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Article

Opioid Overdose Mortality in Kansas, 2001–2011: Toxicologic Evaluation of Intent

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Drug concentration is a factor in the determination of the manner of death, but considerable overlap exists between therapeutic and toxic concentrations. This study aims to quantify opioid mortality in Kansas from use of fentanyl, methadone and oxycodone and to evaluate utility of drug concentrations for the determination of the manner of death. Cases referred to a forensic pathology practice in Kansas for autopsy from 1 January 2001 to 31 December 2011 were considered. The criterion for inclusion was detection of fentanyl, methadone and/or oxycodone in postmortem toxicology. Of 9,789 cases, 3,315 had positive toxicology: 180 of fentanyl, 299 of methadone and 310 of oxycodone. There were 207 single opioid fatalities, 264 polydrug overdoses and 318 deaths where an opioid was present but not contributory to the mechanism of death. In line with published studies, incidence of opioid overdose deaths increased over the time of the study. Drug concentrations within each cause and manner of death covered broad ranges. Non-natural and natural manners had less overlap than existed within non-natural manners in limited comparisons. This study shows that drug concentration is independent of manner for non-natural deaths and although insufficient to identify intent, can provide a guideline in differentiating non-natural from natural deaths.

Introduction

In recent decades, deaths attributed to prescription drug overdose, specifically those involving 'prescription painkillers', have shown marked increase in USA (1–4). The Center for Disease Control reports that the quantity of prescription painkillers sold to pharmacies in the USA quadrupled from 1999 to 2010 (5). States with high per capita sales report high incidence of associated drug overdose (5).

A relationship between opioid-related mortality and prescription patterns has been demonstrated in recent decades (6–8). Comparing the years 2001 and 2010, fentanyl consumption in the United States increased by 159%, from 197 kg in 2001 to 511 kg in 2010, methadone consumption increased by 122%, from 6,874 kg in 2001 to 15,286 kg in 2010, and oxycodone increased by 170%, from 21,871 kg in 2001 to 58,987 kg in 2010 (9, 10). Reasonably speaking, the more a drug was prescribed, the more opportunities existed for adverse events.

This study reports postmortem concentrations in multiple matrices of the three most commonly abused opioids in Kansas: fentanyl, methadone and oxycodone. We quantify overdose-related mortality in Kansas from 2001 to 2011. Drug concentrations in deaths of non-natural and natural manner are compared.

Fentanyl is a highly effective opioid analgesic, indispensable for treatment of chronic pain, and a drug with high potential for abuse (11–13). Indicated for use in the treatment of persistent pain of a moderate-to-severe degree, fentanyl provides therapeutic analgesia and exerts its principal pharmacologic effects on the central nervous system (13, 14). The intrinsic danger of fentanyl lies in its potency; estimates place fentanyl at roughly 50–100 times the strength of morphine (11).

Methadone, a synthetic opioid widely used in opiate addiction management, has seen recent resurgence as an analgesic for chronic pain (15, 16). Methadone has become a first line drug by reason of prolonged pharmacologic efficacy, a direct result of its approximate half-life of 15–40 h, and for cost control (17, 18).

Oxycodone, a semi-synthetic opioid commonly prescribed for moderate-to-severe pain, has become a favored drug of abuse (19). There is high bioavailability of immediate-release formulations, 60–87%, and a relatively fast analgesic effect following oral administration (19, 20). Research into oxycodone abuse has focused heavily on misuse of the sustained-release formulation Oxycontin™ (Purdue Pharma L.P., Stamford, Conn) in recent decades (19, 21, 22).

Methods

Autopsy referral to Frontier Forensics Midwest, LLC, a private practice of forensic pathology in Kansas City, KS, was from County Coroners in 67 of 105 Kansas Counties with referral criteria individual to each Coroner. Each County could adjust death investigative guidelines according to influences of cost, convenience and local interest; some County Coroners referred all deaths to a forensic pathologist, whereas others did so if a death appeared to have a non-natural contributor. The case material presented here represents a sample of deaths with unavoidable selection biases. The Kansas data are not representative of all opioid deaths in Kansas and do not include data from the state's two most populous counties (Johnson and Sedgwick).

Decedents autopsied between 1 January 2001 and 31 December 2011 underwent toxicologic screens when body preservation permitted specimen collection. Femoral blood, brain, liver, urine and vitreous fluid were submitted for analysis, with substitution of alternative sites of blood collection, if necessary. With the exception of deaths not allowing standard collection, such as in cases of advanced decomposition or excessive trauma, the stated specimen collection procedure was consistent among pathologists for the duration of the study. Toxicologic analysis was routinely requisitioned regardless of the potential manner of death.

Toxicologic analyses were performed at the Saint Louis University Forensic Toxicology Laboratory. Case samples were processed as general unknowns by routine toxicologic methods. Whole blood samples were screened preferentially and liver homogenates were screened in the absence of blood or when minimal amounts of blood were available. Analysis allowed for

the screening of approximately 150 known drugs and metabolites and included many classes of drugs such as anesthetics, anticonvulsants, antidepressants, antihistamines, antipsychotics, anxiolytics, non-narcotic analgesics, muscle relaxants, sedatives and stimulants. Confirmations of drugs present were all by gas chromatography/mass spectrometry (GCMS). The routine toxicology reports included the results of all screens and the quantitative results of all positive findings in the various samples of each case.

Data were compiled using an Access® database search of cases from 1 January 2001 to 31 December 2011 with positive toxicology. Deaths with accidental, natural, suicidal and undetermined manners were included and deaths with manner deferred ($n = 38$) or still pending determination ($n = 32$) were not included in the final analysis. Homicides ($n = 291$) with relevant opioid-positive toxicology ($n = 18$) were too few for statistical analysis. Age, race, sex, county of death, cause of death, manner of death and toxicologic findings were tabulated. Cases were excluded from analysis if drug concentrations were not specifically quantified in toxicology reports or the sample source was unspecified. Cases where drug concentrations were reported as 'greater than' or 'less than' a specific value, a very high or very low concentration, could not be included in calculation of drug values; in total, 34 femoral blood samples, 10 other blood and 28 liver values were excluded due to quantitation 'greater than' or 'less than' a specific concentration. If urine or vitreous fluid was positive for the drug studied but blood or tissue concentration was not specifically quantified, the case was counted in the total number of deaths but was not included in tabulation of drug concentrations for blood or tissue. Data presented in Table 2 and Supplementary Tables SI–IV represent both cases with blood and tissue available for analysis, as well as cases with only blood or only tissue. In many cases, one value, such as blood, was specifically quantified and tissue was reported in 'greater than' or 'less than' terms. Paired femoral blood and liver concentration ratios are presented in Supplementary Tables SV and VI for fentanyl and methadone; oxycodone is not included in femoral-to-liver concentration ratios due to the total number of useable paired samples below five.

Interpretation of the cause and the manner of death was by the autopsy pathologist, often in cooperation with the toxicologist. For the purposes of this study, the cause and the manner of death were taken only from the pathologist's final autopsy report. Deaths were classified as single-drug toxicity when the autopsy protocol did not list other drugs as a contributory factor; when other drugs were detected and listed as contributors to the cause of death, the death was classified as polypharmacy. Deaths with fentanyl, methadone or oxycodone detected, when the drugs were not considered contributory to the cause of death at autopsy, were classified by the cause and manner of death assigned by the autopsy protocol.

Cases are classified first by the drug detected, then by the cause of death (single-drug overdose, polydrug overdose or drug not contributory), followed by the manner of death (accident, natural, suicide and undetermined) and the source of sample (femoral blood, other blood, brain and liver). Data from sites of collection with 10 or more samples available for comparison are presented below. Collection sites with fewer than 10 samples are presented in Supplementary Tables SII–IV. For example, in fentanyl overdose deaths of accidental manner, femoral blood ($n = 38$), brain ($n = 20$) and liver ($n = 27$) are reported in the text, but other blood ($n = 5$) is not. The non-natural death category includes accidental, suicidal and undetermined manners, while the natural category contains cases only of natural disease.

A one-way analysis of variance (ANOVA) was conducted in categories containing at least five data points per group. Cases for ANOVA were separated by drug, cause of death, manner and specimen type. For example, in comparing fentanyl concentration in deaths not due to fentanyl, femoral blood in manners of accident ($n = 11$), natural ($n = 14$) and suicide ($n = 5$) were compared, but undetermined ($n = 2$) was not. If a significant difference was found, samples were compared in groups of two. In categories with only two groups eligible for comparison, a two-sample *t*-test assuming equal variance was performed. Alpha was set at 0.05 and calculated *P*-values below 0.05 were compared with a Bonferroni-adjusted alpha.

In Figure 1, deaths listed as 'fentanyl-related', 'methadone-related' or 'oxycodone-related' refer to cases in which the specified drug was involved in a single-opioid or polydrug overdose during a particular year. Cases listed as unrelated to a specific drug include deaths of accident, natural, suicide and undetermined manner where the drug was not contributory to fatality. Deaths indicated as 'opioid-related' represent a combination of fentanyl-related, methadone-related and oxycodone-related deaths over the study period; deaths unrelated to the three specified opioids were combined and represent 'deaths unrelated to opioid'.

Results

From 1 January 2001 to 31 December 2011, 9,789 autopsies were performed; of these, 3,315 (34%) had positive toxicology screens (see Table I). Thirty-one percent ($n = 1,028$) of cases with positive toxicology screens were classified as drug-related, i.e. cases in which the cause of death was drug use or fatalities in which drug use contributed to demise. Of the 1,028 drug-related deaths, 44% ($n = 452$) were polydrug overdoses. Fentanyl-related, methadone-related and oxycodone-related deaths included cases where the drug was either the sole factor in fatality or a contributing factor and cases totaled 10% ($n = 106$), 21% ($n = 217$) and 15% ($n = 151$) of drug-related deaths, respectively. Deaths with positive toxicology for the opioids investigated ($n = 789$) occurred largely in males, 64% ($n = 508$) and lesser numbers in females, 36% ($n = 281$). Age at death ranged from 2 to 92 years, with an average age of 43, median of 44 and mode of 48 years.

Figure 1 demonstrates the numbers of deaths positive for fentanyl, methadone and oxycodone rose from 2001 to 2011 (see Figure 1). Of note, each drug had lowest incidence of drug-related fatalities in 2001 and highest in 2010: fentanyl played a role in 3 deaths in 2001 and 19 in 2010, methadone contributed to 11 deaths in 2001 and 77 in 2010 and oxycodone-related deaths numbered 1 in 2001 and 31 in 2010. Cases where the indicated drug was non-contributory also exhibited an upward trend from 2001 onward.

Fentanyl

From 2001 to 2011, 180 deaths of accidental, natural, suicidal and undetermined manners had positive screens for fentanyl.

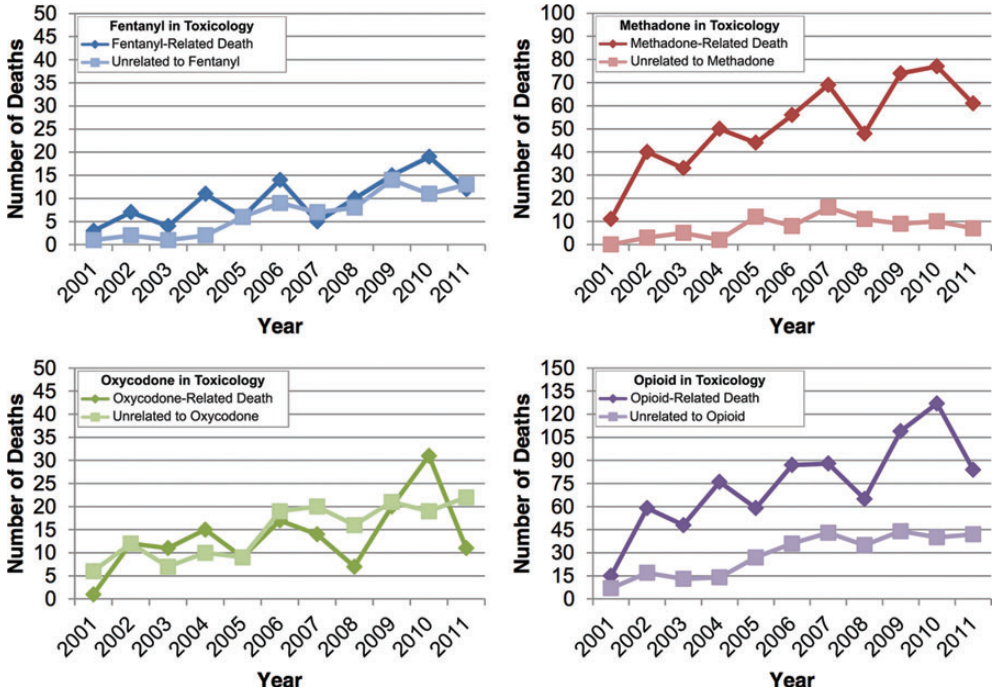

Figure 1. Number of deaths during 2001–2011 containing opioid-positive toxicologic screens.

Fifty-eight percent of cases occurred in males ($n = 104$), and 42% ($n = 76$) occurred in females (see Supplementary Table SI). Age range of decedents was 16 to 92 years, with an average and a median age of 45, mode of 44 years. Blood specimens, of femoral or non-femoral origin, were available for 138 cases (77%). Of the 180 deaths, 33% ($n = 60$) were fentanyl overdose deaths, 26% ($n = 46$) were polydrug toxicity and 41% ($n = 74$) cited fentanyl as non-contributory (see Supplementary Table SII).

In cases of single-drug overdose ($n = 60$), accidental deaths were 82% ($n = 49$), suicides 3% ($n = 2$) and undetermined manner 15% ($n = 9$) of the total sample. In fentanyl overdose deaths, comparison of femoral blood concentration in accidental and undetermined deaths revealed no significant differences ($P = 0.76$). Femoral blood fentanyl in accidental deaths ranged from 3.0 to 69.8 ng/mL ($n = 38$) with a standard deviation of 13.7 ng/mL. Brain tissue in accidental fentanyl overdose ranged from 12.0 to 143.0 ng/g ($n = 20$) with a standard deviation of 33.0 ng/g. The concentration of fentanyl in liver in accidental overdose had a mean of 94.0 ng/g ($n = 27$), a range of 4.4–393.0 ng/g and a standard deviation of 86.1 ng/g. The average femoral blood-to-liver ratio in paired samples ($n = 23$) of fentanyl overdose deaths was 0.16 (see Supplementary Table SV).

Polydrug overdoses involving fentanyl totaled 46 fatalities: 33 accidents (72%), 6 suicides (13%) and 7 undetermined deaths (15%). Comparison of concentration of fentanyl in femoral blood in accident, suicide and undetermined polydrug deaths revealed no significant differences ($P = 0.39$). For fentanyl-related polydrug overdoses, accidental deaths exhibited the widest range in femoral blood concentration, 1.1 ng/mL to 53.0 ng/mL ($n = 30$), of all manners of death in this data set. The concentration of fentanyl in liver did not differ significantly ($P = 0.22$) between accidental and undetermined manners. Fentanyl in liver in accidental polypharmacy deaths ranged 18.3–122.0 ng/g ($n = 11$), had an average of 66.2 ng/g and a standard deviation of 42.8 ng/g. In polydrug deaths, the average femoral blood-to-liver ratio in paired samples ($n = 15$) was 0.26.

Fentanyl was detected but not contributory to the cause of death in 74 cases: 46% were accidents ($n = 34$), 34% natural ($n = 25$), 15% suicide ($n = 11$) and 5% undetermined ($n = 4$). Comparison of femoral blood concentration of fentanyl in accident, suicide and natural deaths revealed no significant differences ($P = 0.24$). The concentration of fentanyl in femoral blood in accidental deaths, cause unrelated to the presence of fentanyl, had a mean of 8.6 ng/mL ($n = 11$), a range from 3.0 to 20.6 ng/mL and a standard deviation of 5.3 ng/mL. For natural deaths, cause also unrelated to fentanyl, femoral blood had a mean of 7.8 ng/mL ($n = 14$), a range from 2.0 to 25.0 ng/mL and a standard deviation of 7.0 ng/mL. In deaths unrelated to presence of fentanyl, the average femoral-to-liver concentration ratio was 0.17 among paired samples ($n = 10$).

In total, 155 non-natural and 25 natural deaths had fentanyl in postmortem fluid or tissue (see Table II). Fentanyl concentration in non-natural and natural deaths showed no significant differences in femoral blood ($P = 0.09$), other blood ($P = 0.20$) and liver ($P = 0.67$). Non-natural deaths had an average fentanyl blood concentration of 13.7 ng/mL ($n = 105$) for femoral blood and 16.0 ng/mL ($n = 14$) for blood obtained from other sources. Natural deaths had a lower average femoral blood concentration of 7.8 ng/mL ($n = 14$). The range of fentanyl concentration in liver values was wide in non-natural deaths, 4.4 ng/g to 540.0 ng/g ($n = 64$) and had an average fentanyl concentration of 86.5 ng/g and a standard deviation of 96.2 ng/g. The average paired femoral blood-to-liver concentration ratio in non-natural deaths ($n = 43$) was 0.19 and 0.25 in natural deaths ($n = 5$).

Table I
Number of deaths during 2001–2011 with positive toxicology screens

Manner	Deaths	Drug-related[a]	Polydrug overdose	Drug-related[b]		
				Fentanyl	Methadone	Oxycodone
Accident	1,251	635	284	82	153	97
Deferred	38	21	7	0	2	1
Homicide	291	3	0	0	0	0
Natural	853	17	0	0	0	0
Pending	32	10	6	0	1	1
Suicide	556	158	80	8	17	18
Undetermined	294	184	74	16	46	34
TOTAL	3,315	1,028	451	106	219	151

[a]Cases in which death resulted from drug use, unaccompanied by more powerful factors, and fatalities in which drug use facilitated demise are classified as 'drug-related'.
[b]Drug-related fentanyl, methadone and oxycodone columns include cases in which the drug was indicated as either the sole (single-drug overdose) or contributing (polydrug toxicity) factor in fatality.

Methadone

For the 11-year study period, 299 accidental, natural, suicidal and undetermined deaths were positive for methadone. Sixty-eight percent of cases occurred in males ($n = 203$), and 32% in females ($n = 96$) (see Supplementary Table SI). Deaths positive for methadone ranged from 2 to 78 years with an average age of 41, median at 43 and a mode of 48 years. Femoral or non-femoral blood specimens were available for analysis in 260 cases (87%). Of 299 deaths, 39% were methadone overdoses ($n = 116$), 33% were polydrug toxicity ($n = 100$) and 28% listed methadone as not contributory to the cause of death ($n = 83$) (see Supplementary Table SIII).

Deaths with methadone as primary toxicity ($n = 116$) numbered 65% accidents ($n = 75$), 10% suicides ($n = 12$) and 25% undetermined deaths ($n = 29$). in methadone overdose deaths, femoral blood concentration between accident, suicide and undetermined deaths did not differ significantly ($P = 0.18$). For accidental methadone overdose deaths, the concentration of methadone in femoral blood ranged from 0.15 to 2.9 μg/mL ($n = 61$) with an average of 0.68 μg/mL and a standard deviation of 0.52 μg/mL. In accidental and undetermined deaths, other blood concentration did not differ significantly ($P = 0.49$). Blood from non-femoral sources in methadone overdoses of accidental manner varied from 0.16 to 5.3 μg/mL ($n = 10$), with an average of 1.19 μg/mL and a standard deviation of 1.49 μg/mL. The concentration of methadone in brain samples could not be evaluated due to insufficient sample size. Liver concentration did not differ significantly ($P = 0.91$) among accident, suicide and undetermined manners. The liver had the widest range of concentration in methadone overdose deaths of undetermined manner, 1.4 μg/g to 21.0 μg/g ($n = 26$) with a standard deviation of 3.8 μg/g. For methadone overdoses with a liver sample size of 10 or more cases, undetermined had the highest average concentration of all manners of death, 3.70 μg/g ($n = 26$). The average femoral blood-to-liver ratio in paired samples ($n = 69$) of methadone overdose deaths was 0.20 (see Supplementary Table SVI).

Methadone was a contributory factor in 100 cases of polydrug overdose: 78 accidents (78%), 5 suicides (5%) and 17 undetermined deaths (17%). Comparison of femoral blood concentration of methadone in accidental and undetermined polydrug deaths did not show any significant differences ($P = 0.17$). For polypharmacy deaths, accidents and undetermined deaths had an overlapping range in femoral blood, 0.1–1.4 μg/mL ($n = 62$) in accidents and 0.26–1.6 μg/mL ($n = 10$) in undetermined. Polydrug deaths of undetermined manner had the highest mean and standard deviation of the methadone femoral blood data set at 0.63 and 0.45 μg/mL, respectively. Insufficient numbers of brain samples were available for statistical comparison. The concentration of methadone in liver differed significantly ($P = 0.02$) between accidental and undetermined manners. In accidental polydrug deaths, the concentration of methadone in liver averaged 2.8 μg/g ($n = 61$), contained values from 0.2 to 9.7 μg/g and had a standard deviation of 2.0 μg/g. Polypharmacy deaths of undetermined manner had a wide range of values in liver, 0.5 to 22.0 μg/g ($n = 15$), a mean of 4.9 μg/g and a standard

Table II
Comparison of drug concentration in non-natural and natural deaths with opioid-positive toxicology[a]

	Blood source (ng/mL)		Tissue (ng/g)	
	Femoral	Other[b]	Brain	Liver
Fentanyl				
Non-natural deaths				
155 Cases				
Mean	13.7	16.0	38.6	86.5
Median	9.0	10.1	28.0	61.5
Range	1.1–69.8	2.3–69.0	5.0–143.0	4.4–540.0
SD	12.7	17.2	34.1	96.2
	$n = 105$	$n = 14$	$n = 42$	$n = 64$
Natural deaths				
25 Cases				
Mean	7.8	5.3	7.5	72.3
Median	4.1	4.0	7.6	35.0
Range	2.0–25.0	2.4–13.0	3.2–11.6	8.3–242.0
SD	7.0	4.4	4.2	83.5
	$n = 14$	$n = 5$	$n = 3$	$n = 9$
Methadone				
Non-natural deaths				
256 Cases				
Mean	0.60	0.76	0.94	3.3
Median	0.50	0.55	0.76	2.7
Range	0.076–3.7	0.1–5.3	0.28–2.5	0.17–22.0
SD	0.49	0.85	0.59	3.1
	$n = 182$	$n = 45$	$n = 18$	$n = 203$
Natural deaths				
43 Cases				
Mean	0.47	0.9	0.47	1.8
Median	0.33	0.25		1.5
Range	0.1–1.5	0.07–3.2		0.28–8.3
SD	0.38	1.28		1.5
	$n = 25$	$n = 8$	$n = 1$	$n = 35$
Oxycodone				
Non-natural deaths				
237 Cases				
Mean	0.40	0.80	1.2	1.9
Median	0.33	0.48	0.98	0.49
Range	0.04–1.6	0.03–5.7	0.03–3.3	0.06–7.5
SD	0.30	1.2	1.0	2.5
	$n = 130$	$n = 30$	$n = 9$	$n = 15$
Natural deaths				
73 Cases				
Mean	0.23	0.24	0.87	0.93
Median	0.17	0.17	0.70	0.70
Range	0.04–0.9	0.05–0.72	0.06–1.9	0.06–2.3
SD	0.20	0.22	0.68	0.79
	$n = 38$	$n = 8$	$n = 8$	$n = 8$

[a]Cases were excluded from analysis if concentration was not specifically quantified by lab or if no preferred sites of collection were available. Cases where urine or vitreous fluid was positive for opioids but blood or tissue concentrations were not specifically quantified are included in case totals.
[b]Other blood samples were obtained from aorta, central source, heart, inferior vena cava, pericardial sac or pulmonary artery.

deviation of 5.8 μg/g. The average femoral blood-to-liver concentration ratio in methadone-related polydrug deaths was 0.20 in paired samples ($n = 60$).

Methadone was detected but played no role in the cause of death in 83 deaths: 27% accidents ($N = 22$), 52% natural ($n = 43$), 7% suicides ($n = 6$) and 14% undetermined ($n = 12$). Accident, natural and undetermined deaths in which the presence of methadone was unrelated to fatality did not differ significantly in femoral ($P = 0.21$) and other blood ($P = 0.46$) concentrations. Sample size was insufficient for separate statistical analysis of femoral and non-femoral blood specimens in accidental, suicidal and undetermined deaths. Natural deaths had femoral blood concentration of 0.1–1.5 μg/mL ($n = 25$), a mean of 0.47 μg/mL and a standard deviation of 0.37 μg/mL. Insufficient numbers of brain specimens were analyzed in this group. Accidental, natural and undetermined deaths in this category did not exhibit significant differences ($P = 0.18$) in liver concentration. Of the manners of death in this data set, accidents had the widest range of liver concentrations, 0.17–8.4 μg/g ($n = 17$), the largest mean concentration of methadone, 2.79 μg/g and the greatest standard deviation, 2.35 μg/g. In deaths where methadone was present but did not play a role in fatality, the average femoral blood-to-liver concentration ratio was 0.23 among paired samples ($n = 33$).

Deaths of non-natural ($n = 256$) and natural ($n = 43$) manners exhibited some overlap (see Table II). The concentration of methadone in non-natural and natural deaths did not differ significantly in femoral blood ($P = 0.19$), other blood ($P = 0.69$) and brain ($P = 0.45$). Femoral blood samples in non-natural deaths ranged from 0.076 to 3.7 μg/mL ($n = 182$), where natural deaths had a narrower range of femoral blood concentrations, 0.1–1.5 μg/mL ($n = 25$). The mean blood concentration in non-natural deaths was 0.60 μg/mL ($n = 182$) in femoral blood and 0.76 μg/mL ($n = 45$) in other blood compared with 0.47 μg/mL ($n = 25$) for femoral blood in natural deaths. Brain specimens were more often analyzed in non-natural than in natural deaths but with inadequate sample numbers for statistical comparison. The concentration of methadone in liver differed significantly ($P = 3.4 \times 10^{-3}$) between non-natural and natural deaths. In methadone overdoses, liver concentration in accidents ($P = 1.2 \times 10^{-2}$), suicides ($P = 1.4 \times 10^{-3}$), and deaths of undetermined ($P = 8.1 \times 10^{-3}$) manner differed significantly from natural deaths. Undetermined deaths unrelated to methadone did not differ significantly ($P = 0.25$) from natural deaths in liver concentration. Liver concentrations in non-natural deaths ranged from 0.17 to 22.0 μg/g ($n = 203$); natural deaths had a narrower range of concentrations, 0.28 to 8.3 μg/g ($n = 35$). The mean concentration of methadone in the liver was 3.3 μg/g in non-natural deaths and 1.8 μg/g in natural deaths; the standard deviation was 3.1 μg/g in non-natural and 1.5 μg/g in natural deaths. The average femoral blood-to-liver concentration ratio in non-natural deaths ($n = 142$) was 0.20; in natural deaths ($n = 21$) the average ratio was 0.25.

Oxycodone

Oxycodone was detected in 310 accidental, natural, suicidal and undetermined deaths from 2001 to 2011. Sixty-five percent of deaths occurred in males ($n = 201$) and 35% in females ($n = 109$) (see Supplementary Table SI). Ages ranged from 15 to 90 years, with an average and a median of 45 and a mode of 48 years. Blood specimens, of femoral or non-femoral source, were available for 206 cases (66%). Of 310 deaths, 10% were oxycodone overdoses ($n = 31$), 38% were polydrug deaths ($n = 118$) and 52% were unrelated to the presence of oxycodone ($n = 161$) (see Supplementary Table SIV).

Deaths with oxycodone as the single-drug cause of death ($n = 31$) had 20 accidents (64%), 3 suicides (10%) and 8 undetermined deaths (26%). Due to the small number of single-drug oxycodone overdose deaths, blood and tissue sample number was small. In comparing overdoses of accidental and undetermined manners, the concentration of oxycodone in femoral blood did not differ significantly ($P = 0.39$). In accidental oxycodone overdoses, femoral blood concentration ranged from 0.12 to 0.98 μg/mL ($n = 16$), with a mean of 0.52 μg/mL and a standard deviation of 0.28 μg/mL. Insufficient numbers of brain and liver specimens were available for accurate statistical comparison in single-drug oxycodone fatalities.

Oxycodone was involved in 118 polydrug overdoses, of which 65% were accidents ($n = 77$), 13% were suicides ($n = 15$) and 22% were of undetermined manner ($n = 26$). The concentration of oxycodone in femoral blood did not differ significantly ($P = 0.39$) between accidental and undetermined polydrug deaths. Accidental and undetermined polypharmacy deaths had a great overlap in range of femoral blood concentrations: 0.05 to 1.6 μg/mL ($n = 55$) in accidents and 0.07 to 1.5 μg/mL ($n = 18$) in undetermined. Accidents averaged 0.37 μg/mL in femoral blood, standard deviation 0.29 μg/mL, and undetermined oxycodone-related polydrug deaths averaged 0.50 μg/mL in femoral blood, standard deviation 0.39 μg/mL. Sample size was insufficient to compare drug concentrations in tissue.

Deaths with oxycodone present, but unrelated to the cause of death ($N = 161$), numbered 46 accidents (29%), 73 natural deaths (45%), 21 suicides (13%) and 21 undetermined fatalities (13%). No significant difference ($P = 0.28$) was found between accidental, natural, suicidal and undetermined manners with regard to femoral blood concentration. Fatalities with accidental and natural manners exhibited a great overlap in concentration of oxycodone in femoral blood: accidents varied from 0.04 to 0.91 μg/mL ($n = 12$) and natural deaths varied from 0.04 to 0.9 μg/mL ($n = 38$). The mean femoral concentration in accidents was 0.34 μg/mL, standard deviation 0.30 μg/mL, compared with 0.23 μg/mL in natural deaths, standard deviation 0.20 μg/mL. The concentration of oxycodone in other blood did not differ significantly ($P = 0.21$) between accidents, natural deaths, suicides and undetermined. Blood sample numbers in suicides and undetermined deaths, femoral and non-femoral sources, were insufficient for comparison of sample averages, ranges and standard deviations.

In total, 237 non-natural and 73 natural deaths tested positive for the presence of oxycodone in postmortem toxicologic screens (see Table 2). The concentration of oxycodone in femoral blood in non-natural deaths differed significantly ($P = 1.4 \times 10^{-3}$) from natural deaths. Femoral blood concentration in oxycodone overdoses differed from natural death concentrations for manners accident ($P = 5.5 \times 10^{-5}$) and undetermined ($P = 6.9 \times 10^{-5}$). The concentration of oxycodone in femoral blood differed significantly from those in natural deaths in polydrug overdoses, manner accident ($P = 1.2 \times 10^{-2}$), suicide ($P = 3.3 \times 10^{-2}$) and undetermined ($P = 9.2 \times 10^{-4}$). Individual comparison of femoral oxycodone in natural deaths with

non-oxycodone-related accidents ($P = 0.16$), suicides ($P = 0.40$) and undetermined deaths ($P = 0.70$) revealed no significant differences. Femoral blood concentration for non-natural deaths ranged from 0.04 to 1.6 μg/mL ($n = 130$) and for natural deaths from 0.04 to 0.9 μg/mL ($n = 38$). The average concentration of oxycodone in femoral blood differed between non-natural and natural deaths: 0.40 μg/mL ($n = 130$) in non-natural and 0.23 μg/mL ($n = 38$) in natural deaths. Oxycodone in non-natural and natural deaths did not differ significantly in other blood ($P = 0.18$), brain ($P = 0.45$) and liver ($P = 0.29$). Non-natural deaths had both the lowest and the highest concentration of oxycodone in a non-femoral blood source, 0.03 μg/mL ($n = 30$) and 5.7 μg/mL.

Discussion

Much current literature on opioid overdose mortality focuses on the occurrence of unintentional drug poisoning with little description of how the manner of death is established (1, 3). Classically, pathologists try to use drug concentrations to assist with determination of the manner of death, as high concentrations typically are believed to be associated with self-destructive intent and lower concentrations with coincidental toxicity. However, a drug can be within the range of concentrations considered potentially lethal but may not play an actual role in the cause of death, as with many trauma and other non-toxicologic cause of death. Detection of licit and/or illicit substances may be from self-destructive effort, attempt for secondary chemical gain or coincidental exposure, and quantitation does not necessarily render clear the intent of the user. The challenge, on review of toxicologic data, is deciphering intent behind a given drug concentration when little relevant case history is available.

Drugs with abuse potential, such as opioid painkillers, present difficulty for toxicologic interpretation of intent since users, both licit and illicit, seek noticeable, positive effects which may be enhanced by increased consumption. In search of a desired effect, abusers may exceed therapeutic ranges, with a consequent increased chance of overdose. Interpretation of drug concentration and relationship of concentration with intent may be clouded by non-quantifiable factors, such as opioid tolerance.

What stands out in the analysis of opioid-related death in Kansas is the variability of concentrations within each manner of death and how much concentrations overlap between manners of death. In comparison of non-natural with natural manners, there is somewhat less overlap; however, statistically significant differences in the data set are limited. With regard to the concentration of fentanyl in postmortem specimens, no significant differences were found in comparison of different causes and manners of death. In deaths positive for methadone, significant differences were found in liver concentration between methadone-related deaths and non-methadone-related deaths. Similarly, oxycodone in femoral blood differed significantly between oxycodone-related deaths and non-oxycodone-related deaths. Paired femoral blood-to-liver concentration ratios in varying causes and manners for fentanyl and methadone suggested no significant patterns.

In line with published studies, incidence of opioid-related fatalities appeared to increase over the course of the study (see Figure 1). Each drug had the lowest incidence of related fatalities in 2001: 3 of fentanyl, 11 of methadone and 1 of oxycodone; however, the frequency which these drugs were screened for in 2001 compared with other years is unknown. Of the three drugs studied, the highest incidence of related deaths was observed in 2010: 19 of fentanyl, 77 of methadone and 31 of oxycodone. The Kansas data also suggest a greater confidence in the identification of deaths with methadone as methadone-related, as evidenced by non-overlapping numbers of methadone-related deaths with unrelated deaths from 2001 to 2011. This differs from fentanyl and oxycodone, where deaths due to or not due to drug were identified with similar, overlapping frequency. The degree to which this difference is due to the availability of relevant case history or local trends in prescription is beyond the scope of this study.

It has been suggested that the small spike in fentanyl-related deaths in 2006 may be a result of the fentanyl-laced heroin epidemic observed in some major metropolitan areas from 2005 to 2007 (23). Review of database information found fewer than five cases from 2001 to 2011 positive for 6-monoacetylmorphine, none of which contained fentanyl. Morphine was present alongside fentanyl in 20 total cases: 5 fentanyl overdoses, 1 morphine overdose, 5 polydrug deaths, 2 deaths of undetermined cause and 7 unrelated to the presence of any drugs.

This study demonstrates drug concentration is not significantly correlated with manner in non-natural deaths. However, when non-natural and natural manners are compared, drug concentrations display some stratification. As with other studies, the Kansas data are consistent with increasing numbers of deaths, regardless of manner, likely by reason of increased drug availability.

Conclusion

Examination of the results of fentanyl, methadone and oxycodone-related fatalities in Kansas demonstrates that drug concentration can vary significantly within manners of death and there is wide overlap of concentrations among manners of death. Postmortem toxicologic analysis provides useful drug concentration data, but circumstance of drug exposure cannot be deciphered by laboratory methods alone. In order to reasonably evaluate context of opioid consumption, attention must be given to relevant case history with less reliance upon specific drug concentration in determination of intent.

Supplementary data

Supplementary data are available at *Analytical Toxicology* online.

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