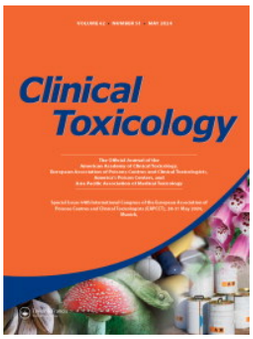

Clinical Toxicology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ictx20

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To cite this article: Merlyn Joseph, Khyati Amin, Courtney Siddens, Gil Jaime, Christina M. Seeger, Kevin Mercer & Terence Chau (12 Jun 2024): Pulmonary edema after naloxone administration for opioid reversal: a systematic review of case reports and causality assessment using the Naranjo scale, Clinical Toxicology, DOI: 10.1080/15563650.2024.2348108

To link to this article: https://doi.org/10.1080/15563650.2024.2348108

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2024.2348108

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REVIEW

Pulmonary edema after naloxone administration for opioid reversal: a systematic review of case reports and causality assessment using the Naranjo scale

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ABSTRACT

Introduction: Pulmonary edema is a rare complication occurring after naloxone administration, but the causal relationship remains insufficiently investigated. We aimed to determine the likelihood of naloxone as the causative agent in published cases of pulmonary edema.

Methods: A literature search was conducted across multiple databases, utilizing database-specific search terms such as "pulmonary edema/chemically induced" and "naloxone/adverse effects." Each case report was evaluated using the Naranjo scale, a standardized causality assessment algorithm.

Results: We identified 49 published case reports of pulmonary edema following naloxone administration. The median total dose of naloxone was 0.2 mg for patients presenting following a surgical procedure and 4 mg for out-of-hospital opioid overdoses. Based on the Naranjo scale, the majority of cases were classified as "possible" ($n = 38$) or "probable" ($n = 11$) adverse reactions, while no "definite" cases of naloxone-induced pulmonary edema were identified. Many patients were classified as "possible" due to limited patient information or other potential risks, such as fluid administration or airway obstruction. Forty-six of 49 patients survived (94 percent).

Discussion: Pulmonary edema may occur after both low and high doses of naloxone; however, low doses were primarily reported in the surgical population. Despite this complication, the majority of patients survived. Furthermore, no case report in our analysis was classified as a "definite" case of naloxone-induced pulmonary edema which limits the establishment of causality. Future studies should explore patient risk factors, including surgical versus outpatient setting and opioid-naïve versus opioid-tolerant for developing pulmonary edema and employ a causality assessment algorithm.

Conclusions: These case reports suggest pulmonary edema can occur following naloxone administration, irrespective of dose. According to the Naranjo scale, there were no definite cases of naloxone-induced pulmonary edema. Overall, we suggest the benefits of naloxone administration outweigh the risks. Naloxone should be administered to treat opioid overdoses while monitoring for the development of pulmonary edema.

ARTICLE HISTORY
Received 4 February 2024
Revised 22 April 2024
Accepted 22 April 2024

KEYWORDS
Naloxone; pulmonary edema; naloxone-induced pulmonary edema; Naranjo scale; adverse effects; causality analysis

Introduction

Naloxone is a widely used medication for reversing opioid overdoses, playing a crucial role in addressing the escalating opioid crisis [1]. However, its administration may result in the development of pulmonary edema [2]. Pulmonary edema after naloxone administration is believed to occur due to fluid shifts resulting from catecholamine-induced vasoconstriction [3]. This adverse reaction is of concern, as severity can range from self-limiting to life-threatening [4].

A retrospective review conducted by Farkas et al. [5] reported that approximately 1% of patients developed pulmonary edema after receiving naloxone outside of a hospital setting. However, this study primarily focused on the occurrence rate of pulmonary edema after naloxone administration without considering the specific causative factors [5]. Since the causes of pulmonary edema can be multifactorial, it would have been ideal to conduct a systematic assessment to determine the likelihood of naloxone as the causative agent in each patient case.

Assigning causality of adverse reactions to a drug is commonly achieved using assessment tools like the Naranjo scale [6]. The Naranjo scale relies on expert evaluation of patient cases through a series of structured questions. This process enables the categorization of each case into one of four levels: doubtful, possible, probable, or definite adverse reaction. Scores ranging from 0 to 13 are assigned by the Naranjo scale, with higher scores correlating to a greater likelihood of causality. Among the previously published case reports on pulmonary edema following naloxone administration, only three reports have utilized the Naranjo scale to

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/15563650.2024.2348108.

assess causality. One case report was categorized as possible [7], while two case reports were categorized as probable adverse reactions [8,9]. Therefore, published case reports have not conclusively established naloxone as a definitive causative agent using a systematic scoring system. Consequently, our primary objective is to conduct a causality analysis for each published case report to determine the likelihood that naloxone was the cause of pulmonary edema.

Farkas and colleagues [5] identified a nonsignificant trend suggesting an increased risk of pulmonary edema with cumulative doses of naloxone exceeding 4.4 mg. On the other hand, Acus and colleagues [10] found no significant differences in pulmonary complications with low ($\leq$2 mg), moderate ($>$2 mg to $\leq$4 mg), or high ($>$4 mg) doses of naloxone administered to patients presenting to the emergency department. Nevertheless, it is important to note that this study is subject to several methodological limitations, particularly in accurately identifying patients experiencing opioid overdoses and encompassing pneumonia within the category of "pulmonary complications" [11]. Consequently, our secondary objectives include identifying the specific doses of naloxone administered in each case of pulmonary edema, aiming to investigate the potential impact of naloxone dose and administration route on the occurrence of pulmonary edema, particularly in surgical and out-of-hospital opioid overdose settings.

By thoroughly examining the available literature and conducting a comprehensive causality analysis using the Naranjo scale, we aim to shed light on the likelihood of naloxone as the causative agent in cases of pulmonary edema. Our analysis will carefully consider potential contributing risk factors and acknowledge the limitations inherent in the available data.

Methods

Search

A systematic search for case reports and case series was conducted to identify instances of pulmonary edema following naloxone administration. The search encompassed multiple databases, including PubMed, CINAHL, Embase, SciFinder, and Google Scholar (Supplemental Table 1) with no language restrictions. Additional searches were performed through relevant organizations and citation tracing to ensure a comprehensive search (Supplemental Figure 1). The initial search included articles published through March 1, 2021. An additional search was performed on PubMed using the same search terms on January 25, 2024.

Study selection

Three reviewers conducted title, abstract, and full-text screening independently, with discrepancies resolved by discussion with a fourth reviewer. Case reports documenting noncardiogenic pulmonary edema after naloxone administration in humans were included in the analysis [2,7–9,12–44]. Twelve case reports or studies were excluded based on the following criteria: absence of naloxone administration [45,46], attribution of pulmonary edema to another cause by the original author [47,48], pulmonary edema not reported [13], ARDS with possible alternative etiologies present [49], unavailability of individual patient information [5,10], appearing to be hypothetical patient cases [50], or lack of clearly documented opioid administration or toxicity [51,52]. The case reports were limited to human case reports [53]. Details of the number of included and excluded case reports and the rationale for their exclusion are provided in Supplemental Figure 1.

Data extraction

Comprehensive data extraction was performed to capture relevant information from the included case reports. Patient demographics, including age, gender, and country of authors, were recorded. Details regarding the opioid being reversed, cumulative dose and route of naloxone administration, as well as symptoms indicative of pulmonary edema (pink frothy sputum) and imaging used for diagnosis, were extracted. Additionally, the time interval between naloxone administration and the onset of pulmonary edema, the administration of diuretic treatment, the need for additional respiratory support, and the time to recovery after pulmonary edema were collected.

Classification

Patients were categorized into surgical and out-of-hospital opioid overdose admissions since there were clear differences in these patient populations. Patients were assigned to the surgical group if they presented to the hospital for a surgical procedure or received naloxone as part of a surgical procedure. Conversely, patients were classified as out-of-hospital opioid overdose admissions if their presentation to the hospital was related to an opioid overdose outside hospital.

Dose conversions

We evaluated the average potency of the opioid as determined by the static morphine milligram equivalents factor defined by the United States Centers for Disease Control and Prevention and the Department of Human Services [54]. Since fentanyl was the most common opioid reversed, we converted doses of other opioids to the equianalgesic dose of fentanyl to compare the extent of each overdose.

Descriptive analysis

The statistical software SPSS© 25 (IBM Corporation, Armonk, NY) was used for data analysis. The normality of continuous variables was assessed using the Shapiro–Wilk Test. As the continuous data did not meet the assumptions of normality, non-parametric analysis was conducted. The median and interquartile range (IQR) were used to report the central tendency and dispersion of the data, respectively. No statistical significance was calculated as patients were classified into surgical and out-of-hospital opioid overdose groups in a non-randomized method. Interrater reliability was assessed by calculating Krippendorff's alpha using the Krippendorff package in Python.

Naranjo scale

Causality assessment was performed using the Naranjo scale, a widely recognized tool for evaluating the probability of causality in adverse drug reaction [6]. A score of 0 corresponds to a "doubtful" probability, while scores between 1 and 4 indicate a "possible" probability. Scores ranging from 5 to 8 suggest a "probable" probability, and scores greater than 9 signify a "definite" probability.

Three experienced clinical pharmacists participated in the causality assessment process to ensure a rigorous evaluation. Two of the pharmacists had specialty training in emergency medicine, while the third pharmacist specialized in internal medicine. Each pharmacist independently evaluated all the case reports and calculated the corresponding Naranjo scores. Subsequently, the case reports were categorized as "doubtful," "possible," "probable," or "definite" using the Naranjo scale and based on a majority vote.

Results

Baseline characteristics

Among the 49 patients included in this study, the majority were male (84%), as indicated in Table 1. In the out-of-hospital opioid overdose group, all patients presented to the hospital due to an outpatient opioid overdose (100%). In contrast, within the surgical population, 96% of patients underwent naloxone administration during anesthesia reversal or in the postoperative period following their surgical procedure, with an additional patient receiving naloxone for inpatient opioid overdose 38 days post-procedure. The surgical patients predominantly sought elective surgery (61%).

Many out-of-hospital opioid overdose patients required naloxone reversal for heroin (50%), while fentanyl reversal was commonly observed among surgical patients (78%), as shown in Table 1. Surgical patients received a median converted fentanyl dose of 150 μg. Opioid doses involved in out-of-hospital opioid overdoses were unavailable.

Table 1. Baseline characteristics.

	Out-of-hospital opioid overdose $n = 26$	Surgical admission $n = 23$
Age, median (IQR)	29 (23-35)	23 (18–31)
Male gender	21 (81%)	20 (87%)
Location of primary author on publication		
North America	26 (100%)	9 (39%)
Europe	0	6 (26%)
Asia	0	4 (17%)
Australia	0	3 (13%)
South America	0	1 (4%)
Reason for initial hospital admission		
Opioid overdose	26 (100%)	
Elective surgery		14 (61%)
Semi-urgent		3 (13%)
Emergency surgery		6 (26%)
Opioid reversed		
Fentanyl/sufentanil	4 (15%)	18 (78%)
Heroin	13 (50%)	0
Morphine	0	3 (13%)
Oxycodone	4 (15%)	0
Meperidine	0	2 (9%)
Codeine	1 (4%)	0
Methadone	2 (8%)	0
Other/unknown	2 (8%)	0

Naranjo scale

In total, 11 case reports were assigned a "probable" Naranjo score, while the remaining 38 case reports received a "possible" Naranjo score (Figure 1; Tables 2 and 3). No definite cases of naloxone-induced pulmonary edema were identified using the Naranjo scale. Interrater reliability for Naranjo classification was 0.80. The final Naranjo score for each case report was determined based on three key questions from the Naranjo scale:

1. Did the adverse event occur after the suspected drug was administered?
2. Was the adverse event supported by other objective evidence?
3. Were there alternative causes that could independently explain the reaction? (Table 4).

All instances of pulmonary edema occurred after administering the suspected drug, although the exact time to onset of pulmonary edema in out-of-hospital opioid overdose patients remained unclear in several reports (Tables 2, 3, and 4). Most surgical patients experienced the onset of pulmonary edema within 30 min of naloxone administration.

Chest radiographs objectively confirmed most cases of pulmonary edema, and many patients presented with pink, frothy sputum (Tables 2 and 3). Alternative causes were carefully evaluated for each case report. Commonly identified factors as alternative causes included excessive fluid administration considering age or congestive heart failure, airway obstruction, and uncertain opioid dosage. In cases where repositioning the airway quickly resolved the pulmonary edema, naloxone was considered less likely to be the cause.

While the questions mentioned above influenced the Naranjo score, other aspects of the Naranjo scale had no impact on the patients' scores. None of the case reports employed a placebo to assess if the adverse reaction would reoccur. Drug concentrations were not measured in any of the case reports, and there were no instances where the naloxone dose was increased to observe a worsening of the reaction. Additionally,

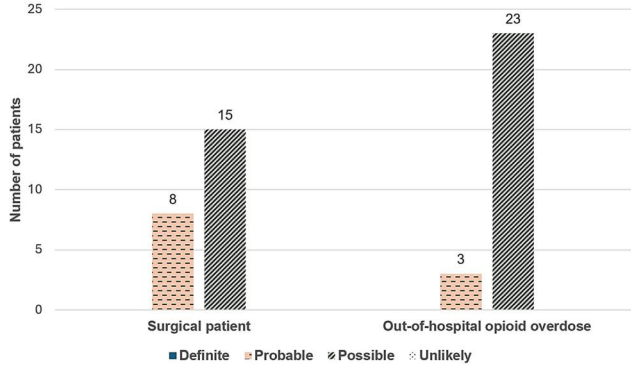

Figure 1. Distribution of Naranjo classification among patients developing pulmonary edema after naloxone administration.

Table 2. Overview of surgical patients developing pulmonary edema after naloxone administration.

Citation	Naranjo classification	Age and gender	Opioid reversed	Actual cumulative naloxone dose	Route of naloxone administration	Pulmonary edema on radiograph or computed tomography	Pink or frothy sputum reported	Time from naloxone administration to onset of pulmonary edema	Diuretic received for pulmonary edema	Additional respiratory support	Time to recovery after pulmonary edema or survival
Andree et al. [13]	Possible	25, Female	Meperidine	0.8 mg	Intravenous	Not reported	Yes	Immediately after 4th dose	Yes	Yes, mechanical ventilation	Died 8 days later
Benavides-Portilla et al. [15]	Probable	56, Male	Fentanyl	0.2 mg	Presumed intravenous administration with other agents during post-operative.	Yes	Not reported	Immediate post-operative period	No	Yes, mechanical ventilation	24 h
Bessè et al. [16]	Probable	34, Male	Fentanyl	0.4 mg	Intravenous	Yes	Yes	10 min	Yes	Yes, mechanical ventilation	48 h
Brimacombe et al. [17] #1	Possible	18, Male	Meperidine	0.4 mg	Presumed intravenous administration with other agents during post-operative.	Yes	Yes	1 min	Yes	Yes, continuous positive airway pressure via mask with progression to mechanical ventilation	<24 h
Brimacombe et al. [17] #2	Possible	69, Male	Fentanyl	0.3 mg	Presumed intravenous administration with other agents during post-operative.	Not reported, clinical diagnosis only	Not reported	1 min after second dose	No	Yes, laryngeal mask airway with progression to mechanical ventilation	~4 h
Flacke et al. [20]	Possible	70, Male	Morphine	0.4 mg	Intravenous	Not obtained at onset of pulmonary edema	Yes	1 min	No	Yes, mechanical ventilation	20 min
Harrington et al. [22]	Possible	17, Male	Fentanyl	0.2 mg	Intravenous	Yes	Yes	Immediate	Yes	Yes, mechanical ventilation	14 h
Horng et al. [23]	Possible	21, Male	Fentanyl	0.08 mg	Intravenous	Yes	Yes	Immediate	No	Yes, oropharyngeal tube to face tent	1.5 h
Jiwa et al. [8]	Probable	22, Male	Fentanyl	0.2 mg	Intravenous	Yes	Not reported	Immediate	Yes	Yes, mechanical ventilation	6 h
Johnson et al. [24]	Possible	13, Female	Fentanyl + sufentanil	0.08 mg	Intravenous	Yes	Not reported	30 min	Yes	Yes, face mask	Not Reported
Lakartidningen [27] #1	Possible	18, Male	Fentanyl	0.16 mg	Intravenous	Not reported, clinical diagnosis only	Not reported	Few minutes	Not reported	Not reported	24-48 h
Lakartidningen [27] #2	Possible	26, Male	Fentanyl	0.04 mg	Intravenous	Not reported, clinical diagnosis only	Not reported	Few minutes	Not reported	Not reported	24-48 h
Lassen et al. [28]	Possible	17, Male	Fentanyl	0.2 mg	Intravenous	Yes	Yes	5 min	Yes	Yes, non-invasive ventilation to mechanical ventilation	71 h
Nath et al. [30]	Possible	28, Male	Fentanyl	0.2 mg	Intravenous	Yes	Yes	60 min	Yes	Yes, mechanical ventilation	24 h
Olsen et al. [32]	Possible	59, Female	Fentanyl	0.4 mg	Presumed intravenous administration with other agents during post-operative.	Yes	Yes	Immediate laryngospasm, pulmonary edema within one hour	Yes	Yes, mechanical ventilation	24 h
Partridge et al. [33]	Probable	19, Male	Fentanyl	0.08 mg	Intravenous	Yes	Yes	Immediately after second dose	No	Yes, mechanical ventilation	14 h
Prough et al. [34] #1	Probable	17, Male	Fentanyl	0.1 mg	Intravenous	Yes	Yes	immediate	Yes	Yes, nasal cannula progressed to face mask	5 h
Prough et al. [34] #2	Probable	16, Male	Fentanyl	0.5 mg (intravenous: 0.2 mg, intramuscular: 0.3 mg)	Intravenous and intramuscular	Yes	No	Symptoms soon after doses administered	Yes	Yes, non-invasive ventilation	Few hours
Puvaneswari et al. [35]	Probable	23, Male	Morphine	0.4 mg	Presumed intravenous administration with other agents during post-operative.	Yes	Yes	1 min	Yes	Yes, non-invasive face mask progressed to mechanical ventilation	3 h
Taff et al. [41]	Possible	26, Male	Fentanyl	0.3 mg	Intravenous	Negative chest radiograph after stabilization on oxygen	Yes	Within a few minutes	No	Yes, non-invasive oxygen mask	Few hours
Vitalone et al. [38]	Possible	23, Male	Fentanyl	0.1 mg	Intravenous	Yes	Yes	5 min	Yes	Not reported	3 h
Wang et al. [36]	Probable	39, Male	Morphine given 38 days after procedure	0.4 mg	Intravenous	Yes	Yes	60 min	No	Yes, mechanical ventilation	Died 1 day later
Wride et al. [37]	Possible	27, Male	Fentanyl	0.2 mg	Intravenous	Not reported, however positive post-mortem	Yes	1 min	No	Yes, mechanical ventilation	Died during resuscitation

Shaded rows indentify “probable” cases

Table 3. Overview of out-of-hospital overdose patients developing pulmonary edema after naloxone administration.

Citation	Naranjo classification	Age and gender	Opioid reversed	Actual cumulative naloxone dose	Route of naloxone administration	Pulmonary edema on radiograph or computed tomography	Pink or frothy sputum reported	Time from naloxone administration to onset of pulmonary edema	Diuretic received for pulmonary edema	Additional respiratory support	Time to recovery after pulmonary edema or survival
Al-Azzawi et al. [12] #1	Probable	29, Male	Heroin	10 mg	Not reported	Yes	Not reported	2 h after naloxone administration on second presentation to emergency department	Yes	Yes, mechanical ventilation	7 h
Al Azzawi et al. [12] #2	Possible	37, Male	Heroin	2.4 mg	Not reported	Yes	Not reported	Not reported	Yes	Yes, bilevel positive airway pressure	"short"
Bansal et al. [14]	Possible	49, Female	Methadone	2 mg	Intravenous	Yes	Not reported	30 min	Yes	Yes, mechanical ventilation	8 h
Carmona et al. [18]	Possible	25, Male	Oxycodone	0.2 mg + unspecified number of repeated naloxone doses	Not reported	Yes	Not reported	Not reported; "shortly thereafter"	Yes	Yes, high flow nasal cannula	<48 h
Cogeni et al. [19]	Possible	37, Male	"Some form of narcotics"	3 mg (intramuscular: 2 mg, intravenous: 1 mg)	Intravenous and intramuscular	Yes	Yes	Not reported; "shortly after arrival to emergency department"	Yes	Yes, non-rebreather mask	<24 h
Elkattawy et al. [2]	Probable	62, Female	Oxycodone	5.2 mg (intramuscular: 4 mg, intravenous: 1.2 mg)	Intravenous and intranasal	Yes	Not reported	Not reported; while in emergency department	Yes	Yes, nasal cannula	72 h
Grout et al. [21]	Possible	3, Male	Fentanyl	0.2 mg/kg	Intravenous	Yes	Yes	30 min	No	Yes, mechanical ventilation	24 h; developed hypoxic ischemic brain injury
Kummer et al. [25,26] #1	Possible	24 Gender not reported for individual patients. Total of eight males and two females.	Heroin	4 mg	Five patients received intravenous initially Five patients received intranasal initially	Yes	Five patients produced pink frothy sputum	Not reported	Not reported	Yes, mechanical ventilation	All patients survived Median duration of hospitalization
Kummer et al. [25,26] #2	Possible	27	Heroin	1 mg	Not reported	Yes	Not reported	Not reported	Not reported	Yes, mechanical ventilation	3 days (IQR 0.8–5)
Kummer et al. [25,26] #3	Possible	23	Heroin	3 mg	Not reported	Yes	Not reported	Not reported	Not reported	Yes, non-invasive ventilation	
Kummer et al. [25,26] #4	Possible	24	Methadone	4.5 mg	Not reported	Yes	Not reported	Not reported	Not reported	Yes, mechanical ventilation	
Kummer et al. [25,26] #5	Possible	23	Heroin	19 mg	Not reported	Yes	Not reported	Not reported	Not reported	Yes, mechanical ventilation	
Kummer et al. [25,26] #6	Possible	28	Heroin	10.2 mg	Not reported	Yes	Not reported	Not reported	Not reported	Yes, mechanical ventilation	
Kummer et al. [25,26] #7	Possible	33	Heroin	8.5 mg	Not reported	Yes	Not reported	Not reported	Not reported	Yes, non-invasive ventilation	
Kummer et al. [25,26] #8	Possible	22	Heroin	14 mg	Not reported	Yes	Not reported	Not reported	Not reported	Yes, non-invasive ventilation	
Kummer et al. [25,26] #9	Possible	20	Heroin	4 mg	Not reported	Yes	Not reported	Not reported	Not reported	Yes, mechanical ventilation	
Kummer et al. [25,26] 10	Possible	18	Oxycodone	2.5 mg	Not reported	Yes	Not reported	Not reported	Not reported	Yes, mechanical ventilation	
Marsalisi et al. [29]	Possible	46, Male	Fentanyl	8.8 mg (intranasal: 4 mg, intramuscular: 0.8 mg, intravenous: 4 mg)	Intravenous, intramuscular, intranasal	Yes	Not reported	60 min	No	Yes, non-invasive ventilation	24 h
Navarro Reynés et al. [31]	Possible	32, Male	Heroin	0.4 mg	Intravenous	Yes	Not reported	8 h	No	Yes, continuous positive airway pressure	24 h
Parekh et al. [7]	Possible	30, Male	Fentanyl	0.44 mg	Intravenous	Yes	Not reported	<1 h	No	Yes, non-rebreather mask	24 h
Patti et al. [9]	Probable	29, Male	Not reported	1 mg	Intravenous	Yes	Not reported	Not reported; After arrival to emergency department	Yes	Yes, mechanical ventilation	24 h
Sallam et al. [39]	Possible	35, Male	Heroin	Not reported	Not reported	Yes	Not reported	Not reported; On route to emergency department	Yes	Yes, non-invasive ventilation	Not reported
Schwartz et al. [40]	Possible	68, Female	Codeine	1.6 mg	Intravenous	Not reported, clinical diagnosis only	Not reported	immediate	Yes	Yes, non-invasive ventilation	10 min
Veet et al. [42]	Possible	27, Male	Oxycodone	6 mg	Intranasal	Yes	Not reported	Not reported: on route to emergency department	Yes	Yes, mechanical ventilation	<48 h
Yarlagadda et al. [43]	Possible	23, Male	Heroin	8 mg	Intranasal	Yes	Yes	Not reported	No	Yes, bilevel positive airway pressure	24 h
Zeba et al. [44]	Possible	34, Male	Fentanyl	4 mg	Intramuscular	Yes	Yes	Immediate	No	Yes, continuous positive airway pressure and bilevel positive airway pressure	48 h

Shaded rows indentify "probable" cases

Table 4. Breakdown of Naranjo responses by question.

	Count
Questions contributing to Naranjo scale	
Did the adverse event appear after the suspected drug was administered?	
Yes	49
No	0
Do not know	0
Are there alternative causes that could on their own have caused the reaction?	
Yes	20
No	11
Do not know	18
Was the adverse event confirmed by any objective evidence?	
Yes	44
No	3
Do not know	2
Questions not contributing to Naranjo score.	*No patients received any points towards the Naranjo scale for these questions.*
• Did the reaction reappear when a placebo was given?	
• Are there previous conclusive reports on this reaction?	
• Did the adverse event reappear when the drug was readministered?	
• Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	
• Was the drug detected in blood or other fluids in concentrations known to be toxic?	
• Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	
• Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	

Table 5. Characteristics of naloxone dose and route administered.

	Out-of-hospital opioid overdose $n = 26$	Surgical admission $n = 23$
Total naloxone dose, median (IQR)	4 mg (2.2 – 8.25) ($n = 23$)*	0.2 mg (0.13 – 0.4)
Naloxone routes of administration		
Intravenous only	6 (23%)	22 (96%)
Intranasal only	2 (8%)	0
Intramuscular only	1 (4%)	0
Intravenous and intramuscular	1 (4%)	1 (4%)
Intravenous and intranasal	1 (4%)	0
Intravenous, intramuscular, intranasal	1 (4%)	0
Unknown	14	0

*Three patients did not have a total naloxone dose reported; IQR: Interquartile range

there were no reports discussing patients who had previously experienced a similar reaction to naloxone (Table 4).

Naloxone dose

In surgical patients, the median total dose of naloxone was 0.2 mg, with intravenous administration being the primary route (96%) (Table 5). On the other hand, out-of-hospital opioid overdose patients received a higher median total dose of naloxone of 4 mg.

Interestingly, during our review of published case reports, we encountered several instances of pulmonary edema in surgical patients occurring even with extremely low doses of naloxone. For example, one case report described pulmonary edema after administering naloxone 0.04 mg [27].

Survival outcomes

The majority of patients survived (94%) (Table 6), and their recovery occurred within 24 h (Tables 2 and 3). However, three surgical patients died during hospital admission [13,36,37]. In all cases of patient deaths, oxygen and rapid intubation were initiated. Diuretic administration was not reported in two out of the three deaths [35,36].

Discussion

The Naranjo scale causality analysis revealed no "definite" cases of naloxone-induced pulmonary edema. Instead, a limited number of cases were classified as "probable" causes of pulmonary edema. Most cases were classified as "possible" due to underreporting or competing reasons for pulmonary edema. Detailed patient information, such as outpatient opioid use, medical history, fluid status prior to administration, and specific medications taken, was often lacking in the case reports, particularly among non-surgical patients admitted for out-of-hospital opioid overdoses. While previous literature has linked pulmonary edema with out-of-hospital opioid overdoses, there is limited evidence of such occurrences with the low opioid doses typically administered during surgical procedures [55–57]. One out-of-hospital opioid overdose classified as "probable" initially showed no signs of pulmonary edema during their first admission for an opioid overdose; however, during their second admission a few hours later, they subsequently developed pulmonary edema after receiving 8 mg of naloxone [12]. Even among surgical cases, there were potential competing factors contributing to the development of pulmonary edema, such as laryngospasm, excessive volume expansion, and the use of other drugs. These findings are consistent with Farkas and colleagues [5],

Table 6. Time to pulmonary edema onset, treatment, and survival.

	Out-of-hospital opioid overdose $n = 26$	Surgical admission $n = 23$
Time from naloxone administration to onset of pulmonary edema		
Immediate to 29 minutes	3 (12%)	19 (83%)
30–59 minutes	2 (8%)	1 (4%)
60–119 minutes	1 (4%)	3 (13%)
>120 minutes	2 (8%)	0
Unknown	18	0
Maximal respiratory support		
Mechanical ventilation	12 (46%)	15 (65%)
Non-invasive (continuous positive airway pressure/ bilevel positive airway pressure/ oxygen mask)	14 (54%)	5 (22%)
Unknown	0	3
Diuretic reported to be administered	10 (39%)	13 (57%)
Survived	26 (100%)	20 (87%)

who documented alternative reasons or contributing factors for many patients developing pulmonary edema.

In our review of published case reports, the timeline of pulmonary edema is interesting. Many patients began producing pink, frothy sputum immediately after naloxone administration. Additionally, imaging was consistent with pulmonary edema. Most patients responded rapidly to oxygen support or ventilation.

Farkas and colleagues [5] also highlighted a potential association between naloxone dose and pulmonary complications. Patients receiving higher doses (>4.4 mg) were found to have a 62% increased risk of developing pulmonary complications, including pulmonary edema, aspiration pneumonia, and aspiration pneumonitis. It is worth noting that the greater doses examined in the retrospective studies were likely related to the availability of the standard 4 mg intranasal formulation of naloxone. In contrast, surgical patients typically receive smaller doses of naloxone via the intravenous or intramuscular route. Overall, our evaluation observed instances of pulmonary edema occurring after both low and high doses of naloxone, with surgical patients receiving a median total naloxone dose of 0.2 mg and out-of-hospital opioid overdose patients receiving a median dose of 4 mg.

Strengths and limitations

Case reports can provide valuable insights as they are typically authored by healthcare professionals involved in the patient's care. They can offer a detailed timeline of events and relevant discussions regarding the patient's evaluation. The included case reports represent a diverse population, reflecting real-world clinical practice. Additionally, causality assessment by three reviewers increases the robustness of this analysis.

The Naranjo scale, used to assess causality in adverse drug reactions, was of limited applicability for naloxone due to its as-needed usage as a reversal agent, rendering questions about improvement upon drug discontinuation or specific antagonist administration irrelevant. Moreover, obtaining serum concentrations of opioids or naloxone is rare, and rechallenge with naloxone is ethically impractical. Inconsistent reporting in case studies resulted in data gaps, particularly regarding the route, dose, and timing of naloxone administration, with missing data in our analysis being reported as "unknown" or "not reported" (NR). This lack of comprehensive information also often hindered conducting a thorough Naranjo analysis to consider alternative causes, as seen in cases with limited patient data, such as the 18 patients mentioned in Table 4. Missing data neither improves nor reduces the Naranjo score but can diminish the possibility of identifying "definite" cases. Consequently, the Naranjo Scale was unlikely to identify any "definite" cases of naloxone-induced pulmonary edema due to a lack of relevant questions, practical constraints outlined, and missing data.

Future studies should aim to address the gaps in knowledge by evaluating specific patient risk factors for developing pulmonary edema and employing a standardized causality assessment algorithm. Additionally, studies should explore the impact of route, dose, and timing of naloxone administration on the occurrence of pulmonary edema. To enhance future research in this field, standardized reporting of case details and adverse events related to naloxone administration should be encouraged. These measures will contribute to a better understanding of the causal relationship between naloxone and pulmonary edema and help guide evidence-based practices for naloxone administration in opioid overdose management.

Conclusions

The compiled case reports suggest that pulmonary edema can occur following naloxone administration, irrespective of the dose administered. Even when pulmonary edema occurred, the majority of patients in these case reports survived. Based on the causality analysis using the Naranjo scale, all case reports were classified as "possible" or "probable." No definite cases of naloxone-induced pulmonary edema were identified using the Naranjo scale. Overall, we suggest the benefits of naloxone administration outweigh the risks. Naloxone should be administered to treat opioid overdoses while monitoring for the development of pulmonary edema.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The authors reported there is no funding associated with the work featured in this article.

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