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Treatment of Acute Respiratory Distress Syndrome with Vasoactive Intestinal Peptide

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Abstract

Purpose: To assess the clinical safety and possible effectiveness of Vasoactive Intestinal Peptide (VIP) in the treatment of Acute Respiratory Distress Syndrome (ARDS) related to sepsis

Methods: Under FDA Investigational New Drug clearance, eight patients with ARDS related to sepsis were treated with 50 pmol/kg/hr-100 pmol/kg/hr of VIP by intravenous infusion for 12 hours. All patients were on mechanical ventilation and full telemetry. Results: No drug related serious adverse events were seen. Hypotension was seen in association with two infusions and diarrhoea in association with one but did not necessitate cessation of therapy. Bigeminy was seen in association with one infusion without sequel. Seven of eight patients demonstrated a successful course during intensive care and were successfully removed from mechanical ventilation and discharged from intensive care. The eighth patient succumbed to purulent secretions in the lungs. Of those who were discharged from the ICU, 6 demonstrated successful 30 day survival. The seventh died from a cerebral infarct at day 30, deemed unrelated to treatment with VIP. Serum levels of Tumour Necrosis Factor α were obtained in 6 patients at baseline and 24 hours and were seen to decrease with treatment in five patients.

Conclusions: Initial clinical treatment results with VIP in patients with ARDS demonstrated a safety profile consistent with previous studies in normal volunteers. The successful clinical course seen in 7 of 8 patients in the expected 50% survival setting may suggest that VIP shows promise in the treatment of other infectious conditions that damage the pulmonary epithelium, particularly COVID-19.

Keywords: Vasoactive Intestinal Peptide; Acute respiratory distress syndrome; Tissue necrosis factor α; Respiratory; Acute lung injury

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Introduction

In March 2020, the US Food and Drug Administration cleared the investigational use of Aviptadil, a synthetic form of VIP, to treat Critical COVID-19 with Respiratory Failure. Among the evidence of human safety included in the Investigational New Drug (IND) application was a previously unpublished study of patients with Acute Respiratory Distress Syndrome (ARDS) in the setting of sepsis. The FDA has subsequently granted Aviptadil a Fast Track Designation, with the initial clinical results in the treatment of Critical COVID-19 with respiratory failure reported. In addition, this manuscript reports the prior clinical experience with the use of VIP in ARDS. The results were previously unreported owing to the retirement and subsequent death of the senior author, Dr. Sami Said.

ARDS is a severe, diffuse inflammatory pulmonary disease with myriad etiologies, for which there is no approved therapy. The underlying condition causes a massive inflammatory response and diffuse edema throughout the lung, culminating in hypoxemia and respiratory distress or failure. Recent mortality estimates for ARDS range from 35%-45%, depending on disease severity, with the only accepted therapy being mechanical ventilation [1-3].

Vasoactive Intestinal Peptide (VIP) is a ubiquitous neuropeptide throughout the human body. Since its discovery by Said et al. in 1970, VIP has been identified in numerous major organ systems

throughout the body but is 70% concentrated in the lung. VIP receptors have primarily been identified within the lung on Alveolar Type II cells, which are critical to surfactant production and recycling. VIP was also shown to reduce inflammatory cytokines. In vitro and in vivo studies using VIP have demonstrated an immunomodulatory effect, particularly in the setting of acute lung injury. In animal models, VIP down regulates numerous macrophage mediated inflammatory cytokines as well as known proinflammatory receptors. Moreover, VIP inhibits cytokine production in T-lymphocytes [4].

In light of these results, VIP was proposed as a potential treatment for ARDS in 1996 but was not synthesized in sufficient quantity for study under FDA Investigational New Drug (IND) permission until 2005. The IND documents prior published and unpublished safety results in normal volunteers without serious adverse events. This manuscript reports results in the first eight patients treated with intravenous VIP under investigator sponsored IND 52,088 issued to author SS registered Phase I clinical trial. These results were not previously published but were reported to and reviewed by the FDA and subsequent regulatory submissions. The objective of this investigator sponsored study was to obtain preliminary data on the maximum tolerated dose of VIP in patients with ARDS and to evaluate the safety and pharmacodynamics activity of this peptide in these patients.

The study initially anticipated recruitment of 18 patients but was terminated after eight patients with Dr. Said's passing. These results are being published after 15 years because of renewed interest in the use of VIP to treat pneumonitis and lung injury associated with COVID-19 [5-19].

Method

Human subjects were treated pursuant to IND 52,088 under a protocol approved by the Institutional Review Board of State University of New York Health Sciences Center, Stony Brook, NY. Patients who met the consensus criteria for diagnosis ARDS in the setting of sepsis were considered for this trial. Patients were observed for a 24 hour period, during which time all inclusion criteria had to be met. The primary inclusion criteria were sepsis or septic shock, diagnosed ARDS, hypotension, and end organ dysfunction. This is a dose escalation study. If all requirements were met once (not necessarily simultaneously), patients were enrolled and received the study drug over 6 hours or 12 hours.

Cohorts of 3 patients each receive escalating doses of VIP over either 6 or 12 hours until the maximum tolerated dose is determined. Patients are followed for 30 days.

The eligibility criteria for the study were

(ARDS) Acute respiratory failure is characterized by: (a) Hypoxemia, refractory to supplemental 02 therapies; (b) Diffuse pulmonary infiltrates (c) Absence of a cardiogenic cause of pulmonary edema and (d) Reduced pulmonary compliance. The severity of lung injury in these patients is quantified by the scoring system of Murray [20].

Diagnosis of Sepsis/septic shock, characterized by two or more of the following:

(a) Fever or hypothermia (core temp >38°C or <36°C); tachycardia (heart rate >90, in the absence of B-adrenergic receptor blockade); tachypnea (respiratory rate >20) or PaCO2<32 mm Hg or requirement of mechanical ventilation. White blood cell count >12,000 cells/mm3 or <4,000 cells/mm3 or immature neutrophils (bands >10%).

(b) Hypotension (systolic blood pressure 90 mm Hg), mean arterial blood pressure <70 mm Hg, or sustained systolic blood pressure decrease of 40 mm Hg, unresponsive to fluid challenge, or the use of vasopressor agents (excluding dopamine at <5.0 mg/kg per min).

(c) Evidence of inadequate organ perfusion or organ dysfunction: acute deterioration in mental acuity (excluding sedative drugs or other nonpeptic causes of altered mental status) or unexplained metabolic acidosis (pH<7.30 or elevated plasma lactate or base deficit of >5 mEq/L) or oliguria (<0.5 ml/kg/hr) for >2 h; or unexplained coagulopathy elevated PT or PTT or platelet count decreased to less than half the baseline value within the past 24 h or <100,000/mm3 or an acute elevation of bilirubin to >2.0 mg/di and an elevation in one of the liver enzymes (alkaline phosphatase, SGOT, SGPT).

(d) Clinical suspicion of infection (to be documented by appropriate and accepted measures such as sputum Gram stain, urinalysis). Documented infections are defined as positive bacterial cultures from normally sterile body fluids or Gram stain and positive cultures together with clinical correlation when sepsis originates from respiratory or genitourinary infections.

Exclusion criteria were as follows: Pregnancy <18 years old. Irreversible underlying condition with a rapidly fatal course. Current or recent (within 30 days) enrollment in another investigational trial. Severe burns or uncontrolled hemorrhage (4 unit transfusion requirement in previous 24 hour period). Acquired immune deficiency syndrome; transplant patients currently immunosuppressed; chemotherapy induced neutropenia (granulocyte count <1000/mm3); weight >100 kg; cardiogenic shock anuria (urine output <50 ml/d). Severe liver

disease with portal hypertension. Recent stroke, head trauma, increased intracranial pressure, or other serious neurologic disorder; inability to obtain informed consent or assent.

Study drug

Preparation and delivery: Sterile, pyrogen free VIP is prepared, as in earlier human studies, at the Karolinska Institute, Stockholm, Sweden (where it was first isolated by the PI in collaboration with Prof. Viktor Mutt) and shipped to New York in sealed ampules or vials. Stock solutions of the peptide are kept at 70°C in the hospital pharmacy, under the direct care of the senior pharmacist in charge of the investigational drug service at University Hospital. Solutions for IV infusion were prepared hours before use, in sterile isotonic saline, containing 0.5% human albumin for each patient, by the pharmacist and delivered by a volumetric infusion pump.

Results

Safety

The objective of this Phase I study was to obtain preliminary data, in an open label study, on the safety of Aviptadil, infused IV. (50 pmol/kg/hr or 100 pmol/kg/hr, infusion time 6 hr to 12 hr) in patients with ARDS induced by sepsis. In total, eight patients were included in the study.

Three patients progressed to the high dose group at 100 pmol/kg/hr, with one patient needing a temporary reduction (to 85 pmol/kg/hr) for hypotension. Infusion in the remaining five patients was maintained at the lower dose of 50 pmol/kg/hr. In 5 cases, there was surgery preceding the infection. Consistent with the polymorbidity of the patients admitted to the trial, they also received a large number of concomitant medications and other supportive measures.

In the low dose group, Aviptadil administration was stopped in one (bronchial obstruction due to hypersecretion considered unrelated to Aviptadil), and the dose was halved in another (Hypotension). In the high dose group with 100 pmol/kg/hr (3 patients). Aviptadil administration was halted in one patient who required temporary reduction (to 85 pmol/kg/hr) for hypotension.

However, the dose was transitorily reduced in two patients due to hypotension (1 case) or bigeminy (observed in the other). In addition, watery stools were observed in one patient in the high dose group. Two patients died during the long term follow up period. Patient #5, aged 87 years, male, was successfully extubated and discharged from the ICU but succumbed to a massive right sided middle cerebral artery infarct three weeks after VIP administration. Supportive measures were stopped at the request of the family. Patient #2, aged 80 years, male, received the Aviptadil infusion for only 2 of the intended 6 hours because oxygen saturation dropped to 85%. The patient, at this point, was suctioned from the endotracheal tube and ventilated with an AMBU bag+bronchodilator nebulizer treatment. The endotracheal tube yielded a large amount of thick, purulent secretions. The arterial oxygen saturation improved to a baseline of 90%-92%, but the Aviptadil infusion was not restarted. He died four days later; the death was considered a direct consequence of underlying sepsis and was deemed unrelated to VIP infusion (**Figure 1**).

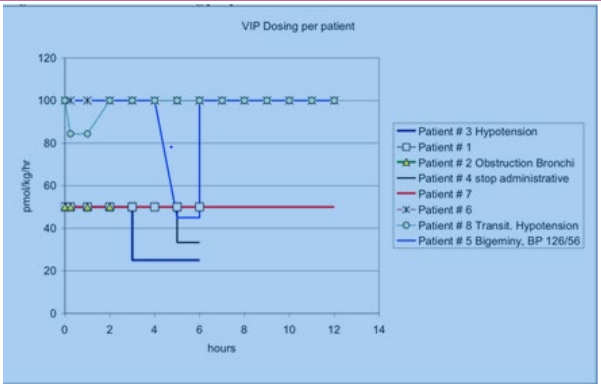

Figure 1 VIP dosing per patient over time.

An intended increase to 150 pmol/kg/hr was not undertaken because the senior author and principal Investigator retired.

Measurement of TNFα

As an exploratory endpoint, Tissue Necrosis Factor α (TNFα) was measured in 6 of 8 patients. In five of those patients, a modest decrease in TNFα was seen, while Patient #6 demonstrated a substantial increase from baseline (**Table 1**).

Table 1 TNFα Level at baseline and 24 hours Post VIP infusion.

TNFα Level			
Patient	**Baseline**	**24 Hours**	**%Change**
BA	49.45	27.01	-45%
GR	25.96	18.73	-28%
DJ	17.69	12.31	-30%
MA	15.82	12.31	-22%
LL	13.87	12.31	-11%
CP	4.65	11.38	-145%

Discussion

This trial aimed to assess the safety of VIP as a treatment for patients with ARDS in the setting of sepsis syndrome. Such patients may or may not have evidence of other organ dysfunction. Mortality of 12.5% during intensive care and 25% at 30 days is lower than the expected mortality in sepsis related ARDS. In addition, only one of the eight patients included this study died from ARDS related causes. The other instance of mortality was

due to a massive hemorrhagic stroke rather than acute lung injury. Until recently, most studies of acute lung injury and acute respiratory distress syndrome have reported a mortality rate of 40 to 60% mortality rate, although some reports suggest that mortality from this disease may decrease.

Although a window of 24-48 hours often exists from when sepsis/septic shock is diagnosed until severe lung and other organ injury occurs, organ injury may develop rapidly. Some degree of lung injury may already be present when sepsis is first diagnosed. The investigators maintained the homogeneity and definition of the study group by limiting the study population to patients with antecedent or associated sepsis/septic shock, excluding those with other risk factors for ARDS such as trauma, drug overdose, acid aspiration, and inhaled toxins.

The adverse events reported above point to possible side effects of IV-infused VIP. However, the number of cases treated is insufficient and too heterogeneous to draw any conclusions regarding dose dependence or the influence of comorbidities of these adverse events. However, previous studies in which VIP was administered to humans identified similar adverse events. In addition, investigations involving the infusion of VIP into healthy subjects yielded reports of flushing, increased heart rate, and liquid/watery stools at higher doses, so it is not surprising that some of the patients in our cohort exhibited some of these events (**Table 2**).

Table 2 Adverse events and outcomes following administration of IV-infused VIP. Gives an overview of the adverse events observed in these severely diseased patients. The adverse events of hypotension and diarrhea are likely attributable to Aviptadil after IV administration.

Patient No.	AEs	Description of Adverse Event	Severity	Serious	Unexpected	Course	Relationship to Aviptadil
CRF #1	No	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
CRF #2	Yes	Hypoxemia, acute	Severe	Yes	No	N.A.	Unlikely
		Death	Severe	Yes	No	N.A.	No
CRF #3	Yes	Hypotension	Mild	No	No	Disappeared after intervention	Possible
CRF #4	Yes	Seizures	Severe	Yes	Yes	N.D.	No
CRF #5	Yes	Bigeminy	Moderate	No	No	Disappeared after intervention	Probable
		Diarrhea	Mild	No	Yes	Spontaneous disappeared.	Probable
		Death	Extreme	Yes	No	N.A.	No
CRF #6	Yes	Seizures	N.A.	No	Yes	N.D.	No
CRF #7	No	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
CRF #8	Yes	Hypotension	Moderate	No	No	Disappeared after intervention	Probable
		Pneumothorax	Severe	Yes	Yes	Disappeared after intervention	No

All adverse events reported were ameliorated shortly after discontinuing treatment as Aviptadil has a very short plasma half-life of one minute with 90% excreted in the urine after 24 hours of infusion [21-26]

Conclusion

Intravenous VIP was generally well tolerated at doses between 50 pmol/kg/hr-100 pmol/kg/hr. In patients treated for ARDS related to sepsis. Although the study was non-randomized, survival was better than expected compared to contemporaneously reported results in this condition. The suggestion of reduced TNFα levels is consistent with nonclinical studies in which VIP was shown to have potent anti-cytokine effects.

These findings are part of the reason that synthetic VIP (Aviptadil) was cleared by the US FDA in 2020 for investigational use in Critical COVID-19 with respiratory failure. As a result, further research was conducted in a randomized clinical trial (RCT) and an

expanded access protocol (EAP). There were 196 patients in the RCT using the same intravenous dosing schedule as the COVID-19 EAP. The 21 patients receiving intravenous Aviptadil under the EAP were compared to non-randomized concurrent controls. The results of the RCT showed a significant survival benefit compared to control, validating the findings of the EAP. The results of the EAP showed an 81% improvement and patient survival compared to the control. A place for further research regarding the efficacy of VIP in non-covid related ARDS is warranted and would hopefully yield similarly promising findings.

Disclosure

Authors JCJ and MJJ have a financial relationship with NeuroRx, Inc., the sponsor of Aviptadil for the Treatment of COVID-19. Author JGY has received funding as an investigator for Aviptadil through his Institution.

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