Aminaphtone, an endothelin-1 synthesis inhibitor: a potential novel therapy for COVID-19

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Abstract

Since the beginning of sars-CoV2 pandemics in late December 2019 the race to find a successful therapy is ongoing. So far, no therapy has focused in reducing cell death directly, which triggers inflammation and if unchecked can lead to cytokine storm, a known phenomenon in ARDS and severe COVID-19 patients. Aminaphtone inhibits the synthesis of endothelin-1, a peptide with vasoconstricting properties and also responsible for triggering several cellular signalling pathways that are implicated in lung and endothelial cell injury such as: synthesis of cytokines, upregulation of adhesion molecules, increasing capillary permeability and diapedesis, downregulation of VE-cadherin and tissue fibrosis. Aminaphtone has shown both in vitro and in vivo potential to disrupt many of the cellular signalling involved in the pathophysiology of COVID-19. It could reduce the severity of the symptoms and if used as prophylaxis, reduce the hospitalization rate. Also, it could help recovering patients by reducing lung fibrosis. Aminaphtone has a tremendous potential and should be readily tested in well designed randomized controlled trail to assess its clinical relevance.

Key words: Aminaphtone, Endothelin-1, COVID-19, ARDS

Introduction

The role of endothelial cells in the development of cytokine storm[1,2] and ARDS[3] in viral infection is well understood and recent research points out to be at a central role in severe COVID-19.[4–7] Stabilizing endothelial cells and avoiding the cascade of consequent signaling is of utmost importance to slow down the progression of severe COVID-19 or even to avoid hospitalization with early intervention.

Aminaphtone a (1,2,4-Naphtalenetriol, 3-methyl-, 2-(4-aminobenzoate)) is a 4-aminobenzoic acid derivative, it downregulates endothelin-1 synthesis interfering with

the Pre-pro-endothelin-1 gene.[8] Endothelin-1 production has many triggers such as shear stress,[9] hypoxia[9], thrombin[9], T cells activated through IFN-γ and TNF-α,[10] angiotensin II[9] and other vasoactive factors,[9] just to name a few.

Endothelin-1 is one of the most powerful vasoconstrictors known in the human body[11] and elicit many changes in the endothelial cells that are linked to the pathophysiology of severe COVID-19 such as upregulating adhesion molecules, downregulating VE-cadherin and increasing the synthesis of cytokines.

Endothelin-1

In vivo and *in vitro* study has shown that endothelial cell damage leads to increased endothelin-1 blood levels.[12] Endothelin-1 is also linked to acute lung injury[13] and pulmonary fibrosis[14] and it is known to induce reactive oxygen species (ROS) production through numerous processes *in vivo.*[15]

Aminaphtone can be used pre-emptively to reduce endothelin-1 release in case of endothelial cell damage. An *in vivo* study using monocrotaline-induced hypertension rat model showed that aminaphtone indeed reduced endothelin-1 levels while significantly improving survival rates compare to control, and at higher dosage seemed to improve both right heart hypertrophy and pulmonary artery wall thickness.[16] Yet another *in vivo* study showed aminaphtone decreased endothelin-1 release in rats undergoing sclerotherapy.[17]

Soluble Adhesion Molecules

Endothelin-1 regulates the expression of soluble adhesion molecules like soluble Endothelial-Leukocyte Adhesion Molecule (sELAM-1), soluble Vascular Adhesion Molecules (sVCAM-1), soluble Intercellular Adhesion Molecule-1 (sICAM-1) as shown in *in vitro* studies.[8] Moreover other *in vitro* studies showed an agonist effect with TNF-alpha, enhancing soluble adhesion molecules expression,[18] and a randomized, open-label pilot study showed a reduction of sELAM-1 and sVCAM-1 after aminaphtone treatment in patients with systemic sclerosis.[19] Soluble adhesion molecules facilitate leukocytes migration to extravascular lung compartments,[20] another suspected hallmark of severe COVID-19 pneumonia.[3]

Cytokines

In vitro studies has shown that aminaphtone and endothelin-1 can downregulate the gene of several cytokines[21]: CCL2 (MCP-1),[22] CSF2 (GM-CSF),[22] CSF3 (G-CSF),[22] CXCL10 (IP-10),[22] IFNA1 (IFN-α),[22] TNF (TNF-α),[22] IL1R1 (IL-1RA),[22] IL-6,[22] IL-7,[22] IL-8,[22] IL-10,[22] IL-15,[22] EGF,[22] FGF2 (FGF-basic),[22] VEGFA (VEGF),[22] as well reduce cytokine-receptor interaction[22], all those effects were elicited at a similar concentration as attained in healthy subjects after taking 75mg of aminaphtone.[19] Cytokine storm is a known phenomenon in severe COVID-19 patients[23] and downregulating cytokines may play a huge role in reducing lung injury. Aminaphtone may also play a role in recovering COVID-19 patients, there is evidence that puts endothelin-1 and as a central orchestrator in lung fibrosis[24–27] as it stimulates profibrotic proinflammatory cytokines

through endothelin-1 receptors in CD4+ T cells.[28] Also, endothelin-1 stimulates TGF-β1[28] and TGF- β2[28] which is known for its role in tissue fibrosis.[29–31]

Vascular Permeability

Endothelin-1 plays a major role in VE-cadherin regulation which is essential to maintain cell to cell adhesion[32–36] and its downregulation is linked to increased capillary permeability,[33–36] Increased diapedesis,[34] and poor outcomes in sepsis[37] and ARDS.[37]

The upregulation of VE-cadherin acts as a stabilizing factor keeping capillary structure and increases endothelial cell viability *in vitro.*[33] Another added effect of avoiding endothelial cell death would be to avoid exposure of subendothelial tissue, which is rich in von Willebrand factor, known to be at high levels in COVID-19 patients.[38]

Also *in vitro* studies suggest endothelin-1 increases capillary permeability signaling to pericytes which tightly regulates permeability and leukocyte migration.[39,40] Furthermore, a case report involving 40 patients showed that aminaphtone was able to significantly reduce albuminuria in the early stages of kidney disease,[41] showing the ability to regulate capillary permeability which most likely involves podocytes[42] which have a homolog function to pericytes.

Discussion

Endothelin-1 seems to be a major player in the development of severe COVID-19 and halting endothelin-1 synthesis might improve outcomes in COVID-19 patients. Although endothelin receptor antagonists seem promising it does not prevent endothelin-1

synthesis, and endothelial cell death which further increases endothelin-1 blood levels. Reducing endothelin-1 synthesis prevents both the physiological release and its disposal upon cell death.

Endothelin-1 vasoconstriction is mediated mainly by ET_A receptors which are, not surprisingly, more abundant in heart, lung, pulmonary artery, aorta and coronary artery.[9] The powerful vasoconstricting action of endothelin-1 added with platelet aggregation caused by subendothelial tissue exposure could be the main drive of ventilation/perfusion mismatch commonly seen in hospitalized COVID-19 patients.

As shown by some *in vivo* studies the use of aminaphtone avoids the increase of endothelin-1 in case of endothelial cell death, this means aminaphtone could be used as a prophylaxis to avoid the initial cascade that leads to lung injury and hospitalization. It fits perfectly as outpatient therapy as it has low toxicity,[43] no known drug-drug interaction,[43] and mild adverse effects such as nausea,[41] headaches,[41,44] and abdominal pain.[41] Endothelial cells play a central role in cytokine storm and COVID-19 so it must be the next logical target for therapy

Conclusion

Aminaphtone might play a huge role in fighting COVID-19, acting upon many processes closely related to its physiopathology which prompt its inclusion in well designed randomized controlled trials both in outpatient and inpatient settings either to investigate

its role as a prophylatic agent to avoid severe disease or as a treatment to reduce the severity of symptoms and course of disease in severe COVID-19 patients.

Conflict of Interest Statement

The author declares no competing interests.

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