

## SCIENTIFIC ADVANCES

### Out-of-hospital Treatment of Opioid Overdoses in an Urban Setting

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#### ABSTRACT

**Objectives:** To investigate clinical outcomes in a cohort of opioid overdose patients treated in an out-of-hospital urban setting noted for a high prevalence of IV opioid use.

**Methods:** A retrospective review was performed of presumed opioid overdoses that were managed in 1993 by the emergency medical services (EMS) system in a single-tiered, urban advanced life support (ALS) EMS system. Specifically, all patients administered naloxone by the county paramedics were reviewed. Those patients with at least 3 of 5 objective criteria of an opioid overdose [respiratory rate <6/min, pinpoint pupils, evidence of IV drug use, Glasgow Coma Scale (GCS) score <12, or cyanosis] were included. A response to naloxone was defined as improvement to a GCS  $\geq$ 14 and a respiratory rate  $\geq$ 10/min within 5 minutes of naloxone administration. ED dispositions of opioid-overdose patients brought to the county hospital were reviewed. All medical examiner's cases deemed to be opioid-overdose-related deaths by postmortem toxicologic levels also were reviewed.

**Results:** There were 726 patients identified with presumed opioid overdoses. Most patients (609/726, 85.4%) had an initial pulse and blood pressure (BP). Most (94%) of this group responded to naloxone and all were transported. Of the remainder, 101 (14%) had obvious signs of death and 16 (2.2%) were in cardiopulmonary arrest without obvious signs of death. Of the patients in full arrest, 2 had return of spontaneous circulation but neither survived. Of the 609 patients who had initial BPs, 487 (80%) received naloxone IM (plus bag-valve-mask ventilation) and 122 (20%) received the drug IV. Responses to naloxone were similar; 94% IM vs 90% IV. Of 443 patients transported to the county hospital, 12 (2.7%) were admitted. The admitted patients had noncardiogenic pulmonary edema ( $n = 4$ ), pneumonia ( $n = 2$ ), other infections ( $n = 2$ ), persistent respiratory depression ( $n = 2$ ), and persistent alteration in mental status ( $n = 2$ ). The patients with pulmonary edema were clinically obvious upon ED arrival. Hypotension was never noted and bradycardia was seen in only 2% of our presumed-opioid-overdose population.

**Conclusions:** The majority of the opioid-overdose patients who had initial BPs responded readily to naloxone, with few patients requiring admission. Noncardiogenic pulmonary edema was uncommon and when present, hypoxia was evident upon arrival to the ED. Naloxone administered IM in conjunction with bag-valve-mask ventilation was effective in this patient population. The opioid-overdose patients in cardiopulmonary arrest did not survive.

**Key words:** heroin; opioid; opiate; overdose; poisoning; naloxone; emergency medical services; EMS, out-of-hospital; paramedic.

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■ Opioid-related overdoses are a common toxicologic overdose in urban settings. The Drug Abuse Warning Network estimates that there were 63,000 opioid-related ED visits in 1993, with 36% of these visits related to an overdose.<sup>1</sup> Reported opioid-related episodes have increased 65% from 1988 through 1993 nationwide and now account for 13% of all drug-related ED episodes.<sup>1</sup> A recent study of preventable deaths from 1986 through 1991 in San Francisco revealed that poisoning and drug overdoses made up 27% of these deaths and was the leading category of preventable deaths.<sup>2</sup> The largest single category of drug causing these deaths was the opioid agents, comprising 23% of the poisoning and drug-related deaths.

Although potentially fatal, the treatment for opioid-related overdoses with naloxone may be one of the more effective therapies rendered in the out-of-hospital arena. However, general management approaches for opioid overdoses have been adopted by emergency medical services (EMS) systems and EDs with limited (often only anecdotal) outcomes data. Hence, a methodical examination of actual practice and outcomes is needed to validate or guide modification of current management approaches. This study evaluates 12 months' experience with presumed opioid-related overdoses initially managed by paramedics in the city of San Francisco and addresses the clinical features that affect outcome.

## ■ METHODS

### Study Design

A retrospective review of EMS records was performed for presumed-opioid-overdose patients who presented in 1993 to the San Francisco EMS system to determine the out-of-hospital therapy and outcome. Reviews of hospital and medical examiner records were used to complement the EMS analysis. The study was approved by the Committee on Human Research of the University of California, San Francisco, the Emergency Medical Services Agency of the city of San Francisco, and the medical examiner's office of San Francisco.

### Setting

The city and county of San Francisco have a single-tiered 2-paramedic advanced life support (ALS) EMS system. The fire department serves as first responder to life-threatening calls (which would include a patient with an altered mental status) and provides basic life support (BLS) intervention as well as semiautomatic defibrillation. An EMS medical record is generated for each patient encounter. The catchment area of the medical examiner's office and that of the paramedic division both include all 49 square miles of San Francisco County. The city and county of San Francisco have an evening pop-

ulation of 750,000, and the EMS system answers approximately 50,000 calls per year. There is a single base hospital that provides on-line medical consultation as needed to all ALS providers.

### Population

Computerized records of the Department of Public Health Paramedic Division were searched for all patients during 1993 who received naloxone as part of their out-of-hospital care. These 1,856 charts were examined by a second-year medical student with prior specific training in reading and interpreting the EMS medical record; any difficult clinical determinations were directly supervised by one of the investigators (KAS).

A diagnosis of presumed opioid overdose required at least 3 of the following clinical criteria: 1) circumstantial evidence of parenteral drug use (syringes, needles, bystander stating heroin use); 2) a respiratory rate <6/min; 3) cyanosis prior to oxygenation; 4) a Glasgow Coma Scale (GCS) score  $\leq$ 12; and 5) pinpoint pupils. The EMS records of all patients which had the above criteria were reviewed and the information was entered into a computerized database.

### EMS Practice for Presumed Opioid Overdose

The altered mental status protocol followed by the paramedics dictates that patients suspected of an opioid overdose are immediately treated with high-flow O<sub>2</sub> via bag-valve-mask to assist ventilation and an IM or IV 2-mg dose of naloxone. A repeat dose is given if no response is seen in 1–2 minutes, and a blood glucose level is checked (Chem-Strip BG, Boehringer Mannheim, Montreal, Quebec, Canada). A patient with an altered mental status of an unknown etiology will receive a blood glucose measurement, and an IM or IV dose of 2 mg of naloxone is given only in the setting of respiratory depression. On-line medical consultation is provided by board-certified emergency physicians at San Francisco General Hospital (SFGH). The use of naloxone or glucose does not require base hospital consultation.

Patients in cardiopulmonary arrest and suspected opioid overdose receive endotracheal intubation, IV or endotracheal naloxone, defibrillation (if ventricular fibrillation is present), and standard ALS medications. If a pulse or persistent ventricular fibrillation is obtained, then the patient is transported to the nearest medical facility. If the patient has pulseless electrical activity or asystole after 20 minutes of ALS, then the patient is commonly pronounced dead in the field after contact with the base hospital physician. Patients found in advanced stages of death (lividity, rigor mortis, or signs of decomposition) by the paramedics are referred to the medical examiner's office.

■ **TABLE 1** Outcomes of Out-of-hospital Opioid Overdoses in 1993, San Francisco

	Number	%
Total	726	100
Opioid overdose with palpable blood pressure	609	84
Transported to base hospital	443	61
Advanced signs of death	101	14
Asystolic arrest (no advanced sign of death)	16	2

### Measurements

The EMS records were reviewed for patient demographics, verification of presumed opioid overdose (see population above), clinical presentation [especially presence of respirations, pulse, and/or blood pressure (BP)], therapy administered, need for ALS therapy (other than naloxone), response to naloxone, survival of out-of-hospital care, receiving hospital, and complications. A response to naloxone was defined as improvement to a GCS  $\geq 14$  and a respiratory rate  $\geq 10$ /min within 5 minutes of naloxone administration. Return of spontaneous circulation (ROSC) was defined as the return of sustained palpable pulses for a minimum of 5 minutes.

Since 74% of the opioid-overdose patients were transported to SFGH, the dispositions of these patients were searched via a separate database that contains demographic and clinical information including diagnosis and disposition. The inpatient charts of those patients

■ **TABLE 2** Characteristics of the Opioid-overdose Groups

	Opioid Overdose with Blood Pressure		Cardiac Arrest		Signs of Death	
	No.	%	No.	%	No.	%
Total	609	84	16	2	101	14
Age (years)						
<20	16	3	0	0	0	0
20-29	90	15	2	13	14	14
30-39	244	40	9	56	37	37
40-49	207	34	5	31	41	41
>50	52	9	0	0	9	9
Race						
White	170	28	4	25	80	80
Black	86	14	2	12	15	15
Hispanic	37	6			6	6
Native American	1	0			0	0
Asian	5	1			0	0
Unknown	310	51	10	63	0	0
Sex						
Male	476	78	11	69	79	78
Female	132	22	5	31	22	22

admitted to SFGH were evaluated. The practice at SFGH is for alert opioid-overdose patients to be evaluated for hypoxia and a recurrence of sedation during a 2-hour observation period before release. Patients with a persistent altered mental status are evaluated as usual with a blood glucose measurement, a repeat dose of naloxone, and a search for other potential causes of their symptoms. Active injection drug users with a documented fever  $>38.3^{\circ}\text{C}$  are admitted to rule out acute bacterial endocarditis.

In addition, all medical examiner's cases for 1993 in the county of San Francisco were reviewed. Those cases seen by paramedics that were deemed to be opioid-related deaths by circumstantial evidence and postmortem toxicologic analysis comprised the out-of-hospital overdose deaths.

### Data Analysis

Descriptive analyses were performed. In addition, the response rates to IV vs IM naloxone in the out-of-hospital setting were compared with chi-square analysis.

### RESULTS

There were 726 EMS responses to presumed-opioid-overdose cases in the city of San Francisco during 1993 (Table 1). Of these, 609 (84%) had initial pulses and BPs and were transported to a hospital. One hundred one (14%) patients were found by paramedics to have evidence of advanced signs of death (lividity, rigor mortis, or signs of decomposition) and were concluded by the medical examiner's toxicologic screening to have experienced opioid-related deaths. Sixteen (2.2%) patients were found in asystolic arrest without advanced signs of death; the deaths were later determined by the medical examiner's office to be opioid-related. The age, sex, and race distributions of these 3 groups are shown (Table 2).

Most patients evaluated by the EMS system (443/726, 61%) were taken to the base hospital (SFGH). Clinical outcomes are not known for the other 166 (26%) patients, but none was reported by the medical examiner's office to be an opioid-related death.

### Out-of-hospital Clinical Characteristics of Opioid Overdoses

The IV route of opioid administration accounted for the majority of the overdoses in which the route was noted (Table 3). Other routes of opioid administration such as IM, subcutaneous, smoked, nasal insufflation, or ingestion accounted for only 4% of the opioid overdoses.

Hypotension defined as a systolic BP  $< 100$  mm Hg was not seen in any patient who had an initial respiratory rate or palpable pulse. Bradycardia was surprisingly rel-

atively rare in opioid-overdose patients who had initial vital signs. A pulse <40 beats/min was never documented and a pulse <60 beats/min was noted in only 2% of this group.

A respiratory rate <6/min was noted in 62% of the opioid-overdose patients and pinpoint pupils were noted in 94%. Large dilated pupils were found almost exclusively among the patients in cardiopulmonary arrest.

**Out-of-hospital Treatment for Opioid Overdoses**

The 2-mg dose of naloxone was used for 58% of the patients, with higher doses such as 3–4 mg used for 28%

■ **TABLE 3** Clinical Characteristics of the Opioid-overdose Patients

	Opioid Overdose with Blood Pressure		Cardiac Arrest	
	No.	%	No.	%
Total	609		16	
Opioid route				
IV	353	58.0	10	63
IM	2	0.3	0	0
Nasal	5	1.0	0	0
Smoked	3	0.5	0	0
Subcutaneous	3	0.5	0	0
Ingestion	3	0.5	0	0
Unknown	240	40.0	6	37
Systolic blood pressure (mm Hg)				
<100	0	0	16	100
100–110	111	18		
111–120	61	10		
121–130	106	17		
>130	293	48		
Unknown	38	6		
Pulse rate (beats/min)				
0–39	0	0	16	100
40–60	13	2		
61–80	79	13		
81–100	229	38		
>100	288	47		
Respiratory rate (breaths/min)				
0	170	28	16	100
2	72	12		
3–6	136	22		
7–10	92	15		
11–20	130	21		
>20	9	2		
Pupils				
Pinpoint	585	96.0	1	6
Equal, reactive to light	14	2.0	0	0
Dilated	3	0.5	11	69
Nonreactive	2	0.3	4	25
Unknown	5	1.0	0	0

■ **TABLE 4** Treatment of the Opioid-overdose Patients

	Opioid Overdose with Blood Pressure	Cardiac Arrest
Total	609	16
Naloxone route		
IM	487 (80%)	2 (13%)
IV	69 (11%)	8 (50%)
Both IM and IV	53 (9%)	2 (13%)
Endotracheal tube	0 (0%)	4 (25%)
Naloxone dose		
None	1 (0.2%)	0 (0%)
0.4 mg	8 (1%)	0 (0%)
1 mg	35 (6%)	0 (0%)
2 mg	353 (6%)	8 (50%)
3–4 mg	172 (28%)	6 (38%)
>4 mg	40 (7%)	2 (13%)
Response intervals		
Average	4.6 min	5.2 min
Median	4.0 min	5.0 min
SD	2.7 min	2.3 min
First responders		
Fire department	429 (70%)	15 (94%)
Paramedics	180 (30%)	1 (6%)

and >4 mg used for 7% (Table 4). For the patients who presented in cardiopulmonary arrest, the naloxone was administered IV more commonly (50%) than it was for the nonarrest patients (11%) and more often in higher doses.

The paramedic response times to these 2 groups were similar. The 90th-percentile response for the opioid-overdose patients who had vital signs was 7 minutes, and that for the opioid-overdose patients who had cardiac arrest was 7.5 minutes. The fire department BLS responders were present in 94% of the cardiopulmonary arrest group and were the first responders for 70% of the group of opioid-overdose patients who had BPs.

Forty-two patients (7%) required restraints for protection of self and staff after receiving naloxone. Only 5 patients escaped from the care of the paramedics post-naloxone and were not transported. Thirty patients (5%) gave a history of simultaneous use of cocaine and opioid (i.e., “speedball”), but no different adverse event such as seizures, arrhythmia, or an increased restraint use was noted in this group.

**Response to Naloxone in Patients with Initial BPs**

Of the 609 patients with any initial BP, 575 (94%) readily responded to naloxone by improving to a GCS ≥14 and a respiratory rate ≥10 within 5 minutes of administration. The response rate for IM naloxone was

■ **TABLE 5** Characteristics of the Opioid-overdose Patients Transported to the Base Hospital (*n* = 443)

	No.	%
<b>Age (years)</b>		
>20	10	2
20-29	66	15
30-39	177	40
40-49	155	35
>50	35	8
<b>Sex</b>		
Male	342	77
Female	101	23
<b>Outcome</b>		
Released	431	97
Admitted	12	3
<b>ED arrival diagnosis</b>		
Pulmonary edema	4	1.00
Pneumonia	2	0.50
Other infections	1	0.25
Altered mental status	2	0.50
Respiratory depression	3	0.75

488/518 (94%) and the rate for IV naloxone was 69/73 (90%) (*p* = NS). Another 52 patients (9%) received naloxone both IM and IV (response rate 98%). This subgroup revealed a similar early response rate to IM naloxone.

### Opioid Overdoses and Cardiopulmonary Arrest

Sixteen (2.2%) patients were found without advanced signs of death and in cardiopulmonary arrest. Standard ALS interventions and naloxone were given, with 2 (17%) patients developing ROSC. One of these 2 patients spent 3 weeks in an intensive care unit before succumbing to multiorgan failure, and the other died in the ED. All of these patients were deemed by the medical examiner to have experienced opioid-related deaths.

### Opioid Overdoses with Hospital Data

Of all the transported opioid-overdose patients, 444 (74%) were taken to the ED of SFGH (Table 5). The age and sex distributions of the transported cohort were similar to those of the total group. Of these patients, the majority (97%) were released after evaluation and observation. Only 12 patients (2.7%) were admitted.

The 4 patients admitted for noncardiogenic pulmonary edema all had obvious symptoms of hypoxia upon admission to the ED. Two of these patients were intubated, and resolution of the pulmonary edema occurred in 1-3 days. All 4 patients with noncardiogenic pulmonary edema were discharged after 2-3 days of hospitalization, all with normal mental status.

Two patients were admitted for pneumonia and 1 was admitted to rule out acute bacterial endocarditis. Two patients were admitted with persistent altered mental status and other medical complications. One patient had toxicologic screening in support of the diagnosis of opioid-overdose and was admitted for persistent hypothermia. This patient had resolution of symptoms in 2 days. The second patient who had an altered mental status was further complicated by the diagnosis of rhabdomyolysis, mild renal insufficiency, and a transient metabolic acidosis, all of which resolved in 2 days. Toxicologic screening was positive for both cocaine and morphine.

Three patients had persistent hypoventilation unresponsive to naloxone. The hypoventilation for 2 of these cases was explained by co-ingestions. One patient was ultimately diagnosed as having wound botulism and underwent prolonged ventilatory support with full neurologic recovery.

### ■ DISCUSSION

The administration of naloxone in an opioid overdose with hypoventilation is probably one of the most effective out-of-hospital treatments. A recent Italian study demonstrated that the mortality from opioid-related deaths was significantly lower in one city that administered out-of-hospital naloxone than it was in the rest of the country's cities that did not use out-of-hospital naloxone.<sup>3</sup> The authors excluded patients with advanced signs of death. Their median response interval for paramedic arrival was 3 minutes (range 1-15). Many [52/126 (41.4%)] of their patients were in respiratory arrest (defined as apnea or gasping) but had spontaneous cardiac activity. They first endotracheally intubated the patients and then gave them IV naloxone in 0.4-mg increments. Most [30/52 (58%)] of the respiratory arrest patients were admitted to the hospital and all 52 patients survived with normal neurologic function. Acute pulmonary edema occurred in only 1 patient (0.8%). Another 77 (53%) patients had altered mental status but little or no respiratory depression and were treated with naloxone. Only 2 (4.3%) of this group were admitted for reasons not stated.

The Italian series had 7 (5%) patients in asystolic cardiopulmonary arrest, and 5 (71%) of these were resuscitated with a combination of naloxone and ALS interventions. The median time delay until treatment for this group was significantly longer than it was for those not in cardiopulmonary arrest. Of these 5 patients, 1 later died of complications secondary to anoxic encephalopathy and the other 4 were released without neurologic impairment.

One U.S. study examined the courses of 124 patients who had opioid overdoses seen in an ED of an urban county hospital.<sup>4</sup> The majority of these patients received

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