COVID-19 and iodide

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Abstract

Currently, no effective treatment or preventive strategy for COVID-19 exists. Medications targeting viral replication are under investigation but additional strategies may be needed to prevent infections in asymptomatic people.

WHO has suggested there is uncertainty concerning feasibility of antibody-based protection against SARS-CoV-2. Therefore, enhancement of innate immunity seems like a natural option to investigate. Iodide has recently been found to enhance antiviral defenses of the respiratory mucosa as a part of a little known nonspecific antiviral mechanism present in saliva and airways. However, its effectiveness in human is as of yet unproven.

Included in WHO Model List of Essential Medicines, iodide is known to be relatively safe. While iodide supplementation is an unproven idea, it might be helpful in the context of COVID-19 pandemic. Given the relatively low toxicity and low cost of production, a randomized controlled trial of supplemental iodide would be feasible.

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Introduction

On April 17th, 2020 the executive director of WHO Health Emergencies Programme Michael J. Ryan noted WHO is not sure whether SARS-CoV-2 infection produces neutralizing antibodies that provide immunity against reinfection. Preliminary information suggested low percentage of population had produced antibodies, providing little sign of "herd immunity". Therefore, Ryan noted antibody-based herd immunity "may not solve the problem of governments".[1]

If the antibody approach is unfeasible, it could also mean that vaccinations may be unfeasible or unreliable. Even if not, their availability may be long time away. Additionally, vaccinations are usually specific to a single virus, even a single strain, requiring yearly redevelopment and revaccinations. A more practical approach would be broad spectrum, effective against several different, not only strains but types of viruses and even other pathogens such as bacteria.

With COVID-19, we would need to find solutions applicable to even the poorest and the most remote populations. This presents an exciting opportunity: what would be the most minimalist solution to general health, including resistance to infections and cancers? This question leads us towards innate immunity, an approach that has received relatively little attention. Nutritional trace element deficiencies are known to influence innate immunity. Would optimizing innate cellular mechanisms, possibly with intakes significantly above dietary reference intake values, provide a benefit against spread of COVID-19?

Iodide and hypoiodite in the respiratory system

Recently, it has been suggested that iodide (I^-) acts as a protective antioxidant in various tissues in the body.[2] It is oxidized by the peroxidase/H_2O_2 system to hypoiodite, which is a potent oxidant for microorganisms. Iodide effectively scavenges reactive oxygen species (ROS) in human blood cells.[3]

I^- is present in saliva, stomach, intestines, kidneys, thyroid, ovaries, placenta, mammary glands, and, the object of interest in this review, airway epithelium. [2] Fischer et. al. demonstrated the ability of I^- to inhibit viral infections by encapsidated and enveloped respiratory virus particles.[4] A single oral dose of 130 mg potassium iodide was shown to accumulate in upper airway secretions. It was suggested that the delivery of I^- to the airway mucosa may augment innate antiviral immunity.

In cultured cells, with added lactoperoxidase enzyme, this mechanism demonstrated robust activity against the two viruses tested, Adenovirus and respiratory syncytial virus (RSV). Adenovirus is a nonenveloped, protein-encapsidated double-stranded DNA virus while RSV is an enveloped negative-sense single-stranded RNA virus. For comparison, SARS-CoV-2 is an enveloped positive-sense single-stranded RNA virus. Because the mechanism is effective against two different types of viruses, it is likely effective against SARS-CoV-2. The authors suggest that the innate oxidative antiviral system present in airways is nonspecific, broad spectrum mechanism applicable to multiple viruses. [4]

Limitations of this study were related to uncertainty about sufficient availability of lactoperoxidase in human airways, and uncertainty about predominance between iodide and thiocyanate in the airway mucosa, as thiocyanate does not lead to the desired antiviral action. Lactoperoxidase is assumed to be present in the airways of most people but it might not be present uniformly in respiratory tract and nasal passages. Also, slightly acidic airway surface liquid provided the best virucidal result. For further study the authors suggested a lamb model which is known to be similar to humans in regard to LPO expression, innate and adaptive immunity, and susceptibility to viral infection.[4]

Another group studied the mechanism in lamb model and stated that high-dose iodide supplementation can be used in vivo to lessen RSV disease severity through the augmentation of mucosal oxidative defenses.[5] Yet another research group studied the mechanism's variability in inactivating various influenza strains in a cell-free system.[6]

An in vitro study on immunomodulatory effects of iodide on human immune cells suggested that optimally iodide saturated cells could enhance the immune system and improve clearance of infections, but current reference level is primarily set to prevent goiter formation, and optimal whole-body sufficiency levels of iodine are unknown.[7]

Iodine, thyroid and safety

Iodine's antioxidant and apoptotic effects in various tissues and immunomodulatory effects on human immune cells are unrelated to thyroid hormone synthesis and depend on the iodide specific mechanism.[8,7]

The practice of using a saturated solution of potassium iodide (SSKI) as an expectorant for patients with difficulty clearing mucus has been commonly used for decades.[9] The practice is still mentioned on many consumer medical websites. Suggested doses for this practice have varied between 1-3.5 g/day. Relative safety of large doses of potassium iodide (KI) has also been demonstrated in dermatology, where continuous doses of 1-6 g/day of potassium iodide are common.[10,11] Significant side effects have been uncommon. For molecular iodine I_2, safety of chronic administration of 3 mg/day has been shown.[12]

While iodide has potential for thyroid suppression, changes in thyroid hormone indicators are usually transient. For patients with a functional thyroid, chronic excess intake of iodine has no effect on thyroid hormone levels.[13] Acute excess transiently raises TSH; the effect disappears in 1-2 weeks. Levels of free T4 and free T3 may slightly decline for a few days but normalize later. For patients with thyroid nodules chronic excess of iodine may cause a risk of hyperthyreosis. On the other hand, an iodine-containing antiarrhythmic medication amiodarone has been shown to often cause permanent harm, not due to its iodine content but to amiodarone itself.[14]

Iodine and cancers

Different chemical forms of iodine have slightly different effects on the body.[12] Potassium iodide is indicated for general iodine deficiency and skin cancer, whereas molecular iodine (I_2) is indicated for thyroid, breast and prostate cancers.[8] A recent randomized controlled trial using iodine as adjunctive treatment for breast cancer showed significant benefit.[15]

Twenty times higher dietary reference intake of iodine has been proposed as prophylaxis of breast cancer.[8,12] Iodine deficiency also exposes individuals to toxic bromide and fluoride accumulation.[16,17,18,19]

Discussion

The COVID-19 pandemic has exposed limitations of current medical practices based on developing single-virus specific vaccinations and targeted pharmaceuticals, rather than pursuing nonspecific, non-patentable methods targeting a broad spectrum of pathogens. To resolve the pandemic in developing countries, simple, affordable, available approaches to enhance innate immunity may be more desirable than difficult-to-produce, unaffordable designer molecules.

If optimization of innate immunity is ignored, overly specific pharmaceuticals and vaccines are a suboptimal solution. Correctable underlying deficiencies in innate immune response should be addressed first. Suboptimal iodine status may be one of these correctable deficiencies. Optimal dosing remains to be investigated. In severe forms of disease, high doses may be needed in order to obtain optimal antiviral effect in the airways.

National reserves of potassium iodide exist for the entire populations of most nations for prophylactic treatment of radioiodine fallout in the event of nuclear emergencies.[20] Using these reserves to address COVID-19 would be a simple, affordable, immediate option, independent of possible issues with antibody-based approaches.

Correlations between country-level and individual-level iodine statuses, other confounding factors such as other deficiencies and air pollution, and COVID-19 prevalence remain an open question. On a general level, it has been suggested that Europe is iodine deficient.[21] Available country-level iodine status data seems inconclusive with respect to what is currently known about country-level epidemic severity.[22] It may be that the current reference level is too low for optimal prevention. On individual level, insufficiency has been observed especially in pregnant women and the elderly.[7,23]

Conclusion

While COVID-19 prevention with iodide is currently an unproven idea, it might prove helpful. Given the relatively low toxicity and low cost of production, a randomized controlled trial of supplemental iodide would be feasible.

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