

Pharmacotherapeutic Challenges in Weaning from Mechanical Ventilation

a report by

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The advent of mechanical ventilation as a necessary therapeutic intervention has revolutionized respiratory care medicine. Mechanical ventilators have evolved from providing rudimentary respiratory controls to microprocessor-controlled devices integrating flow rate and pressure waveform dynamics to optimize pulmonary gas exchange. Based on advances in mechanical ventilation, patient survival has improved, but not without a financial burden on overall healthcare expenditure. Dasta et al.¹ performed a retrospective cohort analysis of more than 51,000 patients from 253 US hospitals. The results determined the mean intensive care unit (ICU) cost and length of stay as \$31,574–42,570 and 14.4–15.8 days for patients requiring mechanical ventilation versus \$12,931–20,569 and 8.5–10.5 days for patients not requiring mechanical ventilation. The mean incremental cost of mechanical ventilation was \$1,522 per day ($p < 0.001$). This high cost of healthcare expenditure requires ICU clinicians to aggressively implement ventilator weaning strategies to decrease days of mechanical ventilation and ICU stay. Factors that influence successful ventilator weaning include:

- pulmonary status, including infection;
- respiratory muscle strength;
- neurological and nutritional status;
- presence of anemia;
- hemodynamic status;
- acid-base abnormalities; and
- severity of critical illness and drug administration.

Discussions about ventilator weaning are traditionally focused on the ventilator and its modes and setting adjustments to achieve a successful outcome. Ventilator weaning incorporating a pharmacotherapeutic component is equally important because of the relationship many drugs have on inhibiting spontaneous ventilation.

Virtually all patients admitted to the ICU requiring mechanical ventilatory support will require concurrent pharmacotherapy to treat a variety of conditions. The challenge to clinicians is to navigate through the information describing common pharmacotherapeutic agent usage and to determine optimum selection. Common end-points described in the literature for therapeutic decision-making include appropriate use, adverse effect profile, and impact of guidelines on cost reduction.^{2–4} Clinicians must balance their expertise of ventilator mode and setting adjustments with knowledge of the pharmacological properties of commonly used drugs to optimize mechanical ventilator weaning outcomes. Patients demonstrating acute agitation, including the inability to synchronize their breathing pattern with the ventilator, often receive pharmacological intervention as the first therapeutic option, and agents traditionally administered include:

- narcotic analgesics (morphine, hydromorphone, fentanyl);
- benzodiazepines (lorazepam, midazolam, diazepam);
- anesthetics (propofol);
- α_2 adrenergic agonists (dexmedetomidine); and
- antipsychotics (haloperidol, quetiapine, olanzapine, ziprasidone, and risperidone).

Neuromuscular blocking agents (NMBAs), including vecuronium, pancuronium, atracurium, and cisatracurium, are reserved for the most critically ill patients, but are generally indicated to facilitate mechanical ventilation, manage increased intracranial pressure, treat muscle spasms, and decrease oxygen consumption. To facilitate weaning from mechanical ventilation, NMBA infusions must be slowly titrated and discontinued to allow for spontaneous ventilation and respiratory muscle conditioning. Based on clinical consensus and expert opinion, NMBA use should be limited and used only as a last resort to manage ventilator patients, and thus will not be discussed in this paper. Clinical practice guidelines are available that provide a more detailed description than is provided here.⁵ Narcotic analgesics, sedatives, antipsychotics, and NMBAs may depress respiratory drive, potentially resulting in direct effects on ventilator weaning outcomes. Each agent has advantages and disadvantages based on pharmacokinetic and pharmacodynamic properties, hemodynamic effects, and duration of analgesic, sedative, amnestic, deleterious, and paralytic responses. Considerations for drug selection, dosage, and dose titration to optimize pharmacological response while minimizing oversedation include: accurate patient assessment (pain, anxiety, delirium); assessment of comorbid disease states, including hepatic and renal dysfunction to limit active metabolite effects; hemodynamic instability; patient age, weight, and medical or surgical condition; potential for drug–drug and drug–disease interactions; and ventilatory goals. The use of analgesics, sedatives, antipsychotics, and NMBAs for patients receiving mechanical ventilation requires a multidisciplinary team of physicians, clinical pharmacists, critical care nurses, and a respiratory therapist. A primary goal of the critical care team is to develop, implement, and access a pre-printed order set, or develop guidelines or protocols using these pharmacological agents to set a standard of care within their critical care environments.⁶ This review will focus on pharmacotherapeutic agents traditionally administered to mechanically ventilated adult patients, and discuss the potential role these agents may have on ventilator weaning.

Analgesia

Mechanically ventilated patients often experience pain and discomfort from multiple sources including surgery, trauma or illness, invasive device insertion, diagnostic procedures, and routine nursing care. Narcotic analgesics are required to maintain patient comfort and acceptance of mechanical

ventilation. Narcotic analgesics primarily interact with the μ and κ opioid receptors, which are required for analgesia. Morphine sulfate is a phenanthrene-derivative opiate agonist that is considered the 'gold standard' compared with other narcotic analgesics. Repeated higher intermittent doses or prolonged exposure to continuous infusion may induce respiratory depression, including decreases in respiratory rate, tidal volume, and minute ventilation, thus inhibiting, delaying, or potentially causing a patient to fail ventilator weaning. Morphine is metabolized via the glucuronidation pathway, resulting in the development of multiple active metabolites, including morphine-6-glucuronide (M6G). M6G is approximately 1.5:1 more potent than morphine administered subcutaneously or intravenously, and may accumulate in patients with renal dysfunction.^{7,8} Morphine also produces significant sympatholytic activity and may produce hypotension and vagally mediated bradycardia in euolemic patients.⁹ Hydromorphone is a piperidine derivative metabolized via the glucuronidation pathway, lacking the production of an active metabolite and histamine release. Hydromorphone would be an optimum therapeutic choice for patients who are intolerant to morphine experiencing hemodynamic instability or renal insufficiency.

Fentanyl is a synthetic phenylpiperidine-derivative opioid. Based on its unique pharmacodynamic profile, clinicians consider this agent to have the quickest onset of effect, shortest duration of action, and the fastest recovery time. Fentanyl is metabolized via the oxidative pathway, lacking the production of an active metabolite. Fentanyl is the preferred agent for patients who are intolerant to morphine and require rapid analgesic control. Due to its lack of histamine release, fentanyl is also preferred for patients experiencing hemodynamic instability or renal insufficiency. Meperidine, also a phenanthrene-derivative opioid similar to morphine, is not as potent and is associated with shorter duration of analgesia. Meperidine is metabolized via the demethylation and hydroxylation pathway, resulting in the formation of an active metabolite, normeperidine. Normeperidine may accumulate in patients with renal insufficiency, producing significant neuro-excitatory sequelae, including seizures, tremors, and delirium.^{10,11} Meperidine is not recommended for chronic analgesia or as an adjunct to sedation for the mechanically ventilated patient.¹⁰

Sedation

Mechanically ventilated patients experience anxiety due to factors such as:

- underlying medical illness;
- endotracheal intubation;
- continuous stimuli from mechanical alarms;
- inability to communicate;
- nursing and healthcare practitioner interventions; and
- sleep deprivation.

Sedation is often required during mechanical ventilation to maintain patient safety and comfort and to optimize acceptance and synchrony of mechanical ventilation. Sedation of the mechanically ventilated patient should be initiated only after adequate analgesia is provided. Optimal sedation end-points have been achieved with the successful integration of common sedation scales including the Ramsay Sedation Scale, the Motor Activity Assessment Scale, and the Riker-Sedation Agitation Scale,¹²⁻¹⁴ although no scale has demonstrated superiority for patient assessment. Clinicians agree that one scale should be used to assess sedation in their ICU setting, and periodic quality assessment should be conducted to achieve sedation goals within their institution.

Benzodiazepines

Benzodiazepines are considered the pharmacological treatment of choice for sedation. Common agents administered to the mechanically ventilated patient include midazolam, lorazepam, and, to a lesser degree, diazepam. The mechanism of action of benzodiazepines is inhibition of gamma-amino-butyric acid, thus producing sedative, anterograde amnesia, and hypnotic properties. Benzodiazepines differ in potency, onset and duration of effect, metabolism, excretion, formulation, and formation of active metabolites. Midazolam is a short-acting benzodiazepine metabolized via the oxidation pathway, resulting in the formation of alpha-hydroxymidazolam or its conjugated salt.¹⁵ The potential result is accumulation and excessive sedation in patients with renal dysfunction. Drugs metabolized by the cytochrome P450 3A4 isoenzyme system, including propofol, diltiazem, conivaptan, and macrolide antibiotics, have been associated with an increased duration of the midazolam effect.¹⁶⁻¹⁸ The benzodiazepine midazolam is considered the first choice for patients experiencing acute agitation where immediate control of the patient is required. During continuous infusion, midazolam is recommended for patients who may require ventilator support for 48-72 hours due to unpredictable awakening and time to extubation.¹⁹ The prolonged effects of midazolam are also associated with hypoalbuminemia and higher volume of distribution, which are both common in the ICU patient.

Lorazepam is metabolized via the oxidative hepatic pathway, resulting in the absence of active metabolites, and has potential for fewer drug-drug interactions. Lorazepam is recommended for patients likely to require prolonged mechanical ventilation, primarily due to its intermediate pharmacological half-life. Unique to lorazepam is its formulation, which includes solvents of propylene glycol and polyethylene glycol. Both solvents have been identified in causing metabolic and lactic acidosis and hyperosmolar state when lorazepam has been used for continuous sedation. Lorazepam doses >18mg/hr for longer than four weeks and in patients with compromised renal function (creatinine clearance <30ml/min) have been identified as risk factors for glycol toxicity.^{20,21} Diazepam is metabolized by demethylation and hydroxylation, resulting in the development of an active metabolite. Diazepam demonstrates rapid onset of effect and limited duration of effect with a single dose. Diazepam usage in the ICU has declined due to advantages of midazolam and lorazepam over diazepam, including the ability to administer both agents as a continuous infusion, shorter pharmacological half-life, and better predictability of pharmacodynamic and pharmacokinetic response. Gesin et al.²² recently performed a prospective, observational study evaluating the use of diazepam, usually administered enterally, as an adjunctive treatment to intravenous lorazepam in 12 mechanically ventilated critically ill trauma patients. Of the 1,077 sedation-agitation scale (SAS) assessments, the mean percent of time with an SAS of 1-2, 3-4, and 5-7 during oral diazepam therapy was 10, 74, and 19%, respectively. No adverse drug events were identified, and no patient required re-intubation due to excessive sedation.

Propofol

Propofol is an intravenous general anesthetic that is used for induction and maintenance of anesthesia, or sedation of the mechanically ventilated patient. Propofol metabolism is via hepatic conjugation, resulting in the absence of active metabolites. Carson et al.²³ evaluated intermittent lorazepam versus propofol with daily sedation interruption in mechanically ventilated patients. Median ventilator days were lower in the daily interruption propofol group compared with the lorazepam group (5.8 versus 8.4; $p=0.04$). Cautions about propofol include hypotension during bolus dosing, risk of nosocomial

infections, and avoidance in patients with severe allergies to eggs, lecithin, soybean, or milk due to its lipid formulation. Propofol has been associated with the development of pancreatitis and requires periodic monitoring of serum triglycerides. Propofol infusion also requires nutritional considerations since the formulation contains approximately 1.1kcal/ml of lipids. Propofol is recommended for sedation in which immediate control is required, or in patients likely to require ventilator support for approximately three days due to its ultra-short half-life.¹⁹

Alpha₂ Adrenergic Agonists

Dexmedetomidine

Dexmedetomidine is an alpha₂ adrenergic receptor agonist that exhibits sedative, analgesic, sympatholytic, and anxiolytic effects without depressing respiratory drive.²⁴ The agent is indicated for continuous infusion (<24 hours) for sedation of initially mechanically ventilated patients. Dexmedetomidine is metabolized via hepatic glucuronidation and cytochrome P isoenzyme 2A6 (CYP2A6), resulting in no active metabolites. Siobal et al.²⁵ evaluated dexmedetomidine to facilitate withdrawal of mechanical ventilation and extubation of five difficult-to-wean trauma/surgical ICU patients, who were either discontinued or maintained on limited narcotic analgesia or sedative agents during dexmedetomidine infusion. Dexmedetomidine infusion was titrated between 0.2 and 0.7mcg/kg/hr to maintain hemodynamic stability and Ramsay Sedation Scale score between 2 and 4. Following dexmedetomidine, propofol infusion was discontinued in four patients, and ventilatory support in all patients was weaned to a continuous positive airway pressure of 5cm H₂O without agitation, hemodynamic instability, or respiratory depression. Dexmedetomidine appeared to maintain adequate sedation without untoward effects on hemodynamics or respiratory drive depression. Dasta et al.²⁶ performed a retrospective observational study evaluating adults receiving dexmedetomidine as part of routine patient care in an ICU. Ten sites from eight states were recruited to participate in the study. The top three reasons for prescribing dexmedetomidine were to assist in weaning from mechanical ventilation (53%), reduce use of narcotic and other sedative drugs (42.6%), and maintain patient alertness (25%). Approximately 60% of patients continued to receive dexmedetomidine following extubation for an average of 11.3 hours.

Based on patient disease variability and requirements, there is no universally accepted protocol or strategy to initiate or wean patients receiving mechanical ventilation off narcotic analgesics or sedatives. Optimally, patients should be initiated with scheduled doses over an 'as needed' dosing regimen to optimize sedation and analgesia. If the patient requires frequency of dosing more often than every two hours, a continuous infusion of either or both agents may be required. After optimum sedation and analgesia is achieved, a generally accepted rule for weaning both classes of agents during continuous infusion is

to decrease the infusion by 10–25% per day, with periodic bolus dosing for breakthrough pain or agitation.¹⁹ Based on impending removal of mechanical ventilation, many clinicians advocate sedation interruption or temporary discontinuation of all narcotic analgesics and sedative agents. Kress et al.²⁷ first documented the impact of daily sedation interruption on patient outcomes. A total of 150 patients were randomly assigned to a sedation interruption group or control group, which was managed by standard practice. The median length of mechanical ventilation was 4.9 days in the sedation interruption group compared with 7.3 days in the control group (p=0.004), and the median length of stay in the ICU was reduced by 3.5 days in the sedation interruption group versus control (6.4 versus 9.9 days; p=0.02).

Delirium

Delirium, which is associated with a change in mental status or disorganized thinking, occurs in 87% of patients admitted to an ICU.²⁸ The *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM IV) criteria are the standard of care for diagnosis of delirium, but the Confusion Assessment Method for the ICU (CAM-ICU) is often utilized by non-psychiatric professionals. The CAM-ICU is used due to its simplicity, accuracy, and convenience. Critical care nurses can complete the CAM-ICU in an average of two minutes with 98% accuracy.¹⁹ If a CAM-ICU score is not used for the assessment of delirium, patients may be inadvertently administered repeated doses of sedatives or analgesics for treatment of agitation. The potential result is increased agitation, confusion, or respiratory depression. Ely et al.²⁹ performed a prospective cohort studying 275 consecutive mechanically ventilated patients admitted to adult medical and coronary ICUs in a US university medical center. Patients who developed delirium had higher six-month mortality rates (34 versus 15%; p=0.03) and spent 10 days longer in the hospital than those who did not develop delirium (p<0.001). Common drug-therapy options for the treatment of delirium in the mechanically ventilated patient include haloperidol, olanzapine, quetiapine, ziprasidone, and risperidone. Although data support the success of these agents for the treatment of delirium, we are not aware of any data evaluating the effects of these agents on ventilator weaning outcomes.

Conclusion

The use of analgesics, sedatives, antipsychotics, and NMBAs agents during mechanical ventilation weaning is challenging to ICU clinicians. Optimizing use requires understanding the full pharmacological profile of these drugs and a daily ventilator plan understood by all healthcare providers involved with the care of the patient. Daily dosage minimization or a 'drug holiday' should be attempted in patients receiving continuous infusions of narcotic analgesics, benzodiazepines, propofol, or NMBAs to optimize synchronization with mechanical ventilation and enhance spontaneous breathing. More prospective, randomized clinical trials evaluating the use of analgesics, sedatives, antipsychotics, and NMBAs on ventilator weaning outcomes are required. ■

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