Cocaine, Myocardial Infarction, and β-Blockers: Time to Rethink the Equation?

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HISTORIC USE OF β-BLOCKADE IN COCAINE TOXICITY

In 1976 and 1977, Rappolt et al1-3 published reports advocating the use of intravenous propranolol in the management of cocaine toxicity because of the “strikingly specific antagonistic effects” they had observed in more than 50 cases of successful treatment of cocaine overdose in San Francisco. At the time, the presumed risks of cocaine overdose included cerebrovascular accident, lethal arrhythmias, and high-output congestive heart failure; the first report of myocardial ischemia and infarction as a result of cocaine use did not appear until 1982.4

Propranolol was widely used as the drug of choice for management of hypertension associated with acute cocaine intoxication, until 1985, when Ramoska and Sacchetti5 proposed that propranolol should be used with caution in cocaine intoxication because of its potential for “unopposed α-stimulation,” causing paradoxic hypertension. This initiated a shift to the current clinical practice of withholding β-adrenergic receptor antagonists (“β-blockers”) in patients with cocaine-induced acute coronary syndrome, a distinct deviation from the standard medical therapy for other patients with myocardial infarction.6-12 The provocative article by Dattilo et al in the current issue of Annals challenges this practice.13 They found that the incidence of myocardial infarction or death was not increased in patients with a positive urinary drug screening test for cocaine (benzoylecgonine). In fact, β-blocker use was associated with a decrease in these measures. Excessive adrenergic stimulation, including that associated with cocaine exposure, causes toxic effects on the myocardium,14-16 and they suggest that the well-established protective effect of β-blockade on cardiac muscle may be more important than its effect on the coronary arteries.17-20 Considered in light of this new data, the Rappolt et al solution to the cocaine–β-blockade equation may actually be correct.

β-BLOCKADE BECOMES CONTRAINDICATED

Since the initial case report in 1982,4 cocaine has been a well-recognized and accepted trigger for acute myocardial infarction. Angiographic studies demonstrating normal coronary arteries among some patients with myocardial infarction after cocaine exposure,21-23 as well as clinical experiments,24-26 supported the hypothesis that vasospasm played a dominant role in the pathogenesis of acute coronary syndromes triggered by cocaine. An influential study by Lange et al27 reported that patients exposed to nasal cocaine during cardiac catheterization and then challenged with intracoronary propranolol had coronary vasoconstriction that was potentiated by β-blockade. A very powerful image from this study demonstrated abrupt occlusion of the left circumflex artery in one subject that was reversed by nitroglycerine. The authors concluded “in patients with cocaine-induced chest pain, β-adrenergic blockade probably should be avoided.”

It is widely accepted that cocaine-induced chest pain equals spasm, and therefore β-blockers are contraindicated. This admonition was emphasized in several clinical reviews on this topic6,27 and in serial statements in the advanced cardiac life support guidelines promulgated by the American Heart Association. These guidelines indicate that the subgroup of patients with acute coronary syndrome caused by cocaine should be evaluated and treated differently than other patients with acute coronary syndrome. Although some authors disagree,28 this advice has been accepted as fact for more than 2 decades.

Two premises underlie the postulate that β-blockers are contraindicated in cocaine-induced chest pain and acute coronary syndrome: first, that cocaine-induced chest pain is predominantly due to vasospasm, and second, that β-blocker administration can, through unopposed α-stimulation, worsen coronary vasospasm and the hemodynamic effects of cocaine stimulation. Both of these hypotheses have a lack of rigorous investigation and instead rely predominantly on uncontrolled observations and clinical experiences.
MYTH 1: COCAINE CHEST PAIN = SPASM

Many of the early cardiac catheterization studies that demonstrated normal coronary arteries in patients with cocaine-induced myocardial infarction were performed before the inception of acute percutaneous coronary intervention. Cardiac catheterizations were performed in a delayed fashion, such that spontaneous thrombolysis of a coronary thrombus could not be excluded. Schachne et al., for example, argued that the finding of normal coronary arteries in a young patient with cocaine-triggered myocardial infarction suggested that "cocaine could cause coronary vasospasm and myocardial infarction"; however, the cardiac catheterization was performed a week after admission. Other catheterization studies have also questioned the role of coronary spasm in this disorder. Furthermore, acute myocardial perfusion imaging rarely demonstrates reversible coronary perfusion defects, consistent with vasospasm, among patients with cocaine-associated chest pain.

Although vasospasm may play a role, the pathophysiology of cocaine toxicity is complex. Cocaine increases blood pressure, pulse rate, and myocardial oxygen demand, but an increasing body of evidence indicates that coronary artery thrombosis may be the major pathway in cocaine-triggered acute myocardial infarction. In a review of 114 published case reports of cocaine-induced myocardial infarction, thrombus was present in 9 of 12 patients who underwent early catheterization, defined as being within 12 hours of presentation. Cocaine use has been reported to increase plasminogen-activator inhibitor, to increase endothelial reported to increase plasminogen-activator inhibitor, to increase endothelial

MYTH 2: COCAINE + β-BLOCKER → UNOPPOSED α EFFECT

The hypothesis of unopposed α receptor stimulation to explain a paradox increase in blood pressure induced by propranolol in cocaine intoxication can also be challenged. This hypothesis was first proposed by Ramoska and Sacchetti to explain their observation of a blood pressure increase from 170/118 to 180/140 mm Hg, with a concomitant decrease in pulse rate from 112 to 104 beats/min, after administration of propranolol in a single subject. Evidence for this hypothesis draws from cardiac catheterization studies showing that cocaine-induced vasoconstriction was exacerbated by propranolol; labetalol, an agent with combined α- and β-blocking activity, had no significant effect. In a series of 7 patients with cocaine intoxication treated with esmolol, a β-1 specific agent, exacerbation of hypertension was noted in 1 patient and hypotension was noted in another patient. Other evidence for deleterious effects of β-adrenergic receptor antagonism in cocaine toxicity relies on rodent or porcine models. Not only are these data limited by small numbers and model systems but also the use of systolic blood pressure, or coronary artery vasoconstriction, as a primary endpoint in assessing the utility of β-adrenergic blockade may not have clinical relevance, because the primary benefit of β-blockers in myocardial infarction is the prevention of reinfarction and ventricular fibrillation. The first problem with the unopposed α effect hypothesis is that blood pressure depends on factors besides vascular tone. An alternate explanation for the hemodynamic changes described in the Ramoska and Sacchetti case report would be that the decreased pulse rate caused increased end diastolic pressure and fiber length, with a resultant increase in ventricular contraction and blood pressure because of Starling's law. The second problem with the hypothesis is that hypertensive responses should be observed in a wide variety of conditions that are routinely treated with β-adrenergic receptor blockade. Catecholamines are liberated from chromaffin cells in the adrenal glands in a "general alarm reaction," causing both α- and β-adrenergic receptor stimulation, because endogenous catecholamines are either nonselective (epinephrine) or have a greater affinity for α-adrenergic receptors (norepinephrine). However, it has long been recognized that the β-adrenergic receptor subtype mediates the deleterious effects of excessive catecholamine stimulation on the myocardium, particularly tachycardia and increased myocardial contractility (which increases oxygen demand). β-Adrenergic overstimulation injures cardiac myocytes by causing calcium overload and necrosis, and the benefit of β-blockade in other conditions characterized by endogenous catecholamine stimulation, including congestive heart failure, subarachnoid hemorrhage, and the perioperative period, is now well established. Recently, 2 large retrospective reviews showed increased survival associated with β-adrenergic blockade in another cohort of patients with increased catecholamine levels: survivors of severe trauma. If there were a deleterious, unopposed α effect caused by β-adrenergic blockade in the presence of sympathetic stimulation, it would logically follow that β-adrenergic blockade would cause this response in any condition accompanied by endogenous catecholamine release.

PRACTICAL PROBLEMS WITH AVOIDING THE POTENTIAL RISK OF β-BLOCKADE

Beyond the theoretical concerns about the β-blocker/cocaine theory, there are practical issues posed by the clinical guidance. Despite the admonition to avoid β-blockers in this setting, patients with cocaine-triggered acute coronary syndrome are routinely treated with β-blockers. Why does this happen? Because illicit drug use is highly stigmatizing. Hollander confirmed that self-report is not reliable in identifying cocaine users. Emergency physician history taking about the cause of chest pain is also highly variable. Although urinary toxicology studies can be obtained to test for cocaine metabolites, these are not available in real time when treating an unstable patient, such as is the case with a patient with an ST-segment-elevation myocardial infarction (STEMI) triggered by cocaine.
POTENTIAL BENEFIT OF β-BLOCKADE?

In this issue of *Annals*, Dattilo et al13 performed a nonconcurrent medical record review study of patients admitted to telemetry, the ICU, and critical care unit during a 5-year period, who had a positive urine toxicology test result for benzoylecgonine. By defining exposure as the administration of β-blockers in the emergency department (ED) or hospital and the outcomes as either myocardial infarction after β-blocker administration or death, the authors sought to examine whether there was in fact evidence favoring either the accepted risk or postulated benefit side of the equation. If coronary vasospasm underlies the pathophysiology of cocaine-triggered myocardial infarction, one would anticipate an increased risk of myocardial infarction and possibly death among those treated contrary to equipoise. Perhaps it is appropriate to remember that in 1975, 4 Swedish investigators reported their positive experience using β-blockers in a cohort of 7 patients with advanced dilated cardiomyopathy who had resting tachycardia.53 Given the well-known effects of β-blockers as negative inotropes, physicians were reluctant to embrace this therapy until prospective clinical trials confirmed these findings.54 Some may argue that the recent results of the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMPETE) study have challenged the use of β-blockers in all patients with acute myocardial infarction, perhaps making the question moot.55 However, the COMMIT trial showed that, overall, β-blockers reduced rates of reinfarction and ventricular fibrillation; rates of cardiogenic shock were highest in elderly patients or those with hemodynamic instability,7 and the use of β-blockade remains a class I recommendation for patients with STEMI and non-STEMI/unstable angina and a core performance measure for the Centers for Medicare & Medicaid Services. The hypothesis that β-receptor blockade could actually be beneficial among those with cocaine exposure has not been tested, nor has the fundamental belief that patients with acute coronary syndrome and a positive urine screening test result for cocaine must be treated differently. Hollander6 observed in a footnote to his initial review of the treatment of cocaine-induced acute coronary syndrome that “there have been no controlled clinical trials of any approach to the initial management of cocaine associated ischemia or infarction.”

IS A CLINICAL TRIAL WARRANTED?

The authors suggest that a clinical trial is a logical next step. Some may reject the thought of studying β-blocker use in the setting of cocaine exposure as dangerous and lacking in equipoise. Perhaps it is appropriate to remember that in 1975, 4 Swedish investigators reported their positive experience using β-blockers in a cohort of 7 patients with advanced dilated cardiomyopathy who had resting tachycardia.53 Given the well-known effects of β-blockers as negative inotropes, physicians were reluctant to embrace this therapy until prospective clinical trials confirmed these findings.54 Some may argue that the recent results of the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMPETE) study have challenged the use of β-blockers in all patients with acute myocardial infarction, perhaps making the question moot.55 However, the COMMIT trial showed that, overall, β-blockers reduced rates of reinfarction and ventricular fibrillation; rates of cardiogenic shock were highest in elderly patients or those with hemodynamic instability,7 and the use of β-blockade remains a class I recommendation for patients with STEMI and non-STEMI/unstable angina and a core performance measure for the Centers for Medicare & Medicaid Services. The hypothesis that β-receptor blockade could actually be beneficial among those with cocaine exposure has not been tested, nor has the fundamental belief that patients with acute coronary syndrome and a positive urine screening test result for cocaine must be treated differently. Hollander6 observed in a footnote to his initial review of the treatment of cocaine-induced acute coronary syndrome that “there have been no controlled clinical trials of any approach to the initial management of cocaine associated ischemia or infarction.”

CONCLUSION

In a discussion of what he termed “toxicomythology,” Dart56 noted, “We must remove entrenched but inaccurate beliefs in the medical literature and challenge new assertions to ensure that they are scientifically valid.” Nordin et al should be recognized for their willingness to question the belief that β-blockade is deleterious among those with cocaine exposure. Emergency physicians must evaluate 2 distinct populations of cocaine-using patients with myocardial infarction: those who are acutely intoxicated by cocaine and those patients with acute
coronary syndrome in the context of previous (and possibly remote) cocaine exposure. The theory and evidence for withholding β-blockade in patients acutely intoxicated by cocaine, as reviewed here, have significant limitations and warrant further investigation. There is no support for extending cocaine, as reviewed here, have significant limitations and apparent beneficial effect of are not acutely intoxicated, clinicians should pursue the coronary syndrome and a positive urine cocaine test result, who are not acutely cocaine intoxicated, and clinicians who hesitate to be doing their patients a disservice. For patients with acute coronary syndrome and a positive urine cocaine test result, who are not acutely intoxicated, clinicians should pursue the apparent beneficial effect of β-blockade. For patients with acute cocaine intoxication, the solution to the β-blocker equation should be elucidated by further research and evidence, not opinion.

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