Fatal Cocaine Interactions

A Review of Cocaine-Related Deaths in Bexar County, Texas

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Abstract: Although cocaine is a widely abused illicit substance that is known to cause death, deaths due to its use appear to occur in a minority of those who use it. This report was designed to review drug-related deaths due to cocaine, and the concomitant use of other drugs/ medications. A retrospective review of drug deaths at the Bexar County Medical Examiner's Office in San Antonio, Texas, was undertaken for cases where cocaine was one of the drugs implicated in causing death. Analysis was performed comparing the concentrations of cocaine and benzoylecgonine present and the absence or presence of other drugs. The data obtained showed that cocaine was toxic over a large range with deaths occurring at concentrations ranging from 0.01 to 78 mg/L. Analyses also indicated an increased lethality when cocaine is used in combination with ethanol, heroin, opiates, and antidepressant/antipsychotic medications, which is consistent with previous reports and research. Antihistamine data showed that there may be relationship between increased toxicity and coingestion, although more research is necessary.

Key Words: cocaine, toxicity, death, ethanol, antidepressant, antipsychotic, opiate, narcotic, heroin, antihistamine

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The effects of cocaine are well known throughout the medical and lay community, including the possibility that the use of cocaine can result in death. Cocaine is derived from *Erythroxylon coca*, a plant indigenous to South America, Mexico, and the West Indies. Historically, it was used for religious and ceremonial purposes and anesthesia, as well as being an additive in several beverages, including wines and Coca Cola. Today, the leaves are still chewed by South and Central Americans to help alleviate altitude sickness and to increase physical endurance. The United States first began to regulate cocaine use in 1906 with the passage of the Pure Food and Drug Act.

Cocaine is a potent central nervous system (CNS) stimulant. It inhibits the reuptake of norepinephrine and epinephrine and increases the release of norepinephrine from adrenergic nerve terminals.[1] Within the CNS, cocaine inhibits dopamine and serotonin reuptake resulting in the euphoria, or "high," perceived by cocaine users. Cocaine also increases aspartate and glutamate within the brain, resulting in increased extracellular dopamine concentration.[1] In addition to the CNS, cocaine can affect the cardiovascular system. The sympathomimetic properties of cocaine result in tachycardia, hypertension, and vasoconstriction that may lead to cardiac and/or cerebral ischemia. Cocaine also acts upon the cardiac sodium channels resulting in prolongation of the QT interval.

Clinical signs and symptoms of cocaine use include hyperthermia, anxiety, agitation, vasoconstriction, tachycardia, hypertension, platelet aggregation, and cardiac dysrhythmias. Cocaine use has been shown to cause death resulting from seizures (convulsions), cerebrovascular accidents (strokes), myocardial infarctions (heart attacks), cardiac dysrhythmias (abnormal heart beats), and respiratory arrest.

In 2007, approximately 2.3% of the US population reported to having used cocaine at least once in the past year, corresponding to 6.9 million people.[2] Accurate national statistics regarding cocaine-related deaths are not kept; however, in San Antonio, Texas (population 1.1 million), during the same period (2007) there were approximately 60 deaths due to drug intoxications involving cocaine. By extrapolating the national data of cocaine use, one can hypothesize that approximately 25,300 people used cocaine at least once in San Antonio, Texas, in 2007 and, of those, 60 people died, or approximately 0.002%. While these statistics are simply estimates and do not reflect actual events, they do highlight the well-known reality that a small percentage of people who use cocaine actually die of that use.

Medical examiners know that deaths due to cocaine can occur in people who chronically use cocaine as well as in people who have never used before; thus, the questions become: Is there a way to predict the lethality of cocaine? Is there a dose relationship? Could drugs taken concurrently with cocaine increase or decrease toxicity and lethality? This study was designed to provide further information regarding these theories and to examine the pharmacologic principles behind them.

MATERIALS AND METHODS

A database review was performed to identify all cases of drug-related deaths at the Bexar County Medical Examiner's Office in San Antonio, Texas, for a 16-year period beginning from January 1, 1993 and ending on December 31, 2005, in which cocaine was one of the drugs implicated in causing death.

At the time of examination, a full toxicology panel was performed on all cases including screens for opiate/opioid, cocaine, alcohol, alkaline, and acid/neutral drugs. The cocaine and opiate screens were performed by fluorescence polarization immunoassay. All positive samples were then extracted by solid phase extraction, confirmed, and quantitated by gas chromatography (GC) paired with mass spectrophotometry. The alcohol quantitation was performed by direct injection method and analyzed by GC/flame ionization detector (FID). All samples positive for ethanol were confirmed by fluorescence polarization immunoassay. The alkaline and acid/neutral drug screens were performed using a liquid-liquid extraction, quantitated by GC/FID, and confirmed by GC/mass spectrophotometry.

The complete toxicologic data for the cocaine-related deaths was compiled and analyzed for cocaine and benzoylecgonine (BE) concentrations and the presence of additional drugs including ethanol. Additional drugs were combined into the following subgroups: ethanol, heroin, opiate medications, anxiolytics, antihistamines, cannabinoids, antidepressant/antipsychotic medications, inhalants, sympathomimetics, anticonvulsants, cardiac medications, and other.

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The data were analyzed for pure cocaine deaths (only cocaine present), cocaine plus 1 additional drug, and cocaine plus multiple additional drugs. Statistical analysis was performed using a Mann-Whitney, 1- and 2-tailed *U* tests. Because of the nonparametric nature of the data, medians and ranges are reported rather than means and standard deviations.

RESULTS

A total of 461 cocaine-related deaths were identified during the study period. The average age of the decedents was 35.3 years, ranging from 15 to 73 years. Men accounted for the majority of the cases (78.5%), whereas women accounted for 21.5%. The median concentration of cocaine in all deaths was 0.19 mg/L with a median BE concentration of 1.5 mg/L. For men, the median concentrations for cocaine and BE were 0.19 mg/L and 2.0 mg/L, respectively, and were 0.19 mg/L and 1.4 mg/L, respectively, for women. There was not a significant difference in the concentrations of cocaine or BE between men and women ($P > 0.05$; Mann-Whitney *U* test).

Cocaine was most commonly used in conjunction with ethanol (42% of cases had ethanol present) followed by opiate/opioid medications, which were present in 29% of cases. Heroin and antipsychotic/antidepressant medications were present in 13% and 12% of cases, respectively. Anxiolytic medications (benzodiazepines, barbiturates, etc) and antihistamines were found in 9% and 7% of cases, respectively. The remaining medications were found in less than 5% of the cases. The data are summarized in Table 1.

Of the 461 cocaine-related deaths, 143 (31%) were purely due to cocaine (no other drugs were present), 146 (32%) were due to cocaine plus 1 additional drug, and 172 (37%) were due to cocaine plus more than 1 drug (Table 2).

Cocaine Only

The concentrations of cocaine and BE in cocaine only deaths were nonparametric in distribution with the curve being skewed to the right. The median cocaine and BE concentrations were 0.89 mg/L and 4.0 mg/L, respectively, with a first quartile limit of 0.19 mg/L for cocaine and 1.3 mg/L for BE and a third quartile limit of 3.8 mg/L for cocaine and 7 mg/L for BE. The concentration of cocaine in cocaine-only deaths ranged from 0.01 to 78 mg/L with BE concentrations ranging from 0.02 to 90 mg/L.

TABLE 1. Summary of Occurrence of All Categories of Drugs

Drug/Drug Class	No. Cases With Drug Present (% of Total)
Ethanol	194 (42%)
Opiate/opioid medications	135 (29%)
Heroin	61 (13%)
Antipsychotics/antidepressants	56 (12%)
Anxiolytics	42 (9%)
Antihistamines	31 (7%)
Dextromethorphan	11 (2%)
Sympathomimetics	8 (2%)
Cardiac medications	7 (2%)
Cannabinoids	2 (<1%)
Anticonvulsants	2 (<1%)
Inhalants	1 (<1%)
Isopropanol	1 (<1%)

TABLE 2. Percentage of Cases With Drugs Present

Number of Drugs Present	No. Cases With Drug Present (% of Total)
Cocaine only	143 (31%)
Cocaine plus 1 additional drug	146 (32%)
Cocaine plus more than 1 drug	172 (37%)

One Drug/Drug Class Plus Cocaine

Of the 146 deaths where only 1 other drug was present in addition to the cocaine, the majority occurred with ethanol (49.3%), followed by opiate/opioid medications (28.8%), antipsychotic/antidepressant medications (6.8%), heroin (5.6%), and antihistamines (4.8%) with anxiolytics, cardiac medications, anticonvulsant medications, sympathomimetics, and dextromethorphan accounting for the remaining cases (4.8%). No deaths occurred with cocaine and cannabinoids alone or with cocaine and inhalants alone. The data are summarized in Table 3.

Analyses were performed comparing the concentrations of cocaine and BE of the only cocaine group with those where only 1 additional drug was present. Because of small sample sizes, comparison could not be made between the only cocaine group and the cardiac, anxiolytic, anticonvulsant, sympathomimetic, and dextromethorphan groups. The remaining analyses are summarized later. All groups showed a nonparametric distribution (rightward skew) of the data.

Ethanol

Cases which had cocaine and ethanol only present had a median cocaine concentration of 0.35 mg/L and a median BE concentration of 1.5 mg/L. The concentration of cocaine was lower in the cocaine plus ethanol group than in the cocaine-only group, but this difference did not reach statistical significance ($P = 0.197$). The concentration of BE was lower in the cocaine plus ethanol group at a statistically significant level ($P = 0.0001$).

Heroin and Opiate/Opioid Medications

Cases which had only cocaine and opiate/opioid medications present had a median cocaine concentration of 0.08 mg/L and a median BE concentration of 1.4 mg/L. Cases which had only cocaine and heroin present had a median cocaine concentration of 0.12 mg/L and a median BE concentration of 1.0 mg/L. Analysis showed statistically significant lower concentrations of cocaine in the heroin and opiate/opioid groups when compared with the pure cocaine group ($P = 0.006$ and $P < 0.0001$, respectively) as well as statistically significant lower concentrations of BE ($P = 0.004$ and $P < 0.0001$, respectively). The opiate/opioid medication group included morphine, oxycodone, methadone, hydrocodone, propoxyphene, and tramadol.

Antipsychotic/Antidepressant

The antipsychotic/antidepressant group included cases with citalopram, fluoxetine, amitriptyline, nortriptyline, desipramine, thioridazine, imipramine, and sertraline present in addition to the cocaine. Cases which had only cocaine and an antipsychotic/antidepressant medication present had a median cocaine concentration of 0.17 mg/L and a median BE concentration of 1.1 mg/L. The concentration of cocaine was less in the antipsychotic/antidepressant group when compared with the cocaine-only group, but this difference failed to reach a level of statistical significance ($P = 0.2$). The concentration of BE was also found to be less when compared with the cocaine-only group, and this difference did reach significance ($P = 0.03$).

TABLE 3. Summary of Deaths Due to Cocaine Plus 1 Additional Drug/Drug Type

Additional Drug/Drug Type	No. Cases	Median Cocaine Concentrations (Range mg/L)	Median BE Concentrations (Range mg/L)
Cocaine only	143	0.89 mg/L (0.01–78)	4.0 mg/L (0.02–90)
Ethanol	72	0.35 mg/L (0.01–82)	1.5 mg/L (0.02–24)
Opiate	42	0.08 mg/L (0.01–3.7)	1.4 mg/L (0.03–6.2)
Heroin	8	0.12 mg/L (0.01–0.83)	1.0 mg/L (0.02–3.7)
Antipsychotics/antidepressants	10	0.17 mg/L (0.03–4.1)	1.1 mg/L (0.29–7.9)
Antihistamines	7	0.33 mg/1L (0.03–0.99)	2.4 mg/L (0.61–3.8)
Anxiolytics	3	0.06 mg/L (0.01–0.11)	1.5 mg/L (0.23–2.8)
Anticonvulsants	1	4.7 mg/L	3.7 mg/L
Sympathomimetics	1	0.91 mg/L	2.9 mg/L
Cardiac medication	1	0.11 mg/L	1.2 mg/L
Dextromethorphan	1	0.48 mg/L	5.2 mg/L

BE indicates benzoylecgonine.

Antihistamines

The antihistamine group included cases where diphenhydramine, doxylamine, hydroxyzine, and promethazine were present in addition to cocaine. Cases which had only cocaine and an antihistamine medication present had a median cocaine concentration of 0.33 mg/L and a median BE concentration of 2.4 mg/L. The concentration of cocaine was less in the antihistamine group when compared with the cocaine-only group, but this difference failed to reach a level of statistical significance ($P = 0.1$). The concentration of BE was also found to be less when compared with the cocaine-only group, and this difference did reach significance ($P = 0.0002$).

Multiple Drugs/Drug Classes Plus Cocaine

In 172 (37%) cases, more than 1 drug was present in addition to cocaine. Although most of these combinations were present in only a small number of cases (less than 10), 2 combinations accounted for 42% of the 172 cases. These combinations were cocaine plus ethanol and opiate/opioid medications and cocaine plus ethanol and heroin.

Cocaine Plus Ethanol and Opiate/Opioid Medications

Cases which had cocaine, ethanol, and opiate/opioid medications present had a median cocaine concentration of 0.08 mg/L and a median BE concentration of 0.48 mg/L (Table 4). Statistical comparison of the cocaine and BE concentrations was made between the cocaine plus ethanol and opiate/opioid group and the cocaine-only, cocaine plus ethanol, and cocaine plus opiate/opioid groups. This analysis showed significantly lower cocaine and BE concentrations between the cocaine and ethanol/opiate/opioid group and the cocaine-only and the cocaine plus ethanol groups ($P < 0.001$). When comparing the cocaine concentrations between the cocaine, ethanol, and opiate/opioid group and the cocaine plus opiate/opioid group, no significant difference was present, though the BE concentration was significantly lower in the former group than the later ($P = 0.002$).

Cocaine Plus Ethanol and Heroin

Cases which had cocaine, ethanol, and heroin present had a median cocaine concentration of 0.09 mg/L and a median BE concentration of 0.42 mg/L (Table 4). Statistical comparison of the cocaine and BE concentrations was made between the cocaine plus ethanol and heroin group and the cocaine only, cocaine plus ethanol, and cocaine plus heroin groups. This analysis showed significantly lower cocaine and BE concentrations between the cocaine, ethanol, and heroin group and the cocaine-only and the cocaine plus ethanol groups ($P < 0.001$). When comparing the cocaine and BE concentrations between the cocaine, ethanol, and heroin group and the cocaine plus heroin group, a significant difference was not found.

DISCUSSION

Dose Effect

Data from this study show a nonparametric distribution of cocaine concentrations in deaths due purely to cocaine intoxication with a range from 0.01 to 78 mg/L. In this study, 50% of deaths occurred at concentrations less than 0.89 mg/L and 75% at concentrations less than 4 mg/L. Because a good majority of deaths occurred at lower concentrations, one might conclude that dose, or at least concentration, does not relate to toxicity. The issue of proving a dose relationship with cocaine is complex. Although a lethal dose 50 for cocaine in laboratory animals has

TABLE 4. Cocaine and BE Concentrations in Deaths Due to Cocaine, Ethanol and Heroin, and Cocaine Ethanol and Narcotic Medications

Drug/Drug Type Combination	No. Cases	Median Cocaine Concentrations (Range mg/L)	Median BE Concentrations (Range mg/L)
Cocaine, ethanol, and heroin	39	0.09 mg/L (0.01–7.6)	0.42 mg/L (0.03–13)
Cocaine, ethanol, and opiates/opioids	39	0.08 mg/L (0.01–3.8)	0.48 mg/L (0.06–16)

BE indicates benzoylecgonine.

been described, human studies are difficult to perform. Bertol et al, in their study looking at cocaine-related deaths, found that the concentrations of cocaine and BE in cocaine-related deaths were significantly increased when compared with deaths where cocaine was present but not causative of death,[3] whereas Karch et al found no such difference when comparing similar populations.[4] Blaho et al developed a Stimulant Intoxication Scale (SIS) to quantify the signs and symptoms of cocaine intoxication to assess the relationship between cocaine toxicity and cocaine concentration.[5] They failed to find a statistically significant relationship between the SIS score and the cocaine and/or cocaine metabolite concentrations nor any element of the SIS and the cocaine/metabolite concentrations.[5]

Proving a causal dose relationship in humans would require that both the dose of cocaine and the concentration be known entities, both of which are difficult to ascertain. Cocaine used as a recreational drug is not a regulated product, and there are no standardized quality control procedures in place regarding its production. Each manufacturer, each batch, each day may result different purities of cocaine resulting in the same amount (weight) of cocaine equating to a different dose of cocaine. Obtaining an accurate postmortem cocaine concentration is also difficult as cocaine is metabolized both in vivo and in vitro. Most medical examiner's offices use sodium fluoride as a preservative to minimize the in vitro component; however, antemortem samples are often used which are not always preserved appropriately. In addition, metabolism can also occur after death but before the collection and preservation of blood. Thus, the cocaine concentrations at the time of death may have been greater than the toxicology results report. The route of administration of cocaine may also play a role in its concentration and toxicity since metabolism can be affected depending upon whether the drug was injected, ingested, inhaled, or insufflated.

The variable of tolerance, whether an individual is a chronic or naive user, must be considered. Chronic cocaine use can cause physiologic changes in the heart as well as other organs, which cause a person to be more susceptible to the physiologic effects of cocaine. For instance, chronic cocaine use can lead to cardiac hypertrophy (enlargement), which is an independent risk factor for developing an arrhythmia; a risk that would be further increased by repetitive cocaine use, which also causes dysrhythmias. The presence or absence of other natural diseases, may also affect how one responds to cocaine. Blaho et al further argue that it is impossible to obtain reliable information from the users regarding all of these variables,[5] making definitive analysis a nonviable possibility.

Cocaine and Other Drugs

Because of sample size constraints, only ethanol, opiate/opioid medications, heroin, antipsychotic/antidepressant medications, and antihistamines could be analyzed in this study. Although other drugs, including anxiolytics, inhalants, and sympathomimetics, may also contribute to cocaine toxicity, no conclusions could be drawn based upon this study alone; therefore, the discussion is limited to those drugs in which this study adds to the current literature.

Cocaine and Ethanol

This study supports the hypothesis that ethanol may increase the toxicity of cocaine. The data show that the concentrations of cocaine and BE in the cocaine-only group were greater than those found in the cocaine plus ethanol group. This is consistent with an autopsy study by Karch et al who compared 72 cases of cocaine-related deaths, 25 of which had ethanol and cocaine present and 47 had cocaine without ethanol.[6] They found lower concentrations of cocaine in the ethanol positive group, but the results were not statistically significant.[6] Several other studies have shown that ethanol and cocaine act synergistically to increase hepatotoxicity, cardiotoxicity, and neurotoxicity.[7–11] Busse and Riley studied the effects of cocaine and ethanol in rats and found that with repetitive dosing, ethanol increased the lethality of cocaine intoxicated rats; although the same was not found after a single dose of each.[12] They hypothesize that the creation of cocaethylene, a toxic metabolite produced only in the presence of cocaine and ethanol, was the cause of the increased toxicity.[12] However, Blaho et al, in their study of emergency room visits for cocaine use, found no relationship between cocaethylene and cocaine-related symptoms or severity.[5] Laizure et al found that in rats pretreated with ethanol the cocaine clearance was decreased, which may explain some of the increased toxicity.[13]

Other studies have demonstrated that ethanol may decrease cocaine lethality. Ethanol is also known to inhibit the glutamate *N*-methyl-D-aspartic (NMDA) receptor site and activate gamma-aminobutryic $acid_A$ $(GABA)_A$.[14] The activation of $GABA_A$ may result in an increase in the seizure threshold, thus protecting the CNS from the pro-seizure (decreased seizure threshold) effects of cocaine. In addition, Shimosoto et al showed that NMDA antagonism decreased the incidence of seizures induced by cocaine,[15] and Matsumoto et al demonstrated that NMDA/glycine site antagonists appear to have a protective effect in the event of cocaine toxicity.[16] It can be hypothesized that the inhibitory effect of ethanol on the NMDA receptor may result in some protection from cocaine-induced seizures, resulting in a decreased lethality of cocaine.

Regarding BE, the present study found results similar to the findings of Karch et al, in that the concentration of BE was lower in the cocaine plus ethanol group.[6] In the present study this difference reached statistical significance while in the study of Karch et al it did not.[6] The differences seen in BE concentrations between the cocaine-only and the cocaine and ethanol groups may be due to the effect of ethanol on cocaine metabolism. There are 2 main enzymes responsible for cocaine metabolism and the formation of its primary metabolites, BE and ecgonine methyl ester (EME). Carboxylesterase hCE1 is responsible for the metabolism of cocaine to BE, and hCE2 is responsible for the metabolism of cocaine to EME.[13] When ethanol is present hCE1 preferentially converts cocaine to cocaethylene rather than to BE.[13] This change in metabolism would cause the cocaine to be metabolized to cocaethylene instead of to BE, leading to lower BE concentrations in individuals who also ingested ethanol. Roberts et al found that in rats given cocaine and pretreated with ethanol there was a 2- to 3-fold increase in peak hepatic concentrations of cocaine, norcocaine, and EME along with a decrease in BE by 2-fold.[17]

Cocaine and Opiate/Opioid Medications and Cocaine and Heroin

The present study supports the findings of Polettini et al, that cocaine enhances the toxicity of heroin,[18] although, for this study, it could be argued that opiates/opioids enhance the toxicity of cocaine. Polettini et al found lower concentrations of morphine in cases of heroin deaths in the presence of cocaine than without cocaine.[18] This study found the corollary that lower concentrations of cocaine are present when opiates/opioids are also present than when opiates/opioids are absent. Blumberg and Ikeda studied the effects of cocaine and opiates/opioids in mice and found that, when combined, morphine increases the effects of cocaine.[19] They also found that this augmentation can be blocked by an opiate antagonist.[19] These studies, in addition to the current one,

support the hypotheses that either cocaine enhances opiate/opioid toxicity, opiates/opioids enhance cocaine toxicity, or both.

Studies and case reports have linked opiates, including heroin, with seizures,[20–27] though the exact mechanism of how opiates cause seizures is not known. Saboory et al showed that, at high concentrations, opiates enhanced seizure activity via the μ and κ receptors, within the hippocampus[24]; Zieglgansberger et al hypothesized that opiate induced seizures may be the result of disinhibition of hippocampal neurons[25]; and Crain et al proposed it was because of enhancement of excitatory neurotransmission.[26] Carlsson et al found that fentanyl decreases the cerebral blood flow and metabolic rate for oxygen in rats, which may lead to cerebral hypoxia and seizures.[27] If both opiates and cocaine have pro-seizure effects, then the use of both together could act synergistically to increase the risk and/or intensity of seizure activity.

Tseng et al showed that cocaine causes central respiratory depression in rats, which may be yet another mechanism of death secondary to cocaine use.[28] Plunkett et al further showed that morphine potentiates the respiratory depression caused by cocaine in guinea pigs.[29] Opiates/opioids may also augment the respiratory depression seen with seizure activity during a cocaine induced seizure, which may further increase the risk of death.

Polettini et al argue 2 additional possible interactions regarding cocaine and heroin.[18] Both heroin and cocaine are hydrolyzed by the same enzyme system, and there may be some competitive inhibition at that enzyme site, resulting in increased duration of action of either cocaine or heroin or both. In addition, they argue that both cocaine and heroin result in increased dopamine release, which has been associated with an increased risk of death (see following discussion on antipsychotics).

Cocaine and Antidepressants/Antipsychotics

As with the opiates/opioids discussed previously, this study supports the hypothesis that antipsychotic/antidepressant medications increase the toxicity of cocaine. This is supported by the concentrations of both cocaine and BE being lower in the deaths with antipsychotic/antidepressant medications present than in the cocaine-only group. Although a previous formal study looking at this effect in humans has not been performed, the compounding effects of cocaine plus antidepressants and/or antipsychotics are pharmacologically logical when one considers the mechanism of action of each of these drugs/drug class. Cocaine acts by inhibiting the reuptake of norepinephrine, epinephrine, dopamine, and serotonin resulting in increased concentrations of each of these monoamines. Most antidepressants and antipsychotics have a similar mechanism of action, resulting in increased concentrations of many of the same monoamines.

The lethality of cocaine seems to depend primarily on its interaction with dopaminergic receptor sites.[30] In addition, dopamine (D1) antagonists have been shown to protect against cocaine-induced lethality.[30,31] Ritz and George further showed that sigma receptor agonists and muscarinic (M1) receptor antagonists can also attenuate cocaine-induced lethality, although the attenuation is not as dramatic as with dopamine antagonists.[30] Antidepressants and antipsychotics often affect the dopaminergic system, usually resulting in increased dopamine levels, which may augment cocaine toxicity and lethality.

O'Dell et al found that antidepressants enhance cocaine toxicity in mice presumably by affecting the reuptake of the catecholamines, dopamine, and norepinephrine, as well as serotonin.[32] They stipulate that cocaine convulsions are mediated by serotonin and that cocaine lethality is mediated by dopamine and showed that antidepressants with high affinity and specificity to serotonin transporters increase cocaine convulsions and the severity of those convulsions.[32] One exception was sertraline that did not alter cocaine-induced convulsions and actually attenuated lethality.[32] This is thought to be due to sertraline's high affinity to sigma receptors, which, as discussed earlier, have been shown to decrease cocaine lethality.[30]

Heard et al showed that mice treated with the antipsychotic medication ziprasidone had higher death rates when combined with cocaine than those rats who used cocaine alone.[33] They postulated that patients taking antipsychotics have an increased susceptibility to cocaine toxicity since long-term administration of antipsychotic medications alters the density of dopamine, glutamate, and serotonin receptors in the brain, all of which are associated with cocaine toxicity.[33] Long-term or chronic antipsychotic administration was also shown to cause an increased sensitivity to cocaine.[33]

Antipsychotic and antidepressant medications may also share cardiac interactions with cocaine. Numerous antidepressant and antipsychotic medications have been shown to increase the QT interval.[34–36] The apparent mechanism of action of medication induced QT prolongation involves the blockade of the outward potassium currents in the heart, causing prolongation of the cardiac action potential.[35] This action may act synergistically with the cardiac channel and sympathomimetic effects of cocaine resulting in an increased risk of cardiac dysrhythmias.

Cocaine and Antihistamines

There is a paucity of data regarding the effects of cocaine and antihistamines. The present study supports the hypothesis that antihistamine medications, when taken concurrently with cocaine, increase the toxicity of cocaine. This is evidenced by the concentrations of both cocaine and BE being less in the deaths with antihistamines present than in the cocaine-only group. Previous studies have shown that both cocaine and H1 antihistamines affect dopamine neurotransmission within the brain leading to positive reinforcement behavior.[37,38] Diphenhydramine and cocaine were found to act as positive reinforcers in the monkey, although the 2 drugs also displayed a stronger, synergistic effect when combined.[37,38] It is possible that this dopaminergic action may also lead to toxicity by the mechanisms discussed previously in the section regarding antidepressant/antipsychotic medications.

First generation H1-antihistamines, which enter the CNS, can result in CNS stimulation, especially when taken in overdose, which can lead to convulsions and death. It can be hypothesized that this may be an additional mechanism of cocaine-antihistamine interaction, resulting in a decreased seizure threshold and increased risk of convulsions.

Like cocaine, antihistamines can cause cardiovascular effects, including rhythm disturbances. Cocaine and H1-antihistamines could act synergistically on the heart creating conduction abnormalities and subsequent death. Both cocaine and some antihistamines (tripelennamine, chlorpheniramine, diphenhydramine, and phenindamine) have been shown to be potent inhibitors of neuronal uptake of norepinephrine.[39,40] By this mechanism, it could be hypothesized that cocaine plus an antihistamine would have a synergistic stimulatory action on the heart by leading to an increase amount of norepinephrine at the receptor causing an increase heart rate and blood pressure that could lead to dysrhythmias or heart attacks. However, not all antihistamines have been shown to have this effect; Davis and McNeill reported that pyrilamine and promethazine had

no effect on norepinephrine uptake.[40] In addition, several antihistamines including astemizole, terfenadine diphenhydramine, and hydroxyzine have been shown to increase the QT interval, which may result in cardiac arrhythmias similar to those produced by cocaine.[34,36] This QT prolongation may be another mechanism by which cocaine and antihistamines may result in fatal cardiac dysrhythmias.

CONCLUSION

This study supports previous reports that cocaine used in combination with ethanol, heroin, opiate medications, and antidepressants/antipsychotics may result in increased toxicity, as evidenced by a decreased concentration of cocaine and BE present in deaths due to a combination of these drugs plus cocaine versus deaths due to cocaine alone. The coingestion of antihistamines and cocaine may result in increased toxicity, although more research is necessary. The question of a dose relationship between cocaine and toxicity is less clear. Although further research is necessary to resolve the dose question, many factors severely limit the ability to conduct research in humans. Understanding the issues related to how and why cocaine can result in death is essential for the forensic pathologist, not only in understanding the dynamics of these deaths but also in communicating with families and other interested parties.

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