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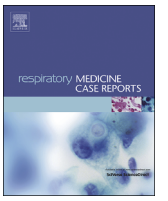

Case Report

Aviptadil: A multifaceted approach to mitigating hypoxemia in acute respiratory distress syndrome

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ABSTRACT

Acute Respiratory Distress Syndrome (ARDS) is a severe and potentially life-threatening lung condition that often leads to Intensive Care Unit (ICU) admissions. Treating ARDS in the ICU involves providing essential support for proper oxygenation and ventilation, often requiring mechanical ventilation using high positive end-expiratory pressure (PEEP) to recruit alveoli. Strategies like prone positioning and extracorporeal membrane oxygenation (ECMO) may be necessary for stubbornly low oxygen levels. Addressing the underlying cause, if known, and employing additional therapies to prevent complications are also integral parts of the management.

Despite advances in critical care, ARDS remains a formidable challenge with considerable risks of mortality and complications. Early recognition, immediate intervention, and comprehensive ICU care are pivotal in enhancing outcomes for ARDS patients. Ongoing research and clinical trials continue to explore innovative treatments and strategies to improve the prognosis of individuals with ARDS. In this series, we share our experience regarding the safe utilization of Aviptadil for treating ARDS arising from causes other than COVID-19.

1. Introduction

Acute Respiratory Distress Syndrome (ARDS) is a critical condition marked by severe respiratory failure, often necessitating mechanical ventilation. The epidemiology of ARDS is broad, with causes ranging from pneumonia and sepsis to trauma and inhalation injuries. The mechanisms underlying hypoxemia in ARDS typically involve one or more of the following factors: 1) surfactant deficiency-induced atelectasis, 2) epithelial damage resulting in a "shunt" effect, 3) endothelial damage leading to increased dead space ventilation, and 4) interstitial damage causing impaired gas diffusion. [1] Despite advancements in medical interventions, the prognosis in ARDS remains discouraging, and mortality rates are still very high. Conventional therapies, while providing life support, often fall short of addressing the underlying complexities of the syndrome. The quest for improved outcomes demands a shift towards unconventional solutions. In this context, we present a case series illustrating the successful application of Aviptadil in treating three instances of non-COVID-related moderate to severe ARDS. We turned to Aviptadil as an unconventional and last-resort measure. We recognize that Aviptadil does not represent a definitive therapy for ARDS but rather serves as an adjunct, and probably helps in buying valuable time until a more comprehensive and definitive treatment takes effect.

Aviptadil is a synthetic form of human vasoactive intestinal peptide (VIP) and theoretically appears to address all four hypoxemia mechanisms in ARDS. This is primarily achieved by restoring the function of damaged alveolar epithelial type 2 cells, leading to increased surfactant production and reduced shunting. Additionally, Aviptadil exerts anti-inflammatory actions that mitigate interstitial damage and enhance gas diffusion.

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The application of Aviptadil has been explored in a wide range of respiratory ailments, including asthma, chronic obstructive airway disease, cystic fibrosis, pulmonary hypertension, ARDS, and sarcoidosis. [2–7] Aviptadil, recognized for its positive impact on respiratory function, was designated as an 'Orphan Drug' by the USFDA in 2001 and by the EMA in 2006. [8,9] It also gained emergency approval from India's CDSCO in April 2022 for COVID-19 ARDS treatment. [10].

1.1. Case 1

A 38-year-old female with a history of diabetes presented at our hospital's emergency department after receiving a day of treatment at another medical facility. She had been experiencing fever and chills for a week. Over the past two days, she also suffered from shortness of breath and epistaxis. On examination, her respiratory distress was evident, necessitating high levels of oxygen support. A chest X-ray revealed bilateral lung infiltrates in the middle and lower zones. With a history of fever, epistaxis and thrombocytopenia (30,000/cu.mm), dengue fever was suspected. This suspicion was confirmed by positive dengue serology results from her tropical fever workup.

In the ICU, her condition deteriorated swiftly. Her oxygen requirements increased, respiratory distress worsened, and noninvasive ventilation (NIV) support proved ineffective. As a result, she was intubated and placed on mechanical ventilation with a FiO_2 of 0.5 and positive end-expiratory pressure (PEEP) of 8 cmH_2O. Prone ventilation was initiated as the patient had a PaO_2/FiO_2 (P/F) of less than 100 on FiO_2 0.8. A 2D echocardiogram indicated a normal ejection fraction of 55% and a normal-sized inferior vena cava with typical respiratory variation. A chest high-resolution computed tomography (HRCT) scan showed bilateral thickening of interlobular septa and ground glass opacities (GGO), primarily sparing the sub-pleural regions. She was ventilated employing lung protective techniques and recruitment maneuvers.

Due to her rapidly deteriorating respiratory condition, we administered Aviptadil after obtaining informed written consent from next of kin. Over three successive days, Aviptadil infusion was administered at increasing doses of 0.166, 0.332, and 0.498 mcg/kg/hour for 10 hours each. By the third day, there was a notable reduction in FiO_2 and PEEP requirements. By day 5, her condition had improved sufficiently to allow a transition from mechanical ventilation to NIV with a FiO_2 of 0.3. On day 10, she was transferred to ward and provided with 1–2 L per minute (LPM) of oxygen via nasal prongs. Her radiological images showed a progressive clearance of lung shadows, which corresponded to her clinical recovery (as shown in Fig. 1).

1.2. Case 2

A 24-year-old male patient, recently diagnosed with diabetes and hypertension, initially sought treatment at another medical facility 10 days before arriving at our emergency department. He had complained of abdominal pain, vomiting, and shortness of breath for the past 10 days. Initially diagnosed with severe community-acquired pneumonia and acute kidney injury (AKI), he underwent dialysis three times at the previous hospital before being transferred. Upon arrival in the ICU, the patient exhibited respiratory distress, agitation, and disorientation, necessitating NIV support with a FiO_2 of 0.7. The patient, however, remained hemodynamically stable. A recent HRCT done elsewhere revealed bilateral GGOs, with a CT severity scoring index of 20/25. Importantly, the patient

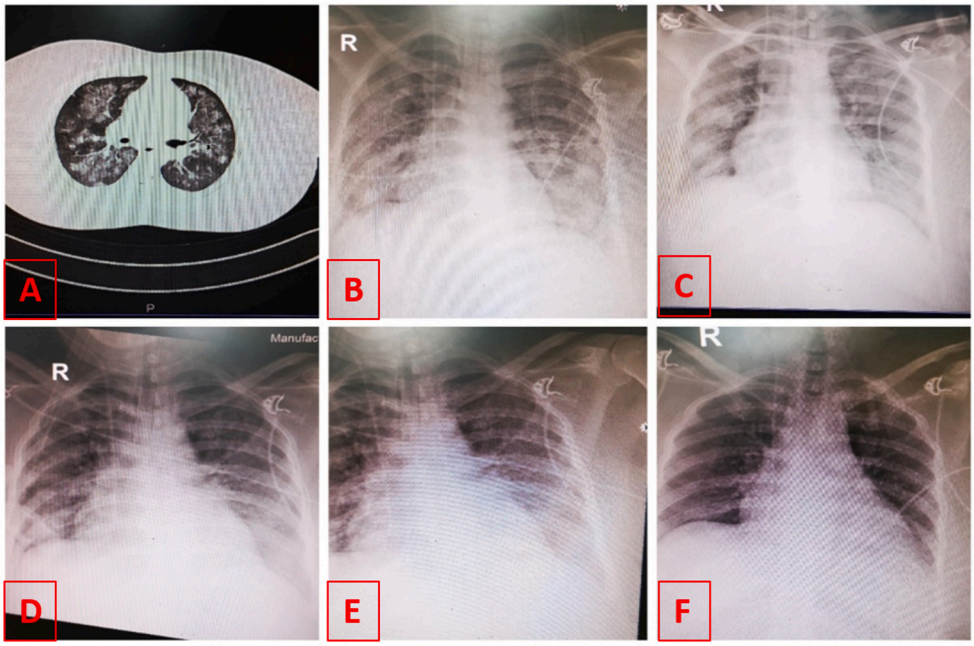

Fig. 1. Showing HRCT scan of case 1 (A), consecutive chest x-ray showing clearance from B to F.

tested negative for SARS-COV-2 (COVID-19). The patient was empirically started on injections of meropenem, teicoplanin, and clarithromycin.

The patient's condition rapidly deteriorated, leading to invasive mechanical ventilation within 24 hours of admission. A consultation with rheumatology specialists was initiated due to suspicion of Pulmo-renal syndrome, given the progressive AKI alongside lung abnormalities. Despite negative results from a respiratory Flu PCR test, the patient was started on steroids while awaiting further laboratory reports.

In spite of high PEEP and lung protective ventilation, the patient's FiO_2 requirement remained elevated, with a P/F ratio of 110. He did not show much response to prone ventilation. His family did not consent to Extracorporeal Membrane Oxygenation (ECMO) support. On day 2, as a desperate measure, Aviptadil infusion at a dose of 0.166 mcg/kg/hour for 10 hours was administered, concurrently with prone positioning. Escalating doses of Aviptadil (0.332 and 0.98 mcg/kg/hour) were administered during the next three days, accompanied by prone positioning. By day 6 (after 2 days of therapy), the patient's FiO_2 requirement decreased, and the patient was successfully extubated on day 9 of ventilation. This was accompanied by radiological improvement as well. Subsequently, the patient was transferred to a ward, receiving minimal oxygen support through nasal prongs and intermittent BiPAP assistance. Extensive rheumatology assessments did not yield any conclusive findings. Concurrently, the patient's AKI resolved, with creatinine levels returning to near-normal and acceptable urine output within the subsequent 2–3 days. A sequence of serial chest X-rays showcasing the improvement is depicted in Fig. 2.

1.3. Case 3

A 65-year-old man with a history of diabetes, hypertension, and coronary artery disease was admitted to our hospital due to symptoms of cough, mucus production, shortness of breath lasting for 4 days, and generalized body swelling for the past 15 days. Due to worsening breathing difficulties, the patient was moved to the ICU. An initial trial of NIV was attempted, but because the patient's respiratory condition continued to deteriorate, he required intubation on the same day. He was started on empirical antibiotics while awaiting definitive laboratory results. Bronchoalveolar lavage (BAL) PCR did not reveal any organisms. HRCT scan of the chest indicated findings consistent with ARDS. Initially, while on invasive mechanical ventilation in the prone position, the patient needed an inspired oxygen concentration (FiO_2) of 0.6 and had a P/F ratio of 110.

The patient's respiratory indicators showed improvement after receiving an Aviptadil infusion for three consecutive days. His P/F ratio increased to 200, and the required FiO_2 was reduced to 0.35. BAL culture showed a pan-sensitive *streptococcus pneumoniae*. The patient was extubated after four days of successful spontaneous breathing trials. He continued to receive oxygen support through HFNC and NIV for an additional two days before being transferred to a general ward with minimal oxygen supplementation through nasal prongs. The patient's radiological progress is shown in Fig. 3.

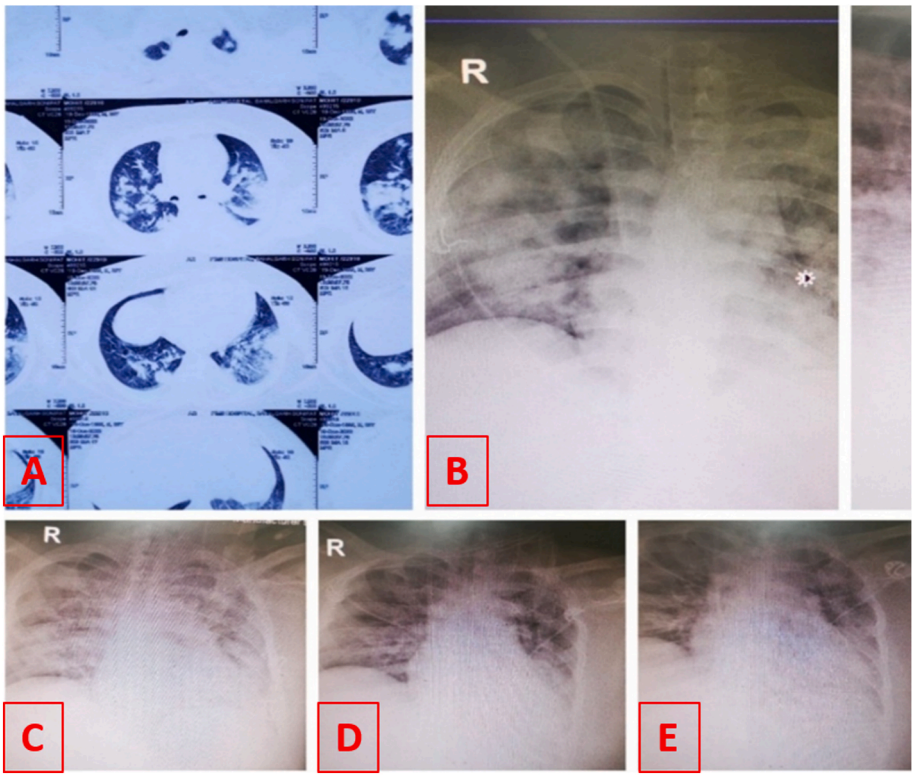

Fig. 2. HRCT scan of case 2 showing bilateral infiltrates (A) with successive clearance of shadows (from B to E).

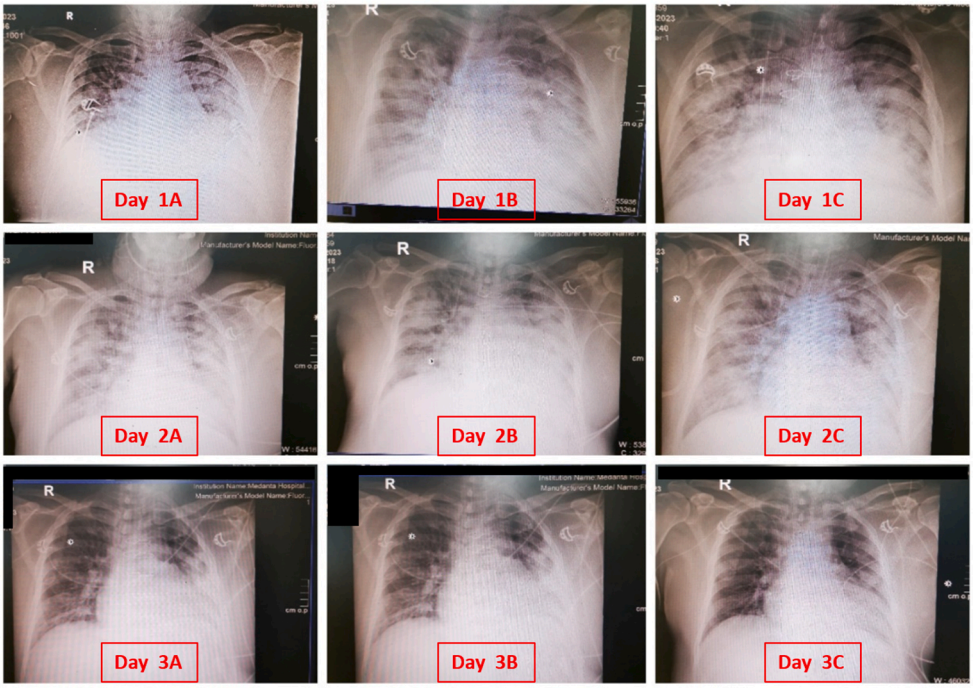

Fig. 3. Consecutive x-rays of case 3 starting from day 1 showing progressive clearance over 3 days of therapy.

No adverse effect was observed with Aviptadil in any of the patients.

2. Discussion

All discussed patients were managed in accordance with established standard-of-care protocols for ARDS, including sedation, neuromuscular blocking agents, proning, and lung-protective ventilation. Despite the diverse etiologies contributing to ARDS, ranging from infectious pneumonia to sepsis, Aviptadil demonstrated a beneficial effect in all of them. These benefits were achieved within the first week of Aviptadil treatment, clinically as well as radiologically. It allowed timely weaning, thereby preventing complications commonly associated with extended ventilatory support such as Ventilator-associated Pneumonia (VAP) or Ventilator-induced Lung Injury (VILI). However, it is important to emphasize that Aviptadil is by no means a panacea; rather, it serves as a supportive measure at best.

In 1970, Prof. Sami Said identified VIP, a molecule abundantly present in the alveoli (around 70%) and nasal mucosa, leading to a groundbreaking discovery. [11] Over the subsequent five decades, VIP's protective role in the lungs has gained significant recognition. VIP interacts with the VPAC1 receptor on Alveolar Type II (AT-II) cells [12], exerting anti-inflammatory effects [13]. It exerts its effects in the bronchoalveolar tissue through VPAC1 and VPAC2 receptors, as well as related receptors like pituitary adenylate cyclase-activating polypeptide. VPAC1 prevails in lung tissue and T lymphocytes, while VPAC2 is prominent in smooth muscle, mast cells, and lung mucosa. [14] VIP binds to VPAC1 receptors on AT-II cells, crucially contributing to surfactant production, [15] which maintains alveolar Type I epithelial cells. VIP further enhances surfactant production by boosting the expression of choline phosphate cytidylyl transferase, an enzyme vital for phosphatidylcholine synthesis—an essential component of pulmonary surfactant. Additionally, VIP prompts c-Fos protein and surfactant protein A expression in AT-II cells, amplifying surfactant production.

Aviptadil exerts several key effects on the lungs in the context of ARDS, a) *Anti-inflammatory action*: The effectiveness of Aviptadil was evident in its notable improvement of inflammatory markers, encompassing LDH, troponin, CRP, ferritin, D-Dimer, and Interleukin-6. [16] There was noticeable improvement across these markers, with CRP (76% ± 3%) and IL-6 (75% ± 3%) displaying the most substantial average percent reduction. This anti-inflammatory effect can potentially contribute to a reduction in alveolar and interstitial edema, resulting in improved gas exchange, a decrease in shunt and low ventilation/perfusion (V/Q) lung units, and consequently an enhancement in the P/F ratio—an indicator of improved oxygenation. The anti-inflammatory action of Aviptadil potentially decreases alveolar and interstitial edema, which might be observed in imaging studies as the resolution of GGOs, reduction in pulmonary infiltrates, and thinning of inter-lobular septa. b) *Increase in pulmonary surfactant production*: The augmentation of surfactant production can lead to increased lung volume, improved lung recruitability, and decreased cyclical alveolar collapse. These factors collectively prevent atelectrauma and contribute to the reduction of shunt fraction in ARDS. (c) *Inhibition of alveolar epithelial cell apoptosis*: Aviptadil inhibits the apoptosis of alveolar epithelial cells. This inhibition of cell death can help preserve the structural integrity of the lung tissue, contributing to overall lung function. d) *Reduction in Ischemia-Reperfusion Injury*: Ischemia-reperfusion injury occurs when blood flow is reinstated to tissue after a period of reduced blood supply, potentially exacerbating tissue damage. The

mechanism of action of Aviptadil includes mitigating this type of injury, thereby contributing to tissue preservation and facilitating the healing process.

The efficacy of Aviptadil in treating ARDS was first substantiated by a randomized controlled trial that showcased a nine-fold increase in the odds of respiratory recovery among patients receiving Aviptadil. [17] The same study also reported an impressive 80% decannulation rate when Aviptadil was administered to patients on ECMO, albeit in the context of COVID-related ARDS cases. Furthermore, another trial involving patients with ARDS caused by sepsis [5] reported equally encouraging outcomes comparable to those observed in the COVID ARDS. Notably, seven out of eight patients (87.5%) in this non-COVID ARDS trial were successfully extubated and transitioned out of the ICU. The substantial positive results have addressed a longstanding void in the treatment of ARDS, prompting us to consider Aviptadil as a vital and urgent intervention for the diverse etiology of ARDS.

Another rationale for the role of Aviptadil in ARDS emerges from its potential impact on a different aspect. Acute cor-pulmonale, a common complication of ARDS, is primarily driven by hypoxemic pulmonary vasoconstriction and the compression of pulmonary capillaries due to positive airway pressure. These factors elevate pulmonary vascular resistance, impeding right ventricular ejection. This situation can lead to right ventricular afterload escalation, causing right ventricle dilation and subsequent septal dyskinesia—detectable by echocardiography. Acute cor-pulmonale is observed in approximately 20% of overall ARDS cases, with a 10% incidence in its severe manifestation. The mortality rates are higher in ARDS cases associated with cor-pulmonale. [18] The potent pulmonary vasodilator effect of Aviptadil potentially lowers the right ventricular afterload which introduces a promising avenue for reducing mortality among ARDS patients. This function of Aviptadil in treating primary pulmonary hypertension has been explored and capitalized on for nearly two decades. Comparative studies, particularly in relation to other inhalational agents like Nitric oxide, could provide valuable insights into the effectiveness of this approach. Large multicenter randomized controlled trials are required before it become the standard of care in ARDS.

3. Conclusion

In essence, Aviptadil shows promise in ARDS treatment, with positive outcomes in reported cases and trials. Its mechanisms targeting inflammation and surfactant production suggest it could play a valuable role as a supplementary intervention. However, it's vital to recognize that Aviptadil is not a standalone solution but rather a complementary element in the broader spectrum of ARDS management. Continued research and well-designed randomized controlled trials will help to define its specific role and contribution in enhancing overall treatment strategies for ARDS patients.

Informed consent

The informed consent was obtained from the legally acceptable representative of the patients.

CRediT authorship contribution statement

Yatin Mehta: Conceptualization, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Chitra Mehta:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Aravind Chandrasekaran:** Data curation, Software, Writing – original draft.

Declaration of competing interest

Authors have no conflicts of interest to declare.

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