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Unexplained Sudden Death and the Likelihood of Drug Abuse

ABSTRACT: The common history of drug abuse in adults with an undetermined cause of death has led us to hypothesize that chronic drug abuse increases the risk of sudden death. To begin evaluating this hypothesis, we conducted a retrospective case-control study of 61 decedents whose cause of death remained undetermined following autopsy matched one to one to a control group of pedestrians or passengers killed in motor vehicle collisions. In 21 pairs, the case subject had evidence of drug abuse but the control did not, and in 5 cases the reverse was true. Analysis showed that individuals with an undetermined cause of death are 4.2 times more likely to have evidence of drug abuse than are victims of a motor vehicle collision.

KEYWORDS: forensic science, forensic pathology, drug abuse, cocaine, death

A few times every year our office investigates the death of a young adult with a history of drug abuse who has died suddenly and unexpectedly and in whom neither anatomical nor toxicological cause for death is found at autopsy. In forensic pathology, these deaths are likely to be classified as undetermined in cause and manner. In 1989 Nademanee et al. reported the occurrence of myocardial ischemia detected by Holter monitor in patients with a history of cocaine abuse who were shown to be free of cocaine at the time of ischemia by urine drug testing (1). Cocaine accounts for much of the illicit drug abuse seen in our practice. In light of the work published by Nademanee et al. we hypothesize that these undetermined deaths, where neither anatomical nor toxicological cause for death is found at autopsy, share a common history of drug abuse because drug abuse induces some change that persists after the drug is no longer detectable in the body. If our hypothesis is true, then this change, which is presumably at the molecular level, would increase the likelihood of sudden death. We have begun investigating this hypothesis by conducting a retrospective case-control study comparing the autopsy findings in these undetermined deaths to a control group who died suddenly as the result of a non-drug related accident. Our purpose in this study was to determine whether drug abuse is more prevalent in individuals who died of undetermined causes than is drug abuse in the general population of individuals dying suddenly and unexpectedly.

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Methods

We conducted a retrospective case-control study of deaths investigated by the Jefferson County Coroner/Medical Examiner Office, Alabama between 1986 and 2002. During this time the medical examiner's office was operating under a consistent medical examiner statute, and all deaths falling under its jurisdiction were certified by one of five forensic pathologists. The statute charges the office with the responsibility of investigating all sudden and unexpected deaths that have occurred in Jefferson County, Alabama. The nature of deaths investigated by our office and the toxicological screening for drugs of abuse remained constant throughout the course of this study. Cases for this study were identified by a computer search of our office database for all individuals between age 10 and 70 years whose cause and manner of death remained undetermined following an autopsy and toxicological analysis for ethanol and drugs of abuse. Decomposed remains were included in the study.

The control group was chosen to most closely represent a random sampling of the population of Jefferson County, Alabama. The decedents chosen for the control group were either pedestrians or passengers killed in a motor vehicle collision, that is, people who died suddenly and unexpectedly while engaged in ordinary pursuits. Every decedent in the control group received an autopsy and toxicology analysis for ethanol and drugs of abuse. The control group was age matched to the study group within 5 years of the age of the decedent in the study group and within 2 calendar years of the date of death of the decedent in the study group (to keep social trends and toxicological methods similar). Three of the study cases could not be matched to a control within these criteria and were therefore excluded from further study. The first suitable control found for a study case was paired with the study case, and then that pair was removed from further consideration for matching.

The charts of all study group and control group cases were reviewed for the circumstances surrounding death, a documented history of drug abuse, and any compelling physical signs at autopsy that indicated drug use, i.e., needle track marks, nasal septum perforation, or polarizing particles in foreign body giant cells within the lungs. In cases where the cause of death remained undetermined

following an autopsy, no physical finding that would reasonably account for death in light of the circumstances surrounding death was found upon review, that is, in none of these cases did the decedent have sufficient disease, such as cardiac hypertrophy, anomalous coronary artery circulation, severe coronary artery atherosclerosis, myocarditis, pneumonia, cirrhosis, intracranial hemorrhage, etc. to explain death. All toxicology results were noted, specifically the presence of cocaine or its metabolites, opiates, amphetamines, and ethanol as well as any other drugs or medications. Cocaine, opiates, and amphetamines were considered drugs of abuse for this study. Propoxyphene and marijuana were not counted as drugs of abuse for this study.

Toxicological analysis for drugs of abuse was done in each case by enzyme multiplied immunoassay (EMIT) for drugs of abuse on the Syva EMIT plus analyzer using EMIT reagents and calibrators according to the manufacturer, Syva, Palo Alto, CA. The EMIT assay detects amphetamines, barbiturates, benzodiazepines, benzoylecgonine, methadone, opiates, propoxyphene, and tricyclic antidepressants. Substances found on EMIT screen were confirmed by gas chromatography/mass spectrometry (GC/MS) performed on blood, liver, brain, or some combination of these matrices. Five mL of blood or 1 g of brain or liver was extracted with 10 mL of *n*-butyl chloride after adjusting the pH to 10 with NH_4OH. The organic layer was acidified by the addition of 5 mL of 1N HCl. The aqueous layer was made basic by the addition of 2 mL of concentrated NH_4OH and extracted with 0.2 mL CH_3Cl (2). Two μL of the CH_3Cl was injected into a Hewlett Packard 5971 GC/MS System (Palo Alto, CA) equipped with a 12.5 m by 0.2 mm HP-1 methyl silicone column. The column temperature was programmed from 70–280°C at 20°C/min. Helium carrier gas flow was 1 mL/min. A total ion scan was performed, in the scan mode from 40 to 400 mev. As an example, specific ions used by MS for identification of cocaine were 303, 182, and 82. In cases with a low concentration of cocaine our procedure would detect only ions 182 and 82; in that case the finding was reported as trace cocaine present, insufficient to quantify, and in this study such a result was interpreted as the individual being positive for cocaine and therefore having a history of drug abuse. A similar approach is taken for other drugs of abuse.

The lower limits for detection varied during the course of the study, with the tests becoming more sensitive as time passed. As an example, in the early years of the study the limit of detection for cocaine was 0.005 mg/L, but in 1999 a new instrument allowed detection of cocaine down to a level of 0.0001 mg/L.

Epidemiologists can compare the risk of an event, such as death, by calculating a risk odds ratio, which is simply a ratio of the risk of a certain event in one group compared to the risk of that same event in another group. In this study some, but not all, individuals in both the study group and the control group had a history of drug abuse. Thus each group could be said to have its own risk for how likely drug abuse was for a given individual within the group. As a simple example, if 15 of 100 individuals in a group had a history of drug abuse, then the chance (or "risk") that any one person in that group would abuse drugs would be 15% (15 in 100). Once the risk for each group is determined, the risks can be compared to each other by means of a ratio, thus forming the risk odds ratio. If the risk is identical in each group, then the ratio would be 1, and thus 1 is the null value. Increased risk is represented by a ratio greater than 1, and decreased risk, which would be a protective effect, is less than 1. In this study, a risk odds ratio of greater than 1 would indicate that decedents in the study group were more likely to have a history of drug abuse compared to the control group; whereas values of less than 1 would indicate the converse. The 95% confidence interval provides an indication of the precision of the relative risk estimate. If the 95% confidence interval straddles the null value of 1, then the significance of that particular risk odds ratio is dubious. Statistical analysis in this matched study is properly done by calculating the risk odds ratio between the control-study pairs that were not identical, that is, in which one member of the pair had evidence of drug abuse but the other did not. A discussion of the mathematical theory and application of this sort of paired analysis is on pages 251–3 of Rothman's *Modern Epidemiology* (3).

TABLE 1—*Evidence of drug abuse found in undetermined (study group) and accidental (motor vehicle collision) deaths. Note that each number in a cell refers to the number of matched pairs that satisfy the condition. For example, in 31 pairs both the study case and the control had no evidence of drug abuse, while in 21 pairs the study case had evidence of drug abuse but the control case lacked such evidence.*

	Control Group without Evidence of Drug Abuse	Control Group with Evidence of Drug Abuse	Total
Study group without evidence of drug abuse	31	5	36
Study group with evidence of drug abuse	21	4	25
Total	52	9	61

TABLE 2—*Summary of findings related to drug abuse in study group (cause of death undetermined) and control group (death due to motor vehicle collision).*

Finding	Study Group (Undetermined Cause)	Control Group (Motor Vehicle Deaths)
History of drug abuse	17	1
Compelling physical signs of abuse	6	0
Cocaine or metabolite in blood, urine, or bile	9	8
Amphetamine in blood or urine	0	1
Opiate in blood or urine	10*	0
Ethanol	27†	36

* 4 methadone, 3 hydrocodone, 2 codeine, 1 oxycodone.
† Includes 16 cases of decomposing remains.

Results

The study consisted of 61 pairs of decedents, and the results are shown in Table 1. In 21 pairs the case subject had evidence of drug abuse but the control did not; in 5 cases the reverse was true. The findings related to drug abuse in both the study group and the control group are shown in Table 2. Sixteen cases of decomposed remains were included in the study group. None of the cases in the control group were decomposed remains.

Comparison of the study group to the control group shows a risk odds ratio of 4.2 (95% confidence interval 1.6–11.1) for a history of drug abuse. In other words, an individual with an undetermined cause and manner of death is 4.2 times more likely to have evidence of drug abuse compared to an individual who dies in a motor vehicle collision as either a pedestrian or passenger. For this study $p = 0.0017$, so chance is an unlikely explanation for these results.

Comparison showed no significant difference between the two groups for the presence of coronary artery atherosclerosis or heart

mass. In multivariate analysis, only a history of drug use proved to be present in a significantly disproportionate number of cases.

Discussion

Unquestionably drugs of abuse can cause or contribute to sudden death independent of their intoxicating properties. Cocaine, for example, causes not only euphoria but also hypertension, contraction band necrosis in myocardium, and acceleration of atherosclerosis (4). Coronary artery atherosclerosis, myocardial hypertrophy, focal necrosis of myocardium, and focal scarring of myocardium can all cause death and occur at the gross or microscopic level rather than at the molecular level. In cases where the manner of death is undetermined, as in this study, these anatomical or microscopic findings (whether present as a result of drug abuse or not) are lacking to explain death. For this reason, we found no significant risk of the study group having an enlarged heart (mass greater than 450 g) or severe coronary artery atherosclerosis (at least one vessel narrowed by at least 50%) in comparison with the control group. Medications or individual drugs of abuse other than cocaine were present in such low numbers that meaningful conclusions about the role of an individual drug were not possible, although all the opiate and opioid drugs taken as a group were present as frequently as cocaine. If a history of drug abuse has increased the risk of sudden death, then cocaine is the single agent most likely responsible for that risk in our patient population.

The blood concentration of cocaine does not correlate to symptoms seen clinically in cocaine abusers (5), nor does the concentration correlate with likelihood of death (6). Clinical findings associated with drug use, such as ischemia, may not even be apparent at autopsy (7). Nademanee et al. examined cocaine addicts who had a high urine benzoylecgonine concentration upon admission to a drug treatment facility (1). The addicts were equipped throughout treatment with a cardiac monitor and were found to have myocardial ischemia manifesting as episodes of ST elevation within the first few weeks of withdrawal when they were shown to be negative for cocaine and benzoylecgonine in both blood and urine, a statistically significant increase in incidence compared to a control group. This research by Nademanee et al. suggests that cocaine can cause myocardial ischemia in long-term drug abusers, even when cocaine or benzoylecgonine is no longer detectable in the blood.

Given that the decedents in our study group lacked gross or microscopic change sufficient to explain death, then what sort of mechanism might be leading to death in light of the findings of Nademanee et al.? A few studies suggest possible mechanisms, but published research has focused on individuals presenting with acute symptoms or on animal models exposed to cocaine daily over a period of time but sacrificed while still receiving their daily dose of cocaine. In human addicts, chronic cocaine use has been shown to alter endothelial cell function, rendering the addicts susceptible to ischemic vascular accidents by thrombosis of injured vessels, accelerated atherosclerosis, or by vasoconstriction and vasospasm (8). In dogs, Jones and Tackett found that chronic cocaine treatment enhances the responsiveness of the left anterior descending coronary artery and the femoral artery to vasoactive substances, enhancing peripheral vasoconstriction and cardiac ischemia (9). Vasoconstriction and vasospasm need not leave visible evidence of occurrence at autopsy. Although vasoconstriction and vasospasm remain only possible mechanisms to explain our results in this study, they serve as guideposts for future avenues of research.

Various factors possibly influenced the results of our study. First, it might seem that the increasing sensitivity in identifying and quantifying drugs of abuse over the course of the study may have influenced our results, but this is not so. Had we chosen all our study group cases from the era where our limit of detection for cocaine was 0.005 mg/L and all our controls from the current era where our limit is 0.0001 mg/L, then our results would be biased. No such bias exists in our study, however, because we matched the controls to the cases in the study group not only by age (within 5 years of the age of the decedent in the study group) but also within 2 calendar years of the date of death of the decedent in the study group. As mentioned in the Methods section, this matching by date of death was done to keep social trends and toxicological methods similar. Therefore, in each pair we are making a similar, and valid, comparison. In other words, although it is always possible that we have missed offending toxicological substances below our limits of detection, our study design means that the chance of missing a low level in a case was equal in each group, thus eliminating systematic error.

The inclusion of decomposed remains in our study group may have caused us not to detect drugs in some cases in the study group. No decomposing remains were included in our control group, however, due to the nature of the control cases. Because decomposition hinders detection of cocaine, decomposition, if present, would artificially lower the risk odds ratio, and thus our finding that drug abuse is more likely in cases where death is undetermined would still be true.

Over the course of our study our office screened cases for fentanyl only if the circumstances surrounding death or history specifically indicated fentanyl as a possible intoxicant. Lacking history or the presence of a patch, we do not routinely screen for fentanyl. It is possible that fentanyl is the cause of some of the undetermined deaths in those with a history of drug abuse. Fentanyl is rarely used as a drug of abuse in our area, however, and our scene investigations reveal pills or empty bottles for methadone, hydrocodone, or oxycodone far more often than the presence of a fentanyl patch.

Finally, it is possible that during investigation of traffic fatalities a complete drug history may not have been sought as diligently as in deaths due to undetermined cause, due to the obvious cause of death in traffic fatalities. If this possibility were true, then drug abuse in our control group may be under counted. If drug abuse went unrecognized in the control group, then the risk odds ratio that we have reported is inappropriately high, and our conclusion that drug abuse is more likely in deaths due to undetermined causes is wrong. We believe that our investigation is diligent, however, and that our results are accurate. Additional studies will either corroborate or refute our findings.

Conclusion

A history of drug abuse is far more common in sudden, unexplained deaths than it is in a control group chosen to represent a random sample of the population, even in the absence of a level of drug sufficient to account for death at the time of death. Research suggests that cocaine use in particular has the potential to induce chronic biochemical and physiological changes that may persist beyond the presence of circulating cocaine in the blood, just as the induction of hepatic enzymes by alcohol persists beyond the presence of ethanol in the blood. We hope that further research in this area will clarify this matter.

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