REVIEW ARTICLE

IJCP THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Practical use of povidone-iodine antiseptic in the maintenance of oral health and in the prevention and treatment of common oropharyngeal infections

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SUMMARY

Aims: To better inform medical practitioners on the role of antiseptics in oropharyngeal health and disease, this article focuses on povidone-iodine (PVP-I), an established and widely-available antiseptic agent. **Methodology:** Review of the anti-infective profile, efficacy and safety of PVP-I in managing common upper respiratory tract infections such as the common cold, influenza and tonsillo-pharyngitis, as well as oral complications resulting from cancer treatment (oral mucositis), and dental conditions (periodontitis, caries). **Results:** Antiseptics with broad-spectrum anti-infective activity and low resistance potential offer an attractive option in both infection control and prevention. While there is some evidence of benefit of antiseptics in a variety of clinical settings that include dental and oral hygiene, dermatology, oncology, and pulmonology, there appears to be discordance between the evidence-base and practice. This is especially apparent in the management and prevention of oropharyngeal infections, for which the use of antiseptics varies considerably between clinical practices, and is in marked contrast to their dermal application, where they are extensively used as both a prophylaxis and a treatment of skin and wound infections, thus minimising the use of antibiotics. **Conclusion:** The link between oral and oropharyngeal health status and susceptibility to infection has long been recognised. The high rates of antibiotic misuse and subsequent development of bacterial resistance (e.g. increasing vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA)) in large parts of the world, especially across Asia Pacific, highlight the need for identifying alternative antimicrobials that would minimise the use of these medications. This, together with recent large-scale outbreaks of, for example, avian and swine influenza virus, further underline the importance of an increasing armamentarium for infection prevention and control.

Review criteria

Data were collected through PubMed using specified search criteria based on efficacy, safety and microbicidal activity of PVP-I. Other health-based search engines that included the Cochrane Library were also used to search for reviews on antiseptic use in defined clinical settings. General searches using Google for non-English articles on PVP-I were also conducted. Expert opinion was sought in areas of limited published information such as optimal duration of PVP-I treatment.

Message for the clinic

While the current evidence-base for antiseptic use in the oropharyngeal setting *per se* is limited compared with other settings, studies of PVP-I demonstrated effectiveness against a broad spectrum of common mouth and throat pathogens and minimised the risk of upper respiratory tract infections, certain dental conditions, and severity of cancer therapy-associated oral complications. Use of PVP-I may thereby assist in the rationalisation of antibiotic prescription.

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Disclosures

Dr Jeeve Kanagalingam is a Consultant to Mundipharma Pte Ltd; Dr Rebecca Feliciano is a Consultant to Mundipharma Pte Ltd; Professor Jeong Hun Hah is a Consultant to Mundipharma Pte Ltd; Dr Hussein Labib is a Consultant to Mundipharma Pte Ltd; Dr Tuan Anh Le is a Consultant to Mundipharma Pte Ltd; Professor Jin-Ching Lin is a Consultant to Mundipharma Pte Ltd. Authors have no other disclosures.

Oral health and disease

The status of the oral and oropharyngeal cavities, which includes the mouth and throat, is inextricably linked to the general health and well-being of an individual (1). Colonisation by pathogenic micro-organisms or an imbalance of the physiological microbiome in the oral cavity can play an essential role in the development and perpetuation of disease (2,3). Indeed, viruses, bacteria, fungi and protozoa can give rise to many common oral and oropharyngeal conditions, as diverse as dental caries, periodontal disease, gingivitis, as well as upper respiratory tract infections such as sore throat, common cold and influenza (2). In the hospital setting, colonisation of pathogens in the oropharyngeal region can result in more serious sequelae in intubated patients, where their spread into the lower respiratory tract can result in ventilator-associated pneumonia (VAP) (4). This underscores the importance of exercising good mouth and throat hygiene as a means of minimising risk in the development of both community-acquired and hospital-acquired infections.

Oral complications are known to develop in cancer patients, either as a direct consequence of the malignancy or because of side effects of therapy (5–9). Appropriate and timely oral care measures have been shown to minimise the severity of complications and improve patient quality of life (10,11). Consequently, several clinical guidelines and systematic reviews sup-

port preventative oral health regimens that include tooth brushing, use of mouthrinses, gargling and professional oral care, as important components to infection control practices (12–16).

Antiseptics appear to be suitable candidates as alternative or adjunctive agents to antibiotics to prevent and treat infections based on evidence of their benefit in dental (17), dermatology (18), and general oral health settings (19). Currently, such practices for oropharyngeal conditions are less well established. The objective of this review was to assess the published evidence on the efficacy and safety of the widely known antiseptic, povidone-iodine (polyvinylpyrrolidone iodine, PVP-I), considered an effective first-line option in the prevention and management of skin infections (20), in common upper respiratory tract infections, oral complications resulting from cancer treatment and in general dental conditions.

Methods

Search methods included electronic databases such as PubMed, library catalogues, the Cochrane Oral Health Group, and the Cochrane Ear, Nose and Throat Disorders Group; as well as Google using a combination of search terms such as: 'antiseptics', 'microbial', 'clinical trials', 'povidone-iodine', 'oral health', 'throat', 'respiratory infections', 'oral mucositis' and 'dental'. The search was not restricted to English language articles.

Antimicrobial activity of PVP-I

The mouth and throat of healthy individuals are known to be inhabited by hundreds of diverse bacteria, fungi, protozoa and viruses that colonise different surfaces of the oral and oropharyngeal cavities (21,22). These micro-organisms may associate to form biofilms, which are resistant to antibiotic treatment. While many micro-organisms can be protective, an ecological shift because of an environmental trigger can initiate a cascade of events that leads to pathogenic changes and ensuing disease (23). Indeed, the transition from an asymptomatic 'healthy' carrier to invasive disease is reflected by a change in the microbial flora (24). The exact mechanism of this change is unclear, although poor oral hygiene, a compromised immune response and genetics are thought to play a part (23). Interestingly, inflammation, the body's defence against injury or infection, has itself been proposed as a mechanism for propagating infection by promoting the growth of dysbiotic microbial communities that have evolved to not only withstand but also exploit the otherwise hostile environment (25).

The oral and oropharyngeal cavities act as reservoirs for a broad variety of potentially pathogenic micro-organisms (Table 1). This indicates a need for antiseptic agents with broad-spectrum activity, as well as oral formulations that ensure whole oral and oropharyngeal antiseptic coverage.

Povidone-iodine is considered to have the broadest spectrum of antimicrobial action compared with other common antiseptics such as chlorhexidine, octenidine, polyhexanide (20) and hexetidine (26) showing efficacy against Gram-positive and Gram-negative bacteria, bacteria spores, fungi, protozoa and several viruses (20). Persistency of effect has also been demonstrated in a study that assessed 1% PVP-I as a preprocedural antibacterial agent in individuals with varying degrees of oral hygiene (27). Reductions in micro-organism concentrations were found to be sustained for at least 4 h (27). Furthermore, there is some evidence that PVP-I is able to restore the natural microbial flora following bacterial infection, as observed in the setting of bacterial vaginosis (28). In a prospective, randomised clinical trial in women with bacterial vaginosis, treatment with PVP-I led to rapid re-colonisation of native lactobacilli (28).

Bactericidal activity

In a study using gargle and mouthwash samples from healthy volunteers, PVP-I was found to elicit stronger bactericidal activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* than benzethonium chloride (BEC) and chlorhexidine gluconate (CHG) (29). PVP-I has also been shown *in vitro* to be effective against highly resistant *Enterococcus faecium* (30), as well as coagulase-negative *Staphylococci* (31), strains of *Proteus*, *Serratia* and *Pseudomonas* (32), and various *Mycobacteria* strains (33).

Moreover, in a study comparing the bactericidal activities of PVP-I gargle with CHG and cetylpyridinium gargles against isolate and standard strains of Gram-positive (MRSA) and Gram-negative bacteria (*P. aeruginosa* and *Klebsiella pneumonia*), PVP-I was found to elicit rapid killing of all three strains after 30 s of exposure and at all dilutions. In contrast, chlorhexidine (CHG) failed to kill any of the strains at any time-point and at any dilution; and cetylpyridinium chloride (CPC) was found to be effective only against Gram-negative strains and only after 60 s of exposure (34). Hexetidine has been shown to have smaller antimicrobial spectra than PVP-I and even CHG (26), and considered less effective in reducing the burden of dental plaque bacteria than CHG (35).

In another comparative study, the bactericidal activity of PVP-I and BEC gargles against *Bordetella*

Table 1 Common oral and oropharyngeal pathogens

Gram-positive bacteria	Gram-negative bacteria	Viruses	Fungi
Streptococcus spp.	*Pseudomonas aeruginosa*	Herpes simplex virus	*Candida albicans*
Staphylococcus spp.	*Neisseria* spp.	Cytomegalovirus	*Candida tropicalis*
Enterococcus spp.	*Escherichia coli*	Varicella zoster virus	*Candida glabrata*
	Bacteroides		*Candida krusei*
	Klebsiella spp.		*Aspergillus* spp.
			Mucormycosis spp.

pertussis strains were assessed. PVP-I showed rapid (20 s of exposure) and high bactericidal activity in contrast to BEC gargle, which had low bactericidal activity against *B. pertussis* (36).

Virucidal activity

Povidone-iodine has been reported as having the highest virucidal activity profile among several antiseptics such as CHG, benzalkonium chloride (BAC), BEC and alkyldiaminoethyl-glycine hydrochloride (AEG) (37). Using a standardised *in vitro* approach, PVP-I gargle was found to inactivate a panel of viruses that included adenovirus, mumps, rotavirus, poliovirus (types 1 and 3), coxsackie virus, rhinovirus, herpes simplex virus, rubella, measles, influenza and human immunodeficiency virus. In this study, CHG, BAC, BEC and AEG were ineffective against adenovirus, polio virus and rhinovirus but generally showed activity against the other aforementioned viruses (37).

In a more recent study, PVP-I products, that included gargle and throat spray, demonstrated rapid virucidal activity against both a highly pathogenic (H5N1) and low pathogenic (H5N3, H7N7 and H9N2) strains of avian influenza A viruses, with viral titres falling below the detection limits of the assay with only 10 s of PVP-I incubation (38). Similarly, these formulations also showed efficacy against a severe acute respiratory syndrome coronavirus strain, with PVP-I mediating rapid inactivation of the virus (2 min of treatment) (39). Furthermore, the results of a study confirmed the virucidal efficacy of PVP-I products including PVP-I gargle against swine influenza viruses (H1N1, H3N2 and H1N2) (40).

Fungicidal activity

Povidone-iodine has also shown rapid activity against *Candida* species *in vitro*, ranging between 10 and 120 s from contact to kill time (41). *Candida albicans*, a major opportunistic pathogen and cause of recurrent oral thrush and oropharyngeal candidiasis, which is a particular problem in HIV/AIDS patients, can require expensive treatment with antifungal medications. PVP-I has been shown to be highly active against this species and its use has been reported to reduce medical costs associated with fungal infections (42).

Taken together, these data support the *in vitro* efficacy of PVP-I in eradicating a broad range of pathogenic micro-organisms that are likely to play an aetiological role in the development of common oral infections.

PVP-I mechanism of action

The active moiety, non PVP-bound ('free') iodine is released into solution from the PVP-I complex. PVP itself has no microbicidal activity but rather delivers the free iodine to target cell membranes. It is this free iodine that mediates the basic mechanism of action (oxidation of amino acids and nucleic acids in biological structures), which is difficult, if not impossible, to counteract. This basic mechanism of action leads to strong microbicidal activity expressed by multiple modes of action that include the disruption of microbial metabolic pathways, as well as destabilisation of the structural components of cell membranes, causing irreversible damage to the pathogen. Consumed free iodine is then replaced by PVP-bound iodine. The concentration of free iodine is the determining factor of the microbicidal action of PVP-I (43–45). PVP-I exposure leads to destruction of cytosolic and nuclear structures in bacteria and damage to the cell wall in fungi (26,46). In a study investigating the virucidal activity of different disinfectants, electron micrographs revealed how exposure to iodine led to degeneration of the nucleoproteins of viral particles, which was the main mechanism of action (47). However, disruption of surface proteins essential for the spread of enveloped viruses has also been noted (48). In addition to a direct killing action on bacteria, PVP-I also inhibits the release of pathogenic factors such as exotoxins, endotoxins and tissue-destroying enzymes (49). Furthermore, iodine is

a scavenger of free radical oxygen species, contributing to anti-inflammatory properties (50).

Microbial resistance of PVP-I

Given the issue of antibiotic resistance, a critical characteristic of an antiseptic is one that has no or low resistance potential (20,51). From our extensive review of the literature, there have been no clinical reports of microbial resistance development in response to PVP-I treatment. This is likely due to its action on multiple pathogenic targets (52). In contrast, bacterial resistance to chlorhexidine has been documented (53). Resistance may result in alteration in bacterial susceptibility, in part, by altering the outer membranes of Gram-negative bacteria and preventing antiseptic adsorption (20). Genes conferring resistance to chlorhexidine and quaternary ammonium compounds have been identified in up to 42% of *S. aureus* isolates in Europe and Japan (54,55); and while there are reports of cross-resistance between antiseptics, PVP-I has remained unaffected (46,52).

The role of PVP-I in common respiratory infections

Upper respiratory tract infections (URTIs) are one of the most common reasons for presentation to primary practice by adults and children, and are a major cause of mild morbidity (56). Symptoms range from the common cold, cough, pharyngitis and fever to occasionally more serious complications, and are associated with high societal costs due to loss in productivity, absenteeism from school and medical resources (57). Most URTIs are caused by viruses, such as adenovirus, rhinovirus, influenza, coxsackievirus, herpes simplex virus, coronavirus and respiratory simplex virus (58). However, current practices do not often consider the aetiological basis of the URTI, leading to inappropriate antibiotic prescription for URTI that are of viral origin (59). This is particularly evident in the treatment of pharyngitis or sore throat, where only 5–30% of cases are because of bacterial infections (60). Inappropriate and overuse of antibiotics further reinforce the importance of identifying alternative anti-infective agents (61) to complement physical and barrier interventions e.g. handwashing and wearing of masks to prevent and interrupt the spread of respiratory pathogens.

The first step in the development of URTIs is the adherence and colonisation of the respiratory pathogen to the oropharyngeal mucosa. Assuming oral entry of such pathogens, gargling offers a practical measure for their eradication (62). Gargling has been strongly advocated for both prevention and treatment of URTIs in Japan, a practice supported by findings from studies that looked at the role of gargling in both healthy individuals and those with frequent or persistent respiratory infections (62–64). In these studies, gargling with either water or PVP-I (four times daily), respectively, were found to reduce the incidence of URTIs. Furthermore, in patients experiencing chronic respiratory infections, PVP-I was found to reduce the episodes of infections with *P. aeruginosa*, *S. aureus* (including MRSA) and *H. influenzae* by half (62). These findings were further corroborated by a non-randomised study in which gargling with diluted PVP-I reduced the incidence of influenza-like illnesses or the common cold and subsequent absenteeism from school and the work place (65). While the mechanism of gargling in the prevention of respiratory infections requires further investigation, an early study suggests that gargling may lead to the removal of oral/pharyngeal house dust mite protease which has been shown to increase infectivity of the influenza virus (64,66). Gargling, intensified by the presence of PVP-I, may therefore play an important role in the prevention or reduction in the incidence of infection through droplet transmission.

Indeed, the benefit of gargling with PVP-I has been noted in Japanese clinical respiratory guidelines that recommend gargling with PVP-I (four times a day) in both inpatients and healthcare workers for the prevention of hospital-acquired pneumonia (67). PVP-I has also been recommended as a preventative measure against pandemic influenza (68,69).

The bactericidal activities of PVP-I gargle were further explored in a study of children attending middle schools in Japan and their effects on absenteeism because of colds or influenza were assessed (34). The mean reduction rate in bacterial count immediately after gargling with PVP-I was 99.4% vs. 59.7% and 97.0% with CHG and CPC respectively. Furthermore, the more effective reduction in bacteria count with PVP-I correlated with lower absence rates because of cold and influenza compared with the other schools where the use of other gargles were encouraged (34).

Respiratory infections in the hospital setting such as aspiration pneumonia or VAP are major issues, especially in elderly people and immunocompromised patients and are associated with high rates of mortality (70,71). Moreover, individuals with gastro-oesophageal reflux disease (10–20%) can develop recurrent or chronic aspiration pneumonia because of aspiration of gastric contents into the lungs (72). Pneumonia is also common in patients on mechani-

cal ventilation resulting from aspiration of salivary bacteria into the lower respiratory tract (73).

In a prospective, randomised study, the efficacy of a PVP-I rinse on the prevalence of VAP in patients with severe head trauma who were expected to need ventilation, was assessed. When compared with those who received saline and control (no rinsing), significantly fewer patients in the PVP-I group ($p = 0.03$ and 0.01, respectively) developed VAP (74).

In another randomised study, the efficacy of PVP-I in mechanical and chemical prophylactic oral cleansing in reducing oral respiratory pathogens in patients requiring endotracheal intubation was assessed. Cleaning with PVP-I resulted in significant reductions in microbial counts of *S. pneumoniae* ($p < 0.05$) and *H. influenzae* ($p < 0.05$) (75). In a separate study assessing the prophylactic use of PVP-I gargle in reducing the risk of nosocomial pneumonia, PVP-I was found to eradicate both general bacteria and MRSA colonies in the pharynx before intubation and at the tip of the tube after extubation (76).

These studies provide a strong rationale for the use of PVP-I as an effective oral care measure to reduce the burden of potential pathogens and minimise the risk of infection in both community-acquired and hospital-acquired settings.

The role of PVP-I in oral mucositis

Oral mucositis (OM) is a common and debilitating complication of cancer therapy, affecting 80% of patients undergoing radiotherapy for head and neck malignancies (77), and over 40% of patients undergoing chemotherapy (78). Significant associations between mucositis and the development of serious clinical outcomes such as pain, infection, impaired nutritional status and weight loss have been observed (79). Importantly, these symptoms can lead to disruption in cancer therapy (80). In a retrospective sample of patients with solid tumours or lymphoma who developed chemotherapy-induced myelosuppression, episodes of infection were significantly more common during cycles with OM (any grade) than during cycles without OM (68% vs. 36%, respectively), and this was directly proportional to the severity of OM (81).

The pathogenesis of oral mucositis involves direct and indirect mechanisms. Direct mucosal injury by radiation and chemotherapy interfere with the average 5- to 14-day turnover time of the oral epithelium and induce apoptosis. Indirect stomatotoxic effects that result from the release of inflammatory mediators, loss of protective salivary constituents and therapy-induced neutropenia have been postulated to contribute to the development of oral mucositis and also to promote the emergence of bacteria, fungi and viruses on damaged mucosa (82).

Several studies have demonstrated that maintenance of good oral hygiene through prophylactic and therapeutic approaches reduces the severity of OM (83–86). Oral decontamination may assist in reducing bacteraemia and infection by opportunistic pathogens (87). The MASCC/ISOO guidelines recommend a combination of toothbrushing, flossing and at least one mouth rinse (88).

The efficacy of PVP-I preparations on radiation-induced OM have been explored in numerous studies. A reduction in the onset (2.25 weeks vs. 1.5 weeks; $p < 0.05$), severity (mean grade 1.0 vs. 3.0; $p < 0.005$) and duration (2.75 weeks vs. 9.25 weeks; $p < 0.001$) of oral mucositis was demonstrated when PVP-I was used four times daily as part of a standard prophylactic mucositis regimen compared with the standard regimen (nystatin, dexpanthenol, rutoside and immunoglobulin) alone (89,90). Similarly, when PVP-I was used in a multi-agent mouthrinse, the incidence and severity of OM was reduced (91). It is therefore legitimate to speculate that anti-inflammatory properties support the antimicrobial characteristics of PVP-I in OM treatment.

In a randomised controlled trial, the effect of three mouthwashes that included PVP-I, chlorhexidine and salt/sodium bicarbonate were assessed on patients with head and neck malignancies undergoing radiation-induced oral mucositis. PVP-I significantly reduced mucositis scores from the first week of radiotherapy compared with the control group. By weeks 4 and 5, mucositis scores in patients treated with PVP-I were significantly lower than the salt/sodium bicarbonate group and the chlorhexidine group respectively (92). These findings are further supported by a systematic review assessing the effectiveness of commonly used mouthwashes in the prevention and treatment of chemotherapy-induced oral mucositis. No beneficial effects of chlorhexidine were noted, while PVP-I was found to reduce the severity of OM by as much as 30% compared with sterile water (93).

While there are no specific recommendations on using mouthwashes for the prevention of oral mucositis in the 2013 MASCC/ISOO guidelines (94), neither the use of chlorhexidine nor antimicrobial lozenges are recommended for OM prevention in patients undergoing radiotherapy. Furthermore, chlorhexidine is not recommended for treatment of established OM. These recommendations are based on conflicting trial results and insufficient evidence respectively (95).

The role of PVP-I in oral surgery and dental conditions

In addition to its broad-spectrum microbial activity and low potential for resistance, PVP-I has also demonstrated haemostyptic and anti-inflammatory effects during minor oral surgery (96–98). In a single-blind randomised study, alveolar sockets of patients following tooth extraction were irrigated with either PVP-I plus saline or saline alone. Significantly, more patients in the PVP-I group experienced spontaneous bleeding cessation than those in the control group ($p < 0.001$). This study highlighted, for the first time, the haemostatic action of PVP-I. This effect was further demonstrated in a prospective pilot study assessing the time to optimal haemostasis in patients undergoing periapical surgery for single-rooted maxillary anterior tooth lesions (97). Compared with saline, when PVP-I was used to irrigate the periapical surgical field with cotton, there was a significant reduction in the time to bleeding cessation at the apex ($p = 0.004$). There were also marked reductions in visual analogue scale scores of oedema on the first two post-operative days and in the use of non-steroidal anti-inflammatory drugs (97).

The efficacy of PVP-I as an anti-oedematous agent was also evident in a randomised controlled clinical trial of 30 patients undergoing mandibular third molar removal (split mouth design) (99) On assessing the postoperative effect of PVP-I (0.5 mg/ml) when used as an irrigant and coolant, a significant decrease in swelling and trismus was observed compared with saline control ($p = 0.001$). No significant difference was observed in pain scores between the treatment groups (99). Similar observations were reported in another study in which the reduced post-operative swelling by PVP-I was attributed to the inhibitory effect on leukotriene B4 and leucocyte extravasation (98).

Use of PVP-I as a prophylactic measure in dental surgery has also been demonstrated. A preprocedural rinse of PVP-I was shown to reduce the level of micro-organisms generated in aerosol and spatter during dental procedures with rotary instruments (100).

Although largely preventable, the most common oral diseases that affect the general population are dental caries and periodontal disease (43). In children with severe early childhood caries, PVP-I led to a significant reduction ($p = 0.001$) in the major cariogenic bacterium *Streptococcus mutans* from postoperative baseline levels to 12 months of oral rehabilitation (101). The reduction in bacterial count subsequently resulted in a decrease in caries relapse, defined as the presence of one or more new smooth surface caries lesion in a primary tooth (101). These data supported earlier evidence of the effectiveness of PVP-I in the prevention of dental caries in 'high-risk' children who required general anaesthesia during oral rehabilitation (102).

The efficacy of PVP-I has also been assessed in the settings of periodontitis and gingivitis. In a systematic review of chronic periodontitis, PVP-I as an adjunct to scaling and root planing was reported to have a small but significant beneficial effect on the enhancement of probing pocket depth reduction (103). Use of PVP-I as an adjunct to non-surgery therapy (using an ultrasonic device) and in retreatment of patients for long-term management of advanced periodontitis was further demonstrated and shown to result in improved gingival conditions, reduced probing pocket depth and significant reductions of probing attachment level losses for up to 13 years (104). In a separate study, PVP-I in combination with hydrogen peroxide as an adjunctive to normal oral hygiene led to marked reductions from baseline in gingival inflammation as reflected in lower plaque and papillary bleeding scores than the water comparator at 24 weeks (105). Use of PVP-I has also been shown to extend to the management of odontogenic and deep fascial space infections such as dento-alveolar abscesses (106).

The role of PVP-I in endodontic practice has also been reported (107,108). Two studies that assessed the effectiveness of a range of antiseptics that included 10% PVP-I in the rapid decontamination of gutta-percha cones artificially contaminated with bacterial cells and spores demonstrated bactericidal effects against *Staphylococcus aureus, Escherichia coli, E. faecalis, and Bacillus subtilis* spores approximately 5 min following PVP-I treatment (107). Rapid decontamination was also demonstrated in a separate study in which 3-s treatment with 10% PVP-I was found to be efficient (108).

More recently, the application of PVP-I to an artificial biofilm of two periodontal pathogens, *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, showed effective suppression of these microbial constituents at concentrations indicated for daily oral rinse (109). Notably, periodontal pathogens, *P. gingivalis* and *Actinobacillus actinomycetemcomitans*, can be transmitted within family members. Periodontal treatment therefore involves elimination or significant suppression of the pathogen in diseased individuals by a high standard of oral hygiene (110). These findings further reinforce the recommendations for preprocedural mouth rinsing in patients undergoing dental procedures to assist in the reduction in oral bacteria load (13,27). This is a particularly important consideration in patients who are at-risk of bacterial endocarditis (111).

Importantly, short-term use of PVP-I has not been shown to irritate healthy or diseased oral mucosa, or exhibit adverse effects, such as discoloration of teeth and tongue and change in taste (16). Other studies reported an absence of irritation or damage to the oral mucosa with PVP-I rinsing over a period of 8 or 10 weeks (89,112); and no discoloration of composite restorations were observed in children receiving PVP-I solution following dental rehabilitation (102).

Overview of PVP-I safety

After almost 60 years on the market, the safety profile of PVP-I is well-established. Although measurable systemic absorption may occur with the long-term use of PVP-I, its clinical manifestation as thyroid dysfunction is not very common (51). Previous studies reported PVP-I mouthwash used four times daily for a short period (2 weeks) or once-daily for a prolonged period (24 weeks) did not affect thyroid function (113,114). However, increases in serum thyroid stimulating hormone concentrations that may occur with prolonged PVP-I treatment (24 weeks), may benefit from a 3-week drug holiday to allow the serum TSH levels to return to baseline levels (114). PVP-I is therefore not to be used in those with hyperthyroidism and other diseases of the thyroid. In addition, the use of PVP-I gargle should only be used during pregnancy and lactation if strictly indicated, and should be kept to the absolute minimum (115). PVP-I was found to be favourably tolerated by children receiving PVP-I for dental conditions (102), and in general was shown to be 20 times better tolerated than other common antiseptics (116). While a few cases of allergic dermatitis after prolonged skin contact with PVP-I have been reported (117), this is considered to be a rare complication and differs to local pruritus and skin irritation (117,118). Overall, the allergenic profile of PVP-I compares well to those of other antiseptics (118).

PVP-I in practice

From a clinical practice perspective, the choice of an appropriate antiseptic product for topical oral use is likely to depend on the oropharyngeal site of disease and infection, as well as the active ingredient and patient preference. While lozenges with analgesic/anaesthetic properties are becoming increasingly popular for use in URTIs for example (119), their perception as being a 'throat sweet' may lead to unintentional over dosing (120,121).

Large, well-designed randomised clinical trials are considered the gold standard for assessing a treatment intervention (122). However, their findings can have limited applicability to patients in clinical practice (122), who are likely to be more heterogeneous. For PVP-I, the number of studies required for the various oropharyngeal conditions and the possible comparators make this an impractical task. Nevertheless, several studies that include *in vitro*, 'real-world' and small-scale randomised studies of PVP-I provide evidence of its efficacy in preventing and treating common oral and oropharyngeal disorders. The benefits of PVP-I are reflected in its broad-spectrum anti-infective profile, its low potential for resistance as well as its haemostatic and anti-inflammatory properties. Furthermore, PVP-I is available in different strengths and formulations: as a 10%, 7.5% and 1% PVP-I gargle and mouthwash across Asia; and e.g. in Japan it is also available as a throat spray (0.45% w/v formulation), thereby allowing flexibility in dosing regimens to suit individual patient's needs.

The regimen and length of PVP-I use will depend on the condition to be treated or prevented, as well as the susceptibility of the offending micro-organisms towards PVP-I. Clearly, the desired effect, the concentration of the solution and the time of exposure need to be balanced. Patient compliance and motivation are essential, especially if longer gargling or rinsing times are necessary. In general, gargling and rinsing with 10-15 mL undiluted PVP-I followed up for a minimum of 30 s is appropriate for the treatment and prevention of sore throats (34) and for prophylactic use before, during and after surgery. Longer rinsing (2 min) is suggested for the treatment of existing mouth lesions; and for oral mucositis, rinsing the mouth with undiluted PVP-I for up to 3 min and after meals is considered optimal (90,92). Given the potential of PVP-I in reducing the incidence of airborne or droplet-transmitted respiratory infections (e.g. SARS, avian flu, swine flu) (38,39), undiluted PVP-I can be used as a protective measure by rinsing the mouth for 2 min up to four times a day.

PVP-I can also be used as part of routine hygiene practices, for which gargling followed by rinsing of the mouth for 30 s using 10–15 ml of diluted or undiluted mouthwash is suggested. While PVP-I gargle or mouthwash can be diluted in defined clinical settings, if done by a patient, careful instructions on proper dilution should be strongly advised.

While there has been no formal study assessing the optimal length of treatment with PVP-I gargle or mouthwash, clinical practice and expert opinion suggests 14 days for URTIs and between 4–10 weeks for oral mucositis. In the oncology setting, patients with laryngeal cancer undergoing radiotherapy are typi-

cally treated with PVP-I for 6 weeks and nasopharyngeal cancer patients are recommended PVP-I for 8 weeks.

Antiseptics, such as PVP-I, address the challenges in many clinical settings, where infectious conditions must be prevented or treated. By mediating a localised effect and sparing or preventing the use of antibiotics, they provide a viable option in the therapeutic armamentarium against common oropharyngeal infections.

Acknowledgements

The authors thank Dr Beejal Vyas-Price for her editorial support in the development of this publication, which was supported by an educational grant from Mundipharma Pte Ltd.

Author contributions

Led by Dr Kanagalingam, each author was part of the publication steering committee, who collectively guided, reviewed and amended the content of the publication according to their specialty. Dr Kanagalingam, Professor Lin and Professor Le guided content in the oncology setting; Dr Feliciano and Dr Hah informed the respiratory setting and Dr Labib guided the dental section.

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Paper received November 2014, accepted July 2015