Drug and Alcohol Dependence 172 (2017) 88–93

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Higher prevalence of detectable troponin I among cocaine-users without known cardiovascular disease

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ARTICLE INFO

Article history:
Received 6 October 2016
Received in revised form
28 November 2016
Accepted 29 November 2016
Available online 19 January 2017

Keywords:
Cocaine
Benzoylecgonine
Cardiac injury
Troponin
cTnI

ABSTRACT

Background: While cocaine use is an established risk factor for acute cardiovascular complications, associations between cocaine use and markers of cardiac injury outside of acute hospital presentation remain poorly characterized. We leveraged advances in cardiac troponin (cTnI) testing to assess low but clinically meaningful levels of cardiac injury among cocaine users and non-users.
Methods: We conducted a case control study comparing cTnI levels by the presence of cocaine among patients presenting for non-cardiac care in an urban safety net hospital. Samples were chosen sequentially among those for which urine drug screens were ordered by providers hospital-wide.
Results: During 2015, 14% of all hospital drug screens ordered were cocaine-positive. Among unique persons providing cocaine-positive (N = 100) and cocaine-negative (N = 100) samples, 37% were female, 45% were African-American and the median age was 51. Detectable cTnI (> 0.02 ng/mL) was observed in 21 samples (11%). It was more common in subjects using cocaine (Adjusted OR = 2.81; 95% CI = 1.03–7.65), but not other drugs. Moreover, there was a significant correlation between concentrations of cTnI and the cocaine metabolite, benzoylecgonine (Spearman Correlation = 0.34, $p < 0.01$).
Conclusions: Among urban safety net hospital patients, 11% had detectable cTnI, and cTnI concentration was significantly correlated with benzoylecgonine concentration. While these preliminary results require additional confirmation, they suggest the potential utility of considering cocaine use as more than just an episodic exposure leading to acute cardiac events. The consideration of cocaine use as an ongoing chronic exposure leading to subclinical cardiac injury may improve risk-stratification and patient outcomes in populations where cocaine use is high.

1. Introduction

Cocaine use leads to 64,000 acute health care visits in the US annually (Maraj et al., 2010), and with a 42% increase in the total number of cocaine-related deaths between 2001 and 2014, it resulted in 5415 deaths in 2015 alone (National Institute on Drug Abuse, 2017). We recently reported a 3% annual mortality rate among homeless and unstably housed adult women living in San Francisco, California (Riley et al., 2013), which is roughly 10 times higher than women of the same age range (ages 45–54) in the general US population (Xu et al., 2010). While rates of co-morbidity were high in this cohort, existing health conditions did not account for the disproportionately high level of mortality. Instead, the most common cause of death was acute intoxication in which cocaine was detected at autopsy. This increase in mortality follows a national trend as deaths due to illegal drug use have increased across the US over the past decade (Miech et al., 2013).

As cocaine is a highly addictive substance, its use is highly prevalent, frequent and sustained over years in some populations, which leads to substantial health risks (Marasco et al., 2014; Spronk et al., 2013; Wolf, 2010). Specifically, the prevalence of crack cocaine use is approximately 50–60% among impoverished women (Riley et al., 2015; Torchalla et al., 2011). Between 30% and 40% of all cocaine

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http://dx.doi.org/10.1016/j.drugalcdep.2016.11.039
0376-8716/

users from communities with a high prevalence of poverty report daily use (Hayashi et al., 2016; Kuo et al., 2014), and the median number of years used among active cocaine users is as high as nine (Parker and Anthony, 2014). In addition, less than 50% of users from low-income communities have ever been in treatment (Booth et al., 2014).

According to the San Francisco Medical Examiner, at least one-third of cocaine-related deaths among San Francisco residents are directly linked to a cardiovascular event (CA Electronic Death Record System, data extracted 8/15/2012), which is consistent with existing research (Maraj et al., 2010; Phillips et al., 2009). Cocaine is a known risk factor for cardiovascular dysfunction (Grund et al., 2010; Lange and Hillis, 2001), and has been linked to a variety of complications, including thrombus formation (Stenberg et al., 1989), enhanced platelet activation (Kugelmass et al., 1993; Rezkalla et al., 1993; Rinder et al., 1994), premature atherosclerosis (Kolodgie et al., 1991), endothelial dysfunction (Gan et al., 1999), hypertrophy (Brickner et al., 1991) and aortic dissection (Hsue et al., 2002). It also exacerbates the effects of other drugs to increase cardiac complications (Tacker et al., 2006; Tacker and Okorodudu, 2004). Life-threatening arrhythmias and sudden death caused by arrhythmia related to cocaine use occur with and without cardiac risk factors (Hollander et al., 1994; Hollander et al., 1997; Hsue et al., 2007; Lange and Hillis, 2001; Minor et al., 1991).

Advances in biomarker testing are creating new opportunities to improve existing knowledge regarding cardiac risks, particularly subclinical conditions. Newer tests with higher levels of sensitivity are expanding the use of cardiac troponins I (cTnI) and T (cTnT), which are current gold standard biomarkers for detecting myocardial infarction (MI), to now detect lower levels of cardiac injury. These advances have led to the establishment of a dose-response association between troponin concentration and degree of cardiac damage (Wu, 1999). Lower concentrations of troponin can now be used to risk-stratify patients suspected of suffering an acute coronary syndrome (Apple and Collinson, 2012; Karras and Kane, 2001), and predict clinical outcomes including death among cardiac surgery patients and those with suspected acute MI (Hochholzer et al., 2011; Lurati Buse et al., 2009). The use of higher-sensitivity assays has led to the understanding that patients with detectable values far below the traditional 99th percentile cutoff, required for the diagnosis of an MI, are at increased risk for morbidity (Zethelius et al., 2006) and mortality (Jaffe, 2006; Waxman et al., 2006). Moreover, cTnI predicts clinical outcomes including death and a first coronary heart disease (CHD) event in individuals free from cardiovascular disease at baseline, indicating the importance of subclinical cardiac damage in the development of CHD and mortality (Zethelius et al., 2006).

More recently, the use of higher-sensitivity troponin has been tested, not only among hospitalized persons or patients receiving cardiac care, but also in the general population. Population-based cohort studies across the United States and Europe report that troponin is a predictor of cardiovascular events (McKie et al., 2014; Zeller et al., 2014), as well as all-cause mortality among individuals aged 30–65 (de Lemos et al., 2010). The addition of troponin to variables of established risk models improves prediction of cardiovascular death and cardiovascular disease in the general population (Blankenberg et al., 2010; Neumann et al., 2014), even in individuals free of cardiovascular disease at baseline (Blankenberg et al., 2016).

While prior work has used cardiovascular magnetic resonance (CMR) examination to indicate a high prevalence of cardiac damage in asymptomatic cocaine users (Aquaro et al., 2011), simpler and lower-cost methods of identifying cardiac injury, such as measuring peripheral cardiac troponin, have received little attention. Given that higher sensitivity troponin is now recognized as a strong predictor of future cardiac events in the general population, significant associations between cocaine and troponin could be used, not only for the treatment of existing cardiac conditions, but for prevention efforts to deter serious future dysfunction. Few studies have compared troponin concentrations by cocaine use outside of acute MI, and those that have, found no significant difference (Epelde et al., 2000; Hollander et al., 1998). However, previous studies evaluating this association are limited by small sample sizes and older, less sensitive troponin assays. Further work in this area has the potential to influence risk assessment and risk stratification in populations that include a high proportion of cocaine users.

To test the hypotheses that cocaine use is associated with detectable concentrations of cTnI, and higher concentrations of cocaine are correlated with higher levels of troponin, we conducted a case-control study of patient samples from inpatient and outpatient health care units, with the exception of cardiology, at an urban safety net hospital.

2. Material and methods

We conducted cTnI testing among remnant serum from patients receiving lab services in health care units throughout San Francisco General Hospital. During two six-week periods occurring from June 1st, 2015 through July 9th, 2015 and December 14th, 2015 through January 25th, 2016, specimens were sequentially obtained among those for which urine drug testing was ordered by a health care provider and accompanied by a serum sample. Drug screens throughout all hospital units, except cardiology, were processed by a single lab, thus specimens for the current study came from patients presenting for non-cardiology care hospital-wide.

To isolate the effect of cocaine, we restricted samples to those negative for amphetamines. This was done to minimize synergistic effects from commonly used stimulants other than cocaine, which are often difficult to analyze and understand in small cross-sectional studies. Given that effects from depressants oppose those of stimulants, and would therefore not likely have synergistic effects with cocaine, depressants were considered as potential confounders and no restrictions on depressant use were imposed during recruitment. The first 100 specimens to test positive for cocaine and/or the cocaine metabolite, benzoylecgonine (cocaine/benzoylecgonine), and negative for amphetamines, were considered cases; the first 100 specimens to test negative for cocaine, benzoylecgonine and amphetamines were considered controls. Samples were de-identified and linked to patient age, race and gender. Based on medical chart review of sequential eligible specimens, patients receiving care for cardiac complications were excluded, and only the first sample provided by any patient was included. Serum samples were batch tested for cTnI after all case and control specimens were collected. The study was considered to have minimal risk to human subjects as data were limited to de-identified retrospective medical records and testing of existing biological specimens. The study protocol was approved by the Institutional Review Board at the University of California, San Francisco, USA.

The primary outcome of the study was cardiac injury measured as cardiac troponin I (cTnI) (Siemens Healthcare Diagnostics, Inc.) >0.02 ng/mL. Measurements were conducted with Siemens ADVIA Centaur TnI Ultra®, a contemporary three-site sandwich immunoassay using direct chemiluminometric technology. Exposure covariates included age, race and gender, each obtained from the electronic medical record, as well as drug use (cocaine, benzoylecgonine, benzodiazepine, methadone, opiates, and oxycodone), which was directly measured by standard competitive immunoassays. Cocaine and benzoylecgonine concentrations were measured using a clinically validated liquid chromatography tandem mass spectrometry method. Due to direct effects of cocaine on