Fatal Fentanyl: One Pill Can Kill

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ABSTRACT

Objective: The current national opioid epidemic is a public health emergency. We have identified an outbreak of exaggerated opioid toxicity caused by fentanyl adulterated tablets purchased on the street as hydrocodone/acetaminophen.

Methods: Over an 8-day period in late March 2016, a total of 18 patients presented to our institution with exaggerated opioid toxicity. The patients provided a similar history: ingesting their "normal dose" of hydrocodone/acetaminophen tablets but with more pronounced symptoms. Toxicology testing and analysis was performed on serum, urine, and surrendered pills.

Results: One of the 18 patients died in hospital. Five patients underwent cardiopulmonary resuscitation, one required extracorporeal life support, three required intubation, and two received bag-valve-mask ventilation. One patient had recurrence of toxicity after 8 hours after naloxone discontinuation. Seventeen of 18 patients required boluses of naloxone, and four required prolonged naloxone infusions (26–39 hours). All 18 patients tested positive for fentanyl in the serum. Quantitative assays conducted in 13 of the sera revealed fentanyl concentrations of 7.9 to 162 ng/mL (mean = 52.9 ng/mL). Pill analysis revealed fentanyl amounts of 600–6,900 μg/pill. The pills are virtually indistinguishable from authentic hydrocodone/acetaminophen tablets and are similar in weight. To date, our county has reported 56 cases of fentanyl opioid toxicity, with 15 fatalities. In our institution, the outbreak has stressed the capabilities and resources of the emergency department and intensive care units.

Conclusions: A serious outbreak of exaggerated opioid toxicity caused by fentanyl-adulterated tablets purchased on the street as hydrocodone/acetaminophen is under way in California. These patients required higher dosing and prolonged infusions of naloxone. Additionally, observation periods off naloxone were extended due to delayed, recurrent toxicity. The outbreak has serious ramifications for public health and safety, law enforcement, and healthcare facilities and resources.

The current nationwide opioid epidemic for both prescription and illicit drugs is a public health emergency.[1] Prescription opioids have now surpassed homicide as a cause of mortality.[2] This epidemic has resulted in multiple agencies, including the U.S. Centers for Disease Control and Prevention (CDC), issuing guidelines aimed at altering prescribing practices in an attempt to decrease morbidity and mortality.[3–5] However, limiting legally obtained prescription opioids only addresses a part of the epidemic. In a 2014 CDC national survey, 10.3 million persons reported taking prescription opioids "recreationally," that is, opioids that had not been prescribed for them.[1,6] These supposed prescription drugs are often purchased illegally and are at risk for drug adulteration.

Previous fentanyl outbreaks exist; however, this outbreak demonstrated pills marketed as a typical pharmaceutical pill but with more severe toxicity.[7–9] Patients

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reported the use of pharmaceutical opioid pills, and thus an opioid presentation was not surprising, but the clinical ramifications were different. In this report, we describe 18 cases of patients taking fentanyl-adulterated pills disguised as hydrocodone/acetaminophen (10 mg/325 mg), that to date have led to 56 overall cases, and 15 fatalities, in a single California county. The consequences of this public health outbreak for hospitals, public health and safety, and federal law enforcement are discussed.

CASE SERIES

Index Patient

Recently, a series of patients presented to a single urban academic emergency department with symptoms suggestive of a severe opioid overdose after reportedly taking hydrocodone/acetaminophen tablets purchased on the street. The index patient was a 24-year-old male who presented on March 23, 2016, with hypotension and hypoxic respiratory failure. Prehospital providers had obtained a history on the scene indicating that the patient had taken hydrocodone/acetaminophen pills and that he complained of "not feeling right" and "feeling really high" from taking his "normal amount." The patient's clinical condition deteriorated during prehospital transport. Naloxone was given via the intranasal route (2 mg) and intravenously (1 mg) without significant response. In the emergency department, the patient continued to be hypotensive (systolic blood pressure 90 mm Hg) and hypoxemic (oxygen saturation 60%–70% on 100% nonrebreather mask). Additional intravenous naloxone (2 mg) did not improve his condition.

The patient was intubated. Chest radiographs revealed evidence of pulmonary edema. He continued to be hypoxemic and developed pulseless electrical activity but responded to 1 mg of epinephrine and cardiopulmonary resuscitation. Ventilation strategies, including neuromuscular blockade with cisatracurium, inhaled nitric oxide, and prone positioning were instituted, but he remained hypoxemic and deteriorated hemodynamically. His B-type natriuretic peptide was normal at 29 pg/mL, suggesting that his hypoxia was unlikely from a cardiac source and more likely from acute lung injury. He was given infusions of norepinephrine, vasopressin, and epinephrine, and venovenous extracorporeal life support was administered. During the next 48 hours, ventilatory and hemodynamic support was decreased and then discontinued. Toxicologic testing revealed no acetaminophen, but the presence of fentanyl, norfentanyl, promethazine, and hydrocodone was revealed.

The patient was extubated on hospital day 7 and transferred out of the intensive care unit. On day 14, he was discharged, ambulating without assistance, and appeared to have normal neurologic function. He admitted to taking 1½ pills, which he had purchased on the street, believing that they were hydrocodone/acetaminophen.

Within the next 8 days after the presentation of the index patient, our institution cared for 18 patients with symptoms of an exaggerated opioid overdose. Additionally, one patient had a repeat respiratory arrest after being off a naloxone infusion for 8 hours requiring a naloxone bolus and repeat infusion. One of the 18 patients died in hospital. Five patients underwent cardiopulmonary resuscitation, one required extracorporeal life support, three required intubation, and two received bag-valve-mask ventilation. Seventeen of 18 patients required boluses of naloxone, and four required prolonged naloxone infusions (26–39 hours). A summary of the patients' clinical course is presented in Table 1. All 18 patients tested positive for fentanyl in the serum, with concentrations of 7.9 to 162.3 ng/mL (mean, 52.9 ng/mL) for those who had samples available for quantification. A summary of complete toxicologic testing of biologic samples as well as pills obtained from the patient are listed in Tables 2 and 3, respectively. Figure 1 shows a comparison of a pharmaceutical hydrocodone/acetaminophen (10/325) tablet (top) and a tablet purchased on the street (bottom).

Pill analysis revealed fentanyl amounts of 600–6,900 μg/pill and smaller amounts of other pharmaceutical medications (Table 3). Pills were obtained from six patients who voluntarily provided them for sampling had a mass ranging from 402 to 489 mg (mean, 454 mg). Pharmaceutical hydrocodone/acetaminophen (M367) was made by Mallinckrodt Pharmaceuticals; weights of 10 pills, weighed by electronic scale (range = 422 to 429 mg; mean = 426 mg) were not significantly different from the weights of the pills obtained from patients.

Early Epidemiologic Investigation

On March 24, 2016, our institution received its fourth patient presenting with opioid toxicity and clinical history similar to that of the index case. We notified our

Table 1
Summary of Clinical Events

Case	Age (y)	Sex	Intubated (Yes/No)	Naloxone Admin (Yes/No)	Naloxone Bolus Dose Prior to Infusion (mg)	Duration of Naloxone Infusion	Length of Stay	Additional Events
1	24	M	Yes	Yes	5	—	296 h 5 m	ECLS
2	25	F	No	Yes	0.4	—	21 h 11 m	BVM
3	50	M	Yes	Yes	5.9	29 h 58 m	67 h 33 m	—
4	28	M	No	Yes	2	—	5 h 42 m	—
5	59	F	Attempted by EMS	Yes	3.2	—	31 h 55 m	—
6	48	F	No	Yes	8	35 h 18 m	43 h 21 m	—
7	55	M	No	Yes	3.4	39 h 41 m	69 h 1 m	—
8	50	M	No	Yes	1.2	26 h 20 m	41 h 33 m	—
9	32	F	No	Yes	2	—	10 h 54 m	CPR
10	32	M	Yes	Yes	3	—	12 m	CPR/death
11	25	M	No	No	0	—	4 h 7 m	—
12	53	F	No	Yes	3.4	—	8 h 9 m	—
13	22	M	No	Yes	2	—	8 h 22 m	CPR
14	28	M	No	Yes	2	—	6 h 40 m	—
15	33	F	No	Yes	2	—	16 h 30 m	CPR
16	16	M	No	Yes	2	—	10 h 49 m	CPR
17	23	F	No	Yes	2	—	6 h 40 m	BVM
18	37	F	No	Yes	1	—	4 h 13 m	

BVM = bag-valve mask respiratory support; CPR = cardiopulmonary resuscitation; ECLS = extracorporeal life support.

county public health officer of our concerns for an adulterated street pill being sold as hydrocodone/acetaminophen. Given the severe degree of apparent opioid toxicity, we would have expected to identify acetaminophen in the blood if this were due to a combination hydrocodone/acetaminophen tablet. However, no acetaminophen was detected suggesting these tablets were not pharmaceutical grade and likely contained some form of opioid. When preliminary testing revealed fentanyl and its metabolite, norfentanyl, a countywide California Health Advisory Notice was issued (March 25, 2016).[10] In addition to traditional public health notification, our poison center notified regional hospitals and three additional California poison centers of our observations. By April 1, this outbreak had spread outside our neighboring counties, and other counties in California began issuing health alerts.[11] At the same time, additional toxicologic testing confirmed our suspicion that the suspect pills contained large amounts of fentanyl. Federal law enforcement officials from the Drug Enforcement Agency (DEA) and the Department of Justice became involved. Results of our pill analyses were shared with law enforcement officials, and further intensive investigation is under way.

Laboratory Evaluation

All patients had urine samples tested for amphetamines, cocaine metabolites, opiates, benzodiazepines, and barbiturates. Samples were tested by automated enzyme assay UniCel DXC800 (Beckman Coulter Inc.). Comprehensive urine toxicology analysis with gas chromatography and mass spectrometry, using the 6890 NPD Agilent ChemStation software (Agilent Technologies), was performed at the University of California, Davis. Biologic samples (serum, plasma, and urine) and pills obtained from patients were sent to the clinical toxicology and environmental biomonitoring laboratory at the University of California–San Francisco. Targeted analysis of 610 illicit and designer drugs with liquid chromatography–quadruple time-of-flight mass spectrometry (Agilent 1260- QTOF/MS 6550) was performed as well as suspect screening of 55 opioid analogs. Confirmation of drugs detected in the samples was done with Agilent MassHunter Qualitative Analysis software. Quantitation of drugs confirmed in both the pill and the biologic samples were done by use of an isotope dilution method with Agilent MAssHunter Quantitative Analysis for data analysis.

Investigation Oversight and Data Collection

This investigation and data collection were part of an emergent public health outbreak. Therefore, they were not considered to be research that required approval from our institutional review board or informed consent from patients.

DISCUSSION

Emergency physicians are on the front line and must realize that often the first clues to identifying public

Table 2
Biologic Sample Results

			Serum Concentration					Urine Concentration	
Case	Urine Drug Screen	Time*	Fentanyl (ng/mL)	APAP (μg/mL)	Hydrocodone (ng/mL)	Promethazine (ng/mL)	Time*	Fentanyl (ng/mL)	Hydrocodone (ng/mL)
1	Fentanyl Hydrocodone Norfentanyl Promethazine	28 h 30 m	39.4	0.01	0	0	28 m	1792.2	295.2
2	Hydrocodone Norfentanyl Promethazine	12 m	22.7	0.82	0	0	1 h 19 m	716.2	59.9
3	Fentanyl Norfentanyl Promethazine	14 h 35 m	16.5	0.17	0	0	3 h 2 m	429.7	0
4	Fentanyl Norfentanyl Promethazine	3 h 35 m	17	0.07	0	0	3 h 38 m	969.2	0
5	Cocaine Fentanyl Hydrocodone Levamisole Methadone Norfentanyl Norhydrocodone Promethazine	7 h 35 m	53.3	0.31	12.1	0	7 h 11 m	646.5	0
6	Fentanyl Hydrocodone Norfentanyl Norhydrocodone Promethazine Trazodone	2 h 13 m	162.3	1.34	0	26.8	2 h 46 m	33754.8	0
7	Fentanyl Hydrocodone Norfentanyl Promethazine Trazodone	2 h 29 m	123.1	1.08	0	3.9	48 m	12036.2	231.3
8	Dihydrocodeine Fentanyl Hydrocodone Norfentanyl Norhydrocodone Promethazine	2 h 22 m	36.3	0.68	55.8	5.1	32 m	3277.1	1217.5
9	Dihydrocodeine Fentanyl Hydrocodone Norfentanyl Norhydrocodone Oxycodone Promethazine	1 h 47 m	51.3	0.41	0	4.7	2 h 27 m	647.2	0
10	Amphetamine Fentanyl Hydrocodone Methamphetamine Norfentanyl Promethazine		NS	NS	NS	NS	Unknown	6776.3	0
11	Dihydrocodeine Fentanyl Hydrocodone Norfentanyl Norhydrocodone Promethazine		NS	NS	NS	NS		NS	NS
12	Fentanyl Norfentanyl Promethazine	3 h 8 m	27.0	0.31	10	O	3 h 8 m	376.3	0
13	Fentanyl Hydrocodone Norfentanyl Norhydrocodone Oxycodone Promethazine	15 m	64.3	0.56	18.6	3.1		NS	NS

(Continued)

Table 2 (continued)

Case	Urine Drug Screen	Time*	Serum Concentration Fentanyl (ng/mL)	APAP (μg/mL)	Hydrocodone (ng/mL)	Promethazine (ng/mL)	Time*	Urine Concentration Fentanyl (ng/mL)	Hydrocodone (ng/mL)
14	Cyclobenzaprine Dihydrocodeine Fentanyl Hydrocodone Norfentanyl Norhydrocodone	5 m	7.9	0.12	22.9	O	5 m	972.2	O
15	Cyclobenzaprine Fentanyl Norfentanyl Promethazine		NS	NS	NS	NS		NS	NS
16	Dihydrocodeine Fentanyl Hydrocodone Norfentanyl Norhydrocodone Promethazine		NS	NS	NS	NS		NS	NS
17	Dihydrocodeine Fentanyl Hydrocodone Norfentanyl Norhydrocodone		NS	NS	NS	NS		NS	NS
18	NS	54 m	65.9	1.01	0	0		NS	NS

The therapeutic (TL) and toxic (TX) serum levels of above drugs are: fentanyl TL = 1–2 ng/mL, TX = 2–20 ng/mL, lethal > 20 ng/mL; acetaminophen TL = 2.5–25 μg/mL, TX = 75–150 μg/mL; hydrocodone TL = 2–50 ng/mL, TX > 100 ng/mL; promethazine TL = 50–100 ng/mL, TX > 1000 ng/mL.[8]
*Time = Time elapsed from patient arrival until sample sent; NS = no sample obtained.

Table 3
Analysis of Pills Obtained from Patients

Pill Source (Case Number)	Pill Mass (mg)	Fentanyl (μg)	Hydrocodone (mg)	APAP (mg)*	Promethazine (mg)
3	453.6	6900	0	137.0	4.27
8	488.9	6320	0	144.8	3.82
10	463.9	6690	0	415.1	4.07
11	420.2	5630	0	105.4	3.66
13	421.9	600	7.41	258.3	0.53
14	473.4	6870	0	102.8	4.61

APAP = acetaminophen.

health outbreaks may occur in the emergency department. Fentanyl is equipotent to morphine at doses that are 50–100 times lower.[12] Importantly, because fentanyl is a fully synthetic opioid, which does not bear a structural resemblance to naturally occurring opiates (morphine, codeine), it is not detected by routine immunoassay urine drug testing typically used as first-line screening.[13] Therefore, without targeted drug testing, fentanyl is difficult to identify and quantify. The mean serum concentrations of fentanyl in our patients (52.9 ng/mL) is markedly higher than therapeutic concentrations of 0.63–2.0 ng/mL.[9,14,15] Reported postmortem serum concentrations of patients who have died from fentanyl overdoses range from 5–120 ng/mL (mean = 36 ng/mL).[16–18] The pills recovered in our series had 600–6,900 μg/pill of fentanyl. Even with oral bioavailability of about 30%, each pill can readily deliver enough fentanyl to result in toxic serum concentrations.[19] Other medications such as promethazine were also found in our patients' biologic samples, which may have contributed to the patients' feelings of euphoria, but, because of their less severe toxicity profiles, those drugs likely played minimal roles in the fatalities or prolonged hospitalizations.

This ongoing outbreak has had several public health ramifications on the regional, state, and federal levels. Eight of the 18 patients arrived in our institution over a 16-hour period. This acute influx placed a serious strain on our emergency department and intensive care unit. Emergency department and hospital

Figure 1. Comparison of pharmaceutical and counterfeit tablets. (*Top*) Pharmaceutical hydrocodone/acetaminophen 10/325 tablet; (*bottom*) counterfeit tablet containing fentanyl. [Color figure can be viewed at wileyonlinelibrary.com]

overcrowding is a nationwide problem that is exacerbated by acute surges regardless the cause.[20–22] In this outbreak, an even more important issue has been that of antidote stocking. Our hospital's supplies of naloxone were quickly depleted because of the large number of patients that presented over a short period of time and the need of some patients for several milligrams of naloxone as bolus dosing and prolonged infusion times. Our hospital required emergency deliveries of naloxone to keep supplies sufficient for patient care. A notable clinical difference we observed was not only the prolonged naloxone infusions but also the recurrence of respiratory depression in the hospital after 8 hours of observation without naloxone. Eight hours is longer than our typical observation period after naloxone administration, and this left of us with the clinical quandary of an appropriate observation time. Patients were observed 6–14 hours based on total naloxone required and social factors. This resource-intense surge also affected care throughout the region. Our institution is the tertiary care referral center for region. Cumulatively, this placed a heavy load on our emergency department and intensive care unit and limited the hospital's ability to provide care for critically ill patients from outside institutions. Outbreaks like this one highlight the importance of not only single-hospital emergency-preparedness plans, but of plans that integrate regional health care systems.[23,24]

The decision to notify public health can be difficult and no criteria exist that are appropriate for every scenario. The CDC has provided a protocol for public health agencies to report disease outbreaks with suggested response times.[25] However, these criteria are mostly for infectious diseases and do not provide guidance to health care providers. Clearly, the more significant the public health risk, the lower the threshold to notify your local public health officer. In our outbreak, we had three similar patients present within a few hours of the index case. We felt these presentations were far more severe than would be expected from ingesting one to two hydrocodone/acetaminophen tablets. This exaggerated toxicity, defined by the severity of illness, in the setting of no detectable acetaminophen, was the key finding that triggered us to contact the local public health officer. This initial public health notification did not immediately lead to the public at large being notified, but emergency response units, hospitals, county coroners, and law enforcement were contacted. After each of these health and law enforcement entities were involved, it became clear we had an ongoing public health event which led to the notification of the public by the public health department. Several months prior in the San Francisco Bay Area, illicit drugs marketed as "Xanax" were also found to contain fentanyl.[26] These outbreaks illustrate the ongoing public health problem that exists with nonpharmaceutical fentanyl. According to the CDC, since late 2013 several states have reported increasing deaths related to fentanyl with most due to illicit manufacturing.[27] All available resources should be used to identify and limit future outbreaks of nonpharmaceutical fentanyl.

Poison centers are a resource that can augment regional care and coordinate with public health. Nationwide, poison centers are linked to all hospitals in a given area and are staffed with a 24-hour-a-day call center with physician toxicologist oversight. In the current outbreak, our poison center notified poison centers statewide of the suspicion of an opioid-related outbreak, and our poison center, in turn, contacted local hospitals. The role of poison centers in public health has been described; the centers can be an invaluable tool during toxicologic outbreaks.[28–30] However, a limitation of poison centers is that for the centers to identify an outbreak, health care providers must initiate contact with the centers. Common causes of overdose, such as those of opioids, which providers feel confident in managing, are often underreported. This underreporting may limit the ability of poison centers to detect outbreaks of opioid poisoning in the

early stages. Thus, providers should be encouraged to report all potential toxicologic issues to a poison center.

Beyond interaction with traditional public health entities, this outbreak intersected with both local and federal law enforcement units. As demonstrated in Figure 1, the tablet involved was visually very similar to that of pharmaceutical-grade hydrocodone/acetaminophen tablets, and the weights of both kinds of pills were similar. Since the pills content was overwhelmingly fentanyl, which does not legally exist in pill form, the pills were no doubt manufactured illegally. Federal law mandates that any machine capable of making and imprinting pills be registered with the Drug Enforcement Administration.[31] It is highly unlikely that illegal operations such as the one used to make these tablets would comply with federal regulations. This leads to concern about ongoing and future outbreaks if fentanyl can be "repackaged" into various pill forms. Our collaboration during this outbreak with the DEA and the U.S. Department of Justice has brought local, state, and federal (CDC) resources together with law enforcement agencies to increase surveillance for fentanyl-related overdoses. This awareness is especially important since identification of fentanyl requires targeted testing; medical personnel, from health care providers to coroners, should be alert to request the appropriate testing.

The magnitude of this public health outbreak is still undetermined, as new cases and fatalities continue to be reported. The reasons for producing such a concentrated fentanyl pill are unclear; whether it represents a concentration error or nefarious intent is unknown. If these pills are produced on a large scale, it is possible that the end distributors were unaware of the degree of adulteration to their customers. This highlighted the importance of our interactions with the DEA and national surveillance as additional outbreaks must be detected early. Nonetheless, alerting the public and health care providers of this serious health issue is paramount to preventing its spread. The importance of public health surveillance, regardless of the cause of an outbreak, cannot be overstated. This series of fentanyl overdoses confirms how healthcare providers on the front lines play an important role in improving public health. In this current opioid epidemic, providers are urged to report all cases to poison centers and public health agencies to better monitor and quantify the scope of the problem and apply targeted interventions.

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