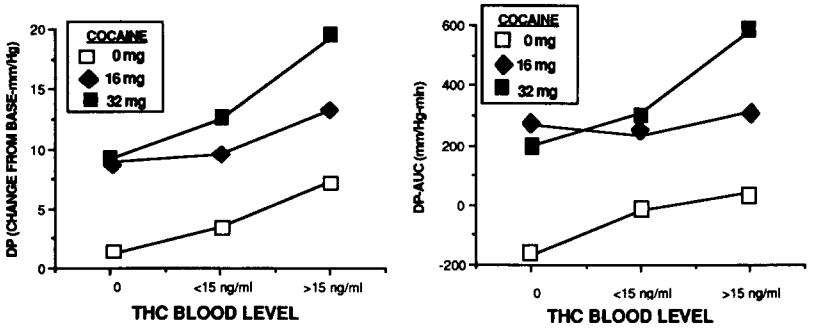

FIG. 6. *Left Panel.* Mean change in peak diastolic pressure (DP) as a function of THC blood level and dose of cocaine. *Right Panel.* Area under the curve for change in diastolic pressure for the first hour after marijuana smoking as a function of THC blood level and dose of cocaine.

DISCUSSION

The results show clearly that the independent administration of either intravenous cocaine or smoked marijuana increases heart rate and blood pressure. When these drugs are given in combination, significant further increments are observed with heart rate increases of up to 50 bpm and blood pressure increases of up to 20 mmHg. The increase in heart rate following independent administration of both drugs replicates previous findings [4,11], and the increase in blood pressure induced by cocaine has also been reported [4]. In contrast, the consistent blood level dependent increases in blood pressure following smoked marijuana differs from some previous reports which have indicated that marijuana produces small and inconsistent changes in blood pressure (e.g., [17]). Protocol differences include the use of blood levels rather than cigarette THC concentrations in the data analysis and the use of experienced research subjects who readily identified the placebo marijuana cigarettes.

Although previous experiments have not reported the effects of cocaine-marijuana combinations, several studies have investigated the interactive effects of *d*-amphetamine and marijuana on cardiovascular activity [3,8]. In the first of these [8], heart rate and blood pressure were measured fol-

lowing various combinations of oral *d*-amphetamine and smoked marijuana. The authors conclude that the increases in heart rate and blood pressure following either drug were "augmented" by the presence of the other drug, but no significant interactions were observed. In the later study [3], it was concluded that the effects of smoked marijuana and oral amphetamine on cardiovascular activity were "additive."

Previous studies have shown that the particular dose-dose combination can be critical in determining the type of drug interaction (e.g., [9, 13, 18, 19]). In the present results all four combinations of cocaine dose and THC blood level produced equivalent, and substantial, increases in heart rate. The peak heart rate observed (i.e., 140 bpm) was below the maximal (or ceiling) safe heart rate for an individual of that age (190 bpm). Thus, one or more other factors were limiting heart rate increases. It is impossible to determine, under the conditions of the present experiment, if the failure to see larger increases in heart rate with large dose-blood level combinations was a result of a drug interaction between cocaine and THC, or an inherent homeostatic mechanism dampening heart rate increases.

The type of interaction was also dependent on the cardiovascular measure. In contrast to the consistent increase in peak heart rate when combinations of cocaine and marijuana were given, only the combination of the highest cocaine dose and THC blood level affected blood pressure differently than when cocaine was given alone. The significant increase in AUC when the high dose-high blood level combination was administered was accounted for by an increase in blood pressure prior to cocaine administration.

In spite of the plateau observed, increases in heart rate following the administration of combinations of cocaine and marijuana were quite large. It is probable that such high dose combinations occur when these drugs are used outside of the laboratory and that such combinations increase heart rate to a greater extent than predicted by the independent administration of either drug. Furthermore, these cardiovascular measures were obtained under resting baseline conditions. The cardiovascular consequences of both cocaine and marijuana have been shown to be increased by task performance [2,7]. Thus, the combination of these drugs under nonresting conditions in high doses may increase the potential for severe cardiovascular toxicity.

ACKNOWLEDGEMENTS

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