



Evidence-Based Analysis and Guideline Development of non-Naloxone Rescue Drugs for Opioid-Induced Respiratory Depression (OIRD)

George Sciple, RN, BSN, SRNA
Faculty Advisor: Dr. Tracy Walker, DNP, APRN, CRNA



Objective

- The purpose of this integrative research review (IRR) is to examine current published evidence regarding the use of non-naloxone rescue drugs for OIRD and assess whether non-naloxone drugs are a safe alternative to naloxone for reversing OIRD

Introduction

- The incidence of OIRD varies among the adult and pediatric surgical population with a reported incidence ranging between 0.5-2% in the adult population and 0.2-0.6% in the pediatric population (Boom et al., 2012; Donempudi, Sprung, and Weingarten, 2018)
- Although the reported incidence is low, OIRD contributes to higher morbidity and mortality rates in the postoperative setting
- Naloxone is a non-selective opioid receptor antagonist that acts by reversing the respiratory depressant effects of opioids while also reversing their analgesic properties
- The reversal of analgesia can be potentially detrimental in those patients who are opioid-dependent and/or in patients experiencing severe pain and/or stress following surgical and diagnostic procedures
- Naloxone has been the gold standard for reversing OIRD, but its administration has been associated with the following potential adverse side effects:
 - Dysthymias
 - Pulmonary edema
 - Seizures
 - Renarcotization
 - Cardiac arrest

Methodology

Databases searched: ScienceDirect, CINAHL, Ovid Medline, Gale General OneFile, Academic Search Complete, and PubMed. **Population Studied:** Adults and/or pediatric patients who experienced OIRD following diagnostic and/or surgical procedures who received Naloxone and/or non-Naloxone drugs for reversing and/or preventing OIRD. **Search Terms:** *opioid-induced respiratory depression, analeptics, respiratory stimulants, doxapram, ketamine, nalbuphine, pentazocine, butorphanol, naloxone, prevention, and reversal.* **Inclusion Criteria:** Publications between 2010-2020 in the English language that examined the incidence of OIRD and whether naloxone and/or non-naloxone drugs were used for reversal and/or prevention of OIRD. Outcomes following the administration of both Naloxone and non-Naloxone drugs were also studied. **Exclusion Criteria:** Articles published earlier than 2010, OIRD outside of the surgical/hospital setting and/or OIRD from neuraxial opioids, non-human subjects, and those in languages other than English. No exclusions were made based on age, gender, race-ethnicity.

Flow Diagram for Study Selection

Literature Search: Science Direct, CINAHL, Ovid Medline, Gale General OneFile, Academic Search Complete, and PubMed
Search Terms: *opioid-induced respiratory depression, analeptics, respiratory stimulants, doxapram, ketamine, nalbuphine, pentazocine, butorphanol, naloxone, prevention, and reversal*

Search Results Combined
(n=1,185)

Articles screened on basis of
Title and Abstract

Articles Excluded (n=1,167)
Written in foreign language: 154
Non-human subjects: 516
Duplicate: 27
Exclusion Criteria: 470

Articles Included (n=18)

Patient factors contributing to higher incidence of OIRD

- Obstructive Sleep Apnea
- Pediatric patients both underweight and/or overweight
- Extremes of Age
- Obesity
- Prematurity
- Developmental Delays
- COPD
- Gender (Females > Males)
- Cardiac Disease
- Neuromuscular Disorders
- Renal Disease
- Opioid-dependance
- Acute Illnesses
- Ingestion of other CNS depressants

Healthcare provider and/or independent factors promoting higher incidence of OIRD

- Type of opioid used and dosage
- Route of opioid administration
- Type and duration of surgical and/or diagnostic procedure
- Coadministration of other CNS and/or respiratory depressant medications in the preoperative and/or postoperative period such as midazolam and/or gabapentin
- Patient controlled analgesia with basal rate
- Inadequate monitoring by provider and/or nursing staff
- Poor handoff communication between anesthesia provider and nursing staff

Discussion

- Non-opioid adjuncts including but not limited to Ketamine, Doxapram, Almitrine, GAL-021, Esketamine, Buprenorphine, CX717, Minocycline, and Ampakines have been examined for their efficacy in preventing and/or reversing OIRD
- While some of these agents have been shown to be efficacious in preventing OIRD by creating an opioid-sparing effect, their action on reversing OIRD has been poorly studied due to inadequate human trials
- The reversal of analgesia and unwarranted withdrawal side effects can be lessened by administering small, incremental doses of Naloxone based on the patient's respiratory rate rather than their level of consciousness
- Patients who are highly opioid-dependent can experience withdrawal symptoms with Naloxone administration with doses as low as 0.08 mg (Kim & Nelson, 2016)
- One study referenced that buprenorphine appears to be a safe alternative to Naloxone for reversing OIRD from opioids with longer half lives. However, while buprenorphine has a reported ceiling effect for respiratory depression, it can still occur in patients with reduced physiological reserve such as the elderly population (Richards, Torre, & Lawther, 2018; Zamani, Buckley, and Hassanian-Moghaddam, 2020)
- Additionally, buprenorphine has a high affinity and slow receptor dissociation so in the event respiratory depression does occur, high doses of naloxone are required for adequate reversal (Richards, Torre, & Lawther, 2018). Thus, the potential for adverse side effects reported with high-dose Naloxone can occur including but not limited to cardiac dysrhythmias, pulmonary edema, seizures, and even death

Conclusion and Anesthetic Implications

- While studies have revealed that there are agents showing promising results for reversing and/or preventing OIRD, multiple studies have suggested that further studies are needed due to their limited use in clinical trials
- For those agents that have shown efficacy in reversing and/or preventing OIRD, their side effect profile has either halted their use in clinical practice or are rarely used by clinicians
- Naloxone, when given in lower doses and titrated to respiratory effect, appears to be the safest and most reliable method for reversing OIRD
- Patients with preexisting comorbidities that places them at higher risk for developing OIRD should be vigilantly monitored, and the use of non-opioid adjuncts should be considered to lessen the likelihood of developing OIRD

References

All references available upon request