Background: Although β-blockers prevent adverse events after myocardial infarction, they are contraindicated when chest pain is associated with recent cocaine use. Recommendations against this use of β-blockers are based on animal studies, small human experiments, and anecdote. We sought to test the hypothesis that β-blockers are safe in this setting.

Methods: We performed a retrospective cohort study of consecutive patients admitted to the San Francisco General Hospital, San Francisco, California, with chest pain and urine toxicologic test results positive for cocaine, from January 2001 to December 2006. Mortality data were collected from the National Death Index.

Results: Of 331 patients with chest pain in the setting of recent cocaine use, 151 (46%) received a β-blocker in the emergency department. There were no meaningful differences in electrocardiographic changes, troponin levels, length of stay, use of vasopressor agents, intubation, ventricular tachycardia or ventricular fibrillation, or death between those who did and did not receive a β-blocker. After adjusting for potential confounders, systolic blood pressure significantly decreased a mean 8.6 mm Hg (95% confidence interval, 14.7-2.5 mm Hg) in those receiving a β-blocker in the emergency department compared with those who received their first β-blocker in the hospital ward (P = .006). Over a median follow-up of 972 days (interquartile range, 555-1490 days), after adjusting for potential confounders, patients discharged on a β-blocker regimen exhibited a significant reduction in cardiovascular death (hazard ratio, 0.29; 95% confidence interval, 0.09-0.98) (P = .047).

Conclusion: β-Blockers do not appear to be associated with adverse events in patients with chest pain with recent cocaine use.

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Cocaine is an illegal substance used by millions of Americans. By preventing reuptake of endogenous catecholamines, cocaine can lead to systemic vasoconstriction, coronary vasospasm, thrombus, and plaque formation, and, by increasing contractility and heart rate, an increase in cardiac oxygen demand. As a sodium channel blocker, cocaine may also be proarrhythmic, potentially resulting in malignant ventricular arrhythmias. Owing to these multiple effects, cocaine may trigger severe hypertension, myocardial ischemia, myocardial infarction (MI), and death. Traditional teaching dictates that β-blockers are contraindicated in the setting of cocaine-associated chest pain. Previous studies suggest that β-blockers may exacerbate coronary vasospasm and the toxic effects of cocaine by creating “unopposed” α-adrenergic stimulation. Recommendations against β-blockers in the setting of cocaine-associated chest pain are common and have been introduced into recent cardiology guidelines. These recommendations are based primarily on case reports and small catheter-based human studies. Of note, the only catheter-based study to show worsening of cocaine-induced vasospasm involved intracoronary propranolol. To our knowledge, no large clinical studies aimed at assessing the safety of systemic β-blockers in cocaine-associated chest pain have been performed.

β-Blockers have definitively been shown to improve outcomes after MI, and evidence to withhold this potentially life-saving therapy in the setting of cocaine-associated chest pain may not be sufficiently robust. While patients with cocaine-associated chest pain given


β-blockers may be at risk, many may also derive the same benefits afforded other populations with ischemic chest pain.

A recent study found a decreased incidence of MI among cocaine users given β-blockers in the emergency department (ED). However, only a small proportion of these patients were admitted with chest pain, and long-term mortality was not assessed. Therefore, to test the hypothesis that β-blockers are safe when administered to patients with chest pain and recent cocaine use, we studied short-term outcomes and long-term mortality in a cohort of patients with chest pain with positive urine toxicologic test results for cocaine, who did and did not receive β-blockers.

METHODS

We performed a retrospective study of consecutive patients admitted to San Francisco General Hospital between January 1, 2001, and December 31, 2006, with chest pain and urine toxicologic test results positive for cocaine. Patients were identified based on International Classification of Diseases, Ninth Revision (ICD-9) codes for chest pain, angina, or chest discomfort and positive urine toxicologic test results for cocaine using a previously established electronic database maintained by the Division of Internal Medicine at San Francisco General Hospital, San Francisco, California (The Health Records Electronic Data Set or “THREDS”). Patients with chest pain diagnosed as pulmonary in etiology while in the ED (such as pneumonia or pulmonary embolus) were excluded. Two reviewers (C.R. and R.G.S.) obtained data for each patient from both paper medical charts and the electronic medical record. A search of the US Department of Health and Human Services National Death Index using patient names, social security numbers, and birth dates was performed to determine deaths that occurred after admission. The primary predictor was receipt of a β-blocker in the ED, and the primary outcome was death. Of note, treatment of chest pain in the setting of recent cocaine use was not dictated by any established protocol, and β-blocker use was determined by the discretion of the treating physicians. Secondary predictors included the receipt of any β-blocker during the hospitalization and discharge on a β-blocker regimen. Secondary outcomes included peak troponin level in the first 24 hours of admission, ventricular fibrillation or ventricular tachycardia requiring defibrillation, need for intubation, and need for vasopressor agents. Cardiovascular death as determined by death certificates from the National Death Index was also a secondary outcome. The systolic blood pressure (BP) and electrocardiogram (ECG) recorded just prior to and just after receipt of a β-blocker was recorded; changes in BP and ECG findings were compared between those receiving β-blockers in the ED (most proximate in time to cocaine ingestion and initial chest pain) and those who only received β-blockers after transfer to the inpatient ward. When available from the index hospitalization or subsequent to the index hospitalization, reports of ECGs, stress tests, and cardiac catheterizations obtained at San Francisco General Hospital were also recorded.

Analyses were performed to examine any abnormal troponin I level (including levels in the “indeterminate” range) and troponin I level in the MI range. The following assays for troponin I were used: the Bayer Immuno 1 system (Bayer Corporation, Diagnostics Division, Tarrytown, New York) before June 2003; the Bayer ADVIA Centaur (Bayer Corporation, Diagnostics Division) from June 2003 to January 2005; and the Siemens Centaur 3-site sandwich immunoassay using direct chemiluminescence (Siemens Medical Solutions, Tarrytown, New York) from February 2005 to December 2006. A positive troponin level lower than 1.5 ng/mL (to calculate as micrograms per liter, multiply by 1.0) was considered indeterminate, and a troponin level higher than 1.5 ng/mL was considered to represent an acute MI. Troponin levels in the indeterminate or acute MI range were considered positive.

A positive test result for cocaine was determined by the presence of the cocaine metabolite benzoylecgonine in urine samples obtained while the patient was in the ED. From June 1993 to October 2003, this was done using the SYVA EMIT method—EMIT II Plus Cocaine Metabolic Assay (Syva Company, Dade Behring Inc, Cupertino, California). After December 2003, the Thermo Scientific Microgenics Cedia Assay (Microgenics Corporation, Fremont, California) was used. The cutoff for detection of benzoylecgonine for both of these assays was 300 ng/mL.

Normally distributed continuous variables are presented as mean (SD); continuous variables that were not normally distributed are presented as median and interquartile range (IQR). Continuous variables were compared using t tests (paired if appropriate) and Wilcoxon signed rank or rank sum tests as appropriate. Categorical variables were compared using the χ² test. Multivariate analysis was performed using linear regression analysis for continuous outcomes (eg, BP) and using a Cox proportional hazards model for time to death. The validity of linear regression models were verified by checking for normality of residuals and for equal variance by each dichotomous predictor. We checked the proportional hazards assumption 2 ways: first, we tested for correlation between scaled Schoenfeld residuals and time, and second, we plotted Kaplan-Meier survival curves against the fitted survival curves under the model, according to receipt of β-blockers. No apparent violations of the assumption were found. Regression coefficients and hazard ratios (HRs) are presented as point estimates with 95% confidence intervals (CIs). Covariates were selected for inclusion in the multivariate model based on convention or “face value” (eg, age and sex) or if they were associated with both the predictor and outcome with a P value of <.20. Two-tailed P values <.05 were considered statistically significant. Statistical analysis was performed using Stata software version 9.2 (StataCorp, College Station, Texas).

BASELINE CHARACTERISTICS

A total of 331 patients were admitted with chest pain and found to have a positive urine toxicologic screening result for cocaine during the 5-year follow-up period. All but 3 were admitted via the ED; of those, 151 (46%) received a β-blocker in the ED. The type and route of β-blocker given for that first dose was intravenous metoprolol in 113 (74%), oral metoprolol in 17 (11%), intravenous labetalol in 18 (12%), oral labetalol in 3 (2%), oral atenolol in 1 (1%), and oral propranolol in 1 (1%). A history of using cocaine within 48 hours of presentation was provided by the patient and documented in the medical record in 94 (30%) patients; per those histories, cocaine was most recently used a median of 24 hours (IQR, 12-48 hours) prior to the ED visit.

Table 1 displays the baseline characteristics of the patients who did and did not receive a β-blocker in the ED. Patients who received β-blockers in the ED were older, had higher presenting systolic BPs, and more of-

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Those who received a β-blocker in the ED experienced a decrease in their systolic BP (median change, −8 mm Hg; IQR, −21 to 3 mm Hg); this was a statistically significantly larger decrease in systolic BP than was observed in those who received their first β-blocker in the hospital ward (median change, +5 mm Hg; IQR, −17 to 4 mm Hg [P = .003]). Other medicines administered to those who did and did not receive a β-blocker in the ED are given in Table 2. After adjusting for other antihypertensive medicines received at the time of first β-blocker administration (including nitroglycerin, calcium channel blockers, ACEIs or ARBs, benzodiazepines, hydralazine, and clonidine) in a linear regression model, those who received a β-blocker in the ED had a mean 8.6–mm Hg greater decrease in systolic BP (95% CI, 14.7– to 2.5–mm Hg greater decrease) than those who received a β-blocker in the hospital ward (P = .006).

There were no significant differences in either baseline ECG findings or subsequent ECG changes between those who did and did not receive β-blockers in the ED (Table 3). The proportions with either positive troponin levels or troponin levels in the MI range were also not different between the 2 groups. The peak troponin level of the 36 patients receiving β-blockers who had an elevated troponin level (median, 1.4 ng/mL; IQR, 0.3 to 6.4 ng/mL) was not significantly different than the peak troponin level of other patients (median, 1.0 ng/mL; IQR, 0.2 to 12.4 ng/mL [P = .78]). Similar results were observed when restricting the analysis to only those who received a β-blocker within 6 hours of presentation (more proximate to the time of cocaine use). There were no significant differences in catastrophic events (such as requiring intubation, vasopressor agents, developing malignant ventricular arrhythmias, or death), nor was there a difference in length of stay between those who did and did not receive a β-blocker in the ED.
**DISCHARGE CHARACTERISTICS**

A total of 124 patients were discharged on a β-blocker regimen: 68 (55%) on a metoprolol regimen, 31 (25%) on an atenolol regimen, 19 (15%) on a labetalol regimen, and 31 (25%) on a propranolol regimen. Those discharged on a β-blocker regimen were more likely to be older, have a history of hypertension, and have a history of coronary artery disease; they were more likely to be discharged on a regimen of aspirin, statins, and nitrroglycerin.

**MORTALITY**

Of the 317 patients with information available from the National Death Index, 45 (14%) died over a median follow-up of 972 days (IQR, 555-1490 days). Eighteen (12%) of those who received a β-blocker in the ED and 27 (16%) of those who did not receive a β-blocker in the ED died (P = .38). Fourteen (12%) of those discharged on a β-blocker regimen died vs 29 (15%) of those not discharged on a β-blocker regimen (P = .44). Based on death certificate data, 19 (42%) of these patients died of cardiovascular causes. Neither receipt of a β-blocker (whether in the ED or any time during the hospitalization) nor being discharged on a β-blocker regimen was associated with incident mortality (Table 4). These findings persisted after eliminating those receiving or being discharged on a regimen of labetalol. Those with congestive heart failure, end-stage renal disease, a positive troponin level, and moderate to severe systolic function were more likely to die. No clear benefit or harm of β-blockers could be detected when restricting the analysis to those with congestive heart failure, a positive troponin level, MI, or reduced systolic function.

Adjusting for potential confounders did not meaningfully change any of the results related to either β-blocker receipt in the ED or at any time during the hospital stay as predictors of incident mortality. After adjusting for potential confounders (including age, race, sex, end-stage renal disease, outpatient ACEI or ARB use, and discharge on a regimen calcium channel blockers), discharge on a β-blocker regimen exhibited a trend toward lower risk of death (hazard ratio [HR] 0.53; 95% CI, 0.26-1.08 [P = .08]).

Being discharged on a β-blocker regimen did not significantly affect incident cardiovascular death (hazard ratio [HR] 0.64; 95% CI, 0.2-2.0 [P = .44]). After adjusting for potential confounders (including age, race, sex, history of end-stage renal disease, outpatient ACEI or ARB use, a positive troponin level, and discharge on a calcium channel blocker regimen), discharge on a β-blocker regimen was associated with a statistically significant 70% reduction in the risk of cardiovascular death (of HR, 0.29; 95% CI, 0.09-0.98 [P = .047]). Removing individuals dis-
charged on a regimen of labetalol and carvedilol from this analysis did not change the results.

COMMENT

β-Blockers did not appear to be harmful to patients with cocaine-associated chest pain. Specifically, there was no evidence of increased BP, increased troponin levels, worsening ECG changes, a greater need for intubation or vasopressor agents, more frequent malignant ventricular arrhythmias, or more death in patients with cocaine-associated chest pain who received β-blockers in the ED vs those who did not. This finding persisted after restricting the analysis to those who received β-blockers within the first 6 hours of presentation. In addition, patients with cocaine-associated chest pain discharged on a β-blocker regimen exhibited a nonsignificant point estimate in favor of decreased overall mortality, and, after adjustment for potential confounders, exhibited a statistically significant 70% reduction in cardiovascular mortality.

There are thought to be approximately 2 million cocaine users in the United States, and the drug is estimated to be involved in more than 300,000 ED visits a year. Cocaine is a powerful sympathomimetic drug that works by blocking reuptake of norepinephrine, dopamine, and epinephrine at adrenergic nerve terminals, leading to vasoconstriction, increased heart rate, and increased cardiac contractility. Coronary artery thrombus formation following cocaine abuse has been described, and the sodium channel–blocking properties of cocaine increase the risk of dangerous arrhythmias.

Despite the proven efficacy of β-blockers in the setting of MI, they are thought to potentially exacerbate the cardiovascular toxic effects of cocaine, leading to official recommendations against their use in the setting of cocaine-associated chest pain. The evidence against β-blocker use in chest pain in the setting of recent cocaine use rests on animal studies, which have shown a higher risk of mild seizures, increased mortality, and increased vascular smooth muscle constriction; the other study failed to show worsening or improvement of vasoconstriction with intravenous labetalol. A recent clinical study supported the safety of β-blockers in the setting of cocaine but did not specifically examine patients with chest pain and was not designed to assess long-term mortality. To our knowledge, our study is the first investigation of the effects of β-blockers in the setting of clinical chest pain associated with cocaine use, and we were unable to demonstrate any adverse effects.

Despite concerns that β-blockers might result in “unopposed” α-adrenergic stimulation in the setting of cocaine and lead to hypertensive crises, we found that β-blocker use resulted in a significant reduction in BP, even after adjusting for the use of concomitant antihypertensive drugs. Of note, the starting BP was higher in those receiving β-blockers in the ED, therefore making a decrease in BP potentially easier to detect, but the important finding is that the addition of β-blockers did not cause a rise in BP as might be expected in the event of true unopposed α-receptor stimulation. Despite examining multiple outcomes, including troponin levels, ECG changes, and length of hospital stay, we could not detect any evidence of β-blocker toxicity. There were also no differences in catastrophic events, such as those requiring intubation, vasopressor agents, or leading to malignant ventricular arrhythmias or death.

A somewhat alarming 14% of this relatively young patient population died over a median follow-up of just over 2.5 years. Importantly, those who were discharged on a β-blocker regimen had a 47% decrease in the likelihood of death (P = .08) and a statistically significant 70% decrease in the risk of cardiovascular death (P = .047), demonstrating that these drugs may in fact have beneficial properties in this patient population. Of note, the point estimate decrease in cardiovascular death is likely overinflated and in part related to relatively small numbers in this subgroup analysis—it is important to emphasize that the upper end of the 95% CI for this estimate includes an HR of 0.98 (a 2% decrease in cardiovascular mortality).

Our study has several limitations. Because this was an observational study and the prescribing physician determined use of β-blockers, we cannot exclude the possibility that those prescribed β-blockers were somehow healthier or less prone to β-blocker toxicity in ways we did not measure. We attempted to address this by reporting differences in patient characteristics, demonstrating that those receiving β-blockers were in fact generally less healthy (eg, older, more hypertension) than those not receiving β-blockers. In addition, we performed multivariate analyses adjusting for potential confounders when appropriate. In fact, since approximately half of all patients with cocaine-associated chest pain received β-blockers in the ED, even if confounding by indication was present, the drugs were clearly safe in a large proportion of these patients. Although the number of patients was likely sufficient to confidently exclude large effects (eg, we had 80% power to detect a difference of proportions of 5% vs 11%, with a 2-tailed α level of .05), we cannot exclude the possibility that β-blockers are harmful in some subgroups. Although we used the gold standard of urine toxicologic tests to determine the presence of cocaine, we were unable to confirm the exact time of last ingestion. However, in those patients in whom the reported time of last ingestion was documented, there were no differences between those who did and did not receive β-blockers. In addition, our analyses were not significantly different when restricted to those who received β-blockers within 6 hours of initial triage (more proximate in time to the last cocaine ingestion). As the urine toxicologic test provides a dichotomous “yes” or “no,” we cannot exclude the possibility that those receiving β-blockers ingested lower doses of cocaine—however, given the lack of baseline differences in BP and clinical outcomes, a clinically significant difference in dose did not appear to be present. While some β-blockers, such as labetalol and carvedilol, have α-blocking properties that might minimize cocaine-related toxic effects, these were the least commonly used β-blockers and eliminating them from our analyses did not meaningfully change...
any of our results. Finally, we were unable to assess interim behaviors and treatments after discharge and relied only on data obtained from the index hospitalization and the National Death Index to determine long-term mortality. Only a prospective randomized trial can definitely address the majority of these limitations.

In conclusion, administration of β-blockers to patients with cocaine-associated chest pain appears to be safe and may even be beneficial. Our patients with cocaine-associated chest pain exhibited a high mortality rate, and outpatient β-blockers may help protect against cardiovascular death.

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