Respiratory Infections Early-Stage Medication: Inhalation Formulation & Dosage of PVP Iodine

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Abstract

The Covid-19 pandemic calls for a rethink of pharmaceutical options for treatment of viral respiratory infections. Respiratory infections start primarily at the surface epithelial cells. Being in direct contact with the ambient air, the respiratory system tissue surface is amenable to topical treatment approaches. We evaluate and define options of translating effective wound care treatments into the realm of respiratory infections treatment and preventions. The goal is a broad-range, safe and cheap anti-viral respiratory infections medication, which can be made globally available for early-stage home use.

We propose a new mode of use of the topical antiseptic PVP Iodine (PVP-I). Unlike nasal sprays or oral gargle, we present a controlled inhalation protocol and calculated aerosol dosage, using ultrasonic mesh nebulizers, to disinfect in one treatment modality both the bronchial tree, upper respiratory nasal and throat tissue simultaneously.

Molecular iodine is absorbed from the respiratory system within about 10 minutes. Yet, iodine effectively disinfects most viruses within 1 minute, including SARS-CoV-2. Moreover, the slower to absorb PVP-I complex provides a continuously eluting reservoir maintaining the the airways surface fluids iodine concentration for several hours. We provide: **(i)** Dosage calculation and delivery protocols; **(ii)** Safety analysis based on guidelines, animal trials and WHO review reports; **(iii)** Evaluation of published pilot clinical trials of SARS-CoV-2 with related nasal spray or oral gargle PVP-I treatments; **(iv)** outline potential use and required modification of existing off-the-shelf market products to render the proposed treatment immediately and cheaply available on a global scale – patent free.

Introduction

For developing pharmaceutical treatments for acute respiratory infections (ARI), a significant difficulty is that ARI is not one disease. Rhinoviruses are the most frequent agents and are mostly limited to the naso-pharyngeal tissue. Other common respiratory viruses include influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, human metapneumovirus, human coronavirus, and enteroviruses, all of which have the capacity to spread deeper and induce a more severe illness.

The Covid-19 pandemic highlighted the factual status of lack of widely accessible, cheap and safe, broad spectrum anti-viral medication for respiratory infections. The preferred clinical goal is to have a first-line mild medication treatment available over the counter (OTC) for home use by patients with the appearance of early symptoms, when the suspected infection is primarily limited to the extrathoracic (nasal and throat tissue) and upper bronchial tree regions, for early prevention of the respiratory infection spread and exacerbation.

Figure 1: Most respiratory infections are initiated in the upper respiratory system – extrathoracic & tracheobronchial airways – before propagating deeper in advanced stages of the infection.

Conceptual Approach

There have been some discussions and even clinical explorations of respiratory infections treatment with topical application of disinfectants, particularly PVP-Iodine, limited to spray for nasal infections and/or oral gargles. Our proposed treatment formulation and associate use of ultrasonic nebulized aerosol inhalation delivery have multiple advantages:

- Reach into the bronchial tree and the even the deep lungs.
- Controlled dosage delivery.
- Controlled and predictable deposition in different locations of the respiratory system.
- Uniform dosage deposition over airway surface.
- Simultaneous treatment of the respiratory tract, throat, and nasal cavities.
- Low dependence and low variance in the application of the human end-user.
- Formulation optimized for anti-viral respiratory tract application (unlike prior formulations which were mostly left in the form for topical skin bacteria disinfection).

Pathogenesis of Respiratory Infections

Viral respiratory infections are initiated when virus particles are inhaled and infect primarily the respiratory mucosal surface epithelial cells [5]. It is common in medicine to regard the bronchial tree and the lungs as internal organs. Yet, topologically the respiratory system surface is in direct constant contact with the ambient air in the same way and level of contact as the nostrils. Therefore, at a clinical conceptual level, the respiratory system may be thought of as an external tissue surface amenable to topical treatment. Consequently, we proclaim that topical treatment substances, such as applicable to wound care infection treatment and prevention, might also be applicable to respiratory infections. The main issues to consider are of (i) safety and side effects specific to the respiratory system tissue; and (ii) the technical method of delivery of the required effective antimicrobial inhibitory concentration (IC) to the target inner regions of the respiratory system.

In Covid-19, peak SARS-CoV-2 viral load in the upper respiratory system is at the time of symptom onset in the first week of illness (see Figure-2), declining thereafter (even as symptoms may get aggravated, with infections spread

deeper into the lungs and other body organs), indicating the highest infectiousness potential within the first five days of symptom onset [6]. The pathogenesis of respiratory infections and the Covid-19 pandemic highlights the need for early-stage home medication as key to (i) prevent both the interpersonal spread of infection to avoid future epidemics; and (ii) prevent the intrapersonal spread of infection from the original more benign upper respiratory system location to the more severe deep lungs and other body organs.

Figure 2: The SARS-CoV-2 viral load in the upper respiratory peaks in the first week of infection and declines significantly thereafter, even as symptoms become more severe. Viral culture from PCR positive upper respiratory tract samples has been rarely positive beyond 9 days of illness (adapted from [7]). Therefore, we estimate that the window of opportunity is essentially limited to the first week of infection and early symptoms, for focused upper respiratory system treatment to prevent progression and spread of the Covid-19 infection.

Advantages of PVP-I for Airway Disinfection

PVP-I safety profile is very promising, being already in medical use for sensitive tissue disinfection, including ophthalmic and nasal treatments. Little more needs to be done to formally establish PVP-I safety as aerosol inhalation medication. From the effectiveness perspective, a key advantage is due to an anomalous property of PVP-I. As illustrated in Figure-3, contrary to common intuition, under dilution of PVP-I 10% solution, the disinfecting free iodine concentration does not decrease, but actually *increases with dilution*, following a bell-shaped curve, reaching a maximum at approximately 0.1% strength PVP solution and only then decreasing with further dilution. Therefore, unlike with common antibiotics, we expect the treatment is not sensitive to the dilution factors of deposition in the target airway surface liquid (ASL) which may vary among individual patients or infection development stages.

Analysis

PVP-Iodine: A Unique Disinfection Solution

In more than 150 years of use for medical disinfection, including application to wounds, oral, nasal, and ophthalmic tissue, Iodine hasn't elicited bacterial or viral resistance. Iodine may have too many mechanisms of action for bacteria to adapt to [8]. Presently on the market there are three primary formulations of iodine: (a) A tincture, commonly at 2% concentration; (b) "Lugol's iodine", which has no alcohol, has twice the mass of potassium iodide as of elemental iodine; and (c) PVP-Iodine (PVP-I) water-based solutions, commonly at pH 2.0<pH<5.5. The focus of our analysis is on the potential use of PVP-I solutions. We shall argue that, for anti-viral respiratory infection purposes, it may be **beneficial to implement concentration around 2%, and delivered near neutral pH (pH~7)**.

PVP-I Special Properties

Povidone-iodine (PVP-I) is globally available for sale over the counter. PVP-I is an iodophor solution comprising a water-soluble complex of iodine and the solubilizing polymer carrier polyvinylpyrrolidone (PVP). In aqueous solution, a dynamic equilibrium occurs between free iodine and the PVP-I complex. In terms of concentration labeling, a 10% w/v PVP-I solution, contains 1% w/v total titratable iodine. Yet, this is not the actively available iodine. The PVP-I complex functions as an eluting reservoir, releasing iodine to maintain a stable equilibrium concentration of free iodine. It is only the free iodine which is an active disinfectant, exhibiting a broad range of microbicidal activity against bacteria, fungi, protozoa, and viruses [9]. As the dissolved free iodine is used up when binding to other molecules, further iodine is released from the PVP-I complex, until the available iodine is exhausted. Therefore, its residual antimicrobial activity is maintained stable over an extended period, while side effects associated with iodine such as irritation and brown staining on mucous membranes are reduced.

PVP-I solutions have an important “concentration anomaly”. Over a certain range of PVP-I concentrations, the free iodine concentration actually increases in more diluted concentrations of povidone-iodine. This paradoxical effect follows a “bell curve” (see Figure-3 below): at low concentrations less than 0.05% lose their povidone-iodine complex characteristics and behave like aqueous iodine, the free iodine concentration rises until peaking at 0.1% PVP-I, then decreasing with further increase PVP-I concentration. Correspondingly, in vitro bactericidal efficacy of povidone-iodine has been shown to increase at more dilute concentrations peaking around 0.1% to 1%, with relatively faster killing rates. **An important beneficial consequence in our context of interest is that, unlike the common situation with disinfection and antibiotic substances, as the deposited PVP-I solution is diluted in the respiratory system airway surface liquid (ASL), the microbicidal effectiveness of the PVP-I may not necessarily be diminished.**

Figure 3: Free molecular iodine dependence on PVP-I solution concentration and pH (adapted from data presented in [10,11]).

All of the presently available commercial PVP-I solutions sold on the market are with pH<5.5 (most actually at pH<3.5). Yet, as we argue in the following section, there may be preference for pH~7 for respiratory infections, not only for better safety matching to the pH of the respiratory tissue, but also increased anti-viral potency in spite of the lower free iodine concentration.

The iodine mass portion of the PVP-I complex is about 1/10. i.e., a 1% concentration PVP-I contains 0.1% (i.e., 1 mg/ml = 1,000 mg/L) of iodine. From Figure-3 we can see that for PVP-I solution at pH~7 the equilibrium concentration of free iodine is roughly 1 mg/L. Therefore, initially upon deposition, the PVP-I complex contains a reservoir of 1,000x the free iodine content, which can be eluted continuously to replace used up free iodine.

Optimizing the Antiviral Effectiveness of PVP-I

Iodine solution stability in water is sensitive to pH. A commonly neglected aspect is that the free iodine in the water solution is not present in one form. Dissolved iodine reacts with the water and can adopt a range of oxidation states, such that various iodine species exist in an aqueous environment: -1 to $+5$, e.g., -1 (iodide, I^-); $+1$ (hypoiodous acid, HOI); $+5$ (iodate, IO_3^-), of which only hydrated iodine (I_2), hypoiodous acid (HOI) and iodine cation (H_2OI^+) possess anti-microbial activity [37]. Of key importance to us will be the balance between elemental I_2 and hypoiodous acid (HOI) content, which can be tuned by pH (see Table-1). In particular – **HIO is approximately 40 times more effective than elemental iodine I_2 against viruses** [12] – a fact that is largely neglected in the medical infections treatment literature and research data. The misguided common wisdom and consideration of USP requirements, in present market commercial products, seems to be that the target active ingredient is just the elemental I_2 content. Therefore, **low pH (pH<5) useful for high elemental I_2 content (see Table-1), is the present commercial market products standard. In contrast, we argue that a different standard, of around neutral pH~7, is preferred for an anti-viral medication formulation for respiratory infections** in order to, (a) not alter the respiratory tract natural pH, and (b) increase anti-viral potency with higher content of the HIO.

pH	Iodine		
	I_2 (%)	HIO (%)	OI (%)
5	99	1	0
6	90	10	0
7	52	48	0
8	12	88	0.005
9	-	-	-

Table 1: Effect of pH on the speciation of iodine (0.5% titratable iodine) [12]

Generally, elemental iodine is primarily effective against bacterial spores and protozoan cysts, whereas hypoiodous acid (HIO) is known to be an effective bactericide and virucide. For example, elemental iodine was found to be 2–3 times more effective against *Entamoeba histolytica* cysts than HIO, whereas HIO was found to be approximately 40 times more effective than elemental iodine against viruses [12].

Microbial group	Disinfection effectiveness of different iodine species
Bacteria (vegetative)	HIO > I_2
Bacteria (spores)	I_2 > HIO
Viruses	HIO > I_2
Protozoa ^a	I_2 > HIO

Table 2: Trends in the disinfection power of different iodine species [12].

An important factor is the absorption time from the lungs into the blood stream. Elemental iodine is absorbed to the blood with a half-life of about 10 minutes. Therefore, low concentrations of PVP-I <0.1% would have an effective action time of about 10 minutes post inhalation. The absorption of larger molecules is mostly proportional to the molecular size. PVP used for PVP-I solutions is on average of size 40 kDa. Drawing from information on inhaled albumin (68 kDa) and α 1-antitrypsin (45–51 kDa) having a half-life of multiple hours (since T_{max} in the blood is reached after more than 12 hours) [13], we can assume at least one hours of near original PVP concentration after the initial deposition. Therefore, moderate PVP-I concentration of 1% or more are expected to maintain the eluted free iodine concentration roughly stable for at least 1 hour post initial deposition.

In-Vitro PVP-I Tests of Respiratory Infections Pathogens including SARS-CoV-2

There are multiple published reviews of in-vitro testing of the deactivation effectiveness of PVP-I on both viruses and bacteria. Most relevant respiratory infection pathogens show high susceptibility to PVP-I, with better than 4Log10 (>4Log10) reduction within 30 seconds [14], including multiple recent tests with SARS-CoV-2 [15]. For in-vitro test, it is important to distinguish clean from dirty conditions, where the dirty conditions include interfering substances. Already from bacterial tests, it appears the total reservoir of Iodine is important, leading to 1% PVP-I being significantly more effective than 0.1% under dirty conditions [16]. Recall, this is in contrast with the naïve expectation that the higher free Iodine content of 0.1% PVP-I would make it more effective.

There are several recently published SARS-CoV-2 in-vitro tests of PVP-I application. Off-the-shelf PVP-I products of the concentrations w/v of 10%, 7.5%, 1.0% and 0.45%, were tested adapting the protocol from the EN14476 disinfectant testing methodology. All products demonstrated virucidal activity against SARS-CoV-2, corresponding to ≥ 4 log10 reduction of virus titre, within 30 seconds of contact [18].

Clinical Trials with PVP-I

PVP-I is commonly used to sterilize the ocular surface prior to surgical procedures, and as treatment for adenoviral conjunctivitis. In a pivotal clinical trial published in 1991, during an 11-month period, topical 5% PVP-I was used in over 3,000 patients to prepare the conjunctiva, in addition to customary prophylactic antibiotics. A significantly lower incidence of culture-positive endophthalmitis ($P < 0.03$) was observed. Use of topical 5% PVP-I in the eye in over 3000 patient was not associated with any adverse reactions [20].

3M company developed a PVP-I 5% gelling product pre-operative nasal and skin antiseptic. In a clinical trial, the 3M product sustained a greater than 2Log10 reduction in *S. Aureus* CFU from nasal swabs even 12h post treatment [21].

Figure 4: 3M Skin and Nasal Antiseptic reduction of *S. aureus* in the nares post-prep for subjects with baseline counts of at least 3.4 Log10 [21].

In preoperative cataract surgery 5% vs. 1% PVP-I solutions antiseptics comparison was conducted in a randomized double-blind study of 100 patients. The ocular surface was irrigated with PVP-I for 1 minute. After a further minute a second swab was taken. Bacterial cultures showed a decrease in median colony forming units (CFU) pre-irrigation to post-irrigation drop of 96.7%, compared with a lesser reduction, drop of 40%, when using 1% PVP-I. The authors speculated that PVP-I 1%, although initially more bactericidal, has a lower reservoir of available iodine which is exhausted when the bacterial load is increased [22].

The bactericidal activities of PVP-I, chlorhexidine gluconate (CHG) and cetylpyridium chloride (CPC) gargles were compared. In vivo, with 6 subjects in each group, reduction rate in the oral bacterial count after gargling was measured. The mean reduction rate in bacterial count immediately after gargling was 99.4% for PVP-I, 59.7% for CHG and 97.0% for CPC [23], establishing the effectiveness of PVP-I in-vivo oral secretions environment.

Covid-19 Clinical Trials of PVP-I

Presently there are multiple clinical trials underway around the world of PVP-I treatment or prophylaxis for Covid-19, all of them evaluating oral gargle or/and nasal spray methods of application. Some published pilot trials are already available. The outcome of these clinical trials is indicative of both (a) the realistic disinfection potential, and (b) the safety, of PVP-I on live respiratory system tissue similar to bronchial tree, nasal, and throat tissue.

In a clinical study from 2020, a total of 6,692 patients were evaluated for feasibility, usability and tolerability of the 0.5% PVP-I gargles and nasal drops. Tolerance was assessed in terms of altered taste, staining of teeth or nasal skin or irritation in the nose. None reported any serious reactions or adverse effects following use of 0.5% PVP-I [25].

A pilot, open labeled, randomized, parallel study compared the effect of 30 seconds, 3 times/day gargling using 1% commercial PVP-I and tap water on SARS-CoV-2 viral clearance among COVID-19 patients. Already at day 4 in 100% of patients for the PVP-I tested negative, compared with 40% for tap water gargle, and 20% control group [26].

In contrast, there was no observed effect on Covid-19 PCR test outcome in another recent pilot study, with 12 patients in each arm, also using a 1% PVP-I solution [27].

Inhalation safety of PVP-Iodine

Iodine is an essential nutrient, with well-established mechanisms of absorption and clearance. Allergic reactions to iodine are rare. An inhaled dosage of 1 mL of a 1% concentration PVP-I contains 0.1% Iodine (i.e., 1 mg/mL = 1,000 mg/L) of Iodine. The PVP carrier component safety profiling has been extensively documented in the literature. National regulatory bodies have concluded that PVP usage is safe as both a food-grade additive and also as a pharmaceutical excipient. Absorption studies revealed that there is no or very limited absorption of PVP in humans. Extensive toxicity studies confirmed that the PVP is a biologically inert substance. PVP is found to be non-toxic, non-irritant, non-sensitizer. PVP was found to be safe for oral and topical applications in any manner, including ocular. PVP-I is routinely used in ophthalmology for both treatment and prophylaxis of eye infections [28].

In a study of 23 adult patients in Japan, with chronic respiratory diseases showing repeated infections, patients gargled PVP-I, 4 times/day over periods lasting from several months up to over 2 years. From the safety point of view this clinical study indicates remarkable tolerance of oral and throat soft tissue to daily repeated and extended duration topical exposure to PVP-I contact in respiratory infected patients [29].

Absorption into the Body

The recommended daily intake of iodine by the WHO is 0.15 mg, with acceptable daily intake of PVP up to 50 mg/kg body weight [30]. When healthy patients were given more than 100 times the recommended intake of iodine (i.e., 15 mg) daily for 38 days, there were no deleterious effects [31]. Therefore, even 15 times per day applications of our proposed treatment are established to be safe as far as absorption to the body is concerned. Hence, there remains to consider the organ specific safety considerations for the respiratory tract tissue.

pH Balance

A healthy lung has neutral pH~7 [30]. Reduced airways surface liquid pH facilitates respiratory bacterial infection. Increasing a commercial PVP-I product from an original pH~4 to a desired pH~7 with phosphate buffer decreased ocular irritancy of the antiseptic [30]. Present commercial PVP-I products comprise a pH buffer which stabilizes their pH to 2<pH<5, most commonly around pH~3. Consequently, even a 1/10 dilution with water does not change much the pH level [32]. pH values below 7.0 decrease ciliary beating in vitro (50% at pH = 5.5 and almost 100% at pH = 3.5) [33]. We speculate that when sensitivity of ciliated cells to PVP-I solutions was found in various tests or clinical trials, it was due to the pH of the solution and not the iodine. Therefore, if starting with a commercial PVP-I product solution, it is highly preferred to adjust the pH to pH~7.

Inhalation of PVP-I Clinical & Animal Testing

To our knowledge, deep inhalation testing (i.e., into the bronchial tree) was thus far explored only with iodine vapor inhalation (not droplet aerosol, which is our intended treatment). Rapid absorption of iodine vapor following inhalation is supported by studies in rats, mice, dogs, sheep and monkeys, with a half-life of 10 min [12]. Similarly, human volunteers exposed to radioactive elemental iodine vapor by inhalation showed clearance with a half-life of 10 minutes, with the iodine being removed by mucociliary clearance to the gastrointestinal (GI) tract [12].

As previously noted, there is a large body of human clinical research and experience with sinonasal and throat application of PVP-I, and the associated safety considerations have been recently reviewed [31]. For example, 1% PVP-I sinus rinses were very well-tolerated similar to saline irrigations, when used twice daily for 30 days, for post-surgery treatment with acute exacerbations of chronic rhinosinusitis and gram-positive bacteria on culture [34].

Targeted Dosage Deposition by Aerosol Inhalation

Aerosol droplets deposition distribution is dependent upon the droplet size (See Figure-5). Ultrasonic nebulizers generate a well-defined stream of fixed sized droplets. Common market products have droplets around 5 μm , but this can be easily manufactured to have a different value anywhere between 3 μm - 10 μm . Nasal inhalation (with a mask) would result with most aerosol deposited in the nasal cavity. Therefore, for the treatment of any non-nasal section of the respiratory system, oral inhalation is recommended. Moreover, since typically about 25% of inhaled aerosol gets exhaled, exhalation through the nose can deposit significant aerosol in the nasal cavity target even when inhalation is done orally.

At droplets size of $\sim 5 \mu\text{m}$, a nearly even depositions of 25% is delivered to each of bronchial tree (BT), extrathoracic (ET), deep lungs (alveoli) (see Figure 5), and in exhalation also to the nasal tissue. Therefore, the available common market mesh nebulizer products, having droplets size of about 5 μm are quite suitable for our purpose. Hence, for dosage calculations, e.g., of delivery to a target bronchial tree (BT) tissue, we shall assume 25% deposition efficiency.

Figure 5: Primary structures of the respiratory system and associated nanoparticle deposition fractions when breathing at rest. Adapted from [35].

Distribution of Dosage in the Bronchial Tree

The bronchial tree is a branched tubing system. Antimicrobial drugs exhibit concentration-dependent efficacy. Ensuring an appropriate inhibitory concentration (IC) of these drugs in the relevant body fluid is important for obtaining the desired therapeutic action. For inhaled antimicrobials, the relevant body fluid for drug concentration purposes is the airway surface liquid (ASL) [36], also referred to as epithelial lining fluid (ELF). The delivered dose is deposited onto and diluted by the ASL. We argue that dosage planning, correction, and controlled verification can all be achieved by examining the easily accessible trachea and/or primary bronchi (first generation, G1). Based on deposition models (see Fig. 6), the trachea can serve as a good concentration estimator (to within a predictable factor) and effective lower bound for the local delivery concentration in all 10 first generations of the bronchial tree. Therefore, tracheal concentration is an effective, well-defined, and measurable representative of target IC.

Figure 6: Local concentration of inhaled aerosol in different generations of the bronchial tree, where the trachea is generation 0. Adapted from [36].

Dosage Quantification for Achieving Target Disinfection Inhibitory Concentration (IC)

We focus attention on the bronchial tree (BT) as the key new target tissue for disinfection presented in this article. The total surface area of the bronchial tree is about 1 m^2 ($10,000 \text{ cm}^2$). Using the surface area and mucosal thickness data [36], we estimate the combined mucosal volume in the top half of the bronchial tree to be about 1 mL in a healthy adult.

Table 3: Surface area and mucosal thickness in parts of the bronchial tree (Adapted from [36]).

Generation (k)	Average Thickness (μm)	Airway surface area (cm^2)
0	6.0	71
1+2	5.2	72
3+4+5	4.2	178
6+7+8	3.5	374
9+10+11	3.1	871
12+13+14	2.8	1631

It follows that the disinfection liquid is diluted upon deposition, as illustrated for example in Table-4.

Table 4: Dilution of inhaled PVP-I 1% solution aerosol upon deposition onto the ASL in the bronchial tree (BT) and resulting effective concentration of PVP-I in the BT ASL. 25% deposition fraction in the BT is assumed for typical 5 μ m aerosol.

Inhaled solution [ml]	BT deposited solution dosage (DSD) [ml]	Resulting dilution factor in the ASL of the bronchial tree (BT)	Resulting PVP-I concentration in the ASL from an original initial solution concentration ISC=1% aerosol
1 ml	0.25 ml	20%	0.2%
4 ml	1 ml	50%	0.5%

The dilution may be larger in an inflammation state with excess bronchi secretions. Therefore, it is advantageous to have a disinfection liquid like the PVP-I with a wide range of effective inhibitory concentrations and safety.

Breathing Cycle Losses in Aerosol Delivery

Inhalation represents less than half of the duration of a full breathing cycle. Hence, when aerosols are delivered continuously, we assume about 50% loss by common market ultrasonic nebulizers. This can be ameliorated with the use of breath-actuated nebulizers.

Conclusions: Proposed Formulation & Dosage of PVP-Iodine for Inhalation Treatment

We culminate the analysis with a specific proposal of optimal formulations and delivery protocols for a treatment of viral respiratory infections. First, we collect the threads from our analysis thus far. Then we integrate the conclusions into a specific quantitative frame of a treatment protocol. In addition, we provide a tentative evaluation and guidance for the potential repurposing use of widely available existing market products to realize our proposal.

Collecting the Threads

Goal: A first line, home use, broad range, cheap and widely available (potentially OTC) antiviral respiratory infections medication.

Safety: PVP-I solutions at concentrations 0.5% - 5% and buffered to pH~7 have high safety and tolerance level for deposition in the respiratory tract.

Efficacy: PVP-I solutions at a concentration ~2% and buffered to pH~7 can be assumed to have high virucidal effectiveness within about 10 minutes of active disinfection time after deposition in the respiratory tract, since

- Tests of PVP-I in concentrations between 0.5% to 5% in clinical settings on human nasal, oral, and ocular tissue showed significant active disinfection properties on both viruses and bacteria. Significant disinfection occurred within 1 minute in multiple test cases.
- At pH~7 there is about 50% of the free iodine in the form of hypoiodous acid (HIO) which is about 40x more virucidal than elemental iodine (I_2).
- Elemental iodine showed clearance from the lungs with a half-life of 10 minutes. Therefore, low concentrations of <0.1% PVP-I would have an effective ~10min of action. Yet, with PVP-I complex molecular weight of ~40K Dalton, solutions at concentrations >0.5% would likely maintain free iodine concentration in the airway surface liquid for at least 60 min and possibly multiple hours.

Dosage calculation: Using common ultrasonic nebulizers with 5 μ m droplet size, only about 50% of aerosolized ASD quantity is inhaled, and only 25% of the inhaled quantity is deposited in the BT tissue and another 25% is deposited in the ET tissue. Hence, only around 1/8 of the dosage quantity nebulized continuously by common market nebulizing devices gets deposited into the trachea-bronchial tree and diluted into the airway surface liquid (ASL).

Therefore, by way of example, we outline two possible protocols, one based on a 5% solution and the other based on a 1% solution concentration of PVP-I.

Example Protocol-1: Nebulizing 2 mL, 5% concentration PVP-I for inhalation with a continuous nebulizer. 0.25 mL (1/8 of 2mL) gets deposited onto the trachea-bronchial tree (TB), getting diluted into a preexisting 1mL of ASL, resulting with a 1% PVP-I concentration in the ASL of the trachea-bronchial tree.

Example Protocol-2: Nebulizing 4 mL, 1% concentration PVP-I for inhalation with a continuous nebulizer. 0.5 mL (1/8 of 4mL) gets deposited onto the trachea-bronchial tree (TB), getting diluted into a preexisting 1mL of ASL, resulting with a 0.33% PVP-I concentration in the ASL of the trachea-bronchial tree.

Using Present Market Products – An Immediate Realization Potential

There is availability on the market of commercial PVP-I solutions at concentrations of 5%, 1% and also some 0.5%, most of which are labeled for use as “oral gargle”. These can be used without any dilution. Yet, the most widely available PVP-I solutions are 10% and 7.5% PVP-I solutions, which can be routinely found for OTC purchase in pharmacies, drug stores, and online stores. These can be diluted 1/2 with distilled water. All are buffered at pH<5.5, mostly around pH~3.0. The key preparation step is to adjust the pH of the available market products to 6.5<pH<7.5 by using a pH buffer.

Bacterial Micro-Aspiration Pneumonia Prevention: Elderly Population & Hospital Ventilator Associated Pneumonia (VAP)

Bacterial respiratory infections due micro-aspiration occurs when oral secretions penetrate into the trachea (instead of the esophagus) in sensitive populations. It is a significant risk factor for ventilator associated pneumonia (VAP) in hospital intensive care settings [41] and for the elderly population with dysphagia [38,39,40]. The same formulations and delivery protocols, which we elaborated above for viral respiratory infections, are expected to be applicable also for bacterial infections prevention in the upper half respiratory system (top 10 sections of the bronchial tree). The upper sections of the bronchial tree are exactly the location where bacterial micro-aspiration aspiration start.

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