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PAPER

TOXICOLOGY; PATHOLOGY AND BIOLOGY

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Concentrations of Opiates and Psychotropic Agents in Polydrug Overdoses: A Surprising Correlation Between Morphine and Antidepressants

ABSTRACT: The relationship between postmortem concentrations of morphine and co-detected psychoactive drugs in fatal overdoses is examined. Morphine and other drugs were detected in 161 medicolegal autopsy cases. Subsets of these morphine-positive cases based on drug class were established, including opioids, antidepressants, ethanol, benzodiazepines, and "other." Each subset was split into high or low concentration groups based on median drug concentrations. Morphine concentrations of the [high] and [low] groups were compared, with no significant difference in morphine concentration identified in the opioid, ethanol, or benzodiazepine subsets. The "other" drug class was too heterogeneous for statistical assessment. Morphine concentrations did show a significant direct relationship ($p = 0.01$) with antidepressants, namely increased concentrations of antidepressant drugs are associated with an increased concentration of morphine. This trend probably remains even after excluding cocaine-positive cases. The unsuspected finding that postmortem concentrations of antidepressants positively correlate with morphine levels may be important in the treatment of depression in drug addicts.

KEYWORDS: forensic science, forensic pathology, toxicology, opiates, antidepressants, drug overdose

A study by the Boston Public Health Commission has found that deaths from drugs and alcohol have risen dramatically from 2005 to 2006 mainly because of an increase in inexpensive heroin and the growing addiction to prescription medications. In 2006, 176 people died from substance abuse in Boston, MA, reflecting a 32% increase in deaths since 2005. Substance abuse is now considered the fifth leading cause of death (with a rate of 176 deaths per 100,000 population) among Bostonians behind cancer, heart disease, injuries, and stroke, respectively (1). By comparison, a 2003 study by the Drug Awareness Warning Network of six participating states (Maine, New Hampshire, Vermont, Maryland, Utah, and New Mexico) found opiate misuse fatality rates between 7.2 and 11.6 per 100,000 people (2).

A suspected cause for the increasing fatal overdoses is a resurgence of the popularity of heroin throughout New England since the late 1990s, presumably because of its low price (3). Furthermore, opiates were not commonly the sole factor in death; rather the deaths more often resulted from a combination with other drugs (2). Morphine is rarely the only drug detected in autopsy (4,5). This polydrug use may be a result of an individual's substance abuse "career," with drugs used in early stages carried through and used along with the drugs of later stages (6). The major drugs associated with heroin overdose include alcohol, benzodiazepines, and antidepressants (7). Combinations with additional respiratory depressants are of particular risk (8).

Although the phenomenon of fatal polydrug overdoses is widely recognized, few studies have investigated the importance of the postmortem concentrations of individually involved drugs. It is widely held that concurrent opiate and other central nervous system depressant drug use is more dangerous than opiate use alone. In this study, medicolegal autopsy cases of polydrug overdoses that include an opiate as well as another psychotropic drug are examined. This article proposes that the postmortem concentration of morphine will be indirectly proportional to the concentration of the coadministered central nervous system depressant drug. In other words, in polydrug overdoses in which high concentrations of a central nervous system depressant drug are detected, we expect morphine levels to be comparatively lower, and vice versa.

Methods

All postmortem examinations with toxicologic analysis performed by the Commonwealth of Massachusetts Office of the Chief Medical Examiner (MA OCME) (Boston, MA) between January 1, 2006 and December 31, 2006 in which the term "opiate" was a part of the cause of death were investigated for possible inclusion in this study. By convention in our practice, overdoses involving morphine (or heroin) are usually certified "acute opiate intoxication" or "acute intoxication because of the combined effects of opiates [and other drugs]." A chart review was performed for each identified case, with abstraction of the following

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information for each decedent: age, height, weight, sex, manner of death, cause of death, whether drug paraphernalia was present at the scene, and other unique circumstances. Toxicologic data, including biological matrix and qualitative/quantitative drug analyses, was also determined. Ultimately, to be included in this study, an opiate (morphine, heroin, 6-monoacetylmorphine, or codeine) along with at least one other psychotropic drug had to be detected in a blood matrix. A determination was then made as to whether the opiate use was licit or illicit, with only cases of illicit use included for analysis.

Toxicologic analysis for all medicolegal postmortem examinations conducted by the MA OCME was performed by the University of Massachusetts Memorial Medical Center Forensic Toxicology Laboratory. As previously described (9), multiple specimen types per postmortem examination were submitted as appropriate and may have included: heart blood, femoral blood, urine, vitreous humor, and other tissues and fluids. The laboratory's analytical scheme includes: presumptive six drug/drug class blood analysis by enzyme-linked immunosorbent assay (Venture Labs, Redwood City, CA) for benzodiazepines, cocaine, fentanyl, methadone, opiates, and oxycodone; presumptive 10 drug/drug class urine screening by enzyme multiplied immunoassay technique (EMITÒ II Plus; Dade-Behring, Deerfield, IL) for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, 3,4-methylenedioxymethamphetamine (MDMA), methadone, opiates, phencyclidine, and propoxyphene; an alkaline extractable drug screen in blood by gas chromatography/mass spectrometry (GC/MS); and volatile analyses for methanol, ethanol, acetone, and isopropanol by headspace dual column GC/flame ionization detection. Confirmation and quantitation for (free) morphine was performed by GC/MS-selected-ion monitoring using a deuterated internal standard following solid-phase extraction and derivatization with *N,O*-bis(trimethylsilyl)trifluoroacetamide with 1% trimethylchlorosilane (BSTFA + 1% TMCS). The lower and upper limits of quantitation for morphine are 20 ng/mL and 2000 ng/mL, respectively. All other drug analyses were performed either in house when possible or at a national reference laboratory. The preferred analytical algorithm is presumptive screening in heart blood and confirmatory quantitative analyses in a single unpooled blood source, generally peripheral blood when available.

Cases were subsequently divided into subsets based on, along with opiates, the codetection of other psychotropic drugs classes, namely benzodiazepines, ethanol, opioids, antidepressants, and "other" (Table 1). Each drug class subset was then divided into "high" and "low" concentration groups based on whether or not each individual drug within the subset had a higher or lower concentration than the median for that drug. If the drug concentration equaled the median, then it was assigned to the "low" concentration group. If multiple different drugs of a single drug class subset (for example, if the opioid subset included methadone, hydrocodone, and oxycodone) were identified in the postmortem analysis of a particular case, that case would be classified as "high" concentration within its subset if at least one of the co-detected drugs was above the median. Given that drug metabolites are often pharmacologically active, for the purpose of this analysis, the various metabolites were treated independent from the parent drug.

To test the hypothesis that the concentration of morphine detected in a given case would be inversely proportional to the concentration of co-detected central nervous system depressant drugs, statistical comparison was made between morphine concentrations associated with the "high" versus "low" concentrations of a particular drug class subset. Probability testing included both a Mann–Whitney *U* (MW) test (http://elegans.swmed.edu~leon/stats/utest.html) and a one-tailed *t*-test (TT) with Microsoft Excel 2000 (Microsoft Corporation, Redmond, WA). Given the reliance on median value for the bulk of this analysis, MW calculations are probably the more reliable determination. Significance is considered $p < 0.05$.

Other factors were also evaluated and include age, height, and weight of each decedent. Also, to determine the impact of cocaine intoxication, each subset of cases was evaluated with and without the inclusion of cocaine and/or its major metabolite benzoylecgonine (BE) (abbreviated "cocaine/BE")-positive cases.

TABLE 1—*Drug class subsets. Listing of drugs included in each subset of drugs co-detected with opioids. Ethanol and cocaine are not shown.*

Co-Detected Drugs in Each Drug Class Subset			
Opioid Subset	Benzodiazepine Subset	Antidepressant Subset	"Other" Subset
Hydrocodone	Chlordiazepoxide	Citalopram	D-9 THC
Hydromorphone	Diazepam	Sertraline	11H D-9 THC
Oxycodone	Nordiazepam	Amitriptyline	D-9 Carboxy THC
Oxymorphone	Oxazepam	Nortriptyline	Olanzapine
Fentanyl	Lorazepam	Bupropion	Quetiapine
Norfentanyl	Temazepam	Fluoxetine	Chlorpromazine
Methadone	Alprazolam	Norfluoxetine	Mephobarbital
EDDP	Clonazepam	Doxepin	Phenobarbital
Norpropoxyphene	7-amino	Nordoxepin	Butalbital
Tramadol	Clonazepam	Fluvoxamine	Amphetamine
		Trazodone	Diltiazem
		Paroxetine	Metoprolol
			Cyclobenzaprine
			Carisprodol
			Diphenhydramine
			Hydroxyzine
			Trimethobenzamide
			Doxylamine
			Dextromthorphan
			Quinine
			Meprobamate

Results

In 2006, 13,422 cases were reported for investigation to the Commonwealth of Massachusetts OCME. Autopsy or external examination with or without toxicologic analysis was performed on 4396 of these cases. Of the 210 cases having autopsy reports that included the keyword "opiate" in the cause of death, 49 were eliminated from further evaluation. Reasons for elimination included: no detection of an opiate in available specimens (26 cases), availability of only matrices unacceptable for study inclusion including urine, decompositional fluid, or tissue samples (10 cases), fetal demise (1 case), manners of death that were not accidental or undetermined (4 cases), and insufficient information (8 cases). Ultimately, of the 210 cases in which the cause of death was found to be at least partially because of acute opiate intoxication, 161 (76.6%) cases were included for analysis.

Of the cases analyzed, 72.0% were men ($n = 116$) and 28.0% were women ($n = 45$), a ratio of 2.6. The age of the population ranged from 18 years to 79 years, with an average of 38.8 years. The manner of death was deemed accidental in 156 cases (96.9%) and undetermined in five cases (3.1%). Drug paraphernalia was documented at the location of death in 58 cases (36.0%), reportedly absent in 28 cases (17.4%) and was not confirmed present or absent by investigative reports in 75 cases (46.6%).

Quantitative analyses were performed using heart blood in 87 cases, femoral blood in 49 cases, a combination of heart and

femoral blood in eight cases, an unspecified blood source in seven cases, antemortem blood in seven cases, and pooled cavity blood, "peripheral blood," and subclavian blood in one case each.

Morphine was present in 159 cases (98.8%) and ranged from less than the limit of quantitation (20 ng/mL) to greater than the limit of quantitation (2000 ng/mL) with a mean concentration of 261.1 ng/mL and a median concentration of 168 ng/mL. In two cases where morphine was not identified, codeine was detected; no further analysis was performed on these cases. Morphine concentrations in cases that quantitated femoral blood (median = 124 ng/mL; mean = 202.9 ng/mL) versus cases that quantitated heart blood (median = 220 ng/mL; mean = 286.8 ng/mL) were significantly different (MW = 0.0004; TT = 0.0558).

There was no significant difference in the body weights of the decedents that corresponded to morphine concentrations equal to or less than the median morphine value (median = 78.9 kg; mean = 83.9 kg) versus those greater than the median morphine concentration (median = 83.9 kg; mean = 86.2 kg) (MW 0.2973; TT = 0.2416). The heroin metabolite, 6-monacetylmorphine, was detected in 11 cases with a mean concentration 17.8 ng/mL and a median of 16 ng/mL. Codeine was identified in 21 total cases (12.9%) with a mean concentration of 65.8 ng/mL and a median of 26 ng/mL.

Opioid Subset

Opioids were present in 30 cases (18.6%) (Table 2). The following opioids were present: hydrocodone, hydromorphone, oxycodone, oxymorphone, fentanyl, norfentanyl, methadone, EDDP, norpropoxyphene, and tramadol. Morphine concentrations ranged from <20 ng/mL to 1071 ng/mL with a mean of 206.7 ng/mL and a median of 124 ng/mL. In nine cases, cocaine/BE was also detected. There was no significant difference in morphine concentrations identified in samples with detectable postmortem concentrations of opioids equal to or less than the median value ("low" concentration) of the specific opioid (median = 155.5 ng/mL; mean = 243.4 ng/mL) versus those greater ("high" concentration) than the median (median = 103 ng/mL; mean = 172.3 ng/mL) (MW = 0.2161; TT = 0.2093) (Table 3).

Ethanol Subset

Ethanol was present in 50 cases (31.1%) and had mean and median concentrations of 0.11 gm% (Table 4). Morphine concentrations ranged from 30 ng/mL to >2000 ng/mL with a mean of 292.7 ng/mL and a median of 202 ng/mL. In 23 cases, cocaine/BE was also detected. There was no significant difference in morphine concentrations identified in samples with detectable postmortem concentrations of ethanol equal to or less than the median value of ethanol (median = 176.5 ng/mL; mean = 241.4 ng/mL) versus those greater than the median (median = 220; mean = 361.1 ng/mL) (MW = 0.1562; TT = 0.1313) (Table 3).

Benzodiazepine Subset

Benzodiazepines were present in 35 cases (21.7%) (Table 5). The following benzodiazepines were detected: chlordiazepoxide, diazepam, nordiazepam, oxazepam, lorazepam, temazepam, alprazolam, clonazepam, and 7-amino clonazepam. Morphine concentrations ranged from <20 ng/mL to 633 ng/mL with a mean of 215.7 ng/mL and a median of 143.5 ng/mL. In 14 cases, cocaine/BE was also detected. There was no significant difference in

TABLE 2—*Opioid-positive cases, including number of cases (*n*), median and mean opioid concentrations, and range of morphine concentrations corresponding to that particular opioid.*

Opioid Subset			
Co-Detected Opioids	*n*	[Opioid] Median/ Mean (ng/mL)	[Morphine] Median/ Mean (range) (ng/mL)
Methadone	16	153.5/238.4	126.5/199.4 (32–573)
EDDP	11	77.5/51.4	116.5/208.6 (32–573)
Fentanyl	6	21/18.9	80/74.5 (<20–124)
Oxycodone	5	58/72.8	181/216.4 (35–573)
Oxymorphone	2	88/54	64, 229
Norfentanyl	2	3.3/3.3	<20, 49
Norpropoxyphene	2	0.61/0.61	185, 412
Hydrocodone	1	58/58	1071
Tramadol	1	486/486	288

TABLE 3—*Summary table showing the number of cases detected in each drug class subset (*n*), mean and median morphine concentrations for the [High] and [Low] groups of each subset, and the corresponding* p *value (Mann–Whitney* U*).*

Morphine Concentrations Corresponding to [High] and [Low] Drug Class Subsets				
Drug Class Subsets	*n*	Morphine Conc. of [High] Drug Class Subset Median/Mean (ng/mL)	Morphine Conc. of [Low] Drug Class Subset Median/Mean (ng/mL)	*p*
Opioids	46	103/172.3	155.5/243.4	0.216
Ethanol	50	220/361.1	176.5/241.4	0.156
Benzodiazepines	59	165/243.8	135/184.1	0.186
Antidepressants	53	321.5/514.6	120/202.9	0.032

TABLE 4—*Ethanol-positive cases, including number of cases (*n*), median and mean ethanol concentrations, and range of corresponding morphine concentrations.*

Ethanol Subset			
Co-Detected Ethanol	*n*	[Ethanol] Median/ Mean (gm%)	[Morphine] Median/Mean (range) (ng/mL)
Ethanol	50	0.11/0.11	202/292.7 (30–>2000)

TABLE 5—*Benzodiazepine-positive cases, including number of cases (*n*), median and mean benzodiazepine concentrations, and range of morphine concentrations corresponding to that particular drug.*

Benzodiazepine Subset			
Co-Detected Benzodiazepine	*n*	[Benzodiazepine] Median/Mean (ng/mL)	[Morphine] Median/ Mean (range) (ng/mL)
Nordiazepam	19	200/352.8	130/200.4 (35–745)
Alprazolam	12	35/76.2	159/170.5 (<20–412)
Diazepam	10	160/337.6	129.5/186.4 (111–633)
Chlordiazepoxide	5	2000/2732	185/304 (76–745)
7-amino Clonazepam	5	71/112.2	170/224.8 (64–573)
Oxazepam	3	61/75.7	129/147.7 (122–192)
Temazepam	2	86/86	122, 129
Clonazepam	2	8.8/8.8	64, 88
Lorazepam	1	11/11	168

morphine concentrations identified in samples with detectable postmortem concentrations of benzodiazepines equal to or less than the median value of the specific benzodiazepine (median = 135 ng/mL; mean = 184.1 ng/mL) versus those greater than the median (median = 165 ng/mL; mean = 243.8 ng/mL) (MW = 0.1311; TT = 0.1859) (Table 3).

Antidepressant Subset

Antidepressants were present in 29 cases (18.0%) (Table 6). The following antidepressants were detected: citalopram, sertraline, amitriptyline, nortriptyline, bupropion, fluoxetine, norfluoxetine, doxepin, nordoxepin, fluvoxamine, trazodone, and paroxetine. Morphine concentrations ranged from 22 ng/mL to >2000 ng/mL with a mean of 358.8 ng/mL and a median of 221.5 ng/mL. In 13 cases, cocaine/BE was also detected.

There was a significant difference (MW = 0.0108; TT = 0.0318) in morphine concentrations identified in samples with detectable postmortem concentrations of antidepressants equal to or less than the median value of the specific antidepressant (median = 120 ng/mL; mean = 202.9 ng/mL) versus those greater than the median (median = 321.5 ng/mL; mean = 514.6 ng/mL) (Table 3). This difference in morphine between the "high" and "low" antidepressant concentration groups remained even after excluding the trazodone- and fluvoxamine-positive cases (MW = 0.0064; TT = 0.0285).

Within the antidepressant subset, there was not a significant difference between the ages (MW = 0.4652; TT = 0.4724) or genders (MW = 0.3234; TT = 0.3022) associated with the antidepressant concentrations equal to or less than the median values (median = 45 years, mean = 42.5 years, number of men = 9, number of women = 6) versus those greater than the median antidepressant values (median = 46.5 years, mean = 42.8 years, number of men = 7, number of women = 7). There was also not a significant difference between the morphine concentrations in cases that analyzed heart blood (median = 108 ng/mL; mean = 508.7 ng/mL) versus those that analyzed from femoral blood (median = 229 ng/mL; mean = 284 ng/mL) (MW = 0.2503; TT = 0.2312). There was a significant difference between the body weights associated with the antidepressant concentrations equal to or less than the median values (median = 83.9 kg; mean = 74.8 kg) versus those greater than the median values (median = 94.3 kg; mean = 99.3 kg) (MW = 0.0334; TT = 0.0214).

TABLE 6—*Antidepressant-positive cases, including number of cases (*n*), median and mean antidepressant concentrations, and range of morphine concentrations corresponding to that particular drug.*

Antidepressant Subset			
Co-Detected Antidepressant	*n*	[Antidepressant] Median/Mean (ng/mL)	[Morphine] Median/ Mean (range) (ng/mL)
Nortriptyline	8	330/557.1	689.5/822 (108–>2000)
Norfluoxetine	8	450/1808.8	111/121.6 (46–297)
Amitriptyline	6	395/475	379/786.4 (108–>2000)
Citalopram	6	405/562.3	258/320.1 (22–1000)
Fluoxetine	6	365/391.7	130/100.6 (46–165)
Doxepin	4	605/837.5	165/190 (46–384)
Nordoxepin	4	340/377.5	165/190 (46–384)
Paroxetine	4	230/375	252/402 (104–>1000)
Bupropion	3	140/170.7	214/465 (110–1071)
Sertraline	2	2100/2100	773, 1071
Trazodone*	1	0.61/0.61	104
Fluvoxamine	1	2800/2800	170

*Concentrations of trazodone reported in mcg/mL.

Other Subset

A heterogenous group of CNS depressant drugs that could not be classified in the other subsets of this study were included in the "other" category and account for 29 of the cases (17.8%) (Table 7). Meaningful statistical analysis of this group was precluded because of the low number (often only one) of each individual identified compound and the wide diversity of drug mechanisms. Morphine concentrations ranged from <20 ng/mL to 1071 ng/mL with a mean of 240.3 ng/mL and a median of 155 ng/mL. In 13 cases, cocaine/BE was also detected.

Cocaine-Positive vs. Cocaine-Negative Groups

Cocaine and/or its major metabolite, BE, were present in 71 cases (44.1%) and absent in 90 cases (55.9%). The average age of decedents with detection of morphine and cocaine/BE is 37.3 years (median = 39 years) while the average age for those without detectable cocaine/BE is 40 years (median = 43 years) (MW = 0.0665; TT = 0.0692). Morphine concentrations in the cocaine/BE-positive group ranged from less than (20 ng/mL) to greater than (1000 ng/mL) the limits of quantitation, with a median morphine concentration of 129 ng/mL and a mean morphine concentration of 198.8 ng/mL. Morphine concentrations in the cocaine/BE-negative group also spanned the limits of quantitation with a median morphine concentration of 197 ng/mL and a mean of 305.6 ng/mL. The morphine concentrations between the cocaine/BE-positive and negative groups did vary significantly (MW = 0.0021; TT = 0.0057). There was no significant difference (MW = 0.1395; TT = 0.2385) between the morphine concentrations corresponding to cocaine/BE-negative cases and cases positive for BE (but not the parent drug).

When cases with cocaine and/or its metabolites were excluded from analysis, there was no significant difference between morphine concentrations in cases with "high" versus "low" concentrations of co-detected opioids (MW = 0.4387, TT = 0.2809),

TABLE 7—*Number of cases present for each "other" drug detected (*n*), median and mean "other" drug concentrations, and range of morphine concentrations corresponding to that particular drug.*

Other Subset			
Co-Detected "Other" Drug	*n*	[Other] Median/ Mean (ng/mL)	[Morphine] Median/ Mean (range) (ng/mL)
D-9 Carboxy THC	13	12/16	138/231.9 (22–1000)
D-9 THC	6	3.7/9.5	89.5/111 (22–278)
Diphenhydramine	4	460/702.5	58/50.7 (30–168)
Olanzapine	2	84/84	41, 111
11H D-9 THC	2	2/2	41, 199
Chlorpromazine	1	140/140	207
Mephobarbital	1	0.79/0.79	49
Phenobarbital	1	1.8/1.8	49
Butalbital	1	3.2/3.2	202
Amphetamine	1	86/86	168
Diltiazem	1	890/890	1071
Metoprolol	1	180/180	773
Cyclobenzaprine	1	700/700	1071
Carisprodol	1	6/6	392
Quetiapine	1	1000/1000	207
Hydroxyzine	1	310/310	392
Trimethobenzamide	1	0.95/0.95	<20
Doxylamine	1	64/64	58
Dextromethorphan	1	150/150	258
Quinine	1	2.8/2.8	185
Meprobamate	1	13/13	392

benzodiazepines (MW = 0.1121, TT = 0.1601), and ethanol (MW = 0.0955, TT = 0.4516). While significance is not established, there does appear to be a trend toward a difference in morphine concentrations in the "high" and "low" concentration groups of antidepressants (MW = 0.0704, TT = 0.1124).

Discussion

The frequency of fatal heroin overdoses is increasing throughout Massachusetts and nationally (2,3). This study investigates trends in drug concentrations of opiates and other psychotropic drugs in the setting of fatal polydrug overdose. Similar to other heroin overdose studies, men were over-represented (72.3%) in our population (4,5,10). The average age of victims of fatal heroin overdose typically falls between the late twenties and early thirties (5). However, similar to the average age of 38.9 years in our population, a study by Oppenheimer et al. (11) has reported an average age of victims of fatal heroin overdose as 38 years. This further supports that most fatal heroin overdoses occur in older, experienced heroin users rather than younger, and inexperienced users (5).

There was a significant difference between the morphine concentrations quantified from heart blood versus those quantified from femoral blood. While this observation is between cases rather than within a single case, the finding is still not unexpected. Morphine is primarily metabolized and distributed throughout the organs of the torso, which after death redistribute the drug by diffusion into central (heart) blood, causing an increase in postmortem concentrations. The femoral vessels are less susceptible to postmortem redistribution because the only theorized source of concentrated drugs is the surrounding muscle tissue. Therefore, femoral blood will typically have a lower concentration (that purportedly better mirrors antemortem concentration) than heart blood (12).

Contrary to the hypothesis that the concentration of morphine would be inversely proportional to the concentration of co-detected central nervous system depressant drugs in the setting of polydrug overdoses, this study does not identify distinct trends in the opioid, ethanol, and benzodiazepine-positive subsets. Specifically, it was expected that the concentration of morphine would be lower in the "high" concentration cases of a particular central nervous system depressant drug class subset, and higher in the "low" concentration cases. This expectation was based on the belief that given their similar mechanisms and effects, central nervous system depressant drugs would react synergistically in a concentration-dependent manner with morphine and that the cumulative result would be an overdose fatality. Particularly, the presence of opioids was believed to result in a fatal overdose with a lesser concentration of morphine, because each targets the same μ receptors with resulting respiratory depression (13). Benzodiazepines (and barbiturates) produce effects by targeting the GABAA receptor complex, which also decreases the respiratory rate. Although the respiratory inhibition of benzodiazepines alone is not as great as the effect of opioids alone, significant respiratory depression can occur when both the μ and GABAA receptors are stimulated simultaneously (13). Alcohol also acts through the GABAA receptor but binds through an alternate site than benzodiazepines. Like benzodiazepines, alcohol has respiratory depressive effects that are compounded with the addition of opiates (13). However, in this study, there were no significant findings among these subsets that demonstrate evidence of quantitative synergism with morphine.

It is possible that trends were not uncovered in the opioid, ethanol, and benzodiazepine subsets because of a lack of statistical power. In small populations, the addition of extra values to the set can of course have a considerable effect on the mean, and to a lesser degree on the median. The use of a nonparametric statistical test (Mann–Whitney *U*), which relies upon median values, is useful in this regard.

Concomitant use of heroin and antidepressants were detected in 17.8% of the total cases in this study. This figure is much higher than those discovered in an earlier study by Darke et al. (14) where antidepressants were detected in only 7% of fatal heroin overdoses. A separate study by Darke and Ross (15) investigated the habits of current heroin users, citing depression as the most common reason (42%) heroin users ingested antidepressants. Other heroin users reported that antidepressants were taken for intoxication (12%), sleep, anxiety, management of heroin withdrawal, and to reduce benzodiazepine use (15).

Within the antidepressant subset in this study, a direct relationship was found between the morphine values corresponding to an antidepressant concentration equal to or below the median antidepressant concentration versus the morphine concentrations corresponding to antidepressant concentrations greater than the median antidepressant concentration. In other words, morphine concentrations were higher in the "high" concentration group of the antidepressant drug class subset and lower in the "low" concentration group. These findings may suggest that the lethal dosage of heroin is increased through heavier concomitant antidepressant use.

Earlier studies have linked tricyclic antidepressants to potentiation of the effects of opiates because of the interaction with serotonin and other neurotransmitters that activate the endogenous opioid system and increase endorphin levels (16). Selective serotonin reuptake inhibitors (SSRI) also have toxic effects when used with heroin although to a lesser degree than tricyclic antidepressants (17).

A study by Fialip et al. (18) with mice found that the effects of morphine on the central nervous system were enhanced by the administration of clomipramine, a tricyclic antidepressant, but only if the clomipramine was administered simultaneously or shortly before the morphine. Alternatively, the same study found that chronic administration of clomipramine inhibited the effects of morphine. The authors concluded that the inhibitory effects of chronic clomipramine administration on morphine analgesia are time-dependent for a given dose and suggested some type of "gradual neurobiochemical changes first suppressing the potentiating effect and then reversing it." They proposed that their findings might be due to a specific loss of opiate receptor binding sites in the cerebral cortex after chronic tricyclic antidepressant administration. After 21 days of administration of a tricyclic antidepressant (desimipramine) in rats, Reisine and Soubrie (19) showed a significant decrease in sensitivity to opiates because of the loss of the specific opiate receptors in the cerebral cortex but not the corpus striatum or the hippocampus.

It was beyond the scope of this study to determine the length of antidepressant use prior to fatal overdose. Regardless, the finding that chronic tricyclic antidepressant administration decreases the quantity of opiate receptors in the cerebral cortex thus inhibiting the euphoric effects of morphine by Reisine and Soubrie (19) serves as a possible explanation for the direct relationship seen in our study between morphine and antidepressant concentrations. Heroin users on antidepressant therapy may increase their dosages in an unsuccessful attempt to gain heightened euphoria, when in actuality their opiate receptors in the cortex are subsensitive. Meanwhile, the opiate receptors of the corpus striatum and hippocampus, which seem relatively unaffected by chronic antidepressant use, become overwhelmed by the increase in opiate dosage. Although the hippocampus is not typically considered to have a direct role in respiration, the hippocampus does play a part in the rate and timing

of breathing. A study by Harper et al. (20) has shown that the theta waves produced by the hippocampus increase during inspiratory activity following a pause in the normal breathing pattern. This finding suggests that the hippocampus plays a critical role in mediating changes in the breathing pattern by producing the "drive" to breathe. Activation of the opiate receptors of the hippocampus can apparently inhibit the driving force to restart inspiratory activity following an anoxic period, thus leading to fatal respiratory depression.

Selective serotonin reuptake inhibitors were developed as a safer alternative to tricyclic antidepressants and their efficacy remains even when combined with morphine (21–23). One study found that the effects of morphine were unchanged in rats during the chronic administration of fluvoxamine (22). Another study found that fluoxetine actually increased the analgesic effects of morphine in healthy humans (23). Given the conflicting available data, as well as the results of this work, more studies are essential to determine whether antidepressants may inhibit the pleasurable effects of morphine in the cerebral cortex, thus requiring users of both to increase morphine doses. Alternatively, it could be postulated that antidepressant use may actually protect against respiratory depression, thus allowing the heroin user to increase morphine doses.

A striking finding of this study was the large number of cases of fatal overdose involving cocaine and heroin. Both morphine and cocaine (or BE) were present in nearly half (44.1%) of the cases in this study; a combination often termed a "speedball." A study by Foltin and Fischman (24) found that drug users prefer to use speedballs because the combination reduces the severity of the "crash" after cocaine use, takes the "edge" off of cocaine, and prolongs the "high" of the drugs, although the combined effects were not determined to have a significantly greater effect than each drug alone. However, a more recent study found that the combination of heroin and cocaine resulted in lower concentrations of morphine causing a lethal effect (25). These results correspond to the findings of this study, namely that significantly lower morphine concentrations are found in cocaine-positive cases and vice versa. Polettini et al. (25) speculated that these findings are the result of heroin and cocaine interfering with the metabolism of one another as they are metabolized through the same liver carboxylesterases. Further studies are needed to verify this hypothesis, as well as to further characterize the mechanism of fatality from this drug combination.

There are limitations to this study. It is retrospective; therefore, particular valuable information may not have been collected. The small number of cases in some of the subsets may have precluded the ability to detect important statistical differences. The use of keyword searching of causes of death may have omitted cases that fit the inclusion criteria. The route of administration was not determinable in every case, thus precluding insight into current usage trends or speculation as to how the rate of absorption may have played a role in the lethal event. Studies have shown that smoking rather than intravenously injecting heroin may be increasing in popularity and that different routes of administration cause a drug to achieve different levels of effects (5). Toxicological analyses in this study were performed on a variety of biological matrices samples, which affects the overall uniformity of the results. The use of antemortem samples ($n = 7$), although ultimately allowed in this study and not particularly outliers, may skew results. Even though the antemortem samples were not exposed to postmortem redistribution, they were included because they represented samples taken at a hospital immediately prior to the expiration of the patient and therefore, may be the most accurate representation of drug concentrations at the time of death. A similar prospective study that accounted for these variables may be of value.

Conclusion

Drug abuse is prevalent nationwide with heroin-related fatalities on the rise particularly. In the fatal heroin overdose population, polydrug fatalities where opiates are combined with other central nervous system agents are very common. This study reveals that there is no detectable relationship between postmortem morphine concentrations and the concentrations of other central nervous system depressants, namely opioids, benzodiazepines, and ethanol. Surprisingly, there is a directly proportional relationship between postmortem morphine and antidepressant concentrations. This relationship may be related to the decrease of opiate receptors in the cerebral cortex after chronic antidepressant treatment. While certainly further studies are needed, these findings may prove useful in understanding addiction and polydrug overdoses, as well as may be important in the treatment of depression in heroin addicts.

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