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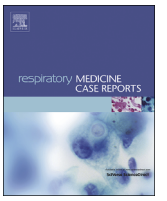

Case Report

Octreotide as a novel agent for the management of bronchorrhea in mechanically ventilated patients: A case series and review of literature

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ABSTRACT

Excessive bronchial secretions pose a challenge in mechanically-ventilated patients and may prolong the time to extubation, increasing the risk for pneumonia. Octreotide, a somatostatin analog, has been used to decrease bronchial secretions especially for the symptomatic management of patients with lung cancer. We describe three patients in the form of a case series and discuss effect of octretotide on bronchial secretions and management of bronchorrhea in the intensive care unit. Similar to reports of its utilization in palliative care in patients with lung cancer, we observed a clinically significant decrease in the rate of bronchial secretions.

Keypoints

1. Question: To study the effectiveness of octreotide for the management of bronchorrhea.
2. Findings: Significant decrease in rate of bronchial secretions was observed with use of octreotide in mechanically ventilated patients.
3. Meanings: Need for further investigation of octreotide's effectiveness in clinical trials.

1. Introduction

Bronchorrhea, arbitrarily defined as voluminous nonpurulent watery sputum production greater than 100ml/day, can be associated with lung malignancies, infectious causes (tuberculosis), and bronchiectasis [1]. Bronchial gland hypertrophy associated with smoking may also increase the risk of bronchorrhea [2]. An abundance of secretions can be a challenge during mechanical ventilation, as it can lead to complications such as atelectasis, pneumonia, and difficulty in oxygenation, which can lead to prolonged intubation. Minimal secretions and the ability to maintain airway patency are important considerations before deciding to extubate a patient [3]. Traditional therapies for the treatment of bronchorrhea are limited: the most widely used class is varying doses of corticosteroids; however, the use of anticholinergics, mucolytics, inhaled indomethacin, erythromycin, octreotide, epidermal growth factor receptor tyrosine kinase inhibitor (gefitinib and erlotinib) has also been described [4]. We describe our experience with the use of octreotide, a somatostatin analog for the management of bronchorrhea in mechanically ventilated patients.

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In this case series, we report on three patients who participated in the treatment arm of a randomized control study. The study was open-label and conducted at a single center, with patients who were being weaned from mechanical ventilation and had excessive bronchial secretions (more than 100 ml per 12-h shift), making extubation challenging. Patients who had an increased risk of side effects from octreotide use (persistent bradycardia, Mobitz type II or third-degree heart block, hypertensive urgency or emergency requiring intravenous agents, and cardiac surgery patients) or had started anticholinergic or corticosteroid therapy (inhaled or systemic) within 72 hours before enrollment, were excluded from the study. The intervention group received an octreotide drip (for up to 72 hours at a rate of 12–25 mcg/h) in addition to the standard of care, while the control group only received the standard of care for bronchial secretion management. The primary outcome was measured as the change in bronchial secretion rate from baseline, calculated by subtracting the volume of saline flushes from the total volume in the bedside suction container. As the study had to be discontinued due to low enrollment, we present our results as a case series that highlights our experience with patients in the intervention group.

2. Description of cases

Patient 1: 61-year-old male with a history of chronic kidney disease, mitral regurgitation, and chronic opioid use, presented from a rehabilitation facility with altered mentation, hypoxia, and hypotension. He was admitted to the intensive care unit (ICU) for bilateral pneumonia, worsening metabolic encephalopathy, septic shock, and acute respiratory distress syndrome necessitating mechanical ventilation, which was complicated by bronchorrhea. He was then started on an octreotide drip, and his 12-h bronchial secretion rate decreased from 100 ml to 50 ml; the patient was extubated after 66 hours on the octreotide drip.

Patient 2: 58-year-old man with a history of COPD and aortic valve replacement, presented with acute abdominal pain and distension, and was found to have abdominal wall hematoma and acute blood loss anemia. Subsequently, he developed hemorrhagic shock that required admission to the intensive care unit (ICU) and a massive transfusion. His course was complicated by acute lung injury (TRALI) and bacterial pneumonia requiring mechanical ventilation for respiratory failure, complicated by bronchorrhea despite continued treatment with systemic steroids (methylprednisolone), inhaled bronchodilators, and appropriate intravenous antibiotics. He was started on an octreotide drip, and the baseline bronchial secretion rate of 150 ml/12 hours decreased to 10 ml/12 hours. The patient was subsequently extubated while being transitioned to palliative care.

Patient 3: 54-year-old male with a history of hypertension and frequent hospital/ICU admissions for COPD exacerbations, admitted to the ICU with acute respiratory failure in the context of COPD exacerbation. The course in the ICU was complicated by ventilator-associated pneumonia. As the patient's condition improved, ventilator weaning was initiated. However, bronchorrhea presented as the main barrier to extubation, despite maximal therapy. Octreotide drip was initiated at 25 mcg/hour. Within several hours after octreotide initiation, a significant increase in blood pressure (from 120 to 185 mmHg systolic) was observed and attributed to an adverse reaction to octreotide, which was addressed by decreasing the octreotide infusion rate by 50%. As the patient's blood pressure normalized over several hours, the rate was titrated up. The bronchial secretion rate decreased over 48 hours, from the baseline rate of 150 ml/12 hours to 25 ml/12 hours. Octeotride drip was then stopped, and the bronchial secretion rate increased significantly over 24 hours. The octreotide drip was then re-started, and a decrease in the bronchial secretion rate that was similar to the first octreotide administration was observed, allowing for successful extubation after 48 hours.

3. Discussion

The removal of foreign particles and bacteria from the lungs is a function of the mucociliary system and the cough reflex [5]. There are various reasons for the retention of secretions in the ICU setting which include: epithelial damage from the endotracheal tube, lack of humidification, direct cough impairment, use of anesthetic agents, and consequences of critical illness like: inflammation, immobility, and atelectasis [5–8].

Mechanical ventilation (MV) is an indispensable tool for the treatment of critically ill patients. Excessive tracheo-bronchial secretions during MV cause a vicious cycle of mucus retention, difficulty oxygenation, and infection (ventilator-associated pneumonia) which prolongs the time to subsequent extubation, thus increasing morbidity and mortality. In a 2018 study by Jaber et al., copious secretions were found to be an important cause of airway-related extubation failure (OR 4.066 (2.268–7.292), $P < 0.0001$) [9].

Traditional therapies used for the treatment of bronchorrhea in the ICU include varying doses of systemic and inhaled corticosteroids, mucolytics (N-acetylcysteine, Dornase alfa, hypertonic saline), macrolide antibiotics, and anticholinergics. Cough augmentation with chest physiotherapy, assist devices, high-frequency chest wall oscillation, etc. Are also known treatment options. However, other modalities such as inhaled indomethacin, inhaled aerosolized antibiotics, octreotide and epidermal growth factor receptor tyrosine kinase inhibitor (gefitinib and erlotinib) (lung malignancy/EGFR mutations) have also been described [4,10–15].

Corticosteroids lead to inhibition of the gene encoding inducible cyclooxygenase, inhibition of glycoconjugate secretion, and inhibition of glycoprotein and chloride secretions, leading to decreased bronchial secretions. Indomethacin acts through a similar mechanism by blocking prostaglandin production by inhibiting COX-2, leading to subsequent inhibition of chloride secretion and glandular secretion. Erythromycin is assumed to decrease bronchial secretion by reducing chloride excretion and suppressing mucus secretagogues released from pulmonary macrophages [4,14,16]. Anticholinergics/muscarinic antagonists block muscarinic receptors on bronchial smooth muscles and exocrine gland cells in the bronchial airways. Mucolytics are further divided into two subgroups: classic and peptide respectively. N-acetyl cysteine is the prototype of the classic subtype and hydrolyzes the disulfide bonds attached to cysteine residues in the mucin polymers. The peptide mucolytics, for example, Dornase alfa, depolymerize the DNA polymers or F-actin network and thus reduce mucus viscosity [17].

Table 1
Patient characteristics.

Patient number	Duration of intubation prior to octreotide administration	Rate of octreotide drip (mcg/h)[a]	Duration of octreotide drip(hours)	Bronchial secretions rate change (ml/12 hours)	Smoking history
1.	12 days	12 » 24	66	100 » 50	Never-smoker
2.	46 hours	16 » 24	60	150 » 10	Former smoker
3.	10 days	24 » 12 » 24	48	150 » 25	Active smoker

[a] Up-titration was performed every 3 hours by 3–4 mcg/hour.

In this case series, we describe our experience using octreotide for the management of bronchorrhea which presented as a major barrier to extubation in mechanically-ventilated patients (Table 1). Octreotide is a somatostatin analog and functions as an anti-secretory drug by inhibiting the synthesis of pituitary and gastrointestinal hormones. It has been used in palliative care to manage nausea, gastrointestinal hemorrhage, ascites, and excessive secretions in the setting of fistula, excessive diarrhea, and malignant bowel obstruction. One of the hormones inhibited by octreotide is secretin-a potent stimulant of electrolyte and water movement in the gastrointestinal system. As the lungs also have secretin receptors [18], it has been suggested that inhibiting secretin reduces chloride and water efflux from bronchial epithelial cells, thus reducing sputum production [19]. Consistent with the proposed effect of octreotide on the secretory function of the bronchial epithelium, we observed a clinically significant reduction in the rate of bronchial secretions in all three patients (Table 1). Overall, octreotide is considered to be well-tolerated. We observed a significant increase in blood pressure after the initiation of the octreotide at the target dose in a patient with a history of hypertension. This side effect was not observed when the infusion was initiated at a lower rate and up-titrated. In addition to the favorable safety profile, octreotide has a relatively low cost ($20/day).

Previous reports of octreotide use for the management of bronchorrhea were primarily in patients with lung cancer [19,20]. Hudson et al. [19] described the successful treatment of bronchorrhea with octreotide in a patient with lung adenocarcinoma. The rate of sputum production was more than 1 L/day for which octreotide was started at 300 mcg over 24 hours via a subcutaneous syringe driver. Within 48 hours, the volume of sputum had decreased to 150 ml/day and the dose of octreotide was increased to 500 mcg, and the production of sputum completely subsided. No side effects were reported from the treatment. Pahuja et al. [20] described better control of bronchorrhea in a patient with bronchioalveolar cell carcinoma. The rate of sputum production was approximately 1 L/day even after treatment with bronchodilators, glycopyrrolate, guaifenesin, opioids, and steroids. She received octreotide at 12.5 mcg/h and within 24 hours, her secretion decreased to 150 mL/day, which decreased further over several days. The patient was continued on subcutaneously administered octreotide as an outpatient, with adequate control of her bronchial secretions.

4. Conclusion

We describe our experience with octreotide use for the management of bronchorrhea in mechanically-ventilated patients when it presented as a major barrier for extubation. Similar to reports of its utilization in palliative care in patients with lung cancer, we observed a clinically significant decrease in the rate of bronchial secretions. Hypertension, a possible adverse effect of octreotide, could be mitigated by starting infusion at a lower rate and subsequent up-titration. Although corticosteroids, anticholinergics, macrolides, and mucolytics continue to remain the cornerstone for the management of bronchial secretions, the effectiveness of octreotide use for the management of bronchorrhea in mechanically ventilated patients should be further investigated in controlled trials.

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Declaration of competing interest

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