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The use of Povidone Iodine nasal spray and mouthwash during the current COVID-19 pandemic may protect healthcare workers and reduce cross infection.

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Abstract

In late 2019 a novel coronavirus, SARS-CoV-2 causing Coronavirus disease 2019 (COVID-19) appeared in Wuhan China, and on 11th March 2020 the World Health Organisation declared it to have developed pandemic status. Povidone-iodine (PVP-I) has a better anti-viral activity than other antiseptics, and has already been proven to be an effective virucide *in vitro* against severe acute respiratory syndrome and Middle East respiratory syndrome coronaviruses (SARS-CoV and MERS-CoV). Povidone iodine has been shown to be a safe therapy when inhaled nasally or gargled. We propose that a protocolised nasal inhalation and oropharyngeal wash of PVP-I should be used in the current COVID-19 pandemic to limit the spread of SARS-CoV-2 from patients to healthcare workers (and vice versa) and thus reduce the incidence of COVID-19. There should be regular use in patients with COVID-19 to limit upper respiratory SARS-CoV-2 contamination, but also use by healthcare workers prior to treating COVID 19 patients or performing procedures in and around the mouth/ nose during the pandemic, regardless of the COVID 19 status of the patient. Patients having such procedures should also be treated with PVP-I. The total iodine exposure proposed is within previously recorded safe limits in those without contraindications to its use.

Background

The current COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, represents a significant risk to healthcare workers with infection in this group representing nearly 4% of cases early in the Chinese epidemic[1]. This may place an extra burden on healthcare environments at a crucial time due to staff absence and spread to family members. Additionally, there is a significant risk to non-infected patients already hospitalised, and Wang et al reported in one centre that 41% of their patients had suspected nosocomial transmission[2]. Critical care, for example, represents a high-risk environment for nosocomial transmission of SARS-CoV-2 with procedures such as non-invasive ventilation, intubation and suction[3] causing a bioaerosol that may represent more of a potential inoculum than by community transmission. Saliva contains a high viral load in COVID-19 with up to $1{\cdot}2\times10^8$ infective copies/mL when the saliva of patients was analysed at the time of admission to hospital[4]. It has recently been found[5], through PCR assay techniques, that the nasopharynx appears to have a higher viral load than that found in the oropharynx. As such, we feel it is important that nasal administration of povidone-iodine is of at least as much importance as oral/oropharyngeal treatment. Steps to reduce risk transmission risk from these sources could minimise the overall impact on the healthcare system by reducing transmission from patients to healthcare workers.

Povidone-iodine

Povidone-iodine (iodine with the water-soluble polymer polyvinylpyrrolidone, PVP-I) was discovered in 1955 at the Industrial Toxicology Laboratories in Philadelphia by H. A. Shelanski and M. V. Shelanski. It was developed in order to find an antimicrobial iodine complex that was less toxic than tincture of iodine, which caused burns. The antimicrobial action of PVP-I occurs after free iodine (I_2) dissociates from the polymer complex. Once in the free form, iodine rapidly penetrates microbes and disrupts proteins and oxidises nucleic acid structures. This interaction ultimately results in microbial

death. PVP-I antimicrobial activity is actually enhanced by dilution of the usually available 10% w/w cutaneous solution, from 1:2 dilution up to a 1:100 dilution (0·1%), with a reduction in activity occurring beyond 1:100.[6]

Virucidal activity

PVP-I has higher virucidal activity than other commonly used antiseptic agents including chlorhexidine and benzalkonium chloride[7]. It has been shown to be active *in vitro* against the coronaviruses that have caused epidemics in the last two decades, namely SARS-CoV causing the severe acute respiratory syndrome (SARS) epidemic of 2002–3 and MERS-CoV the agent responsible for causing the Middle East respiratory syndrome (MERS) epidemic of 2012–13.[8,9]

SARS-CoV-2 is highly homologous with SARS-CoV, and as such it is considered a close relative of SARS-CoV[10]. Initial work looking at the virucidal activity of PVP-I against MERS-CoV by Eggers' group[11] showed that the lowest concentration of PVP-I to be effective was (1%) when used for 30 seconds under "dirty" conditions, leading to a reduction of viral activity of ≥99.99%, however this was not effective at 0·1%[11]. In subsequent work by Eggers[12], the concentration tested and yet still effective, was 0·23%. Kariwa showed that treatment *in vitro* of SARS-CoV with various preparations of PVP-I for 2 minutes was enough to reduce viral activity to undetectable levels[8]. The lowest concentration used was 0·23%, found in an over the counter throat spray (Isodine Nodo Fresh®). [11]

Safety and tolerance

Gargled PVP-I is very well tolerated when compared with other gargled antiseptic agents in common use[13]. It has already been shown in clinically successfully trials using nasal inhalation and gargling to reduce the incidence of nosocomial pneumonia by reducing pharyngeal bacterial colonisation[14]. In Japan, iodine intake, largely from seaweeds, averages 1–3 mg per day without significant associated negative health effects, other than the very low possibility of causing or worsening symptoms for people with previously known thyroid autoimmunity or other underlying thyroid issues[15]. Two studies looking at the prolonged use of PVP-I mouthwash showed it did not affect thyroid function, one for a short period used four times daily (2 weeks)[16] and one for substantially longer, used once daily (6 months)[17].

In a study looking at the excretion of iodine in healthy subjects, average ingestion of 88 mg per day for a period of 38 days was undertaken without deleterious effects. They found that the majority of iodine is cleared by the kidneys in urine, but an appreciable amount is excreted in sweat (35% of the plasma concentration) and that faecal excretion is negligible[18]. The renal iodine clearance rate is not influenced by the iodine intake; and the process is neither adaptive nor saturable[19]. The World Health Organisation recommended daily allowance of iodine for an adult is 0·15 mg[20]. PVP-I 10% contains an equivalent of 11 mg/mL of iodine[21]. Our protocol would deliver no more than 6·6 mg per day for the duration of treatment.

With decades of clinical use, the safety profile of PVP-I has been well-established. Allergy to PVP-I is extremely rare[22]; and in a clinical trial only 2 out of 500 patients showed positive contact sensitivity to PVP-I (prevalence: 0·4%)[23] and although there have been occasional reports of type 1 allergy, these are considered exceptional[24]. There have been documented cases of significant iodine toxicity with topical PVP-I use, one after prolonged sinus irrigation[25], the other with prolonged wound application for 3–5 weeks[26], both using a 10% solution of PVP-I.

Clinical Usage

It is in ubiquitous use in the UK and worldwide as a handwashing agent (usually 7.5% solution) and for pre-procedural skin antisepsis (usually 10% solution). *Videne® Antiseptic Solution* (Povidone-

iodine 10% w/w solution, ECOLAB Ltd) is commonly used in the NHS and is licensed for use on skin and mucous membranes. It is used in ophthalmic surgery (often diluted to 5%) and occasionally used in oral surgery at 10%, although chlorhexidine is preferred as it does not alter the colour of the mucosa and is produced as a commercial mouthwash.

The marketing of a PVP-I mouthwash occurred in the 1980s/90s in the UK but it is believed that it was commercially unsuccessful as it caused staining of the teeth. It is still in production in Singapore for use as a 1% w/w mouthwash every 2–4 hours[27] and as a 0·45% w/w 'sore throat spray'[28]. Chlorhexidine mouthwash is used as the main antibacterial mouthwash in the UK, but chlorhexidine is not effective against coronaviruses[7]. We do not know the exact effective concentration of PVP-I in the presence of mucins and saliva, but we assume that using a concentration twice as strong as that found to be viricidal *in vitro* (0.5% versus 0.23%[8,12]).

The topical application of iodine intranasally for the treatment of recalcitrant chronic rhinosinusitis has been described by the St. Paul's Sinus Centre team in Vancouver[29,30]. They used a 0·08% solution, which they found to be beneficial for the management of this condition, but also did not lead to any significant effect on thyroid function, mucociliary clearance or olfaction.

Higher concentrations of 2·2% and 4·4% PVP-I in liposomal dispersions were trialled by Gluck et al in a partially blinded, monocentric, prospective, controlled, randomised, single, 3-fold crossover phase I study. Again, no change in mucosal appearance, olfactory function, ciliary activity or subjective perception of nasal airflow[31]. Additionally, they were able to show that the treatment was tolerable by subjects, and through comet assay that there was no genotoxicity. It is difficult to be certain whether similar observations would be seen in a pure liquid preparation.

The clearance rate of mucin layers in the oral cavity in normal subjects is between 1 and 8 mm per minute which equates to between 200 and 20 minutes in the oral cavity depending on the site and flow rate[32] . Halides including fluoride bind to mucins and would have a similar clearance rate, though the majority would be gone in under 10 minutes[33]. The flow rate of saliva in hospital unconscious patients is very low, and clearance of PVP-I slower than normal.

Method/ Protocol

In the hospital setting, we propose that a 0·5% (5 mg/ml) PVP-I solution be applied to the oral, oropharyngeal and nasopharyngeal mucosa of patients with presumed/confirmed COVID-19 and the healthcare personnel in close contact with this cohort. At these concentrations antiviral activity is still optimal and lasting staining of skin, mucous membranes and teeth is minimal and reversible.

Additionally, we propose the same application of PVP-I for a second cohort that includes all patients having procedures (including examination) in or around the mouth and nose or procedures that transit those areas and the healthcare professional carrying out those procedures. During the current phase (date today 24 Mar 2020) of the COVID-19 outbreak, the second cohort should include all patients, not just those with suspected/confirmed COVID-19 infection. Procedures in the second cohort would include, but not be limited to dentistry and oral surgery, ENT-ORL examination and treatment, endo-tracheal intubation, endoscopy and bronchoscopy.

Exclusion criteria: A history of allergy to PVP-I or its relevant excipients (alkyl phenol ether sulphate (ammonium salt), disodium hydrogen phosphate dodecahydrate), all forms of thyroid disease or current radioactive iodine treatment, lithium therapy, known pregnancy.

Medicament:

There is no commercially available iodine based 'mouthwash' in the UK. Instead, a 10% solution of PVP-I licensed for oral mucosal use (*e.g. Videne® Antiseptic Solution Povidone-iodine 10% w/w solution, Antiseptic Cleanser for Skin and Mucous Membranes, ECOLAB Ltd*) is diluted to 1:20 using sterile water to yield a 0·5% solution.

Pre-administration:

1. Patients are informed of the benefits and risks of the proposed treatment verbally. Exclusion criteria will be checked and verbal consent taken and documented.
2. Healthcare professions will be offered the administration as a form of PPE and they will record their assent on an individual form, akin to that used prior to immunisation (e.g. the 'flu jab').

Method of **application**:

Step 1 – **for all patients/ healthcare professionals in described groups**: The 0·5% PVP-I solution is administered in a dose of 0·3 ml into each nostril, preferably using an atomising device (2 sprays for average device) or if not from a syringe. The contralateral nostril is occluded and the recipient, if conscious, inhales slowly during the atomisation/ instillation. This will give a total dose of 0·33 mg of iodine.

Step 2 – **conscious patients and healthcare professionals**: 9 ml of the 0.5% solution is then introduced into the oral cavity and used as a mouthwash. Care is taken to ensure the solution is distributed throughout the oral cavity for 30 seconds and then gently gargled or held at the back of the throat for another 30 seconds before spitting out. It is assumed that at most 2 ml of the solution will be retained and absorbed, giving an anticipated maximum total dose of 1·1 mg of iodine. If a nasal pump atomising device is used, the volume can be reduced to 0·6 ml (4 sprays), yielding 0·33 mg of iodine. These pumps will not be universally available.

Step 2 – **unconscious patients**. An oral care sponge swab or similar is soaked in 2 ml of 0·5% PVP-I and this is carefully wiped around all oral mucosal surfaces. Most of this solution will be retained in the mouth/ oropharynx (a small amount remaining in the sponge), giving a maximum total dose of 1·1 mg iodine.

Timing of delivery:

Patients hospitalised for confirmed/ suspected COVID 19 and healthcare workers engaged in their care: Steps 1 & 2 should be undertaken every 6 hours for patients and up to four times per day for healthcare workers (maximal frequency two hourly). For healthcare workers, it is advised that steps 1 & 2 are performed prior to contact with the patient/ patients and if repeated contact is occurring, repeated every 2–3 hours, up to 4 times a day.

Patients attending for dentistry/ oral surgery, ENT-ORL examination and treatment, endoscopy and bronchoscopy and any other action to be carried out close/ in the mouth or nose: The patient should undergo steps 1 & 2 prior to examination/ treatment. Healthcare workers conducting the procedure or in close proximity should perform steps 1 & 2 prior to contact with the patient and if multiple patients are being seen, repeat every 2–3 hours, up to 4 times a day.

Discussion

PVP-I is rapidly virucidal in vitro and its use in the manner we propose was recommended by Eggers et al for reduction of coronavirus load in the oral cavity to help prevent MERS-CoV transmission and this has not been contested[11].

There are very few contraindications to using PVP-I as a mouthwash or nasal spray. Its administration is cheap, simple and rapid using our methods. PVP-I is readily available in healthcare worldwide. Sensitisation is extremely rare.

The exact duration of virucidal action of PVP-I once applied to the mucosae is unknown, although thought to be at least 3 hours. Once present on the mucosa the time taken for a viral particle to infect the host cell is also unknown. In addition, in COVID-19, it is not known yet whether the salivary glands are directly infected or what contribution to the salivary virus load is made by plasma passing into the oral cavity via crevicular fluid. Hence in deciding the dosing regimen for patients and healthcare workers we balance the risk of iodine toxicity versus the protective effect of PVP-I.

We do not know the total dose of iodine absorbed by the suggested regimen, however, upon cessation, the extrapolation of excretion data from Nelson et al, suggests complete urinary clearance by 5 days using their slowest clearance data[18].

Conclusion

There is considerable evidence of benefit for the use of PVP-I antiseptic for the maintenance of oral health prevention and treatment of oropharyngeal infections but there is a discordance between the evidence base and clinical practice[34]. As an adjunct to currently recommended PPE, we recommend the immediate and UK-wide use of PVP-I in healthcare workers and their patients as described to minimise the risk of spread of COVID-19.

Contributors

All authors have equally contributed to the design of the paper, the writing of the manuscript and have seen and approved the final manuscript; they all meet the definition of an author as stated by the International Committee of Medical Journal Editors.

Declaration of interests

All authors declare no interests.

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