Colchicine plus fosfomycin in coronavirus infection

Claudio Gustavo Cerati Pharmacist , University of Buenos Aires ,Argentina.

Polymicrocaps

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Authors:
Cerati Claudio

Abstract

Some antibiotics can act as immunomodulators and particularly fosfomycin has an immunomodulatory effect on human B-cell activation. Fosfomycin is considered a unique antibiotic that is chemically unrelated to any other known antibacterial agent. The effect of fosfomycin on human T-cells function was yet studied along with the inhibition of proliferation of human lymphocytes induced by polyclonal T-cell mitogens as a function of fosfomycin dose.

Colchicine is an ancient API with known benefits in several diseases like FMF (Familial Mediterranean Fever) and gout presenting narrow therapeutic margin and side effects when administerd orally. Delivering both Colchicine and Fosfomycin by inhalation, transdermal and intranasal route was the objective of the present study.

Introduction

It was also described the suppression by fosfomycin of mixed lymphocyte reaction and interleukin-2 (IL-2) production by T cells along with the expression of IL-2 receptor (CD25) on the activated T-cell surfaces.Previous research demonstrated that fosfomycin blocks T-cell division during the transition from G1 to S phase of the cell cycle.

Materials and Methods

Both Colchicine USP 29-NF 24 (crystalline) and Fosfomycin (sodium) USP grade were used . Micro and nano-encapsulation was carried on using polymers accepted for injectable dosage forms. Colchcinie and fosfomycin micro and nanocapsules were vehiculized in an apropriate vehicle (water for injection) as used for inhalation route (0,5 mg colchicine/ 50 mg fosfomycin per dose) and also vehiculized in a silicone matrix intended for the controlled release of colchicine (0,5 mg/day/20 day period).

Results

1. Colchicine and fosfomycin were micro-encapsulated separately or co-encapsulated in bi-layered spheres (Fig.1) in order to obtain a uniform dose and stable suspension of the particles in the vehicle for inhalation.

1.2 Particle nebulization through sonication achieve stable and mono-dispersed suspension .

1.3 Micro and nanocapsule interaction with respiratory mucosa can follow a similar pathway than Coronavirus parti--cles.

2. Evidence was provided about SARS-CoV-2 infection of brain tissue, consistent with its multiorgan involvement and viral entry into the brain through the olfactory epithelium. (Ref.1)

2.1 Differential spreading in the CNS could be due to interactions between the spike protein involved in anterograde and retrograde movement along the microtubule tracks, as seen in some human neurotropic viruses.

2.3 Disruption of microtubules with colchicine significantly blocks neuronal transport and reduces viral replication The reduction of viral titer was due to reduced viral spread through neuron, and not due to cytotoxicity caused by colchicine. (Ref. 2)

2.4 Certain strains of human coronaviruses could persist in the human CNS by targeting oligo-dendrocytic and neuroglial cell lines.Covid-19 targeting of the Central Nervous System (possibly via olfactory nerves), caused severe respiratory distress, strokes, impaired cognition, and brain hemorrhages.

2.5 Patients with Allergic Rhinitis exhibited increased numbers of neutrophils in peripheral blood, nasal biopsies and nasal lavage fluid during the pollen season.Activated neutrophils can help activate T cells.

2.6 Mechanisms of neuroinvasiveness involve intranasal infection and both HCoV-OC43 and SARS-CoV were shown to infect the lungs in mice and to be neuroinvasive being detected in the CNS of susceptible mice.(Ref.3)

Viruses may enter the CNS through two distinct routes: hematogenous dissemination or neuronal retrograde dissemination.Reduction of viral titer was due to reduced viral spread through neuron, and not due to cytotoxicity Caused by colchicine. (Fig.1)

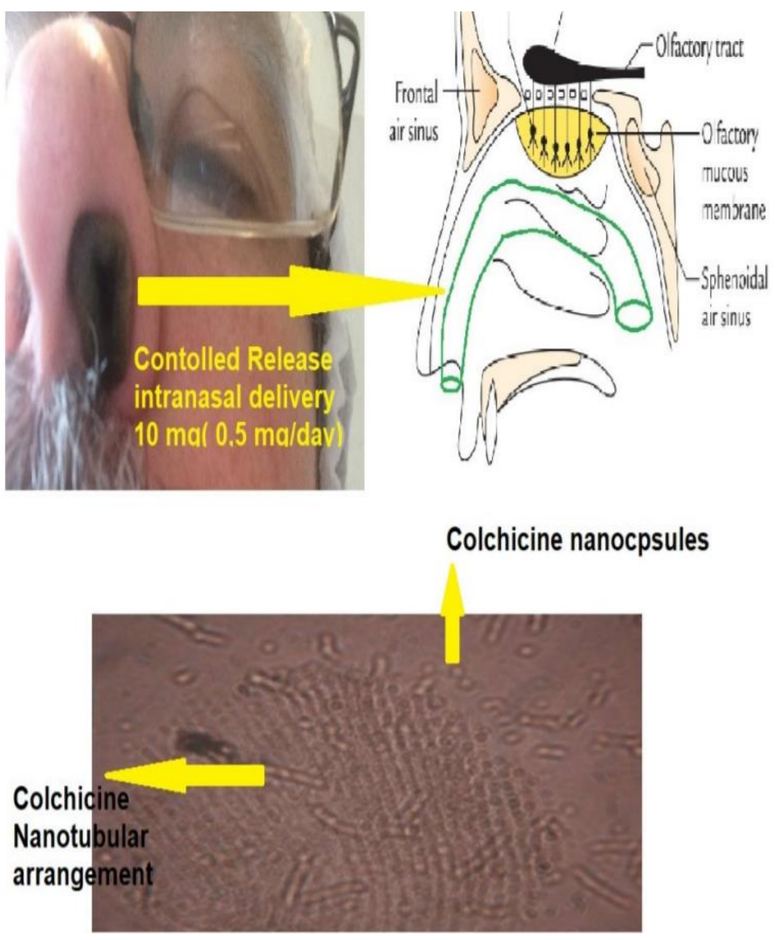

Figure 1 : Colchicine delivery through intranasal device

Low colchicine concentrations such as 10 uM as inhibitor of host cell microtubule dynamics can reduce viral invassion and trasport inside the cell.
3.Colchicine is a medication that acts on inflammasome NLRP3 and can reduce cytokine storm and recently, it has been recognized as an inhibitor of NLRP3 inflammasomes and mitigating interleukin activation.

3.1 In case of co-administration of multiple drugs, the risk of drug interactions increases, however, a more complex disease-drug-drug interaction is expected in Covid -19 infection as the result of high rates of hospitalization and intensive care unit (ICU) admission.

3.2 According to its manufacturer, remdesivir undergoes extensive metabolism by CYPs especially CYP3A4,moreover, other potential candidates for treating Covid- 19 such as Colchicine are also hepatically metabolized being CYP3A4 a key cytochrome in the colchicine metabolism pathway.

4. Colchicine loaded transdermal patch (10 mg / 20 days release) was prepared by nanoencapsulation following Polymicrocaps® technology and inclussion into a silicone matrix .Controlled release followed by Bromocresol green nanoencapsulated along with Colchicine API.Transdermally permeated particles through skin show blue colour.

Discussion
Bacterial and viral interactions within the nasopharynx and whole respiratory tract by coronavirus and bacteriae performs through epithelia colonization via host cell surface receptors, such as the platelet-activating factor (PAF) receptor , upregulation of PAF receptor expression induced by infection with respiratory viruses, including RSV or coronavirus, results in the enhanced adherence of bacteria to respiratory epithelial cells.
Therapeutic association between fosfomycin and colchicine respresent a useful option for administration through Nebulization .
Alternate routes presented for colchicine could be intranasal or transdermal

References

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