Cocaine-Induced Erythrocytosis and Increase in von Willebrand Factor

Evidence for Drug-Related Blood Doping and Prothrombotic Effects

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Background: Mechanisms that mediate cocaine-induced cardiovascular events following vasoconstriction are incompletely understood.

Objective: To examine the effects of cocaine in moderate doses on hematologic and hemostatic parameters that influence blood viscosity and thrombotic potential.

Methods: Changes in hemoglobin concentration, hematocrit, and red blood cell counts were measured in human subjects who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for long-term cocaine abuse, before and sequentially after moderate intranasal and intravenous doses of cocaine. Hemostatic parameters, including von Willebrand factor, fibrinolytic activity, fibrinogen, plasminogen activator inhibitor antigen, and tissue-type plasminogen activator antigen, were sequentially measured after intravenous cocaine or saline placebo with cardiac troponin subunits T and I.

Results: Hemoglobin level ($P = .002$), hematocrit ($P = .01$), and red blood cell counts ($P = .04$) significantly increased from 4% to 6% over baseline from 10 to 30 minutes after intranasal ($n = 14$) and intravenous ($n = 7$) cocaine administration in doses of 0.9 mg/kg and 0.4 mg/kg, respectively, with no change in white blood cell or platelet counts. There was a significant increase ($P = .03$) in von Willebrand factor from 30 to 240 minutes, peaking at 40% over baseline following intravenous cocaine administration in a dose of 0.4 mg/kg ($n = 12$), with no change after 0.2 mg/kg ($n = 3$) or placebo ($n = 6$). Other hemostatic factors, creatinine, blood urea nitrogen, and cardiac troponin subunits T and I showed no changes.

Conclusions: Cocaine induced a transient erythrocytosis that may increase blood viscosity while maintaining tissue oxygenation during vasoconstriction. An increase in von Willebrand factor without a compensatory change in endogenous fibrinolysis may trigger platelet adhesion, aggregation, and intravascular thrombosis.

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As the most frequently used illicit drug among patients presenting with chest pain to hospital emergency departments,1 cocaine may trigger acute cerebral and myocardial ischemia or infarction.2,3 Beyond vasoconstrictive effects shown in human coronary and cerebral circulations,4,5 cocaine may also induce a blood doping effect6 and alter plasma constituents that influence thrombogenicity.8 We therefore measured changes in hematologic parameters in human subjects, before and sequentially after the administration of moderate doses of intranasal and intravenous cocaine sufficient to produce significant changes in blood pressure and heart rate. Hemostatic factors, including von Willebrand factor (vWF), fibrinolytic activity, fibrinogen, plasminogen activator inhibitor (PAI-1) antigen, and tissue-type plasminogen activator (TPA) antigen, were similarly measured after intravenous cocaine or saline placebo to assess changes in thrombotic and fibrinolytic potential. Cardiac troponin subunits T (cTnT) and I (cTnI) were sequentially measured to assess silent injury to the myocardium.

RESULTS

Hemoglobin level ($P = .002$), hematocrit ($P = .01$), and red blood cell (RBC) counts ($P = .04$) significantly increased, from 4% to 6% over baseline following intranasal ($n = 14$) and intravenous ($n = 7$) administration of cocaine in doses of 0.9 mg/kg and 0.4 mg/kg, respectively (Figure 1). Significant elevations in hemoglobin and hematocrit occurred 10 minutes after both routes of cocaine administration and in RBC counts coinciding with peak plasma cocaine concentrations of $476.5 \pm 57.8$ nmol/L ($144.4 \pm 17.5$ ng/mL) and $774.2 \pm 56.8$ nmol/L ($235.1 \pm 23.2$ ng/mL), respectively.
SUBJECTS AND METHODS

Subjects aged 21 to 35 years who met criteria for long-term cocaine abuse, as described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, provided informed consent for participation in studies in the Alcohol and Drug Abuse Research Center of McLean Hospital, Belmont, Mass, under protocols approved by the hospital’s institutional review board and funded by the National Institute on Drug Abuse. Results of comprehensive medical and laboratory examinations were normal, and urine screens for substances of abuse were negative before participation using urine screening kits (Triage; Biosite Diagnostics, San Diego, Calif).

Double-blind studies were conducted with continuous noninvasive cardiovascular monitoring under direct supervision by a physician, with subjects in a resting semi-recumbent position. Cocaine hydrochloride (Mallinckrodt, St Louis, Mo) in powder form was used for nasal insufflation or dissolved in sterile water for intravenous injection after processing through a 0.22-μm millipore filter with negative results of testing for pyrogens using a limulus lysate test (Limulus Amebocyte Lysate assay; Whittaker Bioproducts, Walkersville, Md). Subjects received cocaine hydrochloride, either intranasally in a dose of 0.9 mg/kg using a modified snort-stick device, or intravenously in doses of 0.2 or 0.4 mg/kg in a 1-mL bolus for 1 minute, or saline placebo.

Blood samples were drawn through an indwelling intravenous catheter (Kowarski-Cormed Thrombo-resistant Blood Withdrawal Butterfly Needle and Tubing Set; DakMed, Inc, Buffalo, NY) in the opposite arm. Hemostatic factors and cocaine were assayed without cardiorespiratory symptoms or electrocardiographic changes of ischemia.

There was a significant increase (P = .03) in vWF after intravenous administration of cocaine hydrochloride in a dose of 0.4 mg/kg (n = 12), with no change after 0.2 mg/kg (n = 3) or saline placebo (n = 6) (shown as change in mean percent activity ± SEM in Figure 2). The increase in vWF peaked at 40% ± 18.5% over baseline and lasted from 30 to 240 minutes. Changes were similar among 6 male and 6 female subjects matched for age and body mass index, although baseline values were slightly higher in women. Fibrinolytic activity, fibrinogen, PAI-1 antigen, and TPA antigen showed no significant changes, although a circadian increase in fibrinolytic activity and decrease in PAI-1 were uniformly observed. Levels of cTnT remained within normal limits (<0.10 μg/L) and cTnI was undetectable (<0.35 μg/L) up to 4 hours after cocaine administration, with no changes in creatinine or blood urea nitrogen levels.

nmol/L (234.6 ± 17.2 ng/mL) after intranasal and intravenous routes, respectively. There were no changes in white blood cell or platelet counts after either route of cocaine administration. Cardiovascular parameters, including heart rate (P = .001) and systolic (P = .01) and diastolic blood pressures (P = .03), increased significantly following both routes of cocaine administration without cardiorespiratory symptoms or electrocardiographic changes of ischemia.

Although the practice of chewing coca leaf (Erythroxylon coca) spans centuries—as illustrated by the Andean Indians who measure distance across mountains by the number of “cochitas” required for a given journey—the toxic potential of cocaine has emerged in the modern era, with rapid systemic absorption after smoking, nasal insufflation, and intravenous injection. Since cocaine has been shown to alter hematologic parameters in animals and humans, we investigated sequential changes in complete blood cell counts in human subjects following moderate intranasal and intravenous doses of cocaine sufficient to produce significant changes in blood pressure and heart rate. The increase in hemoglobin levels, hematocrit, and RBC counts of 4% to 6% over baseline after both routes of cocaine administration was quantitatively similar to infusion of 2 units of packed RBCs, use of erythropoietin every other day for 6 weeks in doses of 20 U/kg, or chewing coca leaf during exercise.

Cocaine administration has been shown to induce splenic constriction in humans, with a 20% reduction in volume, as assessed by magnetic resonance imaging, which is temporally concordant with altered hematologic parameters. This constrictive effect contributes to a rapid
of cocaine on hemostatic parameters related to thrombogenic and fibrinolytic potential. There was a significant increase \((P = .03)\) in vWF from 30 to 240 minutes, peaking at \(40\% \pm 18.5\%\) over baseline following intravenous cocaine hydrochloride in a dose of 0.4 mg/kg \((n = 12)\) from 30 to 240 minutes, with no change after a 0.2-mg/kg dose or saline placebo \((n = 6)\), using the same assay for vWF as shown to predict recurrence of myocardial infarction in coronary heart disease.\(^{32}\)

Cocaine-induced coronary vasoconstriction may disrupt unstable atherosclerotic plaques,\(^{33}\) causing release of vWF from damaged vascular endothelium. This process may be mediated by stimulants such as catecholamines, thrombin, vasopressin,\(^{34}\) and cocaine, including production of high-molecular-weight multimers of vWF,\(^{35}\) which were not measured in our study. Cocaine may promote the adhesion and aggregation of platelets that release vWF from fibrils and glycoprotein Ib/IX receptors on platelets.\(^{36}\) Pharmacokinetic analysis of plasma cocaine and adrenocorticotropic hormone suggests that the increase in vWF has a direct effect on vascular endothelium\(^{30}\) similar to the release of immunoreactive endothelin.\(^{40}\)

Fibrinolytic activity, fibrinogen, TPA antigen, and PAI-1 antigen were unchanged after cocaine administration, indicating a lack of a compensatory rise in endogenous fibrinolysis, which has been shown to accompany exercise-enhanced levels of vWF.\(^{31-34}\) Such an imbalance in hemostatic factors, occurring as a consequence of cocaine, has been observed as an independent risk factor for the development of coronary artery disease\(^{48}\) and acute ischemic cardiovascular events.\(^{45-47}\)
Recent evidence supports the improved detection of ischemic myocardial injury using cTnT and cTnI.\textsuperscript{46-50} The diagnostic utility of cardiосpecific troponins for myocardial injury has been demonstrated in patients with unstable coronary artery disease\textsuperscript{51-53} and in cocaine-associated chest pain.\textsuperscript{54,55} Levels of cTnT remained within normal limits (<0.10 µg/L), and cTnI was undetectable (<0.35 µg/L) up to 4 hours after cocaine in these asymptomatic subjects, providing biochemical evidence against silent myocardial injury. Recent reports that an early rise in vWF predicts adverse outcome in patients with unstable angina and that enoxaprin has protective effects by reducing its release\textsuperscript{56,57} suggest a valve for low-molecular-weight heparin in cocaine-induced myocardial ischemia in addition to conventional treatments.\textsuperscript{58}

Based on the small sample size of our study, the hypothesis that cocaine promotes thrombogenesis mediated by altered blood viscosity and an increase in vWF should be regarded as preliminary. Areas for further study regarding cocaine include the measurement of changes in whole blood viscosity, in vitro effects on platelets, vascular endothelium, metabolism of vWF multimers,\textsuperscript{59} and assessment of drug tolerance.\textsuperscript{59} Clinical studies of enoxaprin in patients with cocaine-associated cerebral or myocardial ischemia may be of value. Cocaine-induced changes in blood viscosity from erythrocytosis, and a selective increase in vWF following vasconstriction, may contribute to the abrupt and transient increase in risk for acute MI associated with its use.\textsuperscript{2}

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