A RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED TRIAL: EFFECTS OF METOPROLOL ON ADVERSE OUTCOMES IN PATIENTS WITH COCAINE-ASSOCIATED CHEST PAIN

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A. Study Purpose and Rationale

Among patients seeking care in hospital emergency rooms, cocaine is the most commonly used illicit substance. In 1999, an estimated 1.5 million people reported being current users of cocaine and 3.7 million admitted to using cocaine within the previous year. (Office of Applied Studies, 2000) Cocaine is implicated in numerous cardiovascular events and because of its widespread use, the occurrence of cocaine-related angina pectoris, myocardial infarction, arrhythmias, conduction abnormalities, myocarditis, cardiomyopathy and sudden death from cardiac causes have increased.

The most common cocaine-induced cardiac consequence is chest pain. In 1995, an assessment of cocaine-associated chest pain prevalence revealed that in patients presenting with chest pain, 14-25% in urban hospitals and 7% in suburban hospitals had evidence of cocaine or cocaine metabolites on urine toxicology screening. (Hollander, 1995; Ann Emerg Med)

Several mechanisms are involved in the pathogenesis of cocaine-induced myocardial ischemia or infarction. Cocaine use results in potentiation of the response to sympathetic stimulation which leads to increases in heart rate, systemic arterial pressure and heart contractility, the three major determinants of myocardial oxygen demand. Furthermore, small amounts of cocaine cause vasoconstriction of the coronary arteries, thereby limiting the myocardial oxygen supply even in the face of increased demand. Finally, cocaine use is associated with increases in platelet activation and aggregation as well as plasminogen-activator inhibitor, possibly leading to in-situ thrombus formation. Therefore, in addition to the evidence that long-term cocaine use leads to accelerated atherosclerosis, formation of acute thrombi can occur in patients whether or not underlying coronary artery disease is present. Although these numerous factors have been implicated in the pathophysiology of cocaine-associated myocardial ischemia (CAMI), the relative contributions of each of these mechanisms has not been well defined. Initial case reports cited coronary artery vasoconstriction as the major mechanism but no study consistently demonstrated cocaine-induced vasoconstriction sufficient to cause symptoms or electrocardiographic changes consistent with myocardial ischemia questioning the predominance of vasoconstriction in the pathogenesis of cocaine-related myocardial ischemia. Many patients with CAMI do in fact have atherosclerotic coronary artery disease. (Hollander, 1997) Furthermore, autopsy series have found atherosclerosis in 50-63% of young patients who sustained cocaine-related deaths. (Tardiff, 1989) Therefore, cocaine-induced thrombosis may be an important mechanism in the development of CAMI.

It is estimated that over 64,000 patients are evaluated annually for cocaine-related chest pain in emergency departments. The pharmacologic treatment of patients with ischemic chest pain due to the use of cocaine differs from that of patients who present with myocardial ischemia not in the setting of cocaine use. There have been no well-designed, randomized, prospective clinical trials to compare treatment strategies for CAMI. The paucity of information that does exist includes observational studies, trials in animals, experimental trials in the catheterization laboratory, case series and case reports. In 2002, the ACC/AHA Task Force released their guidelines for the treatment of cocaine-related myocardial ischemia or infarction. (Braunwald, 2002) The guidelines recommend oxygen, aspirin, nitroglycerin and benzodiazepines as first-line agents and phentolamine, calcium antagonists and thrombolytics as second-line agents; beta-blockers are contraindicated.

Based on these guidelines, beta-adrenergic antagonists, one of the mainstays of treatment of acute myocardial ischemia unrelated to cocaine use, are generally avoided in patients with CAMI for fear of exacerbating the cocaine-induced coronary vasoconstriction. This is based on evidence from a single randomized, double-blind, placebo-controlled trial that beta-adrenergic blockade augments cocaine-induced coronary artery vasospasm. (Lange, 1990) This study enrolled patients without a prior history of cocaine use who were undergoing catheterization for evaluation of chest pain. 30 patients were randomized to intranasal cocaine or intranasal saline, followed by randomization of each group to intracoronary propranolol or intracoronary saline. The outcomes included mean change from baseline of the following variables: heart rate, arterial pressure, coronary sinus blood flow, coronary vascular resistance, transcardiac oxygen content difference and diameter of the coronary arteries. Administration of intracoronary propranolol after cocaine administration caused a further decrease in coronary sinus blood flow and an increase in coronary vascular resistance. Based on these findings, it was recommended to avoid beta-blockers in patients with CAMI. However, the data is weak and not clinically applicable. No demographic or historical characteristics about the patients were provided, cocaine-naïve patients were studied in a controlled setting and medications were administered in a non-reproducible fashion, and the variables measured may not necessarily correlate with true clinical outcomes. Despite the lack of applicability of this study, it makes it very difficult to design a randomized controlled trial studying the adverse outcomes versus benefits of beta-blockade in CAMI when expert opinion throughout the last decade has been to withhold beta-blockers from these patients based on the initial data.

Despite the lack of evidence, several reviews and articles go as far as to say that since beta-blockers can worsen vasoconstriction, they may increase the incidence of complications and perhaps even decrease survival in patients with cocaine-associated chest pain. While this hypothesis is reasonable in theory, there is no strong data to support it. Several studies looking at how common cardiac complications such as MI, arrhythmias, and CHF are in patients with cocaine-associated chest pain have shown divergent results. The COCHPA (Cocaine Associated Chest Pain) trial, a large prospective multi-center study determined a 6% prevalence of cocaine-associated myocardial infarction. Of the 246 patients included in the study, 12 patients (4.9%) had arrhythmias, four (1.6%) had congestive heart failure, and 2 deaths (0.8%) occurred. Therefore, adverse reactions totaled 7.3% (Hollander, 1994) A follow-up study by Hollander examining the one-year mortality and incidence of myocardial infarction post-hospital discharge revealed a 98% survival rate (with 6 deaths occurring; none from MI) and a 1% incidence of nonfatal MI over a one-year follow-up period. (Hollander, 1995) A retrospective cohort study of 250 patients also reported a 6% occurrence of MI in these patients but much lower rates of other cardiac complications (2.4% for arrhythmias and 0.4% for CHF). (Weber, 2000) No complication occurred more than 12 hours after arrival to the ED. Further investigations into the short-term morbidity and mortality associated with cocaine-induced myocardial ischemia revealed an even greater incidence of cardiovascular complications. Total adverse events were 36%, including arrhythmias in 31% and congestive heart failure in 5%. Acute in-house mortality was 0%. 90% of complications occurred within 12 hours of presentation. (Hollander, 1995; Arch Intern Med)

Therefore, myocardial infarction in patients who present with cocaine-associated chest pain is not uncommon, occurring in approximately 6% of cases. The risk of MI is highest in the period shortly after cocaine ingestion, estimated at 24 times over the baseline risk in the first hour after cocaine use. (Mittleman, 1999) Incidence of cardiovascular complications resulting from cocaine-related myocardial ischemia appear to vary widely based on studies thus far but also seem to be common, with arrhythmias occurring in 2 to 31% of patients, congestive heart failure 0.4 to 5% and death in less than 1%, especially within the 12 hour period after cocaine use. Therefore, after patients are discharged from the hospital, the subsequent risk of MI, other cardiovascular complications and death in patients with cocaine-associated chest pain appears to be low.

Among the three primary mechanisms that contribute to cocaine-induced ischemia or infarction, it is impossible to determine which mechanism is occurring when a patient presents with cocaine-associated chest pain. Ischemic chest discomfort from cocaine-induced vasoconstriction is indistinguishable from ischemia secondary to coronary atherosclerosis. Because CAMI is multifactorial

and the contribution of each mechanism is poorly understood, atherosclerosis and plaque rupture may be a more important causal factor than was previously believed. Given that beta-blockers are well-studied in non-cocaine-associated ACS, it is worth determining whether they could be beneficial in cocaine-associated ACS as well. Withholding beta-blockers from patients because they worsen the vasoconstriction with cocaine-associated coronary vasospasm may not be applicable to those patients in whom the primary mechanism causing chest pain is a ruptured plaque. In addition, it is unknown how long coronary vasospasm persists given the short half-life of cocaine. The majority of patients with cocaine-associated chest pain will likely come to medical attention at least one hour after the onset of their symptoms. If their episode of coronary vasospasm has terminated, a beta-blocker in this setting may be beneficial in promoting better cardiovascular outcomes in these patients. Furthermore, in patients who have a cocaine-induced elevated sympathetic state with sinus tachycardia and hypertension, beta-blockers may prove beneficial in lowering sympathetic tone.

Metoprolol is a lipophilic beta1-selective antagonist with no intrinsic sympathomimetic activity. In patients with acute myocardial ischemia unrelated to cocaine use, metoprolol decreases the overall mortality by 10% and reduces the odds of death by 23% (Freemantle, 1999). Metoprolol may have a benefit when added to standard treatments in promoting better cardiovascular outcomes even in cocaine-associated myocardial ischemia. I propose a large-scale randomized placebo-controlled trial to investigate whether treatment with metoprolol added to optimum standard therapy lowers the risk of adverse outcomes in patients with cocaine-associated chest pain.

B. Study Design and Statistical Analysis

The study will be a randomized, prospective, double-blinded, placebo-controlled clinical trial of patients with chest pain in the setting of recent cocaine use. It will evaluate the efficacy and safety of the beta-blocker metoprolol when given with standard therapy in such patients. Approval by the hospital's institutional review board will be obtained.

All study patients will be randomized to receive either placebo or treatment with metoprolol 12.5mg by mouth every 6 hours. Randomization as well as medication packaging and dispensing in a double-blinded fashion will be performed by the research pharmacy at the university-affiliated medical center.

The study will include 2000 patients and will have 80 percent power to detect a 5.0% relative reduction in risk. The smallest difference (or treatment effect) of clinical interest (SDCI) was chosen to be a relative risk reduction of 5% (i.e. 20% -> 15%). The power analysis shows that the average number of patients in the study should be 2000, with approximately 1000 patients being randomized to each study arm. This calculation is based on the following assumptions: 20% mean incidence of adverse outcomes in the placebo group and a mean relative risk-reducing effect of 5% of metoprolol.

Categorical variables will be reported as the percentage frequency of occurrence. Ninety-five percent confidence intervals will be reported for the primary outcome, the composite of refractory ischemia, nonfatal myocardial infarction, and death from cardiovascular causes. The results will be analyzed by the Chi-square test.

C. Study Procedure and Outcomes

Both treatment arms will be monitored closely during a 72 hour observation period for occurrence of adverse effects. Cardiac troponin I (cTnI) levels will be measured upon presentation and at six-hour intervals for a total of 3 serum samples. The presence of myocardial infarction will be defined by cTnI levels twice the institutional normal level to account for variation in the different immunoassays. Although cTnI is a specific marker for myocardial damage and an MI, there are variations in the sensitivity and specificity of various immunoassays, which may be related to a lack of standardization. Patients will also undergo telemetry monitoring for the duration of the hospitalization.

These treatments are required as part of the subject's clinical management. The patient may experience pain or discomfort from placement of an intravenous catheter or from blood drawing.

If patients experience no adverse events, they will likely be discharged from the hospital after the 3 day observation period. In the event of an adverse outcome, length of hospital stay will be dictated by the management of the acute event.

The hospital course and occurrence and timing of complications will be recorded. The primary outcome will be a composite of adverse events including refractory ischemia, nonfatal myocardial infarction, and death from cardiovascular causes. Secondary outcomes will be cardiac arrhythmias and congestive heart failure.

Refractory ischemia is defined as recurrent chest pain lasting more than five minutes with new ischemic electrocardiographic changes while the patient is receiving optimal medical therapy (including intravenous nitrate unless such therapy is contraindicated) and leading to additional interventions (such as thrombolytic therapy, cardiac catheterization, insertion of an intra-aortic balloon pump, coronary revascularization). Myocardial infarction is defined by elevation of the serum level of troponin to at least twice the upper limit of the normal reference range. Death from cardiovascular causes is defined as any death for which there is no clearly documented nonvascular cause.

Furthermore, all demographic and historical characteristics of the patients will be recorded. Demographic data will include the age, sex and ethnic group. Historical items documented will be medical histories, cardiac risk factors, past cardiac history, previous episodes of chest pain and time of last cocaine use as well as route of use and drug abuse patterns. Chest pain characteristics noted will consist of duration, quality and location of pain as well as associated symptoms of nausea, vomiting, dyspnea, syncope, diaphoresis or palpitations. Finally, EKG results and laboratory data will be documented as well.

D. Study Drugs

In addition to treatment with metoprolol or placebo, each arm of the study will receive the current standard of care. After treatment with supplemental oxygen and the establishment of intravenous access, aspirin, nitroglycerin and benzodiazepines will be administered to both groups. Dosing schedules are as follows: aspirin 325 mg by mouth once daily, nitroglycerin ointment 1 inch transdermally every 6 hours (for 12 hours on and 12 hours off) and lorazepam 2 mg by mouth every 6 hours. Calcium antagonists or phentolamine will be considered as second-line therapy. If evidence of continued myocardial ischemia persists after medical management, the strategy should then be to establish reperfusion with either thrombolytic therapy or primary angioplasty. All drugs utilized in this study are approved for acute coronary syndromes.

E. Medical Device

No medical devices will be used in this study.

F. Study Questionnaires

No study questionnaires will be used in this study.

G. Study Subjects

Inclusion criteria

- men and women
- over 18 years of age

- present with a complaint of precordial or left-sided chest discomfort less than 12 hours in duration and have a urine toxicology screen that is positive for cocaine
- presentation within 12 hours after the onset of symptoms
- stable hemodynamics at the time of presentation.

Exclusion criteria

- acute myocardial infarction or unstable angina within 28 days before presentation
- indication for treatment with beta-blockade
- contraindication to use of beta-blockers such as sick sinus syndrome, bifascicular block, 2nd or 3rd degree AV block unless treated with a pacemaker
- history of asthma or chronic obstructive pulmonary disease
- peripheral arterial disease with symptoms at rest or current treatment with drugs that have beta-blocking properties such as amiodarone
- beta-blockade within 2 weeks before enrollment
- procedures such as coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty planned or performed in the past 4 months
- unstable decompensated heart failure (pulmonary edema, hypoperfusion)
- supine systolic blood pressure lower than 100mmHg
- any other serious disease that might complicate management and follow-up.

The criteria for eligibility in this study include a complaint of chest pain. It is possible, however, that patients presenting without chest pain may have other symptoms consistent with ischemia (e.g. dyspnea, palpitations) and may be missed.

H. Recruitment of Subjects

ED physicians will initially screen all patients via questioning about recent cocaine use. If the clinical suspicion for cocaine use is high or the patient readily admits to cocaine use, the patient will be considered for this study. The ED physician will notify the study's principal investigator (PI) of the patient's potential eligibility. The PI will contact one of the research assistants who will evaluate the patient themselves and if deemed eligible, will discuss the study with the patient. The research assistant will obtain consent to participate in this study from all willing participants after risks, benefits and alternatives are explained. Patients will be excluded from the study if severely intoxicated. Otherwise, if patients are deemed competent and found to have capacity to make decisions, consent will be obtained from all willing individuals.

After written informed consent is obtained, patients will undergo measurement of cocaine and cocaine metabolites via urine toxicology screening with a highly accurate bedside urine test kit (specificity, 100%, sensitivity, 98%). After cocaine administration, the urine remains positive for cocaine metabolites for 72 hours. (Das, 1993) All eligible patients will be admitted to the hospital.

I. Confidentiality of Study Data

All study data will be coded. Study subjects will be identified with a unique code number. Data will be stored in a secure location, as per IRB regulations.

J. Potential Conflict of Interest

None of the study investigators have a financial interest, nor are they employed in any manner by the company that produces the study drug.

K. Location of the Study

An urban university-affiliated medical center emergency department (ED).

L. Potential Risks

The greatest potential risk in this study is if the potentiation of coronary artery vasoconstriction by the study drug leads to an increase in adverse outcomes. Vasoconstriction is augmented by beta-blockade in previous experimental studies but it is unclear if this has a significant clinical effect. A Data and Safety Monitoring Board, whose members are not affiliated with the institution and are unaware of treatment status, will periodically review the results of the study. Results will be analyzed after 25%, 50% and 75% of the expected number of adverse outcomes have occurred. The study will be terminated if there is significant demonstrated benefit or harm in either group.

M. Potential Benefits

The potential benefits of beta-blockers in patients with cocaine-related chest pain has not been elucidated. However, in patients with myocardial ischemia unrelated to cocaine, beta-blockers significantly alter the risk of morbidity and mortality. Subjects will benefit if we are able to demonstrate similar findings in our study population.

N. Alternative Therapies

The only alternative therapy at the present time is the current standard of care which is being utilized in this study in both treatment arms.

O. Compensation to Subjects

Study subjects will not be compensated for participation in this study.

P. Costs to Subjects

The subject will not incur any additional costs as a result of participating in this study.

Q. Minors as Research Subjects

This study does not include the participation of minors.

R. Radiation or Radioactive Substances

This study does not involve use of radiation or radioactive substances.

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