

Inhaled nebulized sodium pyruvate use in COVID-19 patients

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TO THE EDITOR:

Hydrogen peroxide (H_2O_2) is ubiquitous in human tissues [1]. It is also excreted by airway cells including lung epithelia and its modest generation is part of a healthy immune response. Oxidative damage at cell and tissue level, however, is a serious risk factor for infected patients in intensive care units. If transition metal ions are present, H_2O_2 , which is also generated in infected tissues of the coronavirus disease 2019 (COVID-19) patients, triggers inflammation and promotes oxidative damage of airways and among others of lung alveolar epithelial cells. Large amounts of lipid peroxidation by-products in lung cell membranes have been observed in people who died from SARS-coronavirus infection [2]. It was also noted that these oxidized phospholipid moieties can further trigger cytokine production in macrophages and increase the severity of acute lung injury. This exuberant inflammation, often leading to cytokine storm via autocatalytic process, is thus largely responsible for developing acute severe lung and other multi-organ failures in coronavirus infected thus, also in COVID-19 patients. Cytokine storm has even been suggested as the most probable explanation for the enigma of the high mortality of COVID-19 (the illness that is caused by SARS-coronavirus-2) [3].

Nucleophilic addition of hydrogen peroxide to the alpha-carbonyl group in pyruvate can spontaneously take place under physiological conditions resulting in decarboxylation of pyruvic acid [4]. This nonenzymatic detoxifying chemical

reaction results in fast and complete elimination of H_2O_2 from human tissues [5]. The reaction products, namely H_2O , acetic acid, and CO_2 , are harmless. Pyruvate, one of the most ancient metabolically relevant molecules, is a central player of the intermediate metabolism and, consequently of the biochemical carbon-flux in humans. Pyruvate connects the cytosolic Embden-Meyerhof-Parnas pathway to the Szent-Györgyi-Krebs cycle in the mitochondria and influences several other biochemical pathways. Pyruvate, which is an effective physiologic scavenger of hydrogen peroxide, neutralizes oxygen radicals and reduces the concentrations of superoxide anions and inflammatory molecules. By its H_2O_2 and other reactive oxygen species eliminating function, pyruvate metabolism is important in maintaining the redox homeostasis in cells and organs.

Inhalation therapy with nebulized solutions has been widely used in pulmonary patients. This therapeutic method is advantageous when a direct contact of a water-soluble active ingredient with the human airways and lung epithelia is required. The sodium salt of pyruvic acid – sodium pyruvate (NaP), ($C_3H_3NaO_3$), molecular weight: 110.04 g/mol – is soluble in water (100 mg/ml). The solution is clear/colorless to faintly yellow. In a clinical study (NCT00262652), asthmatic patients were given 0.5 mM NaP in 5 ml 0.9% saline solution, nebulized via a Pari LC Plus® reusable nebulizer powered by a ProNeb® compressor (Midlothian, VA, USA). The scope of the research was the development of a nebulized NaP for the treatment of asthma. Although a pilot clinical study showed that 0.5 mM nebulized NaP resulted in a durable (4 hours) 30% reduction of expired H_2O_2 in asthmatics. The larger clinical study was terminated due to poor response by asthmatic patients. Unlike asthma, the outcome of COVID-19, when it has pro-

gressed to an advanced stage, will more probably be dependent on the oxidative injury provoked lung (and other organs) inflammation. Intracoronary NaP (300 mmol/l, 360 ml/h, over 30 minutes) was safely administered to cardiomyopathic patients (NCT00604331). When taken orally, pyruvate (in form of calcium pyruvate), even in massive doses (22–44 g/day) was not toxic. Therefore, also higher dosages of inhaled nebulized NaP, higher than 0.5 mM NaP / 5 ml normal saline, may safely be administered to COVID-19 patients.

CONCLUSIONS

The administration of inhaled nebulized NaP may provide efficient support for hospitalized COVID-19 patients by reducing their inner oxidative inflammatory milieu via diminishing H_2O_2 action and signaling. The use of inhaled nebulized sodium pyruvate solution in the treatment of hospitalized COVID-19 patients with inflammation-related impaired lung functions is suggested.

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"It is health that is real wealth and not pieces of gold and silver"

Mahatma Gandhi (1869–1948), Indian political and spiritual leader