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A Comparison of the Subjective and Cardiovascular Effects of Cocaine and Lidocaine in Humans

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FISCHMAN, M. W., C. R. SCHUSTER AND Y. HATANO. *A comparison of the subjective and cardiovascular effects of cocaine and lidocaine in humans.* PHARMACOL BIOCHEM BEHAV **18**(1) 123–127, 1983.—Four normal adult volunteers were given intravenous injections of 16, 32 and 48 mg cocaine, lidocaine, or saline, once daily. Heart rate, blood pressure and responses on the Profile of Mood States, Addiction Research Center Inventory, and a locally developed drug effects questionnaire were measured periodically before and after drug or placebo injection. The profile of action of cocaine was significantly different from that produced by lidocaine or placebo whereas the effects of lidocaine were indistinguishable from those of placebo.

Cocaine Lidocaine Humans Profile of action

THERE have been a number of recent reports [5, 7, 9, 16] indicating that at least some of the synthetic local anesthetics can maintain responding in non-human research subjects. These data have been puzzling since, in general, drugs which serve as reinforcers in animals do so in humans, and this property is an important factor in their dependence potential [10]. Despite these reports of local anesthetic self-administration in non-humans, they do not appear to be commonly abused by humans.

There is a recent report [15], however, stating that subjects given matched doses of intranasal cocaine and lidocaine rated them as causing similar "highs," and were unable to discriminate between them. In addition, reports of lidocaine-induced euphoria have appeared when it was administered as an antiarrhythmic [2] and as a local anesthetic [4].

The present study compared the subjective and physiological effects of lidocaine with those of cocaine, a local anesthetic with clear abuse potential. When matched doses of each were administered to four volunteer subjects significant cardiovascular and subjective responses were produced by cocaine but not lidocaine.

METHOD

Subjects

Two male and two female normal adult volunteers ranging in age from 22 to 27 years, with prior histories of intravenous cocaine use participated. Each passed an initial screening consisting of an interview, physical exam, ECG, chest x-ray, urine analysis, and blood chemistry tests. All subjects signed consent forms which described the study, outlined any risks of this procedure, and indicated that cocaine and other drugs structurally similar to cocaine would be administered intravenously.

Procedure

Subjects were housed on the clinical research unit of Billings Hospital for the duration of the study. They participated in testing for approximately three hours each of the nine experimental days, and were free to engage in non-drug recreational activities of their own choice on the ward when not being tested.

Subjects were tested individually and wore appropriate physiological monitoring equipment to measure heart rate and blood pressure. In addition, two teflon intravenous catheters were inserted, one into each arm, prior to the daily experimental session. Drug was injected through one catheter and blood was withdrawn through the other for plasma level assays. Subjects sat alone in the test room, and were monitored from an adjacent room . There was a thirty-minute pre-drug period during which baseline data were collected. ECG was monitored continuously and heart rate

(measured as beat-to-beat time and averaged over two minute periods) and blood pressure were recorded every two minutes. Blood was withdrawn and questionnaires were filled out during this period. This was followed by a three ml intravenous injection of saline or drug dissolved in saline. The session continued for 120 minutes. Blood was withdrawn for cocaine or lidocaine plasma levels at 5, 15, 30, 60 and 90 minutes after intravenous injection. Questionnaires were filled out at those times as well as at 120 and 240 minutes post-drug. These questionnaires included:

Profile of Mood States (POMS)

This is an experimental version of the 65-item POMS described and validated by McNair *et al.* [12], and is a 72-item five-point adjective rating scale, the results of which can be factor analyzed into eight mood clusters: Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness and Elation. Two derived scores can also be obtained: Arousal is the sum of the Vigor and Anxiety scores minus the sum of the Confusion and Fatigue scores, and the Positive Mood score is made up of the Elation minus the Depression scores.

Addiction Research Center Inventory (ARCI)

This is a short form of the 550-item ARCI [6], consisting of 49 items compiled by Martin *et al.* [13], which have been shown to be sensitive to the effects of a number of different stimulant drugs. They were taken from a sedative scale (Pentobarbital Chlorpromazine Alcohol General, PCAG), three stimulant scales (Benzedrine General, BG; Morphine Benzedrine General, MBG; and Amphetamine, A) and a scale measuring dysphoric and psychotomimetic changes (LSD).

Rating

This is a locally developed questionnaire consisting of six lines, each 10 cm long. The lines are labeled "hungry," "down," "sedated," "anxious," "stimulated," and "high." Subjects indicate how they feel by placing a mark along each line labeled, at the left side, "not at all" and at the right side, "extremely." A score is obtained by measuring the percent of the line falling to the left of the subject's mark.

Subjects were asked to indicate what they had received each day: drug, placebo or other. One intravenous injection was administered each day. Saline was always administered on the first day of the study in order to acquaint each subject with the procedures, and the data from this day were not included in subsequent analyses. During the next eight experimental sessions a series of three cocaine or lidocaine doses (16, 32 and 48 mg) plus a saline placebo were administered. Half the subjects received the cocaine series first and half received the lidocaine series first. Doses were arranged according to a modified Latin square balanced for order and the dose regimen is indicated in Table 1. Subject 63 did not receive 48 mg cocaine because of a substantial blood pressure response to 32 mg. Instead, 16 mg was given twice, once on day 7 when 48 mg was scheduled and once on its regularly scheduled day.

Data Analysis

Questionnaires. Results from the two placebo sessions were averaged to obtain placebo session data against which drug data were compared. Scores for each of the POMS, ARCI and Line length subscales were analyzed using separate two-way (Drug × Time) within-subjects ANOVAs.

TABLE 1
COCAINE AND LIDOCAINE DOSE REGIMEN

	Subject Number			
Day	61	62	63	65
1	Saline	Saline	Saline	Saline
2	32L	16C	Saline	48C
3	48L	32C	16L	Saline
4	Saline	48C	32L	16C
5	16L	Saline	48L	32C
6	Saline	48L	32C	16L
7	16C	Saline	16C	32L
8	32C	16L	Saline	48L
9	48C	32L	16C	Saline

L=Lidocaine; C=Cocaine.

When a significant ($p<0.05$) Drug × Time interaction was found, post hoc analyses (using Fisher's LSD) were conducted to determine which drug or doses significantly differed, and at which times these differences occurred. Scores were described as different from placebo only when that difference was found to be significant.

Physiological measures. The data collected prior to each drug or saline injection were averaged each day to obtain a baseline value against which the data collected after that injection could be compared. The data in Tables 2 and 3 were analyzed separately for cocaine and lidocaine using a within-subjects analysis of variance. The missing data for subject 63 at 48 mg cocaine was replaced with that subject's data at 32 mg. When a significant F was found, post hoc analyses (using Fisher's LSD) were conducted to determine which drug doses significantly differed from placebo. Scores were described as different from placebo only when that difference was found to be significant ($p<0.05$).

RESULTS

Cardiovascular Effects

In general, the cardiovascular effects of intravenous cocaine were similar to those reported elsewhere [3,14]. The major physiological change was in heart rate (Table 2) where peak increases over baseline rates during the first 30 minutes after cocaine injection ranged from 34 to 68 beats/min, with one subject reaching peak heart rates as high as 145 beats/min. This is in contrast to the effects of intravenous saline where heart rate never peaked at more than 13 beats/min above its baseline rate. All doses of cocaine had effects significantly ($p<0.05$) different from those seen after placebo. The lidocaine effects were similar to those seen after saline, with changes ranging from a decrease of 3 beats/min to an increase of 11 beats/min. Blood pressure effects were smaller and more variable. Pulse pressure, the difference between systolic and diastolic pressure (mm of Hg) usually showed larger increases after cocaine than after lidocaine or saline (Table 3) and were significantly ($p<0.05$) increased after 48 mg cocaine.

Verbal Report of Drug Effect

In general, when the effects of cocaine were compared

TABLE 2

MEAN BASELINE HEART RATE (±S.D.) AND PEAK CHANGE DURING THE FIRST 30 MINUTES AFTER DRUG INJECTION

Drug and Dose (mg)	Subject 61		Subject 62		Subject 63		Subject 65		
	Baseline	Peak Change	Baseline	Peak Change	Baseline	Peak Change	Baseline	Peak Change	Mean Change
Lidocaine*									
0	76.0 ± 9.2	+ 3.0	50.5 ± 2.5	− 3.5	62.7 ± 3.1	+ 1.2	90.8 ± 7.5	+ 8.8	2.5 ± 5.1
16	74.9 ± 2.7	− 4.9	56.1 ± 4.2	− 3.1	73.4 ± 3.0	+ 0.4	100.4 ± 6.3	+11.4	1.0 ± 7.3
32	68.8 ± 6.8	+10.0	54.0 ± 7.7	− 3.0	66.1 ± 3.0	+ 5.9	92.7 ± 5.2	+ 5.7	3.9 ± 5.5
48	73.1 ± 2.2	+ 5.9	54.7 ± 4.5	− 4.7	63.8 ± 2.5	+ 5.2	85.3 ± 14.9	+ 9.3	3.9 ± 6.0
Cocaine†									
0	78.0 ± 3.0	+ 3.0	59.6 ± 2.0	+ 5.6	74.4 ± 3.7	+12.6	89.6 ± 7.0	+ 5.4	6.7 ± 4.1
16	76.7 ± 2.8	+39.3	51.3 ± 3.1	+41.2	74.2 ± 11.7	+44.8	90.3 ± 3.2	+23.7	37.4 ± 9.4
32	73.7 ± 8.5	+60.3	54.6 ± 2.4	+34.4	74.6 ± 1.8	+60.4	92.6 ± 4.8	+40.4	48.9 ± 13.5
48	77.2 ± 6.4	+67.8	55.7 ± 1.1	+42.3	—	—	68.2 ± 3.6	+55.8	55.3 ± 12.8

*No dose of lidocaine had effects significantly different from placebo.
†All doses of cocaine had effects significantly different from placebo ($p<0.05$).

TABLE 3

MEAN BASELINE (PRE-INJECTION) PULSE PRESSURE (±S.D.) AND PEAK CHANGE DURING THE FIRST 30 MINUTES AFTER DRUG INJECTION

Drug and Dose (mg)	Subject 61		Subject 62		Subject 63		Subject 65		
	Baseline	Peak Change	Baseline	Peak Change	Baseline	Peak Change	Baseline	Peak Change	Mean Change
Lidocaine*									
0	44 ± 10	− 5	40 ± 4	+18	60 ± 3	0	39 ± 8	+12	6.2 ± 10.6
16	42 ± 8	− 2	47 ± 7	+ 8	61 ± 4	3	43 ± 10	+ 3	3.0 ± 4.1
32	41 ± 6	− 2	44 ± 4	+12	66 ± 4	− 6	44 ± 13	−10	− 1.5 ± 9.61
48	38 ± 5	+ 3	43 ± 7	+13	58 ± 8	+ 3	44 ± 9	0	4.8 ± 5.7
Cocaine†									
0	48 ± 8	+ 2	43 ± 5	− 1	57 ± 5	+ 8	54 ± 11	+11	5.0 ± 5.51
16	44 ± 7	0	46 ± 8	+14	60 ± 4	+23	39 ± 8	+14	12.8 ± 9.5
32	41 ± 7	+10	42 ± 5	+25	58 ± 5	+50	47 ± 5	+15	25.0 ± 17.8
48	41 ± 10	+17	38 ± 4	+28	—	—	38 ± 11	+21	22.0 ± 5.6

=No dose of lidocaine had effects different from placebo.
†48 mg cocaine had an effect significantly different from placebo ($p<0.05$).

with those of placebo, there was a dose-related increase in stimulant-related scale scores on all three of the questionnaires used. Lidocaine, on the other hand, did not have this effect. Analysis of variance indicated that the mean POMS scores for Vigor, Elation, Confusion, Friendliness, Positive Mood and Arousal were significantly ($p<0.05$, Fisher's LSD) different from placebo at 5 and 15 minutes after cocaine while the Anxiety, Depression, Anger and Fatigue scores showed no drug related changes. The Arousal and Vigor scores continued to remain significantly elevated through 60 minutes post-cocaine. The same dose-related significant increases after cocaine were seen for ratings of "stimulated" and "high" through 60 minutes post-drug. On the ARCI, at 5 minutes after cocaine administration, the LSD, A and MBG scale scores were significantly elevated above placebo for all doses of cocaine tested. This elevation was also seen at 15 minutes post-cocaine on the MBG and A scales for 16 and 32 mg cocaine, but not 48 mg. Figure 1 presents data for the POMS Vigor score, the line length "high" score, and the MBG score of the ARCI for cocaine over the two-hour experimental session. These data are representative of all those in which a significant Drug × Time interaction was obtained. As can be seen, for the Vigor and "high" scores, the effects of 16, 32 and 48 mg were all significantly different from placebo for at least 30 min after drug administration.

Intravenous administration of lidocaine was not associated with significant changes in any of the ARCI, POMS or line length scores. Figure 2 presents data for the POMS Vigor score, the MBG score of the ARCI, and the line length "high" score after lidocaine and placebo. In no case was a

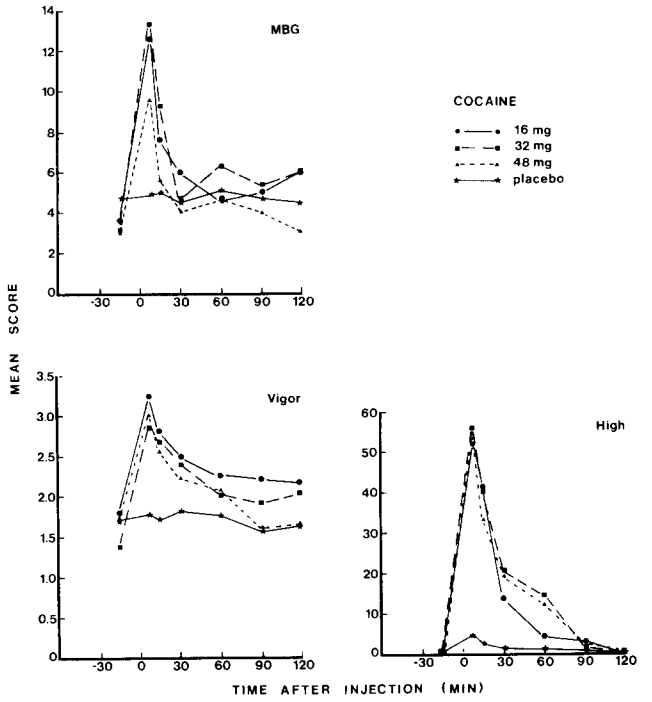

FIG. 1. The effects of intravenous cocaine on verbal report of drug effects. Mean scale score for the four subjects tested is shown for the MBG scale of the Addiction Research Center Inventory, the Vigor scale of the Profile of Mood States and the "High" rating of a locally developed rating scale. Scores on the MBG scale could range between 0 and 16, scores on the Vigor scale could range between 0 and 4, and "High" scores could range between 0 and 100. These questionnaires were administered prior to injection and 5, 15, 30, 60, 90 and 120 minutes after the injection.

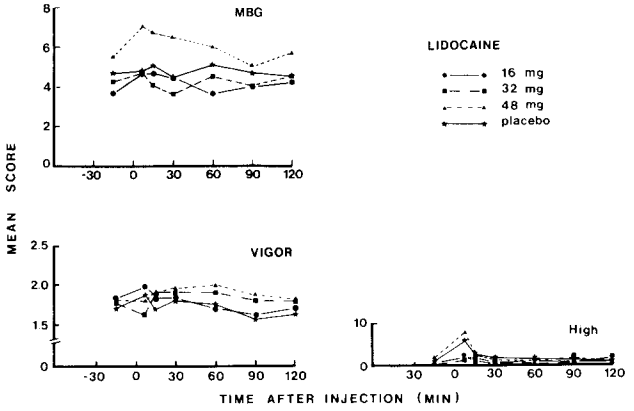

FIG. 2. The effects of intravenous lidocaine on verbal report of drug effects. See Fig. 1 legend for details.

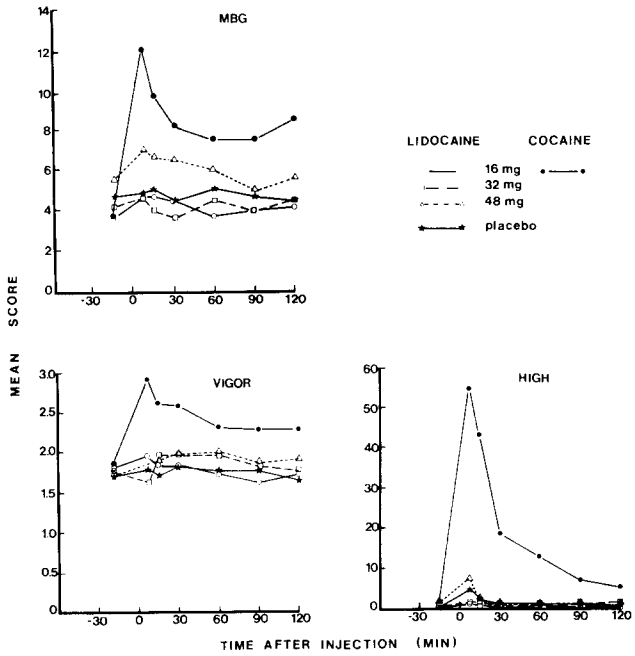

FIG. 3. A comparison of the effects of 16 mg intravenous cocaine with 16, 32 and 48 mg intravenous lidocaine. See Fig. 1 legend for details.

significant drug × time interaction attained. These data are representative of those collected after lidocaine on all three of the questionnaires used.

The effect of an intravenous injection of 16 mg cocaine was compared to the effects of intravenous injections of 16, 32 and 48 mg lidocaine. On the POMS, 16 mg of cocaine caused significantly ($p<0.05$) higher scores on the Anxiety, Friendliness, Vigor, Elation, and Arousal factors from 5 through 60 minutes after injection as compared with any dose of lidocaine. This was also true for the MBG, A and LSD scales of the ARCI and the "stimulated" and "high" scales on the drug effects rating scale (through 90 minutes post-drug). Figure 3 presents data on the POMS Vigor scale, the MBG scale of the ARCI, and the line length "high" scale comparing the mean response to 16 mg cocaine with that to 16, 32 and 48 mg lidocaine. The effects of 16 mg cocaine were significantly greater than any dose of lidocaine for at least the first 60 minutes after drug injection.

When asked to identify the substance they had received each day, all subjects called all cocaine doses "cocaine" and all lidocaine doses and saline, "placebo."

DISCUSSION

The present study was designed to measure the effects of intravenous cocaine and lidocaine in matched doses on selected cardiovascular and subjective measures. The data collected clearly indicated that intravenous injections of 16, 32 and 48 mg cocaine had substantial effects on heart rate and blood pressure as well as on verbal report of drug effect as measured by the Profile of Mood States, Addition Research Center Inventory, and a locally developed questionnaire assessing measures of "high" and "stimulated." Lidocaine, on the other hand, showed no consistent effect on any of the just described measures over the range of doses tested.

These data do not support those presented by Van Dyke *et al.* [15] in which the subjective effects of intranasal cocaine and lidocaine were compared. Those authors reported

that subjects gave similar ratings of "high" to cocaine and lidocaine, given in matched intranasal doses of 0.19, 0.38 and 0.75 mg/kg cocaine and lidocaine. The data they present show a possible trend towards increasing effects of both cocaine and lidocaine, but since no significance testing was carried out, it is not clear whether or not any of the scores obtained were different from those collected after placebo. From inspection of the data it appears that only the highest doses of cocaine may, in fact, have caused a rating of "high" significantly greater than that caused by placebo. In addition, the Van Dyck *et al.* [15] study administered their drug intranasally while in this study all drug was administered intravenously. If we take, for an example, a 70 kg person, their dose range was approximately 15–61 mg intranasal cocaine yielding, at a maximum, peak cocaine plasma levels of approximately 200 ng/ml [8]. In the present study, in which 16–48 mg was administered intravenously, peak cocaine plasma levels at the highest dose reached 700 ng/ml. Cocaine blood levels of that magnitude clearly caused subjective and cardiovascular effects which were significantly different from placebo, and the magnitude of the effect may have made it possible to differentiate the effects of cocaine from those of lidocaine.

Eight mg of intravenous cocaine is sufficient to cause substantial cardiovascular and subjective effects in humans [3]. In contrast, the present study found that doses of lidocaine up to 48 mg were not discriminable from saline. Data from the animal laboratory comparing the potencies of cocaine and lidocaine have been variable, but it has been estimated that comparable effects can be obtained with a lidocaine dose of 3–9 times the cocaine dose [11,16]. It is possible that higher lidocaine doses would have had measurable effects in the present study but the potential cardiovascular toxicity [1,4] of those doses precluded their use.

Based on the data collected with up to 48 mg lidocaine, we would not predict that it will act as a reinforcer in humans. This is in agreement with infra human studies where it has been found that lidocaine is not self-administered [16]. There have, however, been reports of the self-administration of other local anesthetics by non-human research subjects [5, 7, 9, 16]. As pointed out by Ford and Balster [5] only those local anesthetics with an esteratic linkage (e.g., procaine and proparacaine), converted into an alcohol during metabolism, have been shown to be self-administered in the animal laboratory. An investigation of the subjective and reinforcing effects of procaine in humans would therefore be useful in further determining the concordance between the studies in animals and humans.

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