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

J Kirk-Bayley MRCP FRCA EDIC FFICM
Consultant Intensivist & Anaesthetist, Royal Surrey County Hospital

VS Sunkaraneni LLM FRCS (2009)
Consultant Rhinologist, Royal Surrey County Hospital

SJ Challacombe, PhD, FRCPath, FDSRCS, FMedSci, DSc(h.c), FKC
Martin Rushton Professor of Oral Medicine, King's College London

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. In early SARS-CoV-2 infection, viral titres of greater than 10^7/mL in saliva and nasal mucous can be found; minimisation of these titres should help to reduce cross infection. Povidone-iodine (PVP-I) disinfectant has better anti-viral activity than other antiseptics and has already been proven to be an extremely effective virucide *in vitro* against severe acute respiratory syndrome and Middle East respiratory syndrome coronaviruses (SARS-CoV and MERS-CoV). Its *in vivo* virucidal activity is unknown, but it retains its antimicrobial activity against bacteria *in vivo* intraorally and one application can reduce oral microbial flora for greater than 3 hours.

PVP-I disinfectant has been shown to be safe when administered to the nasal cavity and as a mouthwash. We propose a protocolised intra-nasal and oral application of PVP-I for both patients and their attendant healthcare workers (HCWs) during the current COVID-19 pandemic to help limit the spread of SARS-CoV-2 from patients to healthcare workers and vice versa. The aim is to reduce the viral 'load' in two of the key areas from where droplets and aerosols containing the virus are expectorated (the lower respiratory tract being the other). The aim of use in HCWs is to destroy virus that has entered the upper aerodigestive tract before it has the opportunity to infect the host.

We suggest the protocol is considered for routine use during the care of COVID-19 patients, particularly before any procedure that involves the upper aerodigestive tract, including intubation, nasal and oral procedures, endoscopy and bronchoscopy. We suggest it should be considered when such procedures are carried out in all patients during the pandemic regardless of COVID-19 status, due to the reported significant rates of asymptomatic infection

The total iodine exposure proposed is well within previously recorded safe limits in those without contraindications to its use. The intervention is inexpensive, low risk and potentially easy to deploy at scale globally.

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 causing a bioaerosol that may represent more of a potential inoculum than by community transmission[3].

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, through PCR assay techniques, that the nasopharynx appears to have a higher viral load than that found in the oropharynx[5]. As such, we feel that reduction of nasal viral titres is of at least as much importance as in the oral cavity/oropharynx. Minimising, or at least reducing, viral titres in saliva and nasal mucous expectorated by COVID-19 patients should be a key tenet in the battle to reduce transmission of the disease. Doing so may well lessen the overall impact on the healthcare system by reducing cross-infection from patients to healthcare workers and vice versa.

It is appreciated that virus in sputum from the lower respiratory tract is also of importance, but it is not yet clear how viral titres vary between the upper and lower respiratory tracts. One small Korean study[6] found that viral shedding was high during the early phase of illness, as did Zou[7], and was higher in the upper compared with the lower respiratory tract, decreasing after day 7 of illness.

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 antibacterial activity is 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.[8]

Virucidal activity

PVP-I has higher virucidal activity than other commonly used antiseptic agents including chlorhexidine and benzalkonium chloride[9]. 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.[10,11]

SARS-CoV-2 is highly homologous with SARS-CoV, and as such it is considered a close relative of SARS-CoV[12]. Initial *in vitro* work looking at the virucidal activity of PVP-I against MERS-CoV by Eggers' group[13] 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%[12]. In subsequent *in vitro* work by Eggers[14], the lowest concentration tested and yet still effective against coronaviruses, 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[10]. The lowest concentration used was 0·23%, found in an over the counter throat spray (Isodine Nodo Fresh®) available in Japan.

Safety and tolerance

Gargled PVP-I is very well tolerated when compared with other gargled antiseptic agents in common use[15]. It has already been shown in clinically successfully trials using nasal administration and mouthwash to reduce the incidence of nosocomial pneumonia by reducing pharyngeal bacterial colonisation[16]. 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[17]. A study looking at once daily use of 5% PVP-I mouthwash over a six-month period showed no change in thyroid hormone levels (serum T3/T4 and free T4) with a small increase in TSH levels, although all TSH levels remained in the normal range[18].

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[19]. The renal iodine clearance rate is not influenced by the iodine intake; the process is neither adaptive nor saturable[20]. The World Health Organisation recommended daily allowance of iodine for an adult is 0·15 mg[21]. PVP-I 10% contains an equivalent of 11 mg/mL of iodine[22]. Our protocol would deliver less than 6 mg per day for the duration of treatment of patients and less than 4 mg per day for staff, dependent on the method of application as described in 'Method of application' below.

With decades of clinical use, the safety profile of PVP-I has been well established. Allergy to PVP-I is extremely rare[23]; and in a clinical trial only 2 out of 500 patients showed positive contact sensitivity to PVP-I (prevalence: 0·4%)[24] and although there have been occasional reports of type 1 allergy, these are considered exceptional[25]. There have been documented cases of significant iodine toxicity with topical PVP-I use, one after prolonged sinus irrigation[26], the other with prolonged wound application for 3–5 weeks[27], both using a 10% solution of PVP-I.

Clinical Usage

PVP-I is in ubiquitous use worldwide, both as a handwashing agent (usually a 7·5% solution containing foaming agents) and for pre-procedural skin antisepsis (usually simply as a 10% solution). The 10% is commonly used, and is licensed for, use on skin (multiple applications) and mucous membranes (single application – always review summary of product charateristics)It is used in ophthalmic surgery (often diluted to 5%) and occasionally used in oral surgery at 10%.

PVP-I is commercially available in the Far East as a 1% w/v mouthwash for use every 2–4 hours[28] and as a 0·45% w/v 'sore throat spray' for use every 3–4 hours[29]. Chlorhexidine mouthwash is used as the main antibacterial mouthwash in the UK, but chlorhexidine is not effective against coronaviruses[9]. 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 virucidal *in vitro* (0·5% versus 0·23%[10,14]) will be effective, allowing for dilution due to saliva.

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[30,31]. 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. PVP-I use in the nasal

cavity to reduce infection or spread is rational for COVID-19 after two recent trials have demonstrated higher viral load there when compared with the oral cavity.[7,32]

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 were found[33]. 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[34]. Halides, including fluoride, bind to mucins and would have a similar clearance rate, though the majority would be gone in under 10 minutes[35]. The flow rate of saliva in hospital unconscious patients is very low, and clearance of PVP-I slower than normal.

Suggested Protocol

In the hospital setting, we propose that a 0·5% PVP-I solution (0·55 mg/mL available iodine) 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 staining of 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 (April 2020 onwards) 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 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, renal failure and dermatitis herpetiformis. The protocol should not be used in a sustained manner in children, but can be used as a single episode, *e.g.* for dental treatment.

Medicament:

There is currently no commercially available iodine based ‘mouthwash’ in the UK. Instead, a 10% solution of PVP-I licensed for oral mucosal use is diluted to 1:20 using sterile water to yield a 0·5% w/v solution, which has 0·55 mg/mL available iodine. This is an ‘off-label’ use of a licensed product, although a single application of diluted (or un-diluted) PVP-I to mucosa for antisepsis may be on licence – check summary of product characteristics.

Pre-administration:

1. Patients must have exclusion criteria checked and to be informed of the benefits and risks of the proposed treatment, with verbal consent taken and documented.

2. Healthcare professions to be offered the administration as a form of PPE, with risks and potential benefits explained and consent gained akin to prior to immunisation (e.g. the 'flu jab'), again after checking exclusion criteria

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 0·28–0·3 ml into each nostril, preferably using an atomising device (2 sprays for an average device) or if not from a syringe. The contralateral nostril is occluded and the recipient, if conscious, sniffs (with mouth closed) during the atomisation/instillation in order to maximise coverage of the nasal cavity and nasopharynx. 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% PVP-I 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 1 mL of the solution will be retained (based on self-testing using high-accuracy scales, subtracting salivary production) and absorbed, giving an anticipated maximum total dose of 0·55 mg of iodine. If a nasal pump atomising device is used, 7 sprays are used aimed in different directions and then 'licked' around the inside of the oral cavity, yielding 0·54 mg of iodine (0·14 mL per actuation for most commercially available nasal atomisers at 0·077 mg iodine per actuation).

Step 2 – **unconscious patients**. At the time of routine mouthcare, an oral care sponge swab or similar is soaked in 2 mL of 0·5% PVP-I solution and 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 per day. This will give a maximum iodine intake of 3·52 mg for HCW and conscious patients and 5·72 mg for unconscious patients.

Patients attending for dentistry/oral surgery, ENT examination and treatment, endoscopy and bronchoscopy and any other action to be carried out close to or in the mouth or nose: The patient should undergo steps 1 & 2 prior to examination or 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. Dosages are the same as above, but are single exposures for patients.

Discussion

The evidence presented suggests that application of povidone iodine to the nasal and oral mucosae, including the oro/nasopharynx, of patients with COVID-19 may significantly reduce the viral load in those key anatomical areas. This may reduce the risk of transmission to HCW providing routine care as well as allowing a period of time to perform procedures at reduced risk. Further reduction of risk of transmission may be achieved by similar application of PVP-I to the HCW providing the care as a form of prophylaxis. We therefore propose that for the duration of the current COVID-19 pandemic

urgent consideration should be given to the application of PVP-I to patients and HCWs as described above. This includes patients with no symptoms of COVID-19 having procedures in or around the mouth and nose or procedures that transit those areas and the healthcare professionals carrying out those procedures due to the high incidence of asymptomatic infection.

We accept, however, that direct testing and demonstration of the virucidal activity of PVP against SARS-CoV-2 has not been documented. However, the evidence in the literature shows that 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[13]. The proposed protocol is for disinfection of the oral and nasal cavities, akin to the recommended practice of hand sanitisation for transmission reduction, but at the major route of spread (potentially preventing infected patients from passing on the virus) and at a portal of virus entry for HCW (potentially protecting them from being infected via the nose/mouth). It is accepted that aerosolised secretions from the lower respiratory tract almost certainly have a part to play in disease transmission and therefore that this proposal forms only part of the strategy to reduce transmission, as an adjunct to other elements of personal protective equipment.

This intervention is not provided with curative intent for the disease, but may provide a major step to dramatically reduce viral spread within the healthcare workplace. In low and middle-income countries that are soon likely to suffer expansion of the pandemic, the number of healthcare workers per capita is considerably lower, and conventional physical personal protective equipment will probably be in very short supply. Every possible step should be taken to keep HCWs from being infected and able to offer care to reduce mortality from COVID-19. The proposed intervention is applicable to every HCW exposed to both proven or suspected cases to reduce their risk. Additionally, use in clinical scenarios where there is prolonged close proximity of the upper aerodigestive tracts of patients and HCWs combined with aerosol generating procedures, such as general dental practice and ENT clinics, may reduce transmission, especially when treating patients with asymptomatic COVID-19.

It has been assumed that PVP-I shows the same virucidal activity to SARS-CoV-2 *in vitro* as has been shown with other coronaviruses, but the exact duration of virucidal action of PVP-I once applied to the mucosae is currently unknown, as is the length of time for the viral load to recover to pre-treatment levels, or if it does at all. However, in ventilated patients PVP-I solution has been shown to significantly reduce bacterial flora for at least three hours[36]. The high levels of SARS-CoV-2 in both the nose and oral cavity strongly suggest that productive replication is occurring in the mucosae in both sites. Both nasal and oral tissues have been shown to express the ACE-2 receptor[38] and epithelial cells lining salivary duct cells may be early targets of infection by coronaviruses[39] as well as nasal goblet and ciliated cells in the nose[40]. On the basis of these studies and the clearance rate of mucins from both nose and mouth, we suggest that an expectation of a 20-minute window of lowered viral loads is reasonable, although once present on the mucosa the time taken for viral particles to infect host cells and replicate is also unknown. Research is currently being undertaken to determine if PVP-I kills SAR-CoV-2 in the human oral and nasal cavities and, if so, the duration of virucidal action on mucosae.

We consider that it is important to avoid aerosols from either nose or mouth since droplets of even a few microlitres may contain many thousands of infectious virus particles. Thus, the application of the nasal spray requires insertion into the anterior nares and a sniff with concurrent occlusion of the contralateral nose and a closed mouth to avoid bioaerosols from the mouth or nose. The American Dental Association have recently published interim guidelines for minimising the risk of COVID-19 transmission which includes the use of a pre-operative 0·2% PVP-I mouthwash[41].

For the ventilated patient there is possible added value of the suggested PVP-I protocols. Adverse effects of ventilation include rhinosinusitis and aspiration pneumonia. Nasal and oral bacterial loads[37] are significantly reduced by PVP-I and PVP-I use is a recommended therapeutic intervention for recalcitrant rhinosinusitis[30] and for prevention of aspiration pneumonia[36].

The total dose of iodine absorbed by the suggested regimen is not known exactly. If 100% of the nasal spray used were to be absorbed and a similar amount absorbed from the mouthwash, then this would amount to 5·72 mg of iodine per day. For staff, who would be potentially exposed to prolonged use, this figure is 3·52 mg per day. This is far below experimental studies showing lack of any toxicity after ingesting 88 mg daily for 28 days[19] and close to normal dietary intake in Japan[17]. In Ader's study[18], 6 months of use of daily 5% PVP-I mouthwashes, equivalent to 5·5mg per day if 1 mL is retained and absorbed as estimated in this paper, caused no change in serum T3, T4 or free T4. While there was a small increase in TSH, in all subjects this remained within normal range[18]. In addition, upon cessation, the extrapolation of excretion data from Nelson et al[19], suggests complete urinary clearance by 5 days using their slowest clearance data, and our use is far below their maxima, which yielded no ill effects. For perspective, taking 200 mg of amiodarone once per day would be expected to release 7·5 mg of free iodide[42]. Hence we believe that as long as the exclusion criteria are followed, there should be no deleterious effect to HCW or patients due to increased iodine intake from this protocol.

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. 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.

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 noted discordance between the evidence base and translation into clinical practice[37]. As an adjunct to currently recommended PPE used during management of COVID-19 patients, we recommend the consideration of immediate use of PVP-I in healthcare workers and their patients as described to minimise the risk of spread of the disease. We acknowledge that the proposal we present extrapolates *in vitro* finding into the *in vivo* setting and that assumptions are made that under normal circumstances we would confirm with *in vivo* data prior to recommendations for use. However, given the strength of *in vitro* evidence and the low risk, minimal cost and global applicability of the proposed intervention, which amounts to disinfection of the oro/nasal cavities, we feel that there is little to lose and potentially much to gain.

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