Naloxone: Effects and Side Effects

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Naloxone: Effects and Side Effects

- Specificity
- Toxicology
- Unmasking Disease
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ARTICLE

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Crystal structure of the \( \mu \)-opioid receptor bound to a morphinan antagonist

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Opium is one of the world’s oldest drugs, and its derivatives morphine and codeine are among the most used clinical drugs to relieve severe pain. These prototypical opioids produce analgesia as well as many undesirable side effects (sedation, apnoea and dependence) by binding to and activating the G-protein-coupled \( \mu \)-opioid receptor (\( \mu \)-OR) in the central nervous system. Here we describe the 2.8Å crystal structure of the mouse \( \mu \)-OR in complex with an irreversible morphinan antagonist. Compared to the buried binding pocket observed in most G-protein-coupled receptors published so far, the morphinan ligand binds deeply within a large solvent-exposed pocket. Of particular interest, the \( \mu \)-OR crystallizes as a two-fold symmetrical dimer through a four-helix bundle motif formed by transmembrane segments 5 and 6. These high-resolution insights into opioid receptor structure will enable the application of structure-based approaches to develop better drugs for the management of pain and addiction.

Opium extracts from the plant *Papaver somniferum* have been used that it may be possible to develop safer and more effective therapeutic
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N-ALLYLNOROXYMORPHONE: A NEW POTENT NARCOTIC ANTAGONIST

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(From the Departments of Anesthesiology of Mercy Hospital and the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania)

It has been known since 1915, when Pohl described the antagonistic effect of N-allylcodeine on the codeine-induced respiratory depression that N-allyl derivatives of narcotic analgesics are capable of antagonizing narcotic-induced respiratory depression and production of controllable apnea during anesthesia (Foldes et al.). Recently the pharmacological effects of the N-allyl derivative of a potent narcotic analgesic, oxymorphone† (N-morphinan see Fig. 1), were investigated in animals (Blackett et al.3)

CHAPTER 18. OPIOIDS, ANALGESIA, AND PAIN MANAGEMENT:

INTRODUCTION

Pain is a component of virtually all clinical pathologies, and management of pain is a primary clinical imperative. Opioids are a mainstay of pain treatment, but rational therapy may involve, depending upon the pain state, one or more drug classes, such as NSAIDs, anticonvulsants, and antidepressants. The properties of these non-opioid agents are presented in Chapters 34, 21, and 15. This chapter focuses first on the biochemical, pharmacological, and functional nature of the opioid system that defines the effects of opioids on pain processing, gastrointestinal-endocrine-autonomic functions, and reward-addiction circuits. Subsequently, the chapter presents principles that guide the use of opioid and non-opioid agents in the management of clinical pain states.

UPDATE

3/22/2012: Abuse-Deterrent Dosage Formulations

The term opioid refers to compounds structurally related to products found in opium, a word derived from opos, the Greek word for “juice,” natural opiates being derived from the resin of the opium poppy, Papaver somniferum. Opiates include the natural plant alkaloids, such as morphine, codeine, thebaine, and many semisynthetic derivatives. An opioid is any agent, regardless of structure, that has the functional and pharmacological properties of an opiate. Endogenous opioids, many of which are peptides, are naturally occurring ligands for opioid receptors found in animals. The term endorphin is used synonymously with endogenous opioid peptides but also refers to a specific endogenous opioid, 0-endorphin. The term narcotic was derived from the Greek word narkotikos, for “numbing” or “stupor.” Although narcotic originally referred to any drug that induced narcosis or sleep, the word has become associated with opioids and is often used in a legal context to refer to a variety of substances with abuse or addictive potential.
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Clinical Pharmacology

Mechanism of Action
Pure opioid antagonist that competes and displaces narcotics at opioid receptor sites

Pharmacokinetics
Onset of action: Endotracheal, I.M., SubQ: 2-5 minutes; Intranasal: ~8-13 minutes (Kelley, 2005; Robertson, 2009); I.V.: ~2 minutes

Duration: ~30-120 minutes depending on route of administration; I.V. has a shorter duration of action than I.M. administration; since naloxone's action is shorter than that of most opioids, repeated doses are usually needed

Distribution: Crosses placenta

Metabolism: Primarily hepatic via glucuronidation

Half-life elimination: Neonates: 3-4 hours; Adults: 0.5-1.5 hours

Excretion: Urine (as metabolites)
Naloxone: Effects and Side Effects

Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression

Albert Dahan, M.D., Ph.D.,* Leon Aarts, M.D., Ph.D.,* Terry W. Smith, Ph.D.†

This article has been selected for the Anesthesiology CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

ABSTRACT
Opioid treatment of pain is generally safe with 0.5% or less events from respiratory depression. However, fatalities are regularly reported. The only treatment currently available to reverse opioid respiratory depression is by naloxone infusion. The efficacy of naloxone depends on its own pharmacological charge.

opioid use have become well known and may be managed appropriately, with nausea, vomiting, sedation, and respiratory depression being associated commonly with postoperative analgesic doses. However, these side effects should not be trivialized. Postoperative nausea and vomiting is common and distressing.
Identification of two related peptides in brain with potent opiate activity

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Unit for Research on Addictive Drugs, Manchester College, Manchester, UK

A. Fothergill
Department of Biochemistry, Imperial College, London SW7 2AZ, UK

Enkephalin, a natural ligand for opiate receptors, is composed of the pentapeptides D-Phe-Glu-Leu-Gly-Tyr-OH and D-Phe-Leu-Gly-Tyr-Glu-OH. The evidence is based on the determination of the amino acid sequence of natural enkephalin by the Edman–Edman procedure and by mass spectrometry followed by synthetic and comparison of the natural and synthetic peptides.

Trevino and Wahlström*+ and Hughes† have described the existence of an endogenous substance in the brain which acts as an agonist at opiate receptor sites. We have characterized this substance, termed enkephalin, as a low molecular weight peptide. Other workers have also confirmed the presence of a substance in the brain that contains the pentapeptide enkephalin, although not completely characterised, seems similar to enkephalin. A further peptide with opiate agonist activity, larger and chemically dissimilar to enkephalin, has been discovered recently.

Enkephalin was isolated from pig brain as previously been used successfully by Tenerius and Wahlström (Acta physiol. scand., 94, 74; 1975) and by Pasternak, et al. (Life Sci., 16, 1765; 1975), who have also


Brain stem seems to interact strongly with the opiate receptors, suggesting that the mode of action of these drugs does not involve any of these known mech-
Naloxone: Effects and Side Effects

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- Toxicology
- Unmasking Disease
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Toxicology in Rats:

FIGURE 2: Dose-dependent reduction of 1 min stress analgesia but not 4 min stress analgesia by naloxone. *Significantly different from saline controls (p < 0.05).
Naloxone: Effects and Side Effects

Toxicology in People:

- Packaged 0.4 mg/ml and recommended at 0.4-0.8 mg IV.
- We treat opiate overdose in hospital with 0.04 mg IV with repeated doses q2 min as necessary.
- In opiate naïve patients without pain IV doses up to 5.4 mg/kg boluses and 4 mg/kg/h have been administered without adverse effects (Clarke et al., Emerg Med J 22: 616-616, 2005) (although mild elevations in blood pressure and decreased performance on memory tests have been reported with doses over 20 mg)
Naloxone: Effects and Side Effects

**Contraindications**
Hypersensitivity to naloxone or any component of the formulation

**Adverse Reactions**
Adverse reactions are related to reversing dependency and precipitating withdrawal. Withdrawal symptoms are the result of sympathetic excess. Adverse events occur secondarily to reversal (withdrawal) of narcotic analgesia and sedation.

Central nervous system: Narcotic withdrawal
Naloxone: Effects and Side Effects

- Specificity
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**Warnings/Precautions**

**Concerns related to adverse effects:**

- Acute opioid withdrawal: May precipitate symptoms of acute withdrawal in opioid-dependent patients, including pain, hypertension, sweating, agitation, irritability; in neonates: chill cry, failure to feed. Carefully titrate dose to reverse hypoventilation; do not fully awaken patient or reverse analgesic effect (postoperative patient).

**Disease-related concerns:**

- Cardiovascular disease: Use with caution in patients with cardiovascular disease or in patients receiving medications with potential adverse cardiovascular effects (eg, hypotension, pulmonary edema or arrhythmias); pulmonary edema and cardiovascular instability, including ventricular fibrillation, have been reported in association with abrupt reversal when using narcotic antagonists. Administration of naloxone causes the release of catecholamines; may precipitate acute withdrawal or unmask pain in those who regularly take opioids.


**Other warnings/precautions:**

- Opioid overdose: Recurrence of respiratory depression is possible if the opioid involved is long-acting; observe patients until there is no reasonable risk of recurrent respiratory depression.

- Postoperative reversal: Appropriate use: Excessive doses should be avoided after use of opiates in surgery. Abrupt postoperative reversal may result in nausea, vomiting, sweating, tachycardia, hypertension, seizures, and other cardiovascular events (including pulmonary edema and arrhythmias).
Naloxone: Effects and Side Effects

*Addiction* (1994) 89, 1471–1475

**Opiate withdrawal**

MICHAEL FARRELL

National Addiction Centre, 4 Windsor Walk, London SE5 8AF, UK

**Abstract**

Opiate withdrawal is one of the longest studied and most well described withdrawal syndromes. Opiate withdrawal has been described as akin to a moderate to severe flu-like illness. Opiate withdrawal is appropriately described as subjectively severe but objectively mild. This paper describes the mechanisms of opiate dependence and opiate withdrawal and reviews the available instruments for the measurement of withdrawal. The time course of assisted and unassisted withdrawal is described and the range of options for the management of assisted withdrawal are described. This review concludes that the most effective and least time- and resource-consuming approach to opiate withdrawal will substantially contribute to the overall social management of opiate dependence.
Naloxone: Effects and Side Effects

Opiate Withdrawal:

- Agitation
- Anxiety
- Muscle aches
- Increased tearing
- Insomnia
- Runny nose
- Sweating
- Yawning

Early symptoms of withdrawal include:

- Abdominal cramping
- Diarrhea
- Dilated pupils
- Goose bumps
- Nausea
- Vomiting

Terman et al, British Journal of Pharmacology, 2004
# Naloxone: Effects and Side Effects

## Adverse events after naloxone treatment of episodes of suspected acute opioid overdose

Ingebjørg Buajordet\textsuperscript{a}, Anne-Cathrine Næss\textsuperscript{b}, Dag Jacobsen\textsuperscript{c} and Odd Brørs\textsuperscript{a}

### Table 3. Events reported after naloxone treatment.

<table>
<thead>
<tr>
<th>Events</th>
<th>No. of events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 726 )</td>
</tr>
<tr>
<td>Confusion\textsuperscript{a}</td>
<td>235 (32)</td>
</tr>
<tr>
<td>Headache\textsuperscript{a}</td>
<td>157 (22)</td>
</tr>
<tr>
<td>Nausea/vomiting\textsuperscript{a}</td>
<td>66 (9)</td>
</tr>
<tr>
<td>Aggressiveness\textsuperscript{a}</td>
<td>62 (8)</td>
</tr>
<tr>
<td>Tachycardia\textsuperscript{a}</td>
<td>47 (6)</td>
</tr>
<tr>
<td>Shivering</td>
<td>33 (5)</td>
</tr>
<tr>
<td>Seizures\textsuperscript{a}</td>
<td>27 (4)</td>
</tr>
<tr>
<td>Sweating</td>
<td>24 (3)</td>
</tr>
<tr>
<td>Tremor</td>
<td>9 (1)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>66 (9)</td>
</tr>
</tbody>
</table>

\( ^{a} \)Predefined events noted in the reporting charts used by the paramedics.
Naloxone: Effects and Side Effects

Warnings/Precautions

Concerns related to adverse effects:

- Acute opioid withdrawal: May precipitate symptoms of acute withdrawal in opioid-dependent patients, including pain, hypertension, sweating, agitation, irritability; in neonates: chill cry, failure to feed. Carefully titrate dose to reverse hypoventilation; do not fully awaken patient or reverse analgesic effect (postoperative patient).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease or in patients receiving medications with potential adverse cardiovascular effects (e.g., hypotension, pulmonary edema or arrhythmias); pulmonary edema and cardiovascular instability, including ventricular fibrillation, have been reported in association with abrupt reversal when using narcotic antagonists. Administration of naloxone causes the release of catecholamines; may precipitate acute withdrawal or unmask pain in those who regularly take opioids.


Other warnings/precautions:

- Opioid overdose: Recurrence of respiratory depression is possible if the opioid involved is long-acting; observe patients until there is no reasonable risk of recurrent respiratory depression.

- Postoperative reversal: Appropriate use: Excessive dosages should be avoided after use of opiates in surgery. Abrupt postoperative reversal may result in nausea, vomiting, sweating, tachycardia, hypertension, seizures, and other cardiovascular events (including pulmonary edema and arrhythmias).
Naloxone: Effects and Side Effects

Cardiovascular effects

- Withdrawal induced catecholamine release (e.g., sweating)
  - Tachycardia or other arrhythmia (myocardial ischemia) morbidity
    - In patients with other drugs on board (e.g., cocaine)
    - In patients with pre-existing cardiac disease
    - In patients with hypoxia and/or hypercarbia
Naloxone: Effects and Side Effects


Case Report

Should naloxone be prescribed in the ED management of patients with cardiac arrest? A case report and review of literature

Abstract

We report the case of a patient in cardiac arrest with hypoxia and pulseless electrical activity despite resuscitative efforts. The cardiac arrest resolved spontaneously after administration of naloxone. It is possible naloxone may have a role in pulseless electrical activity and cardiac arrest related to hypoxia.

Opioid intoxication is a frequent cause of cardiac arrest.

Clinical paper

Naloxone in cardiac arrest with suspected opioid overdoses

Matthew D. Saybolt\textsuperscript{a}, Scott M. Alter\textsuperscript{a}, Frank Dos Santos\textsuperscript{b,c}, Diane P. Calello\textsuperscript{b}, Kevin O. Rynn\textsuperscript{d}, Daniel A. Nelson\textsuperscript{a}, Mark A. Merlin\textsuperscript{b,*}

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ABSTRACT

Introduction: Naloxone's use in cardiac arrest has been of recent interest, stimulated by conflicting results in both human case reports and animal studies demonstrating antiarrhythmic and positive ionotropic effects. We hypothesized that naloxone administration during cardiac arrest, in suspected opioid overdosed patients, is associated with a change in cardiac rhythm.

Methods: For a database of 22,644 advanced life support (ALS) cases, we examined cardiac rhythm changes...
Naloxone: Effects and Side Effects

Cardiovascular effects

- Withdrawal induced catecholamine release (e.g., sweating)
  - Tachycardia or other arrhythmia (myocardial ischemia) morbidity
    - In patients with other drugs on board (e.g., cocaine)
    - In patients with pre-existing cardiac disease
    - In patients with hypoxia and/or hypercarbia
  - Hypertension morbidity (e.g., vascular aneurysms)
  - Pulmonary edema (e.g., in heart failure)
Naloxone: Effects and Side Effects

Naloxone-Induced Pulmonary Edema

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Received for publication November 21, 1986. Revision received April 27, 1987. Accepted for publication June 16, 1987.

Address for reprints: Max D. Koenigsberg, MD, Department of Emergency Medicine, Illinois Masonic Medical Center, 836 West Wellington Avenue, Chicago, Illinois 60657.

We present the case of a 68-year-old woman with acute pulmonary edema secondary to the administration of naloxone to reverse an inadvertent narcotic overdose. The patient presented following a 12-hour history of increasingly bizarre behavior and confusion. A total IV dose of 1.6 mg naloxone was administered in an attempt to reverse the suspected overconsumption of a codeine-containing cough suppressant. She immediately became agitated, tachycardic, and diaphoretic; a clinical diagnosis of acute pulmonary edema was made. Following treatment with furosemide, nitroglycerin, and morphine sulfate, the patient recovered completely without further incident. Although naloxone is thought to be a safe drug with few complications, it should not be used indiscriminantly, and the smallest doses necessary to elicit the desired response should be used. [Schwartz JA, Koenigsberg MD: Naloxone-induced pulmonary edema. Ann Emerg Med November 1987;16:1294-1296.]

INTRODUCTION

Naloxone is an opiate antagonist without intrinsic agonist activity used for the reversal of narcotic-induced respiratory depression and in the diagnosis of suspected acute opiate overdosage. While being structurally similar to oxymorphone, it is essentially a pure narcotic antagonist that counteracts the effects of narcotics, including respiratory depression, coma, analgesia, pupillary constriction, seizures, and cardiovascular and gastrointestinal effects. Naloxone may precipitate withdrawal symptoms in individuals with physical narcotic dependency. In general, naloxone is widely accepted to be a benign drug with few adverse side effects or contraindications.

We present a case of acute pulmonary edema after naloxone administration, an unusual adverse reaction previously unreported in the emergency medicine literature.

CASE REPORT

A 68-year-old woman was brought to the emergency department because
Negative Pressure Pulmonary Edema Following Naloxone Administration in a Patient With Fentanyl-induced Respiratory Depression

Huei-Chi Horng¹, Min-Tzung Ho², Chih-Hung Huang¹, Chun-Chang Yeh³, Chen-Hwan Chrn³*

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²Division of Otorhinolaryngology, Taichung Armed Forces General Hospital, Taichung, Taiwan, R.O.C.
³Department of Anesthesiology, Tri-Service General Hospital and National Defense Medical Center, Taipei, Taiwan, R.O.C.

Naloxone is commonly used to reverse narcotic intoxication. However, its use is not entirely free of hazards. For instance, pulmonary edema (PE) has been reported to arise with the mechanism of over-sympathetic discharge caused by release of cat-

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CASE REPORT

Negative Pressure Pulmonary Edema after Acute Upper Airway Obstruction

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Department of Anesthesiology, University of Miami School of Medicine, and Department of Anesthesiology, Jackson Memorial Medical Center, Miami, FL, and University of Medicine and Dentistry of New Jersey, Newark, NJ.

Study Objective: To review the clinical characteristics and the pathogenesis of negative pressure pulmonary edema, and to determine its incidence in surgical patients.

Design: Retrospective case report study.

Setting: Operating room, postanesthesia care unit and surgical intensive care of a teaching hospital.


Measurements and Main Results: This study showed a rapid onset of negative pressure pulmonary edema after acute upper airway obstruction, due mainly to laryngospasm in the perioperative period and to upper airway pathology in the postoperative period. Negative pressure pulmonary edema appeared more frequently in healthy ASA physical status I and II, white-male and male patients, with a general incidence of 0.694%. The resolution was relatively rapid after removal of the airway, adequate oxygenation, and positive air pressure ventilation. The clinical course was complicated in all the patients.

Conclusions: In this study, negative pressure pulmonary edema presented a relatively high incidence. Prevention, early diagnosis, and prompt treatment allowed a rapid and uncomplicated resolution.

Keywords: airway obstruction; edema, pulmonary; laryngospasm.

Introduction

The link between acute upper airway obstruction and pulmonary edema was suggested in the late 1920's in animal models. Despite the fact that the pathophysiology of this association began to be understood in the early 1940's, it was not until 1977 that the first case report of pulmonary edema following laryngospasm was published. Even today an underreporting of the cases of negative pressure pulmonary edema (NPPE), after acute upper airway obstruction, still exists.

After a short review of the pathophysiology of NPPE, the results of this case report study, which was performed in 30 adult patients who developed NPPE after acute upper airway obstruction from 1992 to 1995, are discussed.

Materials and Methods

From a total of 51,826 adult patients scheduled for surgery during the period 1992–1995, at Jackson Memorial Hospital-University of Miami, 30 cases of NPPE were reported. The hospital records of these patients and the postanesthesia assessment were reviewed.


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Naloxone: Effects and Side Effects

**Cardiovascular effects**
- Withdrawal induced catecholamine release (e.g., sweating)
  - Tachycardia or other arrhythmia (myocardial ischemia) morbidity
  - In patients with other drugs on board (e.g., cocaine)
  - In patients with pre-existing cardiac disease
  - In patients with hypoxia and/or hypercarbia
- Hypertension morbidity (e.g., vascular aneurysms)
- Pulmonary edema (e.g., in heart failure) – perhaps most commonly post-obstructive
Naloxone: Effects and Side Effects

Seizure effects

- May lower seizure thresholds for patients with prior seizure disorder or immediately post-ictal (i.e., after a seizure).
Naloxone—For Intoxications with Intravenous Heroin and Heroin Mixtures—Harmless or Hazardous? A Prospective Clinical Study

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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 471 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.

Table 4
Complications after Naloxone Administration

<table>
<thead>
<tr>
<th>Case</th>
<th>Events</th>
<th>Sex</th>
<th>Age</th>
<th>Intoxication</th>
<th>Naloxone mg</th>
<th>Survival</th>
<th>Status Pre-naloxone</th>
</tr>
</thead>
</table>
| 1    | asystole             | M   | 21  | heroin/cocaine/cannabis*   | 0.4         | yes      | rhabdomyolysis
      |                     |     |     |                            |             |          | CK 49,200 mmol/L K 5.1 mmol/L aspiration |
| 2    | violent behavior     | M   | 31  | heroin*                    | ?           | yes      | Graves' disease                           |
| 3    | pulmonary edema      | M   | 31  | heroin/ flunitrazepam*     | 0.2         | yes      | hypothermia 30°C K 6.0 mmol/L glucose 27.9 mmol/L rhabdomyolysis, mild |
| 4    | generalized convulsion| M   | 19  | heroin/ flunitrazepam*     | 1           | yes      | suicidal attempt                           |
| 5    | generalized convulsion| M   | 31  | heroin/ alcohol*           | 0.8         | no       | asystole in ED; hypoxemic encephalopathy; hyperthermia 40°C epilepsy |
| 6    | generalized convulsion| M   | 31  | heroin                    | 0.3         | yes      |                                           |
Naloxone: Effects and Side Effects

Endogenous opioids may daloid-kindled rats

HANAN FRENK, JEROME EN JOHN C. LIEBESKIND

Department of Psychology, Tel Aviv University of Medicine and Department of Psychiatry

(Accepted January 11th, 1979)

Nucleus accumbens µ opioid receptors mediate immediate postictal decrease in locomotion after an amygdaloid kindled seizure in rats

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ABSTRACT

Postictal movement dysfunction is a common symptom in patients with epilepsy. We investigated the involvement of opioid receptors in the nucleus accumbens (NAC) in amygdaloid kindling-induced postictal decrease in locomotion (PDL) in rats. Seizures were induced by daily electrical stimulation of the basolateral amygdala until four consecutive stage 5 seizures were elicited. Locomotion was quantified before and after infusion of an opioid receptor antagonist or saline into the NAC. Whereas PDL was induced after a stage 5 seizure in saline-infused rats, pre-infusion of the µ opioid receptor antagonist H-D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH₂ (CTAP, 5 µg/1 µL/side) into the NAC prevented PDL. Pre-infusion of δ (naltrindole, 30 µg/1 µL/side), κ (nor-binaltorphimine, 1.8 µg/1 µL/side), or nonselective (naloxone, 10 µg/1 µL/side) opioid receptor antagonists did not block PDL, but late postictal hyperactivity
Naloxone: Effects and Side Effects

Seizure effects

- Theoretically, may lower seizure thresholds for patients with prior seizure disorder or immediately post-ictal (i.e., after a seizure).
- May unmask seizures from other drugs on board (e.g., cocaine).
- May unmask seizures due to hypoxia or hypercarbia.
Naloxone: Effects and Side Effects

Carbon Dioxide Narcosis and Grand Mal Seizure Complicating Laparoscopic Herniorrhaphy

Quentin M. Nunes, MS, MRCS, Elizabeth H. Emmull, MRCS, Joanna R. Eastwood, BMBS, FRCA, and Dikep N. Lobo, DM, FRCS

Abstract: A 60-year-old man without comorbidity underwent a totally extraperitoneal repair of bilateral inguinal hernias under general anesthesia. Forty minutes after the procedure he developed a slow, shallow respiratory pattern with a respiratory rate of 5/min and a self-limiting grand mal seizure lasting 30 seconds. Arterial blood gas analysis indicated significant hypercarbia and acidosis. The total dose of morphine administered was 50 mg intravenously. Naloxone was administered and the respiratory rate improved. The patient was discharged after 24 hours after making a good recovery and had no further seizures a year after surgery. Although hypercarbia is a well-known complication of laparoscopic surgery when CO₂ is used for insufflation, this, to the best of our knowledge, is the first reported case of a patient sustaining a grand mal seizure resulting from CO₂ narcosis after laparoscopic surgery. The possible mechanisms are discussed.

Key Words: carbon dioxide, complications, hypercarbia, laparoscopic surgery, seizures, totally extraperitoneal hernia repair

Although the use of carbon dioxide (CO₂) to create and maintain a pneumoperitoneum or pneumoperitoneum in laparoscopic surgery is well established, there is a small but significant risk of complications such as hypercarbia, subcutaneous emphysema, decreased pulmonary compliance and vital capacity, and cardiovascular effects such as a diminished cardiac index and increased systemic vasodilatation. Totally extraperitoneal (TEP) laparoscopic inguinal hernia repair involves instillation of CO₂ in the preperitoneal space (preperitoneum). We report a case of hypercarbia associated with seizures in a patient who underwent a TEP repair of bilateral inguinal hernias.

CASE HISTORY

A 60-year-old man without comorbidity underwent an elective TEP repair of bilateral inguinal hernias under general anesthesia. A pneumoperitoneum was created and maintained at a pressure of 10 mm Hg and 3 laparoscopic ports were used. The total operative time was 1 hour 15 minutes and there were no intraoperative anesthetic complications (maximum end-tidal CO₂ recorded was 10.6 kPa). The respiratory rate of the patient varied between 16 and 25/min during the procedure. The patient was transferred to the recovery area with the laryngeal mask airway in situ. However, 40 minutes after the procedure he developed a slow, shallow respiratory pattern with a respiratory rate of 5/min and a self-limiting grand mal seizure lasting 30 seconds. Clinically, the patient had subcutaneous emphysema extending up to his neck. An arterial blood gas analysis (Table 1), at the time indicated significant hypercarbia and acidosis. The total dose of morphine administered was 20 mg intravenously (the last dose being given at least 30 minutes before the seizure). Naloxone was administered and the respiratory rate improved. The patient was discharged after 24 hours after making a good recovery and had no further seizures a year after surgery.

COMMENT

Although hypercarbia is a well-known complication of laparoscopic surgery when CO₂ is used for insufflation, this, to the best of our knowledge, is the first reported case of a patient sustaining a grand mal seizure resulting from CO₂ narcosis after laparoscopic surgery. Liem et al. have shown that pneumoperitoneum for laparoscopic herniorrhaphy results in a rapid increase in PaCO₂ and a consequent decrease in pH. This can be explained by the fact that CO₂ absorption is more extensive in the preperitoneal space, because of a larger gas exchange area as a result of the absence of a natural border which allows diffusion of CO₂ into the subcutaneous tissues and the seroma (as opposed to a pneumoperitoneum). Lateral dissection for placement of the mesh during the repair also increases the total max exchange area. The large pressure gradient for CO₂ as a result of the larger gas exchange area and shorter anatomic distance results in an increased influx of CO₂ into the circulation. Hypercarbia further stresses the cardiovascular system which is already compromised by decreased venous return.
Warning/Precautions

Concerns related to adverse effects:

- Acute opioid withdrawal: May precipitate symptoms of acute withdrawal in opioid-dependent patients, including pain, hypertension, sweating, agitation, irritability; in neonates: chill cry, failure to feed. Carefully titrate dose to reverse hypoventilation; do not fully awaken patient or reverse analgesic effect (postoperative patient).

Disease-related concerns:

- Cardiovascular disease: Use with caution in patients with cardiovascular disease or in patients receiving medications with potential adverse cardiovascular effects (eg, hypotension, pulmonary edema or arrhythmias); pulmonary edema and cardiovascular instability, including ventricular fibrillation, have been reported in association with abrupt reversal when using narcotic antagonists. Administration of naloxone causes the release of catecholamines; may precipitate acute withdrawal or unmask pain in those who regularly take opioids.


Other warnings/precautions:

- Opioid overdose: Recurrence of respiratory depression is possible if the opioid involved is long-acting; observe patients until there is no reasonable risk of recurrent respiratory depression.

- Postoperative reversal: Appropriate use: Excessive dosages should be avoided after use of opiates in surgery. Abrupt postoperative reversal may result in nausea, vomiting, sweating, tachycardia, hypertension, seizures, and other cardiovascular events (including pulmonary edema and arrhythmias).
Naloxone: Effects and Side Effects

NO DEATHS ASSOCIATED WITH PATIENT REFUSAL OF TRANSPORT AFTER NALOXONE-REVERSED OPIOID OVERDOSE

Prehosp Emerg Care, 1999 Jul/Aug

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Abstract

OBJECTIVE: Naloxone is the drug of choice to treat opioid overdose in the out-of-hospital setting. This study examined deaths associated with patient refusal of transport after naloxone reversal of the opioid overdose. METHODS: The authors undertook a retrospective review of medical examiner (ME) reports over a five-year period. The authors examined 1,000 ME reports for deaths where naloxone was used to reverse an opioid overdose. RESULTS: There were 12 deaths associated with patient refusal of transport following naloxone reversal. No deaths occurred in the one-year follow-up period. CONCLUSIONS: Naloxone reversal of opioid overdose is not associated with death when patients refuse transport. Naloxone reversal of opioid overdose is not associated with death when patients refuse transport. Naloxone reversal of opioid overdose is not associated with death when patients refuse transport.

In many emergency medical services (EMS) systems, a patient given naloxone (Narcan) for heroin overdose 1), the patient can be released AMA at the scene by paramedics without base hospital contact. Although
Naloxone: Effects and Side Effects

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Opioid Toxicity Recurrence After an Initial Response to Naloxone

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ABSTRACT

Objective: To determine the frequency and potential predictors of opioid toxicity recurrence after a response to naloxone in adult Emergency Department patients. Methods: A retrospective case-control study of naloxone-treated patients with opioid toxicity over an 8-year period. Both the patient response to naloxone and recurrence of opioid toxicity was determined by an expert Delphi Panel. The frequency of opioid toxicity recurrence was compared by the duration of opioid effect, the route of opioid exposure, and the presence of other CNS depressant drugs. Results: Ninety of 221 (41%) cases with a discharge diagnosis of opioid toxicity were treated with naloxone; six patients were excluded because of a lack of toxicity. There was a response to naloxone in 50% of the 84 cases, and recurrence of toxicity in 31% (95% CI 17–45%) of naloxone responders. The most common opioids were codeine, heroin, propoxyphene, and oxycodone/hydrocodone. Recurrence of toxicity was more common with long-acting opioids (p = 0.04), and was not associated with the route of opioid exposure (p = 0.42), or presence of ethanol and other CNS depressants (p ≥ 0.87). Conclusion: Opioid toxicity recurrence after a response to naloxone occurred in approximately 1/3 of adult Emergency Department opioid overdose cases. Recurrence was more common with long-acting opioids and was not associated with the route of opioid exposure. Other clinically useful predictors of toxicity recurrence were not identified.
Naloxone: Effects and Side Effects

- Specificity (Amazing)
- Toxicology (Forgiving)
- Unmasking Disease: Concerns
  - Opiate Dependence (Withdrawal)
  - Co-ingested Substances
  - Hypoxemia/Hypercarbia
    - Arrhythmias
    - Seizures
  - Post-Obstructive Pulmonary Edema
  - Unrecognized Re-narcotization (perhaps worse with long–acting prescription meds than with other opiates)
- Pain