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## Role of Aviptadil in COVID-19

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### Abstract:

COVID-19 pandemic resulted in large number of death worldwide. Search for effective prevention and treatment option is still evolving. Aviptadil, is a synthetic form of Human Vasoactive Intestinal Polypeptide (VIP) tried in the treatment of COVID-19. It is available for inhalational and intra venous use. Treatment with Aviptadil showed promising results in Corona virus infected critically ill patients.

**Keywords:** Corona virus infection, COVID-19, Human Vasoactive Intestinal Polypeptide, Aviptadil

### Introduction

With widespread infection and increased morbidity and mortality, WHO declared COVID 19, infection with SARS CoV-2, as pandemic on 11 March 2020 [1]. Scientific world is in a rigorous effort to understand more about the disease process and effective treatment options. Hand hygiene, use of masks and social distancing helps to control the spread of infection. Vaccinations have just started. Hydroxychloroquine, favipiravir, ritonavir/ lopinavir, remdisivir, tocilizumab etc are tried in patients with COVID-19 with variable effects [2]. Aviptadil, a VIP analogue has been tried in patients with COVID-19 with success. On 14 July 2020 FDA granted Investigational New Drug (IND) permission for inhaled VIP and awarded FDA Orphan Drug Designation for intravenous VIP, to use in patients with COVID-19. In this article we are reviewing the role of Aviptadil in COVID-19.

### Aviptadil

Aviptadil, also known as RLF-100, is a synthetic form of Human Vasoactive Intestinal Polypeptide (VIP). It is found useful in conditions like asthma, chronic obstructive pulmonary disease (COPD), sarcoidosis, pulmonary fibrosis, acute lung injury, pulmonary hypertension, erectile dysfunction and ARDS [3]. Recent studies showed that treatment with Aviptadil is associated with rapid recovery in

Corona virus infected critically ill patients [4,5,6].

### **Vasoactive Intestinal Peptide (VIP) and SARS-CoV-2**

Vasoactive Intestinal Peptide (VIP) was discovered by Said and Mutt in 1970 [7]. It is a gut peptide hormone, containing 28-residue amino acid peptides. VIP is mainly localized in the myenteric and submucosal neurons and nerve terminals in the GI tract. It belongs to secretin/glucagon hormone superfamily and is produced by neuroendocrine cells in the body, macrophages, B-lymphocytes and T-lymphocytes [8,9]. VIP is widely distributed in the nervous system (both central and peripheral), digestive, cardio vascular, respiratory and reproductive system. It exerts various effects in different system.

VIP acts on two receptors - VPAC1 and VPAC2, which are class B of G-protein-coupled receptors (GPCRs). VPAC1 is mainly present in the lung and T-lymphocytes, whereas VPAC2 is mainly seen in the smooth muscle, mast cells and the basal parts of the lung mucosa [10].

VIP is highly localised in lungs (70%) and binds with alveolar type II (AT II) cells via VPAC1[11,12]. AT II cells constitute only 5% of pulmonary epithelium. Angiotensin Converting Enzyme 2 (ACE 2) surface receptors are present in AT II cells. AT II cells produces surfactant and plays an important role in the maintenance of type 1 epithelial cells. SARS-CoV-2 enters into AT II cells by binding to ACE 2 surface receptors with its spike protein [13].

Plasma level of VIP is higher in patients with severe COVID compared to healthy individuals and those with mild COVID-19 [14]. Survivors of COVID 19 had higher circulating level of VIP compared to non-survivors, indicating its potential role controlling the disease severity.

### **Mechanism of action**

VIP is highly concentrated in the lung and it blocks apoptosis, caspase-3 activation in the lung, inhibits inflammatory cytokines like IL6 and TNF alpha production and reverses CD4/CD8 ratio. VIP increases surfactant production by up regulation of choline phosphate cytidyltransferase, which increase the incorporation of methyl choline to phosphatidylcholine, the major components of pulmonary surfactant [15]. It also up regulate C Fos protein expression in type II alveolar cells, which increase the synthesis of pulmonary surfactant phospholipids and induce surfactant protein A expression [16].

VIP reduces ischemia-reperfusion injury in animal models [17]. It reduces cell death by inhibiting activation induced perforin, granzyme B and caspase activity [18,19]. VIP reduces pulmonary inflammation by reducing the production of pro inflammatory cytokines [9]. It inhibits the synthesis and activation of NF-kB, which block the production of TNF alpha [20].

In addition to that VIP blocks SARS-CoV-2 replication in the lungs and monocyte [8,9,21]. VIP and pituitary adenylate cyclase activating polypeptide ( PACAP) inhibit SARS CoV-2 RNA synthesis in human lung epithelial cell (by 41%) and human primary monocytes (by 33-45%) [9]. It also blocks viral cytopathic effect demonstrated by reduced LDH release (by 40%).

SARS CoV-2 attack mainly type II cells (not type 1 pneumocytes) and results in the death of alveolar type II (AT II) cells which produces surfactant, resulting in profound defect in oxygenation, leading to hypoxia [22]. Aviptadil a synthetic form of VIP results in rapid clinical recovery in patients with SARS-CoV-2 infection. (**Figure 1: A-** Normal alveolar type II (AT II) cells, **B-**After binding of SARS-CoV-2, **C-**Treatment with Aviptadil)

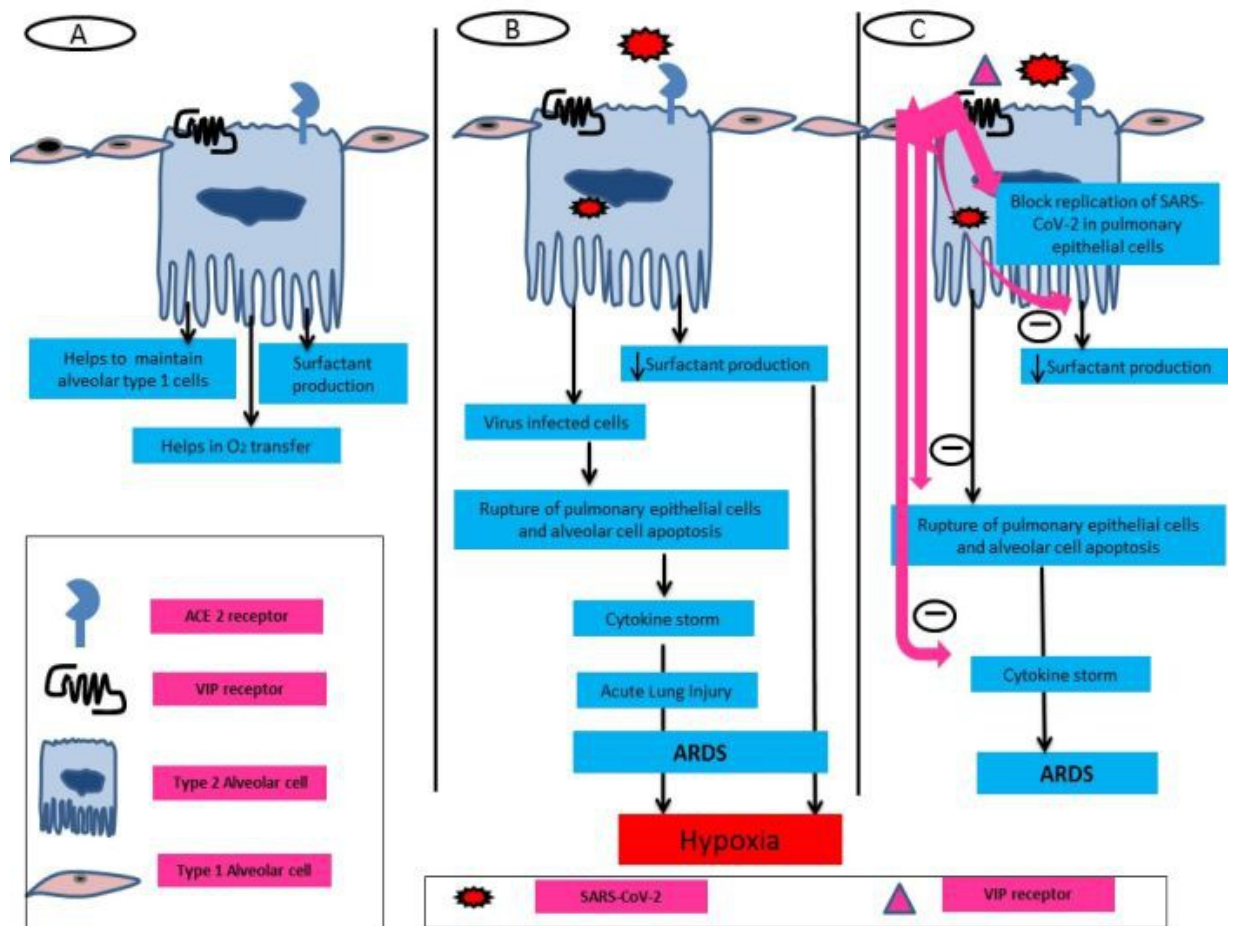


Figure 1

## Preparations

Awiptadil is available both as intra venous and inhalational (nebulisation) preparations.

## Indication

Intravenous Awiptadil is given for critical COVID-19 disease with respiratory failure requiring high flow nasal oxygen, non-invasive ventilation or mechanical ventilation whereas inhalational Awiptadil is given for moderate and severe COVID-19 as a part of the clinical trial.

## Dose

Clinical trial is going on with both inhaled (Clinical Trial NCT0436009- AVICOVID-2) and intravenous (Clinical Trial NCT04311697- COVID-AIV) preparations. Nebulized RLF-100 (awiptadil) 100 µg is given 3 times daily for moderate and severe COVID-19 and intravenous Awiptadil is given as escalating doses from 50 -150 pmol/kg/hr over 12 hours for 3 days for Critical COVID-19 patients with Respiratory Failure.

## Pharmacological features

Awiptadil has a volume of distribution of 14 ml/kg. Its plasma half-life of elimination is 1 to 2 minutes. It is excreted via kidney (35% within 4 hours and 90% within 24 hours).

### **Drug interaction**

There is no significant drug interaction.

### **Pregnancy**

No data regarding the safety of Aviptadil during pregnancy.

### **Adverse effects**

Intra venous administration is associated with side effects like tachycardia, flushing, hypotension, diarrhoea and alterations in ECG (bigeminy).

### **Clinical benefits**

Report from Houston Methodist Hospital regarding rapid recovery of a double lung transplant (with antibody-mediated rejection) patient with critical COVID-19 with respiratory failure is promising [5]. Another 6 patients with critical COVID-19 with respiratory failure, treated with three successive 12 hour infusion of intravenous Aviptadil at 50/100/150 pmol/kg/hr along with other standard care resulted rapid recovery. Critical COVID-19 patients treated with Aviptadil shows rapid clearance of pneumonia on chest X-ray, improvement in blood oxygen level and significant reduction (50% or more) in laboratory inflammatory markers like ferritin, D-dimer, IL-6&TNF alpha [4]. Subsequent reports from same team show dramatic recovery in 19 out of 21 patients from COVID-19 respiratory failure with co morbidity, suggesting 9 fold advantages in survival and recovery from respiratory failure compared to standard care [6]. No serious adverse events reported with Aviptadil. Hypotension and diarrhoea reported in few patients.

### **Other uses of Aviptadil**

Aviptadil is found useful in conditions like Bronchial asthma, chronic obstructive pulmonary disease (COPD), sarcoidosis, pulmonary fibrosis, pulmonary hypertension, acute lung injury, ARDS and erectile dysfunction [3]. Vasoactive intestinal peptide cause bronchodilation and protect against histamine induced bronchoconstriction in patients with bronchial asthma [23,24]. Inhibition of apoptosis of alveolar L2 cells resulting from cigarette smoke-induced cytotoxicity helps to arrest the progression of the disease in patients with chronic obstructive pulmonary disease (COPD) [25,26]. In sarcoidosis, inhaled aviptadil reduce inflammation in the lungs by its immuno regulatory effect [27]. In patients with Pulmonary Arterial Hypertension (PAH) inhalation of Aviptadil cause pulmonary vasodilatory effect and results in mean pulmonary artery pressure reduction, increase in the cardiac output and improvement in the mixed venous blood oxygenation [28]. Treatment with inhaled VIP resulted in Rapid clearance of check point inhibitors induced pneumonitis [29]. In 2005, a trial with aviptadil showed that out of 8 sepsis induced ARDS patients, 7 got recovered, in the setting of an expected 40-60% mortality risk, due to its anti-cytokine effect [14]. Combination of aviptadil with phentolamine is useful as an intracavernosal injection therapy for patients with erectile dysfunction (ED). Aviptadil acts on veno occlusive mechanism whereas phentolamine increases arterial blood flow, resulting in improvement in ED [30].

### **Conclusion**

Synthetic VIP, Aviptadil is found to reduce viral replication in lung tissues, release of inflammatory cytokines and alveolar epithelial cell apoptosis in patients with corona virus infection. On-going clinical trials will be expected to through more light into the role of Aviptadil in COVID-19.

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