Reversal of Opioid-Induced Ventilatory Depression Using Low-Dose Naloxone (0.04 mg): a Case Series

Hong K. Kim¹ · Lewis S. Nelson²

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Abstract

Introduction Naloxone is commonly administered in emergency department (ED) to reverse opioid intoxication. Several naloxone dose recommendations exist for acute management of opioid intoxication based on limited published clinical data. A case series of ED patients with opioid-induced ventilatory depression that was reversed using a low-dose naloxone (0.04 mg with titration) is presented.

Methods ED patients with opioid-induced ventilatory depression requiring naloxone administration were identified through medical toxicology consultation. Retrospective review of medical records was performed. Collected data included history, and pre- and post-naloxone data, including respiratory rate (RR), pulse oximetry (pulse ox), end-tidal CO₂ level (ET-CO₂), and Richmond Agitation Sedation Scale (RASS).

Results Fifteen ED patients with moderate to severe opioid-induced ventilatory depression (median RR, 6 breaths/min) who were managed using low-dose naloxone strategy were identified. Twelve of 15 patients reported ingestion of methadone (range, 30 to 180 mg). The median naloxone dose of 0.08 mg (range, 0.04 to 0.12 mg) reversed opioid-induced ventilatory and CNS depression. Two patients experienced acute opioid withdrawal after receiving 0.08 mg.

Conclusion ED patients with moderate to severe opioid-induced ventilatory depression can be reversed using 0.04 mg IV naloxone with appropriate dose titration.

Keywords Opioid toxicity · Low-dose naloxone · Opioid intoxication reversal

Abbreviations

ET-CO ₂	End-tidal CO ₂ level
ED	Emergency department
CNS	Central nervous system
RASS	Richmond Agitation Sedation Scale
RR	Respiratory rate
IV	Intravenous

Introduction

Naloxone hydrochloride (Narcan®) is a competitive opioid antagonist that is frequently administered in the emergency department (ED) to reverse the adverse effects of opioid intoxication. Naloxone effectively reverses opioid-induced ventilatory and central nervous system (CNS) depression, as well as the euphoric and analgesic effects of opioids. The standard initial naloxone dose is often cited as 0.4 mg. This dose originated from research by anesthesiologists in which naloxone was used to reverse excessive post-operative sedation in opioid naïve patients [1]. However, administration of the standard naloxone dose in opioid-dependent patients may precipitate acute opioid withdrawal [2, 3]. Unlike the relatively benign withdrawal syndrome associated with opioid abstinence, the clinical effects associated with precipitated opioid withdrawal may be life threatening and include acute respiratory distress syndrome, seizure, and cardiac dysrhythmias [2].

✉ Hong K. Kim
hongkimmd@gmail.com

¹ Department of Emergency Medicine, University of Maryland Emergency Medicine Network, University of Maryland School of Medicine, 110 South Paca Street 6th floor, Suite 200, Baltimore, MD 21201, USA

² Department of Emergency Medicine, New York University School of Medicine/Bellevue Hospital Center, 462 First Ave. Room A345, New York, NY 10016, USA

Recognizing this risk, the latest editions of two widely used emergency medicine textbooks recommend using less than 0.4 mg of naloxone to manage opioid intoxication in opioid-dependent patients [4, 5]. One suggests using 0.04 to 0.2 mg of naloxone in opioid-dependent patients with “CNS or respiratory depression [5],” while the other recommends using 0.05 mg of naloxone in opioid-dependent patients “with mental status depression but with minimal respiratory depression [4].” Medical toxicology and anesthesiology textbooks, on the other hand, recommend using an initial dose of 0.04 mg with titration to reverse opioid-induced ventilatory depression [6, 7]. Recent review articles on the management of opioid intoxication also recommends an initial dose of 0.04 mg, and titrating every 2–3 min if no clinical reversal of opioid intoxication is achieved [7, 8].

Despite the recommendations for using low-dose naloxone, there is little documented clinical evidence to support the effectiveness of these recommendations. Since the typical patient in the ED to whom naloxone is administered is less likely to be opioid naïve and may have used other substances concomitantly, there is a need to identify an effective and safe initial dose of naloxone. Here, we present a case series of opioid-dependent patients with acute opioid-induced ventilatory depression that were managed using low-dose naloxone (0.04 mg IV).

Methods

Between January and October 2012, ED providers at an urban medical center were asked to notify medical toxicology service of all ED patients with opioid-induced ventilatory depression who received or planned to administer naloxone. It is routine at the study institution for the ED providers to administer 0.04 mg of naloxone IV with titration (every 2–3 min) to reverse opioid-induced respiratory depression. If naloxone was not administered, a starting dose of 0.04 mg IV every 2–3 min was recommended to reverse the ventilatory depression. Initial clinical data—respiratory rate (RR), pulse oximetry (pulse ox), end-tidal CO₂ level (ET-CO₂), Richmond Agitation Sedation Score (RASS), and the dose of naloxone (if administered)—was obtained during the initial telemedicine consultation. Medical records of all identified patients were retrospectively reviewed within 12 h. Standardized data collection instrument was used to obtain history, ventilatory data (RR, pulse ox, ET-CO₂), and sedation/withdrawal assessment (RASS). RASS was determined by identifying the descriptive terms used for RASS assessment (e.g., alert, drowsy, no response to voice, etc.) during direct provider communication and retrospective chart review. The specific opioid reportedly used by the patient was recorded, but analytic confirmation was not performed. Included patients were >18 years of age with a clinical diagnosis (made by an ED provider) of acute

opioid intoxication from history, and clinical findings of CNS, ventilatory depression (RR<10 breaths/min), and miosis, and who received low-dose naloxone (0.04 mg). Cases were excluded if more than two clinical data elements (RR, RASS, ET-CO₂, or pulse ox) of pre- and post-naloxone administration were missing from the medical charts. Descriptive analysis was performed with Microsoft Excel (Microsoft Inc., Seattle, WA). The institutional review board of the New York University School of Medicine approved the investigation.

Results

A total of 24 ED patients with opioid intoxication were identified. Three patients were excluded due to insufficient data, and four patients did not meet the inclusion criteria (i.e., they received 0.4 mg of naloxone). All cases received naloxone in the ED prior to consultation. No additional naloxone was administered due to medical toxicology consultation. Demographic information and clinical data, including ventilatory variables (RR, pulse ox, ET-CO₂) and mental status assessment (RASS), for the 15 cases meeting the inclusion criteria are summarized in Table 1. The median age was 51 years old (range, 25–61) and 80 % (*n*=12) were men. The majority of patients reported ingesting methadone (*n*=12; 80 %) with a median dose of 60 mg (range, 30 to 180 mg). Eight of the 12 cases were participants in a methadone maintenance treatment program. The most common self-reported co-ingested drug was benzodiazepine (*n*=8) followed by ethanol (*n*=3). All 15 patients experienced significant ventilatory depression (median RR, 6 breaths/min, median pulse ox, 84 %, median ET-CO₂, 50 mmHg) and CNS depression (median RASS, -4). The median total naloxone dose required for clinical reversal of acute opioid-induced ventilatory depression was 0.08 mg (range, 0.04 to 0.12) (Fig. 1). Forty percent of cases (*n*=6) required single dose of 0.04 mg; six cases required total naloxone dose of 0.08 mg, and three cases required 0.12 mg. The median RR after naloxone administration was 13 breaths/min, with corresponding normalization in pulse ox and ET-CO₂ (Table 1). CNS depression was also reversed with a median post-naloxone RASS of 0. Two patients who received 0.08 mg of naloxone developed nausea, vomiting, and acute agitation (RASS, 3 and 2). Bag-valve mask assisted ventilation was performed in six cases prior to naloxone administration. No additional therapy (e.g., dextrose or flumazenil) was administered.

Discussion

There is a growing support for the use of low-dose naloxone as shown by its adaptation in the latest editions of emergency medicine textbooks [4, 5], clinical practice guideline [9], and

Table 1 Clinical characteristics of opioid-intoxicated ED patients before and after naloxone administration

Number	Age	Sex	Opioid	Dose (mg)	Naloxone (mg)	RR	Pulse ox	ET-CO ₂	RASS	RR ^a	Pulse ox ^a	ET-CO ₂ ^a	RASS ^a
1 ^b	54	M	Methadone	110	0.08	6	87	50	−4	14	95	42	3
2	45	M	Methadone	120	0.12	7	95	.	−4	9	99	.	−1
3	38	F	Methadone	30	0.04	6	80	.	−5	12	92	29	0
4 ^b	47	M	Methadone	60	0.08		40	60	−5	13	93	.	2
5	25	M	Methadone	180	0.04	3	92	55	−5	.	94	50	0
6	61	M	Methadone	170	0.12	4	89	50	−4	.	98	29	−1
7	55	F	Methadone	50	0.04	6	84	50	−5	14	89	.	−1
8	40	M	Methadone	40	0.08	3	85	85	−5	14	100	.	−1
9	54	M	Methadone	.	0.04	7	82	41	−4	12	96	31	−3
10	41	M	Methadone	30	0.04	4	84	75	−3	10	93	55	1
11	51	M	Methadone	130	0.08	9	88	40	−4	18	93	33	1
12	46	M	Methadone	60	0.08	3	78	.	.	23	96	.	.
13	56	F	Fentanyl	.	0.08	6	60	.	−4	16	100	.	0
14	34	M	Heroin	.	0.12	3	55	72	−5	9	97	52	1
15	61	M	Heroin	.	0.04	6	85	.	−3	10	95	32	1
Median	51			60	0.08	6	84	50	−4	13	95	33	0

RR respiratory rate (breaths/min), ET-CO₂ end-tidal CO₂ level (mm Hg), RASS Richmond Agitation and Sedation Scale, Pulse ox pulse oximetry (%)

^a Post-naloxone administration

^b Experienced acute opioid withdraw syndrome after naloxone administration

literature [7, 8]. A recent review of 22 medical sources showed that over 50 % ($n=12$) of the medical sources recommend using 0.04 or 0.05 mg (IV) as the initial naloxone dose while remaining sources suggested using 0.4 or 0.5 mg [10]. Many had different dosing schemes based on the likelihood of preexisting opioid dependence while maximum titration naloxone dose also ranged widely from 2 to 20 mg [10]. The lack of consensus in these recommendations is due to the paucity of data outside of the studies involving standard recommended dose (0.4 mg). In addition, the relative safety of administering the standard naloxone dose may have changed over the four decades due to the expanded use of long-acting drugs, such as methadone; extended release formulations of

analgesics such as oxycodone; and an increased concentration of heroin in street drug. Thus, a dose that is sufficiently high to reverse opioid-induced ventilatory depression yet sufficiently low to avoid precipitated opioid withdrawal is optimal. In this case series, low-dose naloxone administration reversed the opioid-induced ventilatory depression in 15 patients. The duration of action following low-dose naloxone administration was not evaluated, but it is expected to be slightly shorter than with higher doses of naloxone.

Although the general concept of gradual escalation of the dose to prevent adverse drug effects is consistent with best practices for safe medication use, the complete safety profile of low-dose naloxone recommendation cannot be adequately assessed with this case series. However, the use of low-dose naloxone may decrease the risk of precipitated opioid withdrawal in those with opioid dependence.

Limitations

There are several methodological limitations. Case identification relied on consultation of medical toxicology service. This may have introduced both referral and selection bias as medical toxicology consultation may have not been obtained for all opioid-intoxicated patients. A single non-blinded investigator abstracted the data. This data abstraction method can introduce abstractor bias, potentially influencing the result and its interpretation. The nature of a retrospective chart review limits the quality of the clinical data that can be obtained due to variable quality (e.g., missing ventilatory data) of

Fig. 1 Change in respiratory rate before and after naloxone administration

documentation. Important question such as the duration of clinical reversal was often not documented. Recall bias may have been introduced when clinical data was collected from the ED providers at the time of consultation. There is no validated method for retrospective assessment of RASS. Clinical opioid withdrawal scale (COWS) also requires direct patient interaction, which was not possible for this case series. However, descriptive terms of RASS allowed assessment of responsiveness (unresponsive vs. awake) and agitation. The safety of using low-dose naloxone as well as the impact of coingestants cannot be assessed from this small case series. A larger prospective study would better assess above questions. The generalizability of our findings may be limited by the predominance of methadone exposure.

Conclusion

This case series demonstrates that low-dose naloxone (0.04 mg IV) can reverse moderate to severe opioid-induced ventilatory depression, and titration may be required. Opioid-dependent patients can experience acute opioid withdrawal after receiving a naloxone dose as low as 0.08 mg. A larger, prospective observational study should be performed to validate this finding and to evaluate the safety of low-dose naloxone.

Conflict of Interest The authors declare that they have no competing interests.

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