Dermatology Online Journal

Dermatology Online Journal
UC Davis

Topical iodophor preparations: Chemistry, microbiology, and clinical utility

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Dermatology Online Journal 18 (11): 1

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Abstract

Iodophor preparations are commonly used in all medical specialties for antisepsis of the skin prior to injections, invasive procedures, and surgery. Povidone-iodine has some very intriguing properties that make it extremely effective as a broad spectrum bacteriocidal agent with no known bacterial resistance, potentially lending itself to broader applications than its current uses. In this article the background, formulations, chemistry, and microbiology of iodine will be reviewed and recent clinical investigations of utility beyond skin antisepsis will be discussed.

Introduction

Iodophor preparations are commonly used in all medical specialties for antisepsis of the skin prior to injections, invasive procedures, and surgery. Povidone-iodine has some very intriguing properties that make it extremely effective as a broad spectrum bacteriocidal agent with no known bacterial resistance, potentially lending itself to broader applications than its current uses. In this article the background, formulations, chemistry, and microbiology of iodine will be reviewed and recent clinical investigations of utility beyond skin antisepsis will be discussed.

Elemental and molecular iodine

Iodine is the heaviest element commonly used by most life forms. It was originally discovered by Courtois (though incompletely characterized) in 1811 as part of a series of experiments aiming to improve the production of gunpowder during the Peninsular Wars waged by Napoleon against the Spanish [**1**]. Though later characterized correctly by both Joseph Gay Lussac and Humphry Davy, both men eventually acknowledged the original work of Courtois and credited him as the first to isolate the new element. Iodine takes its name from *iode*, the Greek word for "violet," as suggested by Gay Lussac, a reference to the deep violet gas that can be seen sublimating from the solid element at room temperature and pressure. Situated at the bottom of the Group VII halogen family on the periodic table (which was not described until 1869 by Mendeleev), iodine derives much of its clinical utility from the combination of its low toxicity, high molecular weight, and ease of reactivity with organic molecules. Like all halogens, its relatively high electronegativity prevents naturally occurring iodine from existing outside of organoiodine complexes, as components of ionic salts, or as part of divalent molecular iodine. This unique chemical reactivity has enabled the development of an array of iodine-containing preparations for use in medicinal chemistry.

From iodine to iodophor

Like fluorine, chlorine, and bromine, iodine is a powerful oxidizing agent that rapidly pulls electrons from less electronegative elements. Although its antiseptic effect in medicinal preparations was recognized soon after its discovery, widespread use was limited by poor aqueous solubility, limited chemical stability, and high local toxicity. Attempts were systematically made to ameliorate all of these shortcomings and these attempts led to the first generation of medicinal iodine compounds. Lugol's solution, first prepared in 1829 by JGA Lugol, sought to overcome the poor aqueous solubility by combining elemental iodine with potassium iodide (KI) salts. This combination shifted the equilibrium distribution of aqueous iodine species to favor increased disproportionation towards easily soluble triiodide (I_3^-). Lugol's solution is an effective microbicide, starch indicator, nuclear stain, and moderator of thyroid activity. Historically it has been used in the treatment of hyperthyroidism by inhibiting the production of iodinated thyroid hormones. Until recently, Lugol's Solution was available as an OTC preparation in most US pharmacies, although its sale is now restricted as it has gained popularity as a precursor in the clandestine production of methamphetamine.

Whereas Lugol's Solution solved the stability problem inherent in the aqueous delivery of elemental iodine as an antiseptic, the solubility problem was more effectively addressed by the development of iodine "tinctures." These formulations also employ KI to force disproportionation towards triiodide but they further address solubility by employing up to 70 percent (w/w or w/v) of alcohol (almost always ethanol). These alcoholic solutions are usually made to include between 2 percent and 7 percent of elemental iodine (as I_2) with a lower KI concentration than the corresponding Lugol's Solution. In this way they achieve higher iodine solubility and deliver a higher concentration of elemental iodine per given aqueous unit.

It took about a hundred years for the next major improvement in the delivery of medicinal iodine compounds. First publicly

"release" free molecular iodine in aqueous systems quickly became the most common way to solve all three problems of stability, solubility, and toxicity.

Chemistry and microbiology of iodophor preparations

What Shalanski first described in 1952 became what we now know as povidone-iodine (PVP-I) or "Betadine." This is a complex of triiodide (I^{3-}) and the organic polymer polyvinylpyrrolidone. PVP-I solved the combined problems of low solubility, poor chemical stability, and local toxicity by wrapping active free iodine in a soluble polymer matrix. This allowed higher effective concentrations to be safely delivered to target tissues without local toxicity.

In aqueous solution systems, the reactions between the PVP-I complex and water leads to the generation of seven iodine forms. Hydrolysis, dissociation, and disproportionation all contribute to the equilibrium distribution of iodine species. Of the seven iodine forms, a bactericidal effect is only attributed to molecular iodine (I_2), hypoiodous acid (HOI), and the iodine cation (H_2O+I). The polyvinylpryrrolidone portion itself has no bactericidal effect, but owing to its affinity for cell membranes is able to deliver the iodophor preparation to the target. For PVP-I, free molecular iodine (I_2) is almost entirely responsible for the observed microbicidal activity [**3**]. Solutions with the same total concentration of iodine but different amounts of free iodine vary greatly in their antiseptic efficacy [**4**]. Irritation, stinging and burning are potential complications of iodine use at higher concentrations but the PVP-I system eliminates these toxicities by carrying the iodine in a complexed, non-irritating vehicle. Most PVP-I used for medicine is standardized to deliver between 0.5 percent and 1.0 percent free molecular iodine on dissolution. Thus the common pre-surgical 10 percent Betadine actually delivers about 1 percent of biocidal, free molecular iodine.

Iodine has been recognized as a broad spectrum, resistance-free biocidal agent for many years. The microbicidal action of povidone-iodine is a result of the non-complexed, freely mobile elemental iodine (I_2). Molecular I_2 can freely enter cells and works via a variety of pathways to eliminate microorganisms in a non-specific manner. Although incompletely understood, it is likely that free iodine poisons electron transport, inhibits cellular respiration, destabilizes membranes, inhibits protein synthesis and denatures nucleic acids. All of these mechanisms derive from fundamental electron-electrophile reactions whose inhibition, though possible, would require mutations inconsistent with the definition of "living organisms" [**5**]. Povidone-iodine kills microorganisms including bacteria, viruses, yeasts, molds, fungi, and protozoa. This is particularly interesting from a dermatological standpoint in that it has the ability to eradicate commonly seen organisms such as *Staphylococcus*, *Pseudomonas*, *Candida*, *Trichophyton*, and *Mycobacterial* species [**6**].

It is of particular interest that lower concentrations of PVP-I have been shown in the chemistry literature to be *more effective* antimicrobials [**7**]. This paradoxical effect is not completely understood but likely stems from the increased free-iodine available in more dilute solutions. It is suggested that as the polymer complex "unwraps" in more dilute solutions, more free iodine is translocated from inner hydrophilic sites to outer solubilized sites, thus generating more free molecular iodine [**8**]. Although the exact mechanism remains elusive, the net effect is incontrovertible: Stock 10 percent PVP-I solutions reach a maximum of antimicrobial efficacy *in vitro* as dilutions of 1/100. Recent interest in using dilute preparations of PVP-I, alone and in combination, has led to some novel therapeutic strategies.

0.10% povidine (= .01% = 100 ppm iodine) is optimal concentration

Clinical utility of iodophor Formulations

There are numerous commercially produced FDA-approved preparations of PVP-I (for a variety of indications (see **Table 1** [**9**]). Although 10 percent PVP-I remains the standard for pre-surgical skin disinfection, lower concentrations of PVP-I are commonly used for a variety of indications. The most common diluted preparation is the 5 percent PVP-I ophthalmic formulation sold by Alcon for use before most invasive ocular procedures including surgery, anterior chamber paracentesis, and intravitreal injection. Recent controlled clinical trials in ophthalmology have established the utility of dilute (less than 2%) PVP-I preparations as prophylactic and therapeutic agents in infant and childhood conjunctivitis [**10**, **11**]. Concentrations as low as 0.4 percent PVP-I have been studied in the treatment of viral conjunctivitis [**12**]. It is notable that even this very low concentration has shown significant effect at reducing adenoviral titers from infected study subjects, thus showing *in vivo* consistency with the paradoxical *in vitro* findings discussed above.

0.4% PVP-I = 0.04% I = 400 ppm

After studies determining the safety of iodine agents as potential otic therapies [**13**, **14**], several investigators have demonstrated the use of dilute PVP-I in otitis media and otitis externa, including difficult to treat cases of chronic otomycosis [**15**, **16**]. Similarly dilute PVP-I preparations have been shown to be safe and effective in indications that include the prevention of respiratory infections [**17**], treatment of human [**18**] and canine sinusitis [**19**, **20**], and prevention of infection in a variety of applications in intraoperative irrigation [**21**, **22**]. These and other studies demonstrate that as PVP-I use has endured and evolved; recently it has been recognized that dilute PVP-I could be employed not only as a disinfectant but also as a topical therapeutic, given the right formulation and regimen.

Clinical utilization in dermatology

In dermatology, 10 percent PVP-I remains a popular pre-surgical skin disinfectant. Other uses have been surprisingly rare. The most common avenue of exploratory use outside of anti-sepsis involves wound care. A variety of studies have proposed dilute PVP-I for use in chronic, non-healing wounds as a means of reducing bacterial colonization. Clinical evidence of efficacy in wound healing remains controversial, although anecdotal reports are not uncommon. Some *In vitro* models employing cultured cells have shown marked cellular toxicity and impaired wound healing [**23**, **24**]. In at least one study, clinically relevant concentrations of PVP-I have demonstrated negative effects on cultured human keratinocytes [**25**].

Other reports suggest that aqueous PVP-I preparations can promote tissue repair in non-healing wounds impaired by polymicrobial flora [**26**]. A new concept in wound repair combining moisture and antisepsis in the form of 2 percent PVP-I liposome hydrogel has

been shown to promote epithelialization of chronic wound beds [**27**]. Compression combined with local PVP-I treatment for chronic wounds has also been found effective as a means of promoting healing [**28**].

Perhaps the most insightful study addresses excessive protease levels in chronic non-healing wounds. At the molecular level, excessive levels of matrix metalloprotease, elastase, and plasmin levels in wound fluid are characteristic of non-healing wounds. The excessive protease activity degrades growth factors and newly formed extracellular matrix, eventuating in a deadlocked wound. SA Eming et al tested the effect of different PVP-I doses on protease activity. There was a clear dose-dependent inhibition of both metalloprotease and neutrophil elastase activity with PVP-I. For plasmin, the inhibition was less pronounced. This result is surprising as microbicidal activity of PVP-I at low concentrations becomes attenuated in the presence of high protein concentrations such as the environment in non-healing wounds. As mentioned above, iodine is strongly oxidative, and the iodine radicals generated lead to denaturation and loss of function of enzymes. Some enzymes are more susceptible to iodine than others, explaining the differences in enzyme deactivation noted above. High overall protein content in richly exudative wounds may inhibit deep penetration of iodine radicals into wound tissue, limiting cellular damages as demonstrated in earlier animal models. The appearance of granulation tissue in the wound bed would signal the need to discontinue the use of PVP-I and continue with the use of moist, occlusive wound healing measures alone [**29**].

Summary

Medicinal iodine has evolved from the toxic, insoluble, unstable form first described over a hundred years ago into the universally known iodophor preparation of povidone-iodine. Newer dilute agents are already under investigation as topical treatments for a range of therapeutic indications, led by uses in otolaryngology and ophthalmology. PVP-I is poised to enter a renaissance in dermatology as newer formulations are embraced for a variety of skin and mucosal applications. With some modifications to achieve better penetration through the stratum corneum already published in the patent literature [**30**], it may not be long before we see newer, dilute formulations of PVP-I as the subject of clinical investigation.

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