The Evolution of Recommended Naloxone Dosing for Opioid Overdose by Medical Specialty

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Abstract

Introduction Opioid abuse and opioid overdose deaths have increased significantly over the past decade. Naloxone is a potentially life-saving medication that can reverse opioid-induced respiratory depression, though precipitated opioid withdrawal can pose acute risks to the patient and medical personnel. The optimal naloxone dose is unclear and few studies address this question.

Methods A convenience sample of commonly available references were queried for the recommended IV naloxone dose. When dosing recommendations were different for opioid-tolerant patients these were also recorded.

Results Twenty-five references were located. 48% recommended a starting dose ≤ 0.05 mg while 36% recommend a dose ten-fold higher. More than half of medical toxicology and general medical sources recommended a low-dose strategy with a starting dose lower than 0.05 mg IV.

Conclusion There are variations in the recommended doses for naloxone with ranges spanning an order of magnitude. Further exploration is needed to determine the dose that

balances reversal of respiratory depression with mitigation of withdrawal.

Keywords Naloxone · Opioid overdose · Opioid withdrawal

Introduction

Over the past decade, prescriptions and overdose deaths due to opioid pain relievers (OPR) have increased markedly. In 2013, 207 million OPR prescriptions were written in the USA, a substantial increase from the 126 million written in 2000 [1]. The increase in opioid prescribing was associated with a quadrupling of opioid overdose deaths, from 6242 deaths reported in 2000 to 28,647 in 2014 [2, 3]. Additionally, there has been a rise in the rate of heroin abuse and heroin-related deaths [3–5]. Considering the widespread availability of opioids and their consequences, the management of patients who present to the emergency department (ED) with opioid toxicity remains an important skill for healthcare providers.

Naloxone became part of standard therapy for opioid-induced respiratory depression shortly after its introduction in 1967 [6]. The initial recommended dose of 0.8 to 2 mg IV naloxone was determined both by studies in animal models and through use by anesthesiologists to reverse postoperative opioid-induced respiratory depression [6]. It has since been widely used in prehospital and hospital-based settings, generally with success in its primary outcome of improving the respiratory effort of patients with opioid overdose. Although naloxone can thereby obviate the need for assisted ventilation, excessive dosing can result in precipitated withdrawal, which carries potentially significant consequences. In the medical setting, with appropriate equipment and personnel, there is little urgency to administer naloxone because oxygenation and ventilation can be maintained with supplemental oxygen

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and bag-valve-mask (BVM) ventilation or endotracheal intubation, respectively, as needed. Once stabilized, there is time and opportunity to slowly and safely titrate naloxone with the goal of producing spontaneous ventilation while avoiding both awakening of the patient and opioid withdrawal.

Precipitated opioid withdrawal is associated with significant increases in circulating catecholamines, even in anesthetized opioid-dependent subjects [7, 8]. Catecholamine excess results in hypertension, tachycardia, ventricular stiffness, and pulmonary capillary permeability, which may combine to cause naloxone-associated pulmonary edema [9]. Vomiting, especially in a patient with co-exposure to a non-naloxone-responsive sedative such as ethanol or a benzodiazepine, may result in pulmonary aspiration. Behavioral disturbance, primarily agitation, anxiety, or aggression, may result in the need for physical or pharmacological restraint to prevent harm to the patient, care team, or property [10, 11]. Furthermore, elopement from healthcare following a transient naloxone-induced improvement in consciousness and respiratory status may be followed by recrudescence of opioid toxicity due to the limited duration of action of naloxone. This is a particular concern in the setting of an overdose of extended release and long-acting (ER/LA) opioid formulations.

A controversial though fundamental question about naloxone is the optimal dose to reverse opioid-induced respiratory depression in a medical setting, particularly the ED. Limited research exists regarding the safety and effectiveness of naloxone when used outside the controlled setting of the operating room. Due to clinicians' relative comfort with its use after approximately 50 years of clinical availability, extensive research into this question is unlikely to occur. We aimed to compare the naloxone dose recommended by the authors of commonly available, respected references to determine trends in dosing and whether these recommendations vary based on medical specialty.

Methods

We reviewed a convenience sample of medical textbooks, study guides, and Internet resources in the fields of internal medicine, emergency medicine, medical toxicology, anesthesiology, pediatrics, pain medicine, and general medicine. These disciplines were chosen due to the likelihood that clinicians in these fields would encounter patients with opioid toxicity. We stipulated that the resources included recommendations for intravenous (IV) naloxone dosing and were published or updated in the past 10 years. Respected and widely utilized textbooks and study guides from the aforementioned medical specialties were selected based on the authors' institutional library holding and subscriptions. Additionally, popular Internet resources (e.g., online textbooks, blogs) were reviewed to more closely approximate what ED providers

would access while working clinically [12–34]. Resources that may have contained dosing information but that had a specific focus within these larger fields (e.g., pictorial guides) were excluded. From each resource, we recorded the recommended initial IV naloxone dose to reverse opioid-induced respiratory depression in the hospital setting and the subsequent dosing regimen or titration protocol. When an alternative dosing strategy or regimen was recommended for the opioid-tolerant patient or those in whom opioid withdrawal was anticipated, both dosing strategies were recorded. When alternate strategies were given for adult and pediatric populations, the adult recommendation was recorded in order to compare recommendations for patients more likely to be opioid tolerant. Percentages of resources with specific ranges of naloxone doses were calculated. Microsoft Excel was used to calculate the R^2 value where recommendations were compared based on year of publication. As there were no subjects involved, this research met criteria for exemption from IRB approval.

Results

Twenty-five resources (Table 1) with an IV naloxone dose recommendation (Fig. 1) were located. Of these, 48 % ($n = 12$) recommended an initial dose of 0.05 mg IV or lower [12–21, 34, 35], 16 % ($n = 4$) recommended a starting dose of 0.1 mg IV [22–24, 36], and 36 % ($n = 9$) suggested 0.4 or 0.5 mg IV [25–33]. Seventy-five percent ($n = 3$) of resources of medical toxicology, 50 % ($n = 2$) anesthesiology, 66 % ($n = 4$) general medicine, and 50 % ($n = 3$) emergency medicine recommended initial doses of ≤ 0.05 mg IV. The pain management textbook recommended a strategy with the lowest initial dose of 0.02 mg IV. All Internet-based resources ($n = 5$) recommended initial doses of ≤ 0.1 mg IV. Twenty-five percent ($n = 1$) of the internal medicine or pediatrics textbooks recommended an initial dose of < 0.4 mg IV.

Two resources provided a low-dose option (≤ 0.05 mg IV) specifically for patients who are opioid-tolerant [12, 19] one recommended “smaller doses” in opioid-tolerant patients [27], and one stated 0.5 mg IV can precipitate withdrawal though did not recommend a lower starting dose [29]. No resource explicitly defined opioid tolerance or dependence. One resource recommended naloxone dosing based on clinical features, suggesting 0.05 mg IV for a patient with spontaneous respirations, 0.2–1 mg IV for an apneic patient, and 2 mg IV for a patient suffering cardiac arrest [15]. There was a tendency towards a lower recommended initial naloxone dose based on the year of publication, with lower doses associated with later publication dates, though the correlation is not strong ($R^2 = -0.21$).

The maximum recommended IV dose also varied between resources. One stated a dose of 0.2 mg IV is rarely indicated

Table 1 Bibliographic information for sources grouped by medical specialty

Sources by medical specialty

Anesthesia

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Emergency medicine

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General medical

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Internal medicine

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Medical toxicology

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Pain management

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Pediatrics

- [23] Lee C, Tschudy M, Arcara K. Drug Doses. In: Tschudy M, Arcara K, editors. *The Harriet lane handbook*. Philadelphia: Mosby; 2011.
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Numbers in brackets indicate reference number

[20], while three recommend maximum doses of 0.8 mg IV [29, 32, 33], seven suggested a maximum dose of 2 mg IV

[13, 17, 22, 23, 25, 28, 31], though one stated that some patients may require much higher doses, nine recommended

Fig. 1 Sources grouped by specialty with the recommended naloxone dosing regimens. Recommendations are in *black*, though when a different regimen was recommended for the opioid-tolerant patient, the regimen is depicted in *gray*. If a range was recommended, bars were graphed between these. If specific doses were recommended, these were graphed as *small filled rectangles*. Maximum doses are indicated by *small empty (white) rectangles*

10 mg IV [14–16, 18, 19, 24, 26, 27, 32], and two noted 20 mg as the highest dose [12, 30]. Seven resources recommended a titration protocol [14, 20, 21, 30, 34–36]. Six recommended redosing naloxone at set time intervals while one recommended incremental dose increases [14], specifically 0.04, 0.4, 2, then 10 mg IV.

Discussion

Wide variation in recommendations from respected medical resources demonstrates how little is accepted or proven about the use of naloxone. A majority of the resources surveyed recommended initial naloxone doses an order of magnitude lower than that suggested in the early 1990s [6]. The highest proportion of low-dose regimens was published in medical toxicology, emergency medicine, and general medical resources. Resources that recommended low-dose strategies (less than the conventional 0.4 mg IV) cite the decreased risk of opioid withdrawal in the opioid-tolerant patient and the ability to redose as needed. Variations in recommendations for initial doses, maximum doses, and titration protocols were generally based on authors' expert opinion rather than clinical data.

Both pediatric textbooks provided recommendations for children and adults, but only one of these recommended a low-dose approach. Dosing strategies for children generally included higher naloxone doses because chronic opioid use, and therefore the risk for opioid withdrawal, is far less common than in the adult population. However, according to the 2015 Monitoring the Future Survey, 5.4 % of 12th graders have use opioids other than heroin, 4.4 % have used hydrocodone, and 3.7 % have used oxycodone in the past year

suggesting that opioid tolerance and dependence may be more common than suspected in older children [37].

It is disconcerting that a tenfold difference in initial naloxone dose recommendations exists in influential textbooks, especially given the risks for adverse effects with inappropriate dosing. It will likely be the learner without significant experience in administering naloxone who will access these resources. With such large variation, there is a significant potential for confusion and inappropriate dosing leading to harm. While some resources provided recommendations for patients suspected to be opioid tolerant, given the current prevalence of chronic opioid use, the use of low naloxone doses in all patients seems most reasonable. The recognition by authors of the increasing numbers of chronic opioid users may explain the trend towards lower doses over time. It is perhaps telling that the pain medicine resource recommended the lowest initial dose, considering the proportion of their patients at risk for precipitated withdrawal. Some medical centers have had success with the low-dose naloxone approach, though wider adoption is limited by the dearth of rigorous data demonstrating the superiority of any specific regimen [38]. Patient-centered clinical studies optimally should be performed to evaluate the efficacy and safety of the various regimens.

Limitations

The data presented are limited by access to textbooks only available through the authors' university libraries and therefore does not include every potential resource. Furthermore, not every Website that discusses naloxone dosing was accessed. Additionally, the recommendations themselves are based on limited experimental data and generally represent expert opinion by the authors and editors of each resource.

Only IV dose data was used for comparison because resources did not reliably include information about other routes of administration, such as intramuscular or intranasal. Thus, direct application of this data to bystander-administered naloxone, which usually occurs by one of these routes, is not appropriate.

Conclusion

Significant variation exists in the initial and maximum dose of naloxone recommended by respected resources for the reversal opioid toxicity. Medical toxicology and general medical resources had the highest percentages of recommendations for initial doses of ≤ 0.05 mg IV, while half of the surveyed emergency medicine and anesthesiology resources recommended this low-dose strategy. There was also a tendency to recommend lower initial doses over time. Given the availability of supportive therapies in the medical setting, low-dose strategies, particularly less than 0.05 mg, should continue to be evaluated through appropriate clinical or observational studies.

Compliance with Ethical Standard

Conflicts of Interest None

Sources of Funding None

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