Acute Opioid Withdrawal Following Intramuscular Administration of Naloxone 1.6 mg: A Prospective Out-Of-Hospital Series

Katherine Z. Isoardi, BMed, FACEM*; Lachlan Parker, GradDipICPP, MHlthSc(OHS); Keith Harris, MBBCh, FACEM; Stephen Rashford, FACEM; Geoffrey K. Isbister, MD, FACEM

*Corresponding Author. E-mail: katherine.isoardi@health.qld.gov.au.

Study objective: Large doses of intramuscular (IM) naloxone are commonly used in out-of-hospital settings to reverse opioid toxicity; however, they are used less commonly in hospitals because of concerns about opioid withdrawal, particularly agitation. We aimed to determine the frequency of severe agitation following a single 1.6 mg IM naloxone dose.

Methods: We undertook a prospective study of adult (>15 years) patients treated by an Australian state ambulance service with 1.6 mg IM administration of naloxone for respiratory depression (respiratory rate <11 breaths/min and/or oxygen saturation <93% in room air) caused by presumed opioid poisoning. The primary outcome was the proportion of presentations with severe agitation (Sedation Assessment Tool score >1) within 1 hour of naloxone administration. Secondary outcomes were the proportion of presentations with acute opioid withdrawal (tachycardia [pulse rate >100 beats/min], hypertension [systolic >140 mm Hg], vomiting, agitation, seizure, myocardial infarction, arrhythmia, or pulmonary edema), and reversal of respiratory depression (respiratory rate >10 breaths/min and saturation >92% or Glasgow Coma Scale score 15).

Results: From October 2019 to July 2021, there were 197 presentations in 171 patients, with a median age of 41 years (range, 18 to 80 years); of the total patients, 119 were men (70%). The most common opioids were heroin (131 [66%]), oxycodone (14 [7%]), and morphine (11 [6%]). Severe agitation occurred in 14 (7% [95% confidence interval {CI} 4% to 12%]) presentations. Opioid withdrawal occurred in 76 presentations (39% [95% CI 32% to 46%]), most commonly in the form of tachycardia (18%), mild agitation/anxiety (18%) and hypertension (14%). Three presentations (1.5%) received chemical sedation for severe agitation within 1 hour of naloxone administration. A single 1.6 mg dose of naloxone reversed respiratory depression in 192 (97% [95% CI: 94% to 99%]) presentations.

Conclusion: Severe agitation was uncommon following the administration of 1.6 mg IM naloxone and rarely required chemical sedation. [Ann Emerg Med. 2022;80:120-126.]

Please see page 121 for the Editor's Capsule Summary of this article.

Readers: click on the link to go directly to a survey in which you can provide **feedback** to *Annals* on this particular article.
A **podcast** for this article is available at www.annemergmed.com.

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2022.03.004

SEE EDITORIAL, P. 127

INTRODUCTION

Background

Naloxone is an opioid receptor antagonist that is widely used as an antidote for opioid poisoning. Despite being available for over 50 years, the optimal dosing regimen of naloxone remains unclear.[1,2] Many clinicians prefer using small titrated intravenous (IV) boluses (eg, 0.04 to 0.1 mg) of naloxone during the initial management of opioid poisoning.[3-5] The reasoning behind this dosing approach is to minimize acute opioid withdrawal, which is thought to contribute to significant morbidity and potential fatality.[1]

In the out-of-hospital setting, which can at times be a chaotic and austere environment, larger intramuscular (IM) doses (eg, 1.6 to 2.0 mg) of naloxone are often used because the IM route is more rapid and reliable.[6,7]

In a recent retrospective study of 117 patients with suspected heroin poisoning who presented to a clinical toxicology unit, Harris et al[6] reported that a single 1.6 mg IM dose of naloxone effectively treated opioid poisoning, with few patients (5/48 [10%] versus 27/69 [29%]) requiring a subsequent naloxone infusion, compared with the patients initially administered with small titrated IV aliquots. However, some authors recommend avoiding large doses of IM naloxone outside of the out-of-hospital setting because of

Editor's Capsule Summary

What is already known on this topic

Naloxone can precipitate withdrawal in opioid-dependent patients in a dose-dependent fashion.

What question this study addressed

What is the rate of precipitated withdrawal following a single 1.6 mg dose of intramuscular naloxone in out-of-hospital patients with opioid overdose?

What this study adds to our knowledge

Nearly 40% of recipients developed withdrawal after receiving this dose, though there were few serious adverse events.

How this is relevant to clinical practice

Although effective in reversing respiratory depression, the incidence of precipitated withdrawal could be decreased by using alternative dosing strategies.

the concern that they are more likely to cause acute opioid withdrawal than the small titrated IV boluses of naloxone.[8]

The clinical effects of acute opioid withdrawal range from mild symptoms, such as dysphoria, vomiting, diarrhea, and muscle pain, to more serious complications, such as agitation and violent behavior.[9] Life-threatening complications, including seizures, myocardial infarction, and pulmonary edema, have also been rarely described.[7]

Importance

There are relatively few studies investigating the frequency of agitation following the administration of naloxone in the out-of-hospital setting. In a large prospective Norwegian series of 1,192 patients who received out-of-hospital naloxone (0.2 to 2.8 mg given through both IM and IV routes), Buajordet et al[10] reported that 8% of the patients demonstrated aggression. In other, smaller out-of-hospital studies of IM naloxone administration, the reported rates of agitation range from 7% to 14%.[11-13] However, none of these studies define agitation or use a validated assessment tool for agitation. Sporer et al,[11] in a retrospective series of 608 patients who received out-of-hospital naloxone (dose range 0.4 to 4.0 mg both through IV and IM routes), found that 7% of the patients required restraint for acute behavioral disturbance following administration of naloxone. Establishing the safety of high-dose IM naloxone may assist in its adoption into the hospital setting, particularly in emergency departments (EDs).

Goals of This Investigation

We aimed to determine the frequency of severe agitation following the administration of a single 1.6 mg IM naloxone dose in patients with opioid toxicity in the out-of-hospital setting.

MATERIALS AND METHODS

Study Design and Setting

This is a prospective observational study of adult patients (>15 years) with presumed opioid poisoning who were attended to by a state ambulance service that responds to approximately 1.2 million cases yearly. The study was set in an urban catchment area of a capital city with a population of approximately 2.2 million people. This study adhered to the Strengthening of Reporting of Observational Studies in Epidemiology guidelines.

Selection of Participants

All the patient presentations in which a single 1.6 mg dose of IM naloxone was administered to reverse respiratory depression (respiratory rate <11 breaths/min or oxygen saturation <93% in room air) caused by suspected opioid toxicity were included in the study from October 2019 to July 2021. Presentations were excluded if IV naloxone was given at any stage during the out-of-hospital care or if there was prolonged (>15 minutes) cardiac arrest before administration of naloxone. Furthermore, presentations were excluded if a dedicated data form (Figure E1 [available at http://www.annemergmed.com/]) was not completed by the paramedic on scene. Ethical approval for this study, including a waiver of consent for the participants, was granted by the Metro South Human Research Ethics Committee (HREC/2019/QMS/53305).

Intervention

The ambulance service administers naloxone as defined by their drug therapy protocol (Figure E2 [available at http://www.annemergmed.com/]). It is available in 0.4 mg/mL glass ampoules. All paramedics within the service can administer 1.6 mg of IM naloxone as a single dose. Critical Care Paramedics with additional postgraduate qualifications and scope of practice can elect to administer naloxone in titrated 0.05 mg IV aliquots. In 2020, naloxone was administered to 424 cases across the state of Queensland, with 308 of 424 (73%) cases receiving 1.6

mg IM naloxone and 116 of 424 (27%) receiving either IV or a combination of IV and IM naloxone.

Measurements

A dedicated data form (Figure E1) was completed by the treating paramedic for each participant, detailing the case number, sex, age (or estimation, if unknown), ingested opioid and its dose (if known), pulse rate, blood pressure, the presence of vomiting, and a sedation score using the Sedation Assessment Tool, a validated scoring tool for agitation (Figure E3 [available at http://www.annemergmed.com/]).[14] Agitation was assessed prospectively by the paramedics on the scene using a Sedation Assessment Tool score. The Sedation Assessment Tool score was documented before administration of naloxone and at 10-minute intervals following naloxone administration, until arrival at the hospital. Other observations of vital signs, including respiratory rate, oxygen saturation, and Glasgow Coma Scale (GCS) score, were assessed by the paramedics on the scene and documented in the electronic ambulance record as part of routine management. Once completed, the data form and the electronic ambulance record were emailed to one of the investigators (L.P.), data was extracted and collected for the study, and any missing or illegible data items were clarified. The administrations of 1.6 mg of naloxone documented in the electronic ambulance record were monitored regularly throughout the study period to ensure that there were no missed cases.

Further data were obtained through review of the electronic ambulance record as well as the ED medical record to include any coingestants, observations upon arrival at ED (respiratory rate, oxygen saturation, and GCS score), complications (seizure, myocardial infarct, arrhythmia, or pulmonary edema), chemical sedation administered (drug and dose), further naloxone administered in hospital, and hospital length of stay. For the patients who were not transported to the hospital, the patients who the treating paramedic assessed as having the capacity to refuse transfer (Figure E4 [available at http://www.annemergmed.com/]), medical records were reviewed to ensure the patient survived the event by identifying the existence of a health care episode following the presentation to our study. A single investigator (K.Z.I.), not blinded to the study objective, abstracted all the data in this study.

Outcomes

The primary outcome of this study was the proportion of presentations with severe agitation (Sedation Assessment Tool score >1) within 1 hour of the administration of naloxone.

Secondary outcomes included the proportion of patient presentations with acute opioid withdrawal, defined as any of the following clinical effects occurring within 1 hour of naloxone administration: tachycardia (pulse rate >100 beats/min), hypertension (systolic blood pressure >140 mm Hg), vomiting, agitation, seizure, myocardial infarction, arrhythmia or pulmonary edema, and the reversal of respiratory depression (respiratory rate >10 breaths/min and oxygen saturation >92% or GCS score 15 if a repeat oxygen saturation was not performed) before arrival at the hospital.

The sample size was based on 2 previous studies, a small ED study (N=25) that reported 13% of the presentations that were administered with titrated low doses of IV naloxone experienced agitation, and a large, out-of-hospital series (N=726) in which 7% of presentations required physical restraint following naloxone administration.[11,15] We estimated a sample size of 177 on the basis of the upper 95% confidence interval (CI) of our study being less than 13% and having a point estimate of approximately 7%.

Analysis

Data are reported using descriptive statistics, including medians, interquartile ranges (IQRs), ranges for continuous data, and proportions with 95% CI for dichotomous outcomes. All analyses were performed in GraphPad Prism 8 for Mac OS (GraphPad Software, San Diego, CA; https://www.graphpad.com).

RESULTS

Characteristics of Study Subjects

Over the 22-month period, there were 232 presentations, of which 35 were excluded (Figure 1), leaving 197 presentations in 171 patients (119 [70%] men) with a median age of 41 years (range 18 to 80 years). The most common opioids were heroin (131 [66%]), oxycodone (14 [7%]), and morphine (11 [6%]) (Table 1). Coingestions were taken in 84 (43%) presentations, with central nervous system depressants being the most common coingestion. Before naloxone administration, the median oxygen saturations were 80% in room air (IQR 70% to 90%), the median respiratory rate was 4 breaths/min (IQR 3 to 6), and the median GCS score was 3 (IQR 3 to 7).

Main Results

Severe agitation occurred in 14 (7% [95% CI 4% to 12%]) presentations, all unique patients. In 3 of the presentations (1.5%), chemical sedation was given for severe agitation within 1 hour of naloxone administration; one of these was given out of the hospital, whereas the

other 2 were given after arrival at the ED. The other 11 presentations settled with verbal de-escalation techniques.

Any feature of opioid withdrawal occurred in 76 presentations (39% [95% CI 32% to 46%]) (Table 2), with the most common, nonspecific features being tachycardia in 35 (18%) (median peak pulse rate 115 beats/min [IQR 107 to 128 beats/min, maximum 152 beats/min]), hypertension in 28 (14%) (median peak systolic blood pressure 149 mm Hg [IQR 145 to 155 mm Hg, maximum 179 mm Hg]), and vomiting in 6 (3%) presentations. Mild agitation or anxiety occurred in 36 (18% [95% CI 13% to 24%]) cases. There were no instances of seizure, myocardial infarction, arrhythmia, or pulmonary edema.

A single 1.6 mg dose of naloxone reversed respiratory depression in 192 (97%) presentations before arrival at the hospital. One hundred and sixty cases (81%) were transported to a hospital for further assessment and management. Of the 37 presentations that were not transported, all were counseled by the treating paramedic and believed to have the capacity to refuse transfer, except for a 52-year–old man who had taken heroin and became highly agitated with a Sedation Assessment Tool score of 3 following naloxone administration. He absconded from the scene before a capacity assessment. Subsequent medical records confirm that this man is alive. All presentations that were not transported to the hospital and had sufficient identifying data recorded on the electronic ambulance records (33/37) were alive on follow-up.

Further, naloxone was given in 47 (24%) presentations following arrival at the ED, with 22 (11%) then receiving naloxone infusions. In those with heroin intoxication, further naloxone was provided in 26 (20%) presentations, with 11 (8%) proceeding to a naloxone infusion (Table 3).

The median length of stay was 6.3 hours. The length of stay was similar in those who experienced opioid withdrawal symptoms compared with those who had no opioid withdrawal symptoms (7.6 hours versus 6.0 hours, difference 1.6 hours, 95% CI 2.3 to 1.7 hours). There were no deaths in this series.

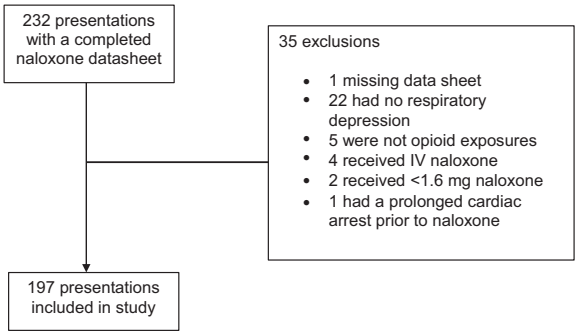

Figure 1. Flowchart of patient enrolment and the reasons for exclusion.

Table 1. Baseline characteristics of 197 presentations with opioid toxicity that received 1.6 mg IM naloxone.

Characteristic	No.	(%)
Total patients	171	
Male	119	70
Female	51	30
Transgender	1	<1
Median Age (y) (range)	41	18-80
Suspected opioid exposure*		
Heroin	131	(66)
Undisclosed opioid	21	(11)
Oxycodone	14	(7)
Morphine	11	(6)
Fentanyl	9	(5)
Buprenorphine	6	(3)
Codeine	5	(3)
Tapentadol	4	(2)
Methadone	3	(2)
Tramadol	1	(<1)
Opium	1	(<1)
Hydromorphone	1	(<1)
Etodesnitazene	1	(<1)
Coingestion†	84	(43)
Benzodiazepine	37	(19)
Alcohol	30	(15)
Pregabalin	19	(10)
Methamphetamine	16	(8)
Marijuana	5	(3)
Other	10	(5)

*Ten reported taking multiple opioids.
†Twenty-six admitted to taking multiple coingested agents.

LIMITATIONS

This study had some limitations, the major one being the predominance of heroin in the study, which may not translate to areas where the primary opioid of concern has a much longer half-life, such as methadone, is more potent like fentanyl, or where the primary opioid is oxycodone. Heroin is the main illicit opioid in Australia, although there is increasing misuse of prescription opioids.[16,17] Australia has not yet experienced a rise in high-potency opioids such as fentanyl that has been seen in North America in recent years. Few signals of illicitly manufactured fentanyl have been identified in Australia, and most misuse is the diversion of pharmaceutical fentanyl.[18]

Table 2. Features of opioid withdrawal that occurred following administration of 1.6 mg IM naloxone in 197 presentations of opioid toxicity.

Feature of Opioid Withdrawal	No.	%
Any feature of opioid withdrawal*	76	39
Tachycardia	35	18
Hypertension	28	14
Vomiting	6	3
Agitation		
Mild agitation/anxiety (SAT 1)	36	18
Severe agitation (SAT 2 or 3)	14	7
Myocardial infarction	0	-
Seizure	0	-
Arrhythmia (excluding sinus tachycardia)	0	-
Pulmonary edema	0	-

SAT, Sedation Assessment Tool.[14]
*Multiple features of withdrawal could occur in the same presentation.

The study conclusions apply primarily to heroin without coingestants, rather than semisynthetic fentanyl or methadone because most of the presentations are caused only by heroin exposure. The subgroups exposed to coingestions, methadone, and semisynthetic fentanyl, which may have different outcomes, were too small to perform any meaningful subgroup analysis.

A further limitation is that the rate of opioid withdrawal may have been underestimated as only objective features of opioid withdrawal were used, and the patient's subjective experience of withdrawal was not considered. Using a subjective rating score like the Subjective Opioid Withdrawal Scale may have been helpful to capture this.[19] Patient height, weight, and ethnicity were not captured in the data, all of which may have influenced opioid and naloxone pharmacokinetics.

Furthermore, though the data collection instrument was created a priori, the secondary outcome data were abstracted by chart review, and there was only one person who abstracted the data. This person was not blinded to the study objective, and there was no interrater reliability assessment because there was only 1 chart abstractor.

Another limitation is that the patients who received IV naloxone were excluded. It is possible that IV naloxone was preferentially given to those who the paramedic believed were at a higher risk of withdrawal. However, only one quarter of the naloxone administrations by the ambulance service are IV; thus it was believed that this effect would be limited. Finally, the opioids and coingestants taken by the patient were not analytically confirmed in most cases, and information was rather based on patient history.

DISCUSSION

Severe agitation was uncommon following the administration of a 1.6 mg IM dose of naloxone, and chemical sedation was rarely required. Milder clinical features of opioid withdrawal were common and appeared to be well tolerated. Initial reversal of respiratory depression was achieved in most presentations.

The frequency of opioid withdrawal is similar to that previously described in the literature following the

Table 3. Recurrence of opioid toxicity receiving further doses of naloxone in the emergency department and naloxone infusion use for individual opioids.

Opioid	Number	Recurrence of Opioid Toxicity Receiving Naloxone in ED N (%)	Naloxone Infusion N (%)
Heroin	133	26 (20)	11 (8)
Oxycodone	14	5 (36)	2 (14)
Morphine	11	3 (27)	2 (18)
Fentanyl	9	3 (33)	1 (11)
Buprenorphine	6	3 (50)	2 (33)
Codeine	5	3 (60)	2 (40)
Tapentadol	4	0	0
Methadone	3	0	0
Tramadol	1	1 (100)	0
Opium	1	0	0
Hydromorphone	1	0	0
Etodesnitazene	1	0	0
Unknown opioid	21	6 (28)	4 (19)

administration of various naloxone regimens.[10,20] Most features of opioid withdrawal are considered unpleasant rather than serious and clinically significant. Severe agitation is the most common clinically relevant feature of rapid opioid withdrawal induced by naloxone and was the focus of this study. This is a common reason for medical staff being reluctant to administer naloxone, particularly large doses of naloxone.[4] We report severe agitation in only 7% (95% CI 4% to 12%) of presentations, which is comparable to other studies reporting agitation and aggression following opioid reversal, irrespective of the dose or route of naloxone used. Surveys of take-home naloxone users report anger or aggression in 9% to 14% of administrations.[21-23)] Naloxone doses in these series vary from 0.4 mg to 2.0 mg delivered by IM and intranasal (IN) routes. A small retrospective series of patients given titrated doses of 0.04 mg IV (median 0.08 mg) naloxone also reported a rate of agitation of 13%.[15]

Most presentations with severe agitation in our series settled with verbal de-escalation techniques employed by the paramedics. Only 3 presentations, or 1.5%, received chemical restraint. This compares favorably to a large retrospective out-of-hospital series of opioid-poisoned patients receiving 0.4 mg to 4.0 mg of naloxone (either IV or IM), in which 7% of patients received physical restraint following opioid reversal.[11] Our study, even more so than this previous study, is in contrast to traditional beliefs, suggesting that larger doses should be avoided in preference to small, titrated doses to limit severe agitation.[1,8] It is possible that the attenuated peak concentration of naloxone following IM injection compared to the much higher peak concentration that results from the same dose delivered through the IV route is protective and reduces the probability of severe agitation.[24]

The 1.6 mg dose of IM naloxone was effective in initially reversing respiratory depression in 97% of opioid presentations; further, naloxone was given in a quarter of cases, and only 11% later received a naloxone infusion. The rate of naloxone infusion use is lower than has been reported in other series of opioid intoxication receiving reversal, in which 16% to 66% of patients received a naloxone infusion during their treatment.[6,25-27] Higher rates of naloxone infusions are seen with opioids that have a long half-life, such as methadone or are slow-release opioid preparations.[26,27] While the low rate of naloxone infusions in our series may be partially explained by the predominance of heroin, it is still lower than other series reporting naloxone infusion rates following heroin intoxication. A retrospective series including 88 patients with heroin intoxication receiving naloxone reported that 16% of patients then received naloxone infusions.[25] In another retrospective series of 117 patients with heroin intoxication receiving naloxone, 27% received a naloxone infusion, although if the patient received 1.6 mg IM naloxone (rather than titrated IV naloxone), this fell to 11%.[6]

Again, it is possible that the kinetics of the IM route may be favorable for treating opioid withdrawal with measurable concentrations of naloxone persisting for 4 hours following the administration of 1.6 mg IM naloxone in a volunteer study.[24] This approach to opioid reversal may have a role beyond the out-of-hospital setting, particularly in smaller centers or in those with limited resources, in which the simplicity of administration and lower likelihood for further naloxone is advantageous.

In summary, severe agitation was uncommon following 1.6 mg IM naloxone in our series, and the use of chemical sedation was rare, with most patients settling following verbal de-escalation. Milder features of opioid withdrawal were common and similar to what is reported following other dosing regimens. Initial reversal of respiratory depression was achieved in most patients.

Supervising editor: Lewis S. Nelson, MD. Specific detailed information about possible conflict of interest for individual editors is available at https://www.annemergmed.com/editors.

Author affiliations: From the Clinical Toxicology Unit, Princess Alexandra, Hospital (Isoardi, Harris), Brisbane, Australia; the Clinical Toxicology Research Group, University of Newcastle (Isoardi, Isbister), Newcastle, Australia; the Faculty of Medicine, University of Queensland (Isoardi, Harris), Brisbane, Australia; and the Medical Director's Office, Queensland Ambulance Service (Parker, Rashford), Brisbane, Australia.

Author contributions: KZI and GKI conceived the study and designed the trial. KZI, LP, KH, and SR supervised the conduct of the trial and data collection. KZI and GKI analyzed the data. KZI drafted the manuscript, and all authors contributed substantially to its revision. KZI takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria:(1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

Dr. Isbister is supported by the National Health and Medical Research Council (Senior Research Fellowship ID1061041).

Publication dates: Received for publication November 22, 2021. Revisions received February 4, 2022; February 19, 2022, and February 22, 2022. Accepted for publication March 2, 2022.

An abstract of this study has been accepted for an oral presentation at EAPCCT Congress held in Tallinn Estonia, May 24-27, 2022.

REFERENCES

1. Connors NJ, Nelson LS. The evolution of recommended naloxone dosing for opioid overdose by medical specialty. *J Med Toxicol*. 2016;12:276-281.
2. Lombardi J, Villeneuve E, Gosselin S. In response to: "The Evolution of Recommended Naloxone Dosing for Opioid Overdose by Medical Specialty.". *J Med Toxicol*. 2016;12:412-413.
3. Kim HK, Nelson LS. Reducing the harm of opioid overdose with the safe use of naloxone: a pharmacologic review. *Expert Opin Drug Saf*. 2015;14:1137-1146.
4. Connors NJ, Nelson LS. In reply: "The Evolution of Recommended Naloxone Dosing for Opioid Overdose by Medical Specialty.". *J Med Toxicol*. 2016;12:414-415.
5. Clarke SF, Dargan PI, Jones AL. Naloxone in opioid poisoning: walking the tightrope. *Emerg Med J*. 2005;22:612-616.
6. Harris K, Page CB, Samantray S, et al. One single large intramuscular dose of naloxone is effective and safe in suspected heroin poisoning. *Emerg Med Australas*. 2020;32:88-92.
7. Rzasa Lynn R, Galinkin JL. Naloxone dosage for opioid reversal: current evidence and clinical implications. *Ther Adv Drug Saf*. 2018;9:63-88.
8. Li K, Armenian P, Mason J, et al. Narcan or nar-can't: tips and tricks to safely reversing opioid toxicity. *Ann Emerg Med*. 2018;72:9-11.
9. Donroe JH, Tetrault JM. Substance use, intoxication, and withdrawal in the critical care setting. *Crit Care Clin*. 2017;33:543-558.
10. Buajordet I, Naess AC, Jacobsen D, et al. Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. *Eur J Emerg Med*. 2004;11:19-23.
11. Sporer KA, Firestone J, Isaacs SM. Out-of-hospital treatment of opioid overdoses in an urban setting. *Acad Emerg Med*. 1996;3:660-667.
12. Kerr D, Kelly AM, Dietze P, et al. Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. *Addiction*. 2009;104:2067-2074.
13. Kelly AM, Kerr D, Dietze P, et al. Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *Med J Aust*. 2005;182:24-27.
14. Calver LA, Stokes B, Isbister GK. Sedation assessment tool to score acute behavioural disturbance in the emergency department. *Emerg Med Australas*. 2011;23:732-740.
15. Kim HK, Nelson LS. Reversal of opioid-induced ventilatory depression using low-dose naloxone (0.04 mg): a case series. *J Med Toxicol*. 2016;12:107-110.
16. Frood J, Paltser G. Types of opioid harms in Canadian hospitals: comparing Canada and Australia. *Healthc Q*. 2019;22:10-12.
17. Roxburgh A, Hall WD, Dobbins T, et al. Trends in heroin and pharmaceutical opioid overdose deaths in Australia. *Drug Alcohol Depend*. 2017;179:291-298.
18. Nielsen S, Dietze PM. What can Australia learn from the North American opioid crisis? The role of opioid regulation and other evidence-based responses. Drug. *Alcohol Rev*. 2019;38:223-225.
19. Handelsman L, Cochrane KJ, Aronson MJ, et al. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse*. 1987;13:293-308.
20. Dettmer K, Saunders B, Strang J. Take home naloxone and the prevention of deaths from opiate overdose: two pilot schemes. *BMJ*. 2001;322:895-896.
21. Enteen L, Bauer J, McLean R, et al. Overdose prevention and naloxone prescription for opioid users in San Francisco. *J Urban Health*. 2010;87:931-941.
22. Banjo O, Tzemis D, Al-Qutub D, et al. A quantitative and qualitative evaluation of the British Columbia Take Home Naloxone program. *CMAJ Open*. 2014;2:E153-E161.
23. Madah-Amiri D, Clausen T, Lobmaier P. Rapid widespread distribution of intranasal naloxone for overdose prevention. *Drug Alcohol Dep*. 2017;173:17-23.
24. Dowling J, Isbister GK, Kirkpatrick CM, et al. Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers. *Ther Drug Monit*. 2008;30:490-496.
25. Morizio KM, Baum RA, Dugan A, et al. Characterization and management of patients with heroin versus nonheroin opioid overdoses: experience at an academic medical center. *Pharmacotherapy*. 2017;37:781-790.
26. Zamani N, Buckley NA, Hassanian-Moghaddam H. Buprenorphine to reverse respiratory depression from methadone overdose in opioid-dependent patients: a prospective randomized trial. *Crit Care*. 2020;24:44.
27. Berling I, Whyte IM, Isbister GK. Oxycodone overdose causes naloxone responsive coma and QT prolongation. *QJM*. 2013;106:35-41.