Journal of Toxicology: Clinical Toxicology

ISSN: 0731-3810 (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ictx19

Naloxone–For Intoxications with Intravenous Heroin and Heroin Mixtures-Harmless or Hazardous? A Prospective Clinical Study

Joseph J. Osterwalder

To cite this article: Joseph J. Osterwalder (1996) Naloxone–For Intoxications with Intravenous Heroin and Heroin Mixtures-Harmless or Hazardous? A Prospective Clinical Study, Journal of Toxicology: Clinical Toxicology, 34:4, 409-416, DOI: 10.3109/15563659609013811

To link to this article: https://doi.org/10.3109/15563659609013811

Clinical Toxicology, 34(4), 409–416 (1996)

Naloxone—For Intoxications with Intravenous Heroin and Heroin Mixtures—Harmless or Hazardous? A Prospective Clinical Study

Joseph J. Osterwalder, MD, MPH

Department of Emergency Medicine and Surgery, Kantonsspital, St. Gallen, Switzerland

ABSTRACT

Background: Naloxone is standard medication for the treatment of heroin intoxications. No large-scale studies have yet been carried out to determine its toxicity in heroin intoxications. Methods: We have undertaken an investigation as to the frequency, type and degree of severity of complications attributable to naloxone administration. Subjects treated between 1991 and 1993 with naloxone for intravenous drug intoxications were prospectively evaluated. Main Outcome Measurements: Development of ventricular tachycardia or fibrillation; atrial fibrillation; asystole; pulmonary edema; convulsions; vomiting; and violent behavior within ten minutes after parenteral administration of naloxone. Results: Six of 453 intoxicated subjects (1.3%; 95% confidence interval 0.4%-3%) suffered severe adverse effects within ten minutes after naloxone administration (one asystole; three generalized convulsions; one pulmonary edema; and one violent behavior). After the ten minute period, no further complications were observed. Conclusions: The short time between naloxone administration and the occurrence of complications, as well as the type of complications, are strong evidence of a causal link. In 1000 clinically diagnosed intoxications with heroin or heroin mixtures, from 4 to 30 serious complications can be expected. Such a high incidence of complications is unacceptable and could theoretically be reduced by artificial respiration with a bag valve device (hyperventilation) as well as by administering naloxone in minimal divided doses, injected slowly.

Correspondence: Dr. Joseph Osterwalder, Leitender Arzt ZNF, Kantonsspital, 9007 St. Gallen, Switzerland. Tel: 41/71-494-1111; Fax: 41/71-494-2870.

INTRODUCTION

Naloxone, a pure, semisynthetic opioid antagonist, is today one of the standard emergency medications, promptly alleviating coma and respiratory depression caused by overdoses of heroin or other opioid agonists. The first published report on naloxone appeared in 1961. Thereafter, it was described as a safe drug, based on the fact that pharmacologic studies with high doses, in the absence of opioids, had revealed no essential pharmacologic changes.[1] Since 1974, however, reports have appeared repeatedly in the anesthesiology literature, describing isolated cases of severe cardiovascular complications, thus questioning the unequivocal safety of naloxone.[2] Similar observations were reported in the 1980s, following treatment of subjects with opioid intoxications. A Medline search disclosed six reports in a total of only seven patients,[3-8] as well as one retrospective case series, describing five complications following 813 treatments with naloxone.[9] These complications consisted of atrial fibrillation and ventricular arrhythmias, pulmonary edema, convulsions, vomiting, violent behavior as well as hypotonia and hypertonia. Furthermore, naloxone was reported to potentiate the effects of cocaine.[8,10]

The reason for this surprisingly small number of reported complications attributed to naloxone may be that these adverse effects are difficult to differentiate from those due to opioid overdoses or cocaine. In most cases any complications are probably attributed to the effects of the intoxication itself.

A treatment mode that may lead to life-threatening complications is contrary to current tenets of medical practice and requires a critical examination. Most overdoses involve young healthy people with a favorable prognosis for spontaneous recovery without medical treatment. Nevertheless, here as well, appropriate investigations are lacking. The prevailing uncertainty is reflected in two different treatment recommendations: 1) administer 0.04 mg IV, to be repeated at 1-2 min intervals until the desired effect has been attained;[11] 2) administer 0.4 mg IV, to be repeated at 2-3 min intervals until the desired effects have been attained.[12] There is a tenfold difference of the two doses.

Several fundamental questions, concerning the treatment with naloxone for intoxications with opioids or opioid mixtures, remain unanswered:

1) What are the potentially life-threatening complications of opioid poisoning?

2) What are the therapeutic effects of naloxone?

3) Does naloxone have any toxic effects?

4) Are there drug interactions between naloxone and opioids?

5) Has naloxone the potential for causing life-threatening complications? If the answer is yes, how often?

6) Are these complications caused by an intrinsic property of naloxone or by an acute withdrawal reaction?

7) What is the safest administration route and dosage regimen?

We undertook a prospective investigation of the frequency, type, severity and magnitude of complications encountered with IV opioid intoxication and subsequent naloxone treatment. We limited our study to intoxications with heroin or heroin mixtures because they are the most common opioid intoxication seen in our Emergency Department (ED) (Table 1). Furthermore, we theorize the mechanism of complications and their prevention. We did not try to answer questions 2 and 4.

METHODS

Setting

The Canton Hospital St. Gallen is a 900-bed municipal hospital, serving 150,000 people as the sole primary care institution, and serving a further 800,000 people as a general hospital. All emergency cases are admitted into an interdisciplinary emergency unit.

Patients and Procedures

From January 1, 1991 until December 31, 1992, all emergency cases admitted for acute intoxications with heroin or heroin mixtures were prospectively included in our study. Moreover, we also investigated the occurrence of delayed complications. The indications for opioid antagonism were: 1) a Glasgow Coma Scale (GCS) score < 14; 2) hypotension; and 3) clinically significant hypoventilation after a trial with mechanical ventilation. Inclusion criteria were GCS score < 14; respiratory rate < 12/min; and improvement of consciousness and respiration after naloxone administration; new injection sites on the body as well as obligatory

Table 1

Substances Used by Drug Addicts (538 visits to the ED)

Substance	Single (%)	Combinations (%)	Total (%)
Heroin IV	357 (66.4%)	127* (23.6%)	484 (90%)
Cocaine IV	4 (0.7%)	39† (7.3%)	43 (8%)
Others	-	6‡ (1.1%)	6 (1.1%)
No data	-	-	5 (0.9%)

*Alcohol, benzodiazepine, cannabis, methadone. †Heroin IV. ‡Methadone IV with cannabis, LSD, alcohol.

confirmation of the clinical observations based on the patient's own or an external source's patient history. We chose the GCS score because it is reproducible, simply applied, and also accepted for the classification of nontraumatic disorders of consciousness. Excluded were patients who recovered spontaneously (after mechanical ventilation) without requiring naloxone administration. Since the presence of an opioid or other drugs is not definitive evidence of clouding of consciousness or respiratory depression, and for logistic reasons, toxicochemical screening tests were carried out only in serious or doubtful conditions.

Measurements

We collected the following demographic and clinical data: date; time of admission; time of discharge; age; sex; number of intoxications in the current year; substances involved (questioning the patients); discharge modality (ambulatory; hospitalized; intensive care); medication and dosage regimen (naloxone and flumazenil); development of ventricular tachycardia or fibrillation; atrial fibrillation; asystole, pulmonary edema; convulsions; vomiting; and violent behavior following administration of naloxone. Naloxone doses or divided dose intervals were not stipulated. Further details concerning the patients could be ascertained from the respective patient histories. Autopsy protocols are available for all deaths.

Statistical Analysis

Calculations were made by means of the Systat® version 5, 1992. The complication rate for naloxone was defined as the number of patients who had developed cardiovascular arrest, pulmonary edema, convulsions, vomiting, or violent behavior within 10 min after naloxone administration relative to the number of intoxications treated with naloxone parenterally. In our experience, a 10 min interval is essential because we give an IV injection slowly; therefore, a dose of 0.4 mg of naloxone reaches effective blood levels only after 5-10 min, thus delaying its action.

To calculate the incidence rate, we projected the number of complications to 1000 intoxications and expressed the results as an absolute 95% confidence interval.

RESULTS

Patients and Clinical Course

Four hundred and eighty-five patients visited the Emergency Department 538 times (92 women; 393 men) with acute IV drug intoxications. Several patients visited the ED on more than one occasion.

The median age was 24 years old (range 15-47 years old), of whom 67% reported to have taken heroin alone, and 31% heroin combined with other substances (Table 1).

Forty-six complications occurred, before or after treatment, in 30 patients (5.6%), i.e., 1.5 complications per patient (Table 2). Seven men and one woman died (1.5%): five due to cardiocirculatory arrest, two due to pneumonia, and one due to pulmonary edema.

Treatment Procedures (Table 3)

No treatment with naloxone was required for 85 intoxicated subjects. In the remaining 453 intoxicated subjects, naloxone was given IV 51 times, IM 49 times, and IV plus IM 350 times. No information is available for three patients. The median IV dose was 0.2 mg of naloxone (range 0.1 mg–2.8 mg); the median IM dose was 0.2 mg (range 0.1 mg–0.9 mg).

Table 2

Complications (30 patients)

Type	No. of Complications
Cardiocirculatory arrest	9
Delayed onset of consciousness and normal respiration	8
Pulmonary edema	8
Aspiration	5
Hyperthermia	4
Generalized seizures	3
Rhabdomyolysis	3
Pneumonia	2
Hypoglycemia	2
Hypothermia	2
Total	46

Table 3

Pharmacologic Treatment (538 Interventions)

Drug	No. of Interventions	%
None*	69	12.8%
Naloxone	414	77.0%
Naloxone and flumazenil†	39	7.2%
Flumazenil	1	0.2%
Unknown	15	2.8%
Total	538	100.0%

*Patients with a GCS score of ≥ 13 and respiratory frequency of ≥ 12 min after mechanical respiration with a bag valve device did not receive naloxone.
†Flumazenil was administered if additional benzodiazepine intoxication was suspected.

Complications

Six patients out of 453 treated with naloxone (1.3%; 95% confidence interval 0.4%-3%), developed severe complications within 5 min after a parenteral injection. Three patients had severe disorders before naloxone administration in addition to their intoxication (Table 4). Despite response to treatment (except Case 1) their conditions rapidly deteriorated further. After this time period, no further complications were encountered. Full details are shown in Table 4 and the following case reports.

Case Reports

Case 1

This 21-year-old man was admitted with a GCS score of 3. The patient's carotid pulse was easily palpable, regular and fast. His respiration rate was < 12; arterial blood gas analysis (ABGA): PaO_2 49.5 mm Hg, SaO_2 54.9%; $PaCO_2$ 106.6 mm Hg, (pH 6.95). An IV injection of 0.4 mg naloxone was administered, followed by an asystole (registered on the ECG monitor) within seconds. After mechanical resuscitation, intubation, and suction of stomach contents, administration of 1.8 mg of epinephrine and 1 mg of atropine, spontaneous circulation was restored. The patient awoke with a blood pressure of 100/65 and a pulse rate of 68/min. He required sedation.

Laboratory values were as follows: Hgb 127g/L (normal 140-180 g/L); Wbc 14.6 x 10^9/L (normal 4-10 x 10^9/L); platelets 229 x 10^9/L (normal 150-300 x 10^9/L); Na 140 mmol/L (normal 130-145 mmol/L); K 5.1 mmol/L (normal 3.4-4.8 mmol/L); Cl 93 mmol/L (normal 95-107 mmol/L); phosphate 4.1 mmol/L (normal 0.8-1.5 mmol/L); creatinine 186 μmol/L (normal 30-120 μmol/L); CK 49,200 U/L (normal 25-170 U/L); CK-MB 1,151 U/L (normal < 8% CK); glucose 10.1 mmol/L (normal 3-6 mmol/L); EMIT® test of serum for opioids, cocaine, and cannabis: positive; morphine blood levels 0.2 mg/L; ECG ST elevation in leads V_3-V_6 as well as in all terminal limb leads. Chest X ray and CT scan of the head were both normal. Patient was discharged in full remission after 4 days.

Case 2

This man, 31 years of age, was vomiting on admission in the ED. He had a GCS score of 5; blood pressure 150/90 mm Hg; pulse 120 bpm and respiratory rate 4/min. After an unknown dose of naloxone IV, the patient woke up in a state of aggressive psychomotor agitation. His respiration was normal. Within 2-3 min, respiratory embarrassment returned. The patient was intubated. Chest X ray showed right superior lobe infiltrates.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.