CURRENT CONCEPTS

THE MANAGEMENT OF COCAINE-ASSOCIATED MYOCARDIAL ISCHEMIA

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THE use of cocaine has reached epidemic proportions. Over 30 percent of men and 20 percent of women between the ages of 26 and 34 have used cocaine at least once.[1] Moreover, 23 million Americans have used cocaine at some time,[1] and 5 million use it regularly.[2] During the 1980s cocaine became the most frequently used illicit drug among patients presenting to hospital emergency departments.[3-5] Chest pain is the most common cocaine-related medical problem[6]; it leads to the evaluation of more than 64,000 patients annually for possible myocardial ischemia. Of these patients, 57 percent are admitted to the hospital,[7] at an annual cost of more than $83 million.

PATHOPHYSIOLOGY

The initial effect of cocaine on the cardiovascular system is vagotonic, producing a transient bradycardia. This is rapidly followed by an increased sympathetic stimulation that produces tachycardia and hypertension. Peripherally, cocaine produces a sympathomimetic response by inhibiting the reuptake of both epinephrine and norepinephrine while stimulating the presynaptic release of norepinephrine. The increased presence of norepinephrine at the postsynaptic alpha receptors accounts for the drug's stimulatory effects. The drug's mechanism of action in the central nervous system is less clearly understood. Cocaine may enhance the release of norepinephrine, block the neuronal reuptake of dopamine and excitatory amino acids, or do both.

Goldfrank and Hoffman have proposed a useful model for cocaine toxicity (Fig. 1).[3] Stimulation of the central nervous system leads to increased neuronal firing, which, coupled with reuptake blockade, exaggerates the sympathetic response. The sympathetic response leads to the peripheral manifestations of cocaine toxicity, including cardiovascular complications, and produces feedback that results in further central nervous system agitation (seizures and hyperthermia). This model helps clarify how the antagonism of cocaine's peripheral effects may be associated with central nervous system toxicity and provides a rationale for the management of cocaine toxicity.

Evidence of cocaine-induced myocardial ischemia, although largely circumstantial, has become more compelling in recent years. The likely principal contributing factors are coronary-artery vasoconstriction, thrombus formation in situ, platelet aggregation, and accelerated atherosclerosis.[8,9] Cocaine produces coronary vasoconstriction that can be reversed by phentolamine, an alpha-adrenergic antagonist,[10] and exacerbated by propranolol, a beta-adrenergic antagonist.[11] Cocaine-induced vasoconstriction occurs in both diseased and nondiseased coronary-artery segments. However, the effect is more pronounced in diseased segments.[12]

Cigarette smoking induces coronary-artery vasoconstriction through an alpha-adrenergic mechanism similar to that of cocaine.[13] Most cocaine users are also cigarette smokers, and the combination of habits has a synergistic effect on coronary vasoconstriction.[14] Cocaine affects platelets directly[15] and indirectly[16] through an alpha-adrenergic–mediated increase in platelet aggregability. Platelet aggregation induced by adenosine diphosphate is enhanced,[17] and concentrations of plasminogen-activator inhibitor are increased,[18] by the presence of cocaine. The formation of thrombi occurs in patients with cocaine-associated myocardial infarction whether or not underlying coronary artery disease is present.[8]

Long-term users of cocaine may be prone to premature atherosclerosis. The ability of cocaine to promote early atherosclerosis has been demonstrated in studies in animals,[19,20] and atherosclerosis is found with increased frequency in autopsies of young cocaine users.[21-24] Large clinical studies have found that 31 to 67 percent of patients with cocaine-associated myocardial infarction have atherosclerotic coronary artery disease.[8,25] Epicardial[26] and intramyocardial coronary artery disease[27] has been found in cocaine users with chest pain but without myocardial infarction.

The ability of cocaine to increase myocardial oxygen demand while decreasing coronary blood flow through vasoconstriction, as well as its enhancement of platelet aggregation, in situ thrombus formation, premature atherosclerosis, left ventricular hypertrophy,[24,28] hypertension, and tachycardia, makes the drug an ideal precipitant of myocardial ischemia (Table 1).

INITIAL EVALUATION

Cocaine causes complications in nearly all organ systems.[3] In addition to chest pain, symptoms such as dyspnea, anxiety, palpitations, dizziness, and nausea are frequent.[6] Because many of these symptoms suggest ischemic heart disease, the initial evaluation is usually directed toward ruling out myocardial infarction. In three retrospective studies of selected cohorts of cocaine users with chest pain, the incidence of myocardial infarction ranged from 0 to 31 percent.[29-31] Two prospective studies found a frequency of myocardial infarction of approximately 6 percent.[7,32]

The typical patient with cocaine-associated myocardial infarction is a young tobacco-smoking man with a history of repetitive cocaine use but few other cardiac risk factors.[8,9] Demographic or historical factors have not been identified that can reliably predict or rule out

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acute myocardial infarction in subjects with cocaine-associated chest pain.[7] Neither the location, duration, or quality of chest pain nor the symptoms associated with it are predictive of myocardial infarction.[7] Although most patients have symptoms within 24 hours of drug use,[7-9,29] cocaine withdrawal may also result in myocardial ischemia.[33]

Interpreting the electrocardiograms of patients with cocaine-associated chest pain is difficult. Electrocardiograms are abnormal in 56 to 84 percent of patients with cocaine-associated chest pain[7,29-31]; and as many as 43 percent of cocaine-using patients without infarction meet the standard electrocardiographic criteria for the use of thrombolytic agents.[31] J-point and ST-segment elevation due to early repolarization or left ventricular hypertrophy often makes the identification of ischemia more difficult in these patients.[31,34]

Myocardial infarction occurs in some cocaine users with normal or nonspecific electrocardiographic findings.[7,32] In one study, patients with myocardial infarction were as likely to present at hospital emergency departments with normal or nonspecific electrocardiograms as with electrocardiograms indicating ischemia, a circumstance that led to the release of 15 percent of patients with myocardial infarction.[7] The sensitivity of the electrocardiogram for myocardial infarction is approximately 36 percent.[7] The specificity and the positive and negative predictive values are 90 percent, 18 percent, and 96 percent, respectively.[7] Because of the difficulty of identifying patients with cocaine-associated chest pain who are at low risk for myocardial infarction, most patients are admitted to the hospital.

Cardiac Chemical Markers

Cocaine use produces increased motor activity, hyperthermia, skeletal-muscle injury, and rhabdomyolysis. As a result, increased concentrations of creatine kinase and creatine kinase MB occur even in the absence of myocardial infarction.[32,35] After using cocaine, approximately 50 percent of patients have elevations in the serum creatine kinase concentration whether or not they are undergoing an infarction.[7] A pattern of continuously rising enzyme concentrations is more likely to occur in patients with myocardial infarction[7,25]; initial elevations that rapidly decline indicate infarction less commonly.[7,32]

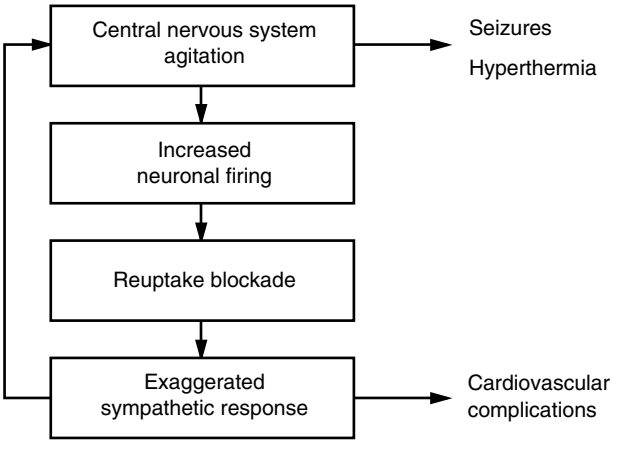

Figure 1. A Model of Cocaine Toxicity.
Reproduced from Goldfrank and Hoffman,[3] with the permission of the publisher.

Table 1. Principal Pathophysiologic Mechanisms of Cocaine-Associated Myocardial Ischemia.

Increased myocardial oxygen demand
Coronary-artery vasoconstriction
In situ thrombus formation
Premature atherosclerosis
Left ventricular hypertrophy

The immunoassay for cardiac troponin I has no detectable cross-reactivity with human skeletal-muscle troponin I, making it a more specific test than that for creatine kinase MB in assessing myocardial injury when concomitant skeletal-muscle injury exists.[36] Use of the immunoassay for cardiac troponin I may therefore enhance the accuracy of a diagnosis of myocardial infarction in patients with cocaine-associated ischemia.[35]

Treatment

The pharmacologic treatment of patients with ischemic chest pain due to the use of cocaine differs in several important ways from that of patients with the usual type of myocardial ischemia. Treatment recommendations based on the pathophysiology of cocaine-associated myocardial ischemia must take into account cocaine's toxic effects on the central nervous system and other vital organs. For example, aspirin must be avoided in patients at risk for subarachnoid hemorrhage. If treatment strategies could be altered by the knowledge of recent cocaine use, rapid bedside toxicologic assays for the drug or its metabolites may be useful, since the patient's own reporting is not entirely reliable.[37,38]

There have been no well-designed, randomized, prospective clinical trials to compare treatment strategies for cocaine-associated ischemia. My recommendations are based on well-controlled trials in animals, experimental trials in the cardiac catheterization laboratory, observational studies, case series, and case reports. Because some of the recommendations may be controversial, the scientific rationale for the suggested approaches to treatment is shown in Table 2.

In experiments in animals, benzodiazepines attenuate the cardiac and central nervous system toxicity of cocaine.[39-41] Long-standing and widespread clinical experience supports their use as a first-line treatment for cocaine-intoxicated patients. In addition to their anxiolytic effects, benzodiazepines reduce blood pressure and heart rate, thereby decreasing myocardial oxygen demand. Benzodiazepines are recommended for pa-

Table 2. The Scientific Basis for the Recommended Approach to the Initial Management of Cocaine-Associated Myocardial Ischemia or Infarction.

Drug	Recommended as Therapy	Source of Evidence*			
		Experiments in human subjects	Case series or observational studies	Case reports	Experiments in animals
Benzodiazepines	Yes			X	X
Aspirin	Yes				
Nitroglycerin	Yes	X	X		
Phentolamine	In selected cases†	X		X	
Calcium-channel blockers	In selected cases†	X			X
Beta-blockers	No	X	X		X
Labetalol	No	X		X	X
Thrombolytic agents	In selected cases†		X	X	
Lidocaine	In selected cases†		X	X	X
Sodium bicarbonate	In selected cases†				X

*There have been no controlled clinical trials of any approach to the initial management of cocaine-associated myocardial ischemia or infarction.

†See the text for specific indications.

tients with cocaine-associated myocardial ischemia who are anxious, have tachycardia, or are hypertensive.

Aspirin should be administered to prevent the formation of thrombi. This recommendation is based on theoretical considerations,[15-17] the drug's good safety profile, and the extensive investigation of aspirin in patients with ischemic heart disease unrelated to cocaine, although there are no clinical data on the use of aspirin in patients with cocaine-associated myocardial ischemia.

Nitroglycerin limits the size of acute myocardial infarction and reduces infarct-related complications in patients with myocardial ischemia unrelated to cocaine. Sublingual nitroglycerin, in a dose sufficient to reduce the mean arterial pressure by 10 to 15 percent, reverses cocaine-induced coronary-artery vasoconstriction[42] and relieves symptomatic chest pain.[43] Therefore, nitroglycerin is recommended as a primary therapy for cocaine-associated myocardial ischemia.

Patients who continue to have severe chest pain after the administration of oxygen, benzodiazepines, aspirin, and nitroglycerin may be treated with either low-dose phentolamine,[44] verapamil,[45] or thrombolytic agents,[46] depending on the electrocardiographic changes and the clinical likelihood of myocardial infarction. Phentolamine, an alpha-adrenergic antagonist, reverses cocaine-induced coronary-artery vasoconstriction,[10] and electrocardiographic resolution of ischemia has been documented in some patients after the administration of phentolamine (unpublished data). The use of a low dose (1 mg) may avoid the hypotensive effects of the drug while maintaining the antiischemic effects.[44]

In studies of cocaine intoxication in animals, calcium-channel antagonists prevent malignant arrhythmias,[47] blunt negative inotropic effects,[48] limit increases in systemic vascular resistance,[48] and protect against myocardial infarction,[49] although the drugs may increase central nervous system toxicity and mortality.[50] In general, calcium antagonists have no proved benefit in acute myocardial infarction unrelated to cocaine. Verapamil, however, does reverse cocaine-induced coronary-artery vasoconstriction[45] and may therefore have a role in the treatment of refractory myocardial ischemia secondary to cocaine use. It should be administered after benzodiazepines to ensure sufficient central nervous system protection.

Beta-adrenergic antagonists, one of the mainstays of treatment of acute myocardial ischemia unrelated to cocaine use, should be avoided in patients who have recently used cocaine. These drugs enhance cocaine-induced coronary vasoconstriction,[11] increase blood pressure,[11] fail to control the heart rate,[51] increase the likelihood of seizures, and decrease survival.[40,52]

Although some patients have been treated with labetalol, a combined alpha–beta antagonist, without adverse consequences,[53,54] controlled experiments in animals and humans do not support its use. The beta-antagonist effects are much more potent than the alpha-adrenergic effects, and patients with pheochromocytoma have had unopposed alpha-adrenergic stimulation when labetalol was used.[55] In studies of cocaine intoxication in animals, labetalol increased seizure activity and mortality.[52] In humans, cocaine-induced coronary vasoconstriction was not lessened by labetalol.[56] Labetalol is therefore not recommended for treatment of cocaine-associated myocardial ischemia.

Theoretically, thrombolytic therapy is attractive for cocaine-induced ischemia because of the enhanced thrombogenesis associated with cocaine. Its safety, however, was questioned after 1 patient died of an intracerebral hemorrhage,[57] although no further major complications have been noted among 36 subsequent patients (frequency of major complications, 2.8 percent).[46] Although thrombolytic agents may be safe, several considerations continue to limit their use: the mortality from cocaine-associated myocardial infarction is extremely low in patients who reach the hospital alive[25]; the clinical benefit of thrombolytic therapy has not been demonstrated[46]; and young patients with cocaine-associated chest pain have a high incidence of early repolarization.[31,34] This last finding may prompt the unnecessary administration of thrombolytic agents to patients without myocardial infarction.[31,34,57]

I recommend a stepped approach to the treatment of patients with cocaine-associated myocardial ischemia. After treatment with oxygen and the establishment of intravenous access, benzodiazepines, aspirin, and nitroglycerin should be administered. Calcium antagonists or phentolamine should be considered as second-line therapy. If evidence of continued myocardial infarction persists after medical management, the strategy should then be to establish reperfusion with either primary angioplasty or thrombolytic therapy. When possible, the patient's current electrocardiogram should be com-

pared with earlier ones. If the ST-segment elevations are unchanged from prior electrocardiograms, diagnostic cardiac catheterization may be indicated and reperfusion, if necessary, can be accomplished with primary angioplasty. If the ST-segment elevations are new, it is reasonable to give the patient thrombolytic agents, in the absence of the traditional contraindications.

Some concern exists about the use of lidocaine to treat cocaine-induced arrhythmias, since both lidocaine and cocaine have proarrhythmic and proconvulsant effects mediated through sodium-channel blockade. Studies in animals have yielded conflicting data regarding the safety of these agents when taken in combination.[58,59] Limited data in humans suggest that lidocaine is safe several hours after cocaine use.[60] Sodium bicarbonate may represent a safer alternative for patients whose ventricular arrhythmias immediately follow cocaine use, since it reverses cocaine-induced QRS prolongation.[61] Cautious use of lidocaine to treat ventricular arrhythmias that do not immediately follow cocaine use is reasonable.

Cardiovascular Complications

Cardiovascular complications secondary to cocaine-associated myocardial ischemia are relatively uncommon,[7,8,25,29] and they usually occur soon after arrival at the hospital.[7,25] Life-threatening ventricular arrhythmias occur in 4 to 12 percent of patients with cocaine-associated myocardial infarction, and congestive heart failure occurs in 5 to 7 percent.[8,25,29] In a study of 136 patients with cocaine-associated myocardial infarction, there were cardiovascular complications in 36 percent; however, most complications (90 percent) occurred within 12 hours of presentation.[25] No patients died after arrival at the hospital. Complications are less common in patients with chest pain who do not have infarction, and patients who require treatment are usually identified by the time of arrival at the hospital.[7] Because of the low risk of late complications, patients with cocaine-associated chest discomfort may be ideal candidates for a 12-hour observation period.

Observation of Patients

The use of cost-effective evaluation techniques, such as 9- to 12-hour observation periods, to rule out myocardial infarction in low-risk patients with chest pain unrelated to cocaine use has become more common. A similar observation period may be appropriate for many patients with cocaine-associated chest discomfort because these patients appear to have a low incidence of cardiovascular complications, whether or not they have myocardial infarction.

Patients without infarction have an extremely low frequency of late complications.[7,32] Of patients with cocaine-associated chest pain, 6 percent have myocardial infarction.[7,30,31] Although 36 percent of patients with cocaine-associated myocardial infarction have cardiovascular complications, 94 to 100 percent of these patients can be identified by the use of electrocardiography, serial creatine kinase MB measurements, and observation for 12 hours.[25]

One retrospective study found that electrocardiographic evidence of ischemia, elevated creatine kinase MB concentrations, and cardiovascular complications in the first 12 hours after arrival successfully predicted late complications.[25] Hence, patients with these findings should be admitted to monitored beds. Estimates suggest that fewer than 1.6 of every 1000 patients with cocaine-associated chest pain who do not meet these criteria will have late cardiovascular complications. These estimates support the use of a 12-hour observation period.[25] However, this triage strategy still requires a prospective study for validation.

Long-Term Prognosis

The possibility that cocaine may accelerate atherosclerosis has important implications for the management of cocaine-associated myocardial ischemia. In a review of 24 patients with cocaine-associated myocardial infarction who were followed for a median of 4.5 months, 12 had recurrent ischemic chest pain and 8 had a second myocardial infarction, which suggests that such patients are at high risk for subsequent adverse events.[8]

There are analogies between cocaine-using patients without infarction and patients with unstable angina unrelated to cocaine. Many patients (40 percent) with cocaine-associated myocardial infarction have had prior episodes of chest pain,[8] and patients with cocaine-associated chest pain of new onset are at increased risk for infarction.[7] Cocaine-associated myocardial infarction, like unstable angina, has a circadian rhythm.[62] Despite these similarities, cocaine-associated chest pain may not need to be managed as intensively as unstable angina unrelated to cocaine. Moreover, drug rehabilitation may be at least as important for cocaine users as cardiovascular-risk assessment.

Patients with cocaine-associated chest pain have a one-year actuarial survival of 98 percent and an incidence of late myocardial infarction of only 1 percent.[63] Most deaths occur as a result of concurrent medical problems, such as infection with the human immunodeficiency virus. Since patients who have an episode of cocaine-associated chest pain are not at high risk for myocardial infarction or death during the ensuing year, urgent cardiac evaluation is probably not necessary for patients in whom acute myocardial infarction has been ruled out. Continued cocaine use, however, is associated with an increased likelihood of recurrent chest pain, and aggressive drug rehabilitation may therefore be useful.[63]

Diagnostic Evaluation

The diagnostic assessment of potential coronary artery disease in cocaine users remains poorly studied. Many clinicians have assumed that coronary vasoconstriction and vasospasm are the principal mechanisms responsible for cocaine-associated myocardial ische-

mia. The failure to recognize coronary artery disease in patients with cocaine-associated myocardial ischemia may contribute to the infrequency of diagnostic workups.[7]

Most patients with reversible defects revealed on exercise tests have underlying coronary artery disease.[64,65] On the other hand, negative results on stress tests may have limited value, because of the poor exercise tolerance of these patients.[65] Studies of coronary-artery anatomy have been done in cocaine users, predominantly in patients with myocardial infarction due to drug use, 31 to 67 percent of whom were found to have coronary artery disease, despite average ages ranging from 32 to 38 years.[8,25]

Secondary Prevention

Cessation of cocaine use is the key to secondary prevention. Recurrent chest pain is less common in patients who stop using cocaine, and fatal or nonfatal myocardial infarction is rare.[63] Since tobacco smoking enhances cocaine-induced coronary-artery vasoconstriction[14] and is associated with a more rapid onset of chest pain after cocaine use,[66] it too should be avoided. Modification of traditional risk factors may provide additional benefits. Aspirin prophylaxis may be useful to prevent platelet aggregation and the formation of thrombi. The value of oral nitrates or calcium-channel blockers remains unproved. Beta-adrenergic antagonists, although useful in other populations, should be avoided in patients who may again use cocaine. Unfortunately, patients with cocaine-associated chest pain often continue to use the drug; 60 percent report cocaine use in the year after an episode of chest pain.[63]

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