Opioid toxicity

TERMINOLOGY

CLINICAL CLARIFICATION [1]

- Opioid toxicity results in severe, sometimes fatal, toxic effects that most commonly occur after overdose
- Primary toxic effect of opioid overdose is decreased rate and depth of respiration leading to pulmonary edema
  - May result in death from hypoxia and respiratory arrest before development of pulmonary edema
- Effects on other organs include hypotension, bradycardia, and decreased body temperature

CLASSIFICATION

- Toxicity caused by short-acting opioids, such as:
  - Morphine sulfate
  - Fentanyl
  - Oxycodone
  - Hydrocodone
  - Codeine
  - Heroin
- Toxicity caused by longer-acting and delayed-release opioids, including:
  - Extended-release morphine sulfate
  - Methadone
  - Oxymorphone
- Toxicity caused by opioid receptor agonist-antagonist drugs, such as:
  - Agonist at 1 opioid receptor/antagonist at a different opioid receptor
    - Pentazocine
    - Butorphanol
    - Nalbuphine
    - Dezocine
  - Partial agonist at a single opioid receptor
    - Buprenorphine
    - Meptazinol

DIAGNOSIS

CLINICAL PRESENTATION

- History [2]
  - History of nonprescribed opioid use/abuse
    - Medical records may indicate previous use/abuse
    - Family or friends may confirm opioid use
    - Needles or other paraphernalia found near patient
  - History of prescribed opioid use
    - Pills, pill bottles, or paraphernalia found near patient
  - Common symptoms even without any available history
    - Apnea
    - Depressed consciousness
      - Can range from drowsiness to coma
- Physical examination [3]
  - Common signs
    - Depressed respiratory rate is the most specific sign
      - A respiratory rate of 12 breaths or fewer per minute, with stupor, is highly suggestive of acute opioid toxicity, especially when accompanied by miosis or depressed consciousness
    - Reduced size and reactivity of pupils
      - Pupil constriction to less than 2 mm in diameter [4]
      - Not always present, particularly if opioids were ingested along with other substances
    - Hypotension, bradycardia, and hypothermia usually present [3]
  - Other examination findings
    - Skin
      - Evidence of fentanyl patches [1]
      - Needle track marks
        - Recent injection marks are small, red, inflamed, or surrounded by slight bruising
        - Old injection sites show pigmentation change and atrophied skin

- Neurologic
  - Seizures often associated with overdose of tramadol, propoxyphene, and meperidine, particularly if used concomitantly with medicines that lower seizure thresholds[1]
- Mucous membrane cyanosis is a late sign of hypoxia and hypotension[3]
- Pulmonary
  - Pulmonary edema in patients with apnea or severe bradypnea
    - Rales and frothy sputum are a late sign of severe opioid toxicity[1]

CAUSES AND RISK FACTORS

- Causes
  - Overdose of opioid drugs[2]
    - Opioid drugs are substances that bind to 1 or more of the 4 opioid receptors (δ, κ, μ, and nociceptin receptors)
    - Toxicity is not necessarily dependent on dose of opioid used
      - Tolerance may be dramatically different in patient subpopulations
    - More overdose deaths are due to prescription opioids than nonprescription forms[2]
      - Commonly prescribed opioids[5]
        - Hydrocodone
        - Oxycodone
        - Morphine
        - Codeine
        - Hydromorphone
        - Oxymorphone
        - Methadone
        - Fentanyl patch
        - Tapentadol
        - Diphenoxylate
      - Commonly prescribed opioid receptor agonist/antagonist or partial-agonist drugs
        - Pentazocine
        - Butorphanol
        - Nalbuphine
        - Dezocine
        - Buprenorphine
        - Meptazinol
      - Most common nonprescription opioids
        - Heroin
        - Fentanyl (diverted or illicitly produced; typically added to heroin)
        - Carfentanil (diverted from veterinary sources; typically added to heroin)
        - Loperamide (in supratherapeutic doses)
  - Overdose of buprenorphine does not cause lethal respiratory depression in adults unless administered intravenously or combined with another respiratory depressant[6,7]
    - Death from buprenorphine in children results from unintentional exposure secondary to medication being stored in sight, accessed from a bag or purse, or not being stored in its original packaging[8]
  - Effects of toxic metabolites[9]
    - Normeperidine from meperidine: lowers seizure threshold and accumulates with repeated dosing
    - Morphine-3-glucuronide from morphine: lowers seizure threshold and may be responsible for myoclonus and allodynia
- Risk factors and/or associations[2]
  - Age
    - Higher incidence of opioid poisoning deaths in those aged 25 to 64 years, with highest incidence among those aged 45 to 54 years[10]
    - Advanced age is associated with reduced clearance of morphine, fentanyl, codeine, and oxymorphone, increasing the risk of overdose (and requiring more caution with prescribing)[9]
    - Children are more likely than adults to experience respiratory depression and death after unintentional exposure to agonist/antagonists like buprenorphine[8,11]
    - Children may be more sensitive to codeine dosing and be accidently overdosed owing to the existence of rapid metabolizers of the prodrug codeine to the active drug morphine[12]
  - Sex
    - Incidence higher in men

- Ethnicity/race
  - Death rates in white populations are 4 times higher than in Hispanic or black populations [10]
- Other risk factors/associations
  - Opioid toxicity is most highly associated with persons who are prescribed high doses of opioid analgesics (over 100 mg of morphine or equivalent per day) [13]
  - Also associated with persons who seek care from multiple physicians or receive early refills
    - Risk of distribution to other persons
  - Prescription opioid death rates are highest in rural populations [10, 2]
  - Heroin death rates are highest in large central metropolitan areas
  - Populations at greatest risk for opioid toxicity [2]
    - Persons with mental illness
    - Persons who report long-term medical use of opioids
    - Persons who report nonmedical use (ie, use without a prescription or medical need) of opioids in the past month
  - Hepatic impairment [9]
    - Especially important to consider when using oxycodone, morphine, oxymorphone
    - Lower risk of toxicity with fentanyl and methadone
  - Renal impairment [9]
    - Particularly important with morphine, hydromorphone, and other opioids with active metabolites
    - Less risk with fentanyl and methadone

DIAGNOSTIC PROCEDURES

- Primary diagnostic tools [14]
  - Primary diagnosis is based on:
    - Classic symptoms of opioid overdose
      - Respiratory depression, often accompanied by central nervous system depression and miosis
    - Responsiveness to naloxone
- Laboratory
  - Urine toxicology tests [14]
    - Screen for acetaminophen levels
    - Do not rely on toxicology screens for the initial management of suspected opioid overdose
    - A positive screen for opioids does not confirm toxicity
    - While positive toxicology results can indicate the presence of opioids, negative results do not necessarily mean absence of opioids
      - Some opioids such as fentanyl may not be detectable using typical toxicology screening methods
- Imaging
  - Obtain chest radiographs in opioid-toxic patients with rales or hypoxia to evaluate for pulmonary edema or aspiration pneumonia
- Functional testing
  - ECG can be used to monitor bradycardia [14]
  - QTc prolongation is noticed in some patients receiving methadone (which typically increases the QTc by 12 milliseconds), increasing the chance of developing a ventricular arrhythmia, particularly torsades de pointes [15]
    - Doses above 100 mg daily produce a dose-dependent QTc prolongation
      - Regular monitoring of the QTc is recommended for patients receiving therapy with methadone
    - QTc prolongation may also occur with loperamide toxicity [16]

DIFFERENTIAL DIAGNOSIS

- Most common
  - Clonidine and oxymetazoline toxicity (particularly in pediatric patients)
    - Both drugs are centrally acting α-1 blocking agents that cause depressed mental status, bradycardia, hypotension, and miosis
    - Partial response to naloxone is common
      - No easy or consistent way to differentiate from opioid toxicity
      - Urine test for these drugs is typically only available at reference laboratories
        - Results will not change management of patient
    - Most children with clonidine or oxymetazoline toxicity will be treated as opioid toxic and vice versa
  - Acute subdural hematoma [14]
    - Common presentation is depressed mental status
    - CT scan results differentiate pure opioid toxicity from subdural hematoma

- Other central nervous system depressant toxicity (eg, alcohol, barbiturate, benzodiazepine, cannabinoid)[17]
  - Cannot differentiate easily by symptoms alone
  - Differentiate by ineffectiveness of naloxone
    - Combined with quantitative alcohol serum levels, narrows diagnostic considerations
- Meningitis and encephalitis
  - Present with confusion and depressed mental status
    - Additional symptoms include headache, vomiting, and fever
  - No response to naloxone
  - Differentiate by CT scan result revealing meningeal inflammation and lumbar puncture showing evidence of infection
- Hypoglycemia
  - Presents with confusion and depressed mental status
  - Differentiate using a bedside blood glucose test and response to oral glucose ingestion

TREATMENT

GOALS

- Reverse opioid toxicity
  - Treat with reversal agent
  - Secure airway
  - Restore respiratory status
  - Reverse central nervous system depression
- Avoid precipitating withdrawal

DISPOSITION

- Admission criteria
  - Respiratory depression
    - Occurs after nonresponse to naloxone or during resedation after naloxone wears off
    - May be accompanied by stupor and hypotension
    - Admit children aged 3 years or younger exposed to opioids other than immediate-release formulations for 24-hour observation if ingestion of agents is suspected from history but cannot be confirmed[18]
  - Criteria for ICU admission[1, 19]
    - Patients whose toxicity is due to long-lasting and extended-release opioids
      - Long-lasting and extended-release opioids cause resedation after naloxone wears off
      - Patients require prolonged observation for respiratory depression and airway compromise
    - Patients who require a naloxone infusion
    - Patients with respiratory problems who require orotracheal intubation
- Recommendations for specialist referral
  - Refer to medical toxicologist for specialty management of opioid toxicity
  - Refer to pain or addiction specialist to prevent recurrence and treat addiction

TREATMENT OPTIONS

- First priority is to restore respiration using a bag-valve mask or orotracheal intubation if necessary[1]
- Drug treatment is the same regardless of causative opioid
  - Naloxone therapy is the standard treatment for opioid toxicity[1]
  - Naloxone prescriptions or access to OTC naloxone is an important treatment option for high-risk individuals
- Drug therapy
  - Naloxone[1]
    - Dose is empiric and depends on the amount of opioid the patient received or has taken
    - IV administration is most common and preferable method of delivery
      - IV naloxone continuous infusion is difficult and has several drawbacks
        - Difficult to titrate adequate dose to maintain adequate respiration but avoid withdrawal
          - Recommended infusion strategy of hourly dose to match dose required to reverse apnea has not been validated
        - Relying on an IV infusion of drug to maintain ventilation
          - IV catheters can become kinked, be pulled out, or become otherwise dysfunctional
        - Patients still require ICU admission for monitoring
    - Intramuscular, intranasal, or pulmonary administration should be used when IV is not an option
    - Oral administration is not recommended because of high first-pass metabolism rate of drug
    - Patient should be observed for 4 to 6 hours before discharge is considered[20, 21]

- Toxic effects often reappear within 30 minutes, requiring further naloxone because of its short half-life
- A gradual titration in naloxone dose is preferential to isolated larger doses to avoid withdrawal
- Opioids that require larger doses of naloxone [20]
  - Natural opium derivatives
    - Codeine
    - Methadone
  - Synthetic opiates
    - Diphenoxylate
    - Propoxyphene
  - Mixed opioid agonist-antagonists
    - Pentazocine
    - Butorphanol
    - Nalbuphine
- Intermittent Intravenous, Intramuscular, Subcutaneous, or Intraosseous dosage (standard syringe):
  - Naloxone Hydrochloride Solution for injection; Neonates: 0.1 mg/kg/dose IV/IM is recommended in clinical guidelines; may require repeated doses. FDA-approved labeling recommends 0.01 mg/kg/dose IV, IM, or subcutaneously initially; may repeat every 2 to 3 minutes.
  - Naloxone Hydrochloride Solution for injection; Infants and Children younger than 5 years or weighing 20 kg or less: 0.1 mg/kg/dose IV/IO (PALS recommendation); may require repeated doses. FDA-approved labeling recommends 0.01 mg/kg/dose IV, IM, or subcutaneously initially; may repeat every 2 to 3 minutes.
  - Naloxone Hydrochloride Solution for injection; Children and Adolescents 5 to 17 years or weighing more than 20 kg: 2 mg IV/IO (PALS recommendation); may require repeated doses. FDA-approved labeling recommends 0.01 mg/kg/dose IV, IM, or subcutaneously initially; may repeat every 2 to 3 minutes.
  - Naloxone Hydrochloride Solution for injection; Adults: 0.4 to 2 mg IV, IM, or subcutaneously, up to a total dose of 10 mg; doses may be repeated every 2 to 3 minutes PRN. In emergency settings, guidelines recommend 0.4 to 2 mg IV; alternatively, 0.4 to 0.8 mg may be given IM/subcutaneously if systemic perfusion is adequate.
- Endotracheal dosage:
  - Naloxone Hydrochloride Solution for injection; Infants and Children younger than 5 years or weighing 20 kg or less: Optimal ET dosage has not been determined; a dose of 2 to 3 times the IV dose has been recommended (equivalent to 0.2 to 0.3 mg/kg/dose ET).
  - Naloxone Hydrochloride Solution for injection; Children and Adolescents 5 to 17 years or weighing more than 20 kg: Optimal ET dosage has not been determined; a dose of 2 to 3 times the IV dose has been recommended (equivalent to 4 to 6 mg/dose ET).
  - Naloxone Hydrochloride Solution for injection; Adults: Optimal ET dosage has not been determined. In emergency settings, guidelines recommend 0.4 to 2 mg via ET tube.
- Intranasal dosage (Narcan nasal spray):
  - Naloxone Hydrochloride Nasal spray, solution; Adults, Adolescents, Children, Infants, and Neonates: 1 spray (2 mg or 4 mg of naloxone) by intranasal administration. Seek immediate medical attention after administration of the first dose. May repeat dose in alternate nostrils every 2 to 3 minutes as needed; each device contains a single dose. Monitor closely until emergency medical personal arrive; continue to monitor pediatric patients for at least 24 hours.
- Continuous Intravenous or Intraosseous Infusion dosage:
  - Naloxone Hydrochloride Solution for injection; Neonates, Infants, Children, and Adolescents: Limited data available. If repeated intermittent doses are required, calculate initial infusion rate based on effective intermittent dose; use two-thirds up to the full intermittent dose as initial hourly infusion rate (i.e., if a 0.02 mg/kg IV dose was effective, initiate infusion at 13 to 20 mcg/kg/hour [0.013 to 0.02 mg/kg/hour]). Titrate as needed. A continuous infusion rate of 2 to 160 mcg/kg/hour IV/IO has been suggested; however, most reports have utilized 24 to 44 mcg/kg/hour IV. When appropriate, wean in 25% increments while closely monitoring patient.
  - Naloxone Hydrochloride Solution for injection; Adults: Loading dose of 0.005 mg/kg IV followed by 0.0025 mg/kg/hour IV.

- Naloxone can precipitate withdrawal symptoms including: [22]
  - Anxiety, irritability, and restlessness
  - Gooseflesh
  - Hot and cold sweats
  - Muscle, bone, and joint aches
  - Tremor
  - Nausea, vomiting, and diarrhea
  - Increased resting pulse rate

- Nondrug and supportive care
  - For apnea of fewer than 12 breaths per minute [1]
    - Provide ventilation with a bag-valve mask
    - Perform chin-lift and jaw-thrust maneuvers to diminish hypercarbia
  - Procedures
    - Orotracheal intubation [1]
      - General explanation
        - Insertion of a tube into the trachea to restore respiration
        - Safely ensures oxygenation and ventilation while providing protection against aspiration
      - Indication
        - To gain definitive control of the airway to restore respiration
- Special populations
  - Children
    - Overdose characterized by: [1]
      - Unexpectedly severe poisoning based on dose received
      - Prolonged toxic effects
    - Admit children aged 3 years or younger exposed to opioids other than immediate-release formulations for 24-hour observation if ingestion of agents is suspected from history but cannot be confirmed [18]
    - Children who ingest opioids may require larger doses of naloxone because they often ingest a higher dose than adults per kilogram of body weight [1]
  - Elderly
    - Age-related changes in physiology and body composition may cause persistent intoxication [1]

MONITORING

- For patients with opioid toxicity, monitoring of respiratory adequacy and cardiovascular stability is mandatory
  - Pulse oximetry or end-tidal CO_2 monitoring to monitor respiration
  - Periodic (every 15 minutes) blood pressure monitoring to assess for hypotension

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS

- Respiratory depression and apnea
  - Apneic patients who receive naloxone frequently develop noncardiogenic pulmonary edema [1]
- Central nervous system depression with airway compromise
  - Vomiting can result in aspiration of gastric contents into the lungs
- Head trauma or brain injury due to falls related to loss of consciousness
- Multiple complications can occur secondary to prolonged hypotension, bradycardia, and hypothermia
- Death may occur in severe cases

PROGNOSIS

- Recurrence is likely in patients with opioid abuse history [2]
- Mortality rate is 5.1 per 100,000 with opioid analgesics [23]

SCREENING AND PREVENTION

SCREENING

PREVENTION [24, 25]

- Reduce the following by educating doctors and implementing prescription drug monitoring programs:
  - Inappropriate prescription of opioid analgesics
  - Chronic prescription of opioids for acute pain
  - Prescription of high-dose opioid analgesics
- Use prescription and insurance data to screen and reduce opioid prescription for:
  - Persons seeking care from multiple physicians
  - Persons obtaining early refills
    - At risk of providing opioids to others
- Increase availability of opioid-dependence treatment, especially office-based medication-assisted treatment with buprenorphine/naloxone
- To decrease risk of death, distribute naloxone and promote education on its use in communities where opioid toxicity is likely
- Provide naloxone to patients receiving chronic opioid therapy, particularly those requiring higher doses, and train patient and family members in intranasal application when overdose is suspected

- Refer opioid abusing/dependent patients to Narcotics Anonymous or similar support programs
  - Inpatient and outpatient rehabilitation counseling is an important aspect of prevention

SYNOPSIS

KEY POINTS

- Opioid toxicity causes respiratory depression, generally accompanied by depressed consciousness and miosis
  - Diagnosis is made on these 3 primary symptoms, which may not always present together, paired with a positive response to naloxone
- Opioid toxicity is often coupled with ingestion of other substances, such as acetaminophen or ethanol
- Treatment involves restoration of respiration using a bag-valve mask or intubation (if necessary)
- Treatment with IV naloxone, a competitive opioid antagonist, is the gold standard reversal agent
- Continuously observe patients receiving naloxone because naloxone has a short half-life
  - Observation should be longer than expected elimination time for naloxone (minimum observation time 1-2 hours)
- Naloxone, while necessary, can cause withdrawal symptoms, which can be stressful to patients and caregivers; cautious titration to desired effect (reversal of respiratory suppression) is recommended
- Recurrence is likely in patients with opioid abuse history

URGENT ACTION

- First priority is to restore respiration
- If symptoms are present, begin treating with naloxone to reverse opioid toxicity; do not wait for urine drug screen or immunoassay results to confirm diagnosis
- Admit to ICU if patient is intoxicated by long-lasting opioids, has recurrent respiratory depression, requires naloxone infusion, or requires intubation

PITFALLS

- Naloxone can precipitate opioid withdrawal and is titrated for best effect
- Altered mental status should not be attributed to opioid toxicity solely based on positive drug screen results; the screen is qualitative not quantitative
- May present along with head trauma, which can hinder the restoration of consciousness

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