

Introduction

Iodine is a highly effective topical antimicrobial that has been used clinically in the treatment of wounds for more than 170 years. It has a broad spectrum of antimicrobial activity with efficacy against bacteria, mycobacteria, fungi, protozoa and viruses and can be used to treat both acute and chronic wounds¹. It is also relatively inexpensive and easy to use, but is often underused as a topical antiseptic due to its perceived toxicity.

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What is iodine?

Iodine is a natural dark violet, non-metallic element that plays a key role in human metabolism. It is essential for the production of thyroid hormones and an iodine deficiency can result in hypothyroidism. Iodine occurs naturally in the form of iodide ions in sea water, fish, oysters and certain seaweeds². It can also be found in vegetables grown in iodine-rich soil and dairy products. It has been described as 'the most potent antiseptic available'³.

What is the history of iodine in wound healing?

In the 4th century BC, before iodine had been discovered, Theophrastus, a pupil of Aristotle, recorded that iodine-rich seaweeds could be used to reduce the pain of sunburn⁴. One of the first antiseptic iodine preparations to be used in wound care was Lugol's solution containing elemental iodine and potassium in water, which was developed in 1829⁵. This solution was also used to treat wounds in the American Civil War.

The antimicrobial properties of iodine were first demonstrated in 1882 by Davaine⁶. In the First World War, iodine was found by Alexander Fleming to reduce the incidence of gas gangrene in the wounds of soldiers when compared to carbolic acid⁷. Since the mid-19th century, iodine-based preparations have also had an important role in the prevention of surgical site infections. Povidone iodine preparations are popularly used as an antiseptic to prepare the patient's skin before surgery and are also used by

surgeons and theatre staff as a skin cleanser and antiseptic in preoperative hand scrubs.

Early uses of iodine involved aqueous and alcoholic iodine preparations, which were associated with unpleasant side effects including pain, irritation and skin staining.

Why is iodine safer today?

Iodophors were developed in the 1950s to overcome the side effects associated with elemental iodine. These were found to be safer and less painful, but just as effective as elemental iodine, allowing widespread use.

Bonding iodine with another molecule makes it less toxic and instead of high concentrations of iodine being released in a single application, the iodine is slowly released from the reservoir carrier molecule over a sustained period of time.

Iodophors are preparations that bind iodine to a solubilising agent or carrier. The water-soluble complex allows the slow release of a low concentration of free iodine when the carrier comes into contact with wound exudate. This controlled release of low concentrations of iodine helps to minimise the negative side effects of using free elemental iodine.

Modern iodine preparations

The two most commonly used iodophors in modern wound dressings (Table 1) are:

- **Povidone iodine (PVP-I): a chemical complex of polyvinylpyrrolidone (also known as povidone and PVP) and elemental iodine. Examples include dressings such as Inadine® (Systagenix) and solutions such as Betadine® (Purdue Products) and BraunoI® (B Braun)**
- **Cadexomer iodine: an iodine and polysaccharide complex, such as Iodoflex® (Smith and Nephew) and Iodosorb® (Smith and Nephew), which can be used as antiseptic fillers, particularly in cavity wounds.**

Povidone iodine preparations were introduced in the 1960s and it is now the most common iodophor in clinical use. It is available in different formulations, including solution, cream, ointment, spray and wound dressings.

What is the evidence to support iodine use?

There is extensive evidence to support the use of povidone iodine in wound healing⁸ (Table 2), but its use is not without controversy due to perceived issues with toxicity, systemic

Iodine made easy



Table 1 Wound dressings containing iodine (adapted from Boothman, 2010⁸)

Product	Distributor	Iodine form	Available iodine content	Description
Braunovidon® ointment/ ointment gauze	B Braun	PV-1	10% per 100g ointment	Colloidal ointment base
Inadine®	Systagenix	PV-1	1.0% w/w	Knitted viscose mesh
Iodosorb®	Smith & Nephew	Cadexomer iodine	0.9% w/w	Matrix dressing
Iodosorb® ointment	Smith & Nephew	Cadexomer iodine	0.9% w/w	Macrogol ointment base
Iodosorb® powder	Smith & Nephew	Cadexomer iodine	0.9% w/w	Cadexomer iodine beads
Iodoflex®	Smith & Nephew	Cadexomer iodine	0.9% w/w	Macrogol ointment base with gauze backing
Iodozyme®	ArchiMed	Iodine	<0.04% w/w	Hydrogel dressing
Repithel®	Mundi-Phama	PVP-1	0.3% w/w	Liposome hydrogel

Note: % w/w describes the percentage solution

absorption and delayed healing. It has been suggested that iodine has a negative impact on cells involved in the wound healing process and because of this its safety and efficacy have been questioned.

Some reviews have analysed the conflicting evidence and have found that studies based on animal models tend to support the argument for iodine's cytotoxicity, whereas human studies suggest that PVP-I can help the wound healing process by reducing bacterial load and decreasing infection rates^{9,10}. One study demonstrated that not only does PVP-1 significantly improve the healing rates of chronic venous leg ulcers, but also that it lacks cytotoxicity *in vivo*¹¹.

The efficacy of cadexomer iodine has been demonstrated using both animal models and clinical studies. Cadexomer iodine was found to significantly reduce symptoms associated with infection (eg exudate, erythema, oedema and pain) in patients with pressure ulcers¹² and venous leg ulcers¹³.

In addition to providing an antimicrobial effect, *in vitro* studies have reported a lack of toxicity for human fibroblast activity¹⁴ and that cadexomer iodine may increase epithelialisation of chronic wounds^{15,16}. However, its mode of action is not understood and further research is needed to determine whether wound aetiology has a contributory role⁹.

How does iodine work as an antimicrobial?

Iodine's exact antimicrobial mode of action is not fully understood, but it is believed to be associated with its ability to rapidly penetrate the cell wall of micro-organisms¹⁷.

Schreier et al³ also investigated the effects of PVP-1 on microbial cells and found that it affects the structure and functions of enzymes and cell proteins and damages bacterial cell function by blocking hydrogen bonding and altering the membrane structure¹. These multiple modes of action ensure the rapid death of microbes and help to prevent the development of bacterial resistance. Because the microbicidal action of iodine is related to several directly toxic effects on the cell wall, rather than through specific molecular pathways (as used by antibiotics), resistance is highly unlikely and reports of iodine-resistant strains are exceptionally rare (Figure 1)⁸.

Is iodine effective against MRSA?

There is substantial *in vitro* evidence demonstrating that PVP-I is a highly effective and broad spectrum antimicrobial. Activity has been demonstrated against both common bacterial wound isolates^{18,19} and antibiotic-resistant species²⁰. Lacey and Catto²¹ determined that more than 99% of methicillin-resistant *Staphylococcus aureus* (MRSA) cells were killed within 10 seconds of exposure to PVP-I. Mertz et al²² found that cadexomer iodine significantly reduced MRSA and total bacteria in partial thickness porcine wounds compared with a no-treatment control and a vehicle group.

Is iodine effective against biofilms?

At the most basic level, a biofilm can be described as being bacteria embedded in a slimy, protective mucopolysaccharide glycocalyx²³. The effectiveness of iodine in the management of biofilm is currently unclear, although it is known that low dose, slow release iodine is effective in killing free-floating planktonic micro-organisms²⁴ and is therefore likely to be a good choice of

Table 2 Clinical studies featuring iodine (from 1980 to present)

Study reference	Therapy	Design	Selection criteria	Clinical outcomes
Homann HH, et al. <i>Ann Plast Surg</i> 2007; 59(4): 423–7	Liposome PVP-I hydrogel vs silver sulfadiazine	Randomised controlled trial (n=43)	Partial-thickness burns	Healing was found to be significantly faster in the hydrogel group ($p<0.015$) and an improved cosmetic result was also noted. Without the inclusion of a non-antimicrobial control, it is difficult to determine whether the PVP-I hydrogel does increase the rate of healing or alternatively if silver sulfadiazine may have a delaying effect.
Eming SA, et al. <i>J Invest Dermatol</i> 2006; 126(12): 2731–3	Different concentrations of PVP-I on fluid collected from chronic venous leg ulcers incubated with a range of povidone iodine concentrations	<i>In vitro</i> research on wound fluid from seven patients	Chronic venous leg ulcers	At the higher PVP-I concentrations, elastase and plasmin activity was reduced significantly in the four wound fluids examined. It is proposed that this beneficial effect may contribute towards improved healing rates in chronic wounds
Kumar BP, et al. <i>Int J Oral Maxillofac Surg</i> 2006; 35(8): 765–6	Irrigation with PVP-I vs saline	Randomised controlled trial (n=50)	Oral surgery wounds	Cessation of bleeding was achieved in 19 patients treated with PVP-I (76%) and 5 in the saline group (20%) ($p<0.01$)
Fumal I, et al. <i>Dermatology</i> 2002; 204 (Suppl) 1: 70–74	Povidone-iodine vs silver sulfadiazine or chlorhexidine digluconate for six weeks	Comparative study (n=17 patients with at least two similar leg ulcers)	Chronic leg ulcers	Compared with the control lesions, both the healing rate and time to healing of the leg ulcers showed a modest improvement at the sites receiving silver sulfadiazine (2–7%) or chlorhexidine digluconate (-1 to 5%). By contrast, PVP-I increased significantly the healing rate (4–18%, $p<0.01$), and the time to healing was reduced by 2–9 weeks ($p<0.01$)
Vogt PM, et al. <i>Wound Repair Regen</i> 2001; 9(2): 116–22	A novel liposome PVP-I hydrogel complex vs chlorhexidine gauze	Monocentric, randomised, open, phase II pilot study (n=36)	Meshed skin grafts	Treatment with the PVP-I hydrogel resulted in significantly faster epithelialisation ($p=0.005$), better antiseptic efficacy ($p=0.002$), improved wound healing quality ($p=0.004$) and a lower incidence of graft loss ($p=0.001$) in comparison with chlorhexidine gauze
Miyachi Y, Imamura SJ. <i>Dermatol Treat</i> 1997; 1: 191–93	Sugar (70%) and povidone-iodine (3%) paste for a three-year period	Clinical study treating refractory cutaneous ulcers (n=168)	Traumatic, venous and ischaemic, post-burn and diabetic ulcers	Increased granulation tissue formation and a reduction in the size, depth and bacterial contamination of wounds of mixed aetiology
Konig B. et al, <i>Dermatology</i> 1997; 195 Suppl 2: 42–8	PVP-I and the effect on exotoxins and enzymes	<i>In vitro</i> study	Not specified	Endotoxins and exotoxins released by bacteria have been implicated in delayed wound healing; povidone iodine was found to inactivate bacterial exotoxins such as phospholipase C and lipase and inhibit their further generation. Furthermore, destructive cytokines and enzymes released by neutrophils in response to bacterial colonisation were also found to be inactivated.
Piérard-Franchimont C, et al. <i>Dermatology</i> 1997; 194(4): 383–7	PVP-I in combination with hydrocolloid dressings vs hydrocolloid dressings alone for four weeks	Clinical study in 15 female patients (age range 57–73)	Chronic leg ulcers	PVP-I accelerated the rate of venous leg ulcer healing when evaluated against hydrocolloid dressings alone. After four weeks the wounds treated with PVP-I also had a smaller amount of micro-organisms present than the hydrocolloid-only group
Lammers RL, et al. <i>Ann Emerg Med</i> 1990; 19(6): 709–14	Use of 1% povidone iodine solution to soak the wound before cleansing and debridement vs normal saline and no treatment	Randomised controlled study (n=33 wounds; 29 patients)	Contaminated traumatic wounds (seen within 12 hours of injury)	Tissue samples were taken before and after soaking and bacterial counts were conducted. While bacterial colonisation was reduced with PVP-I solution, there was no significant difference when compared with the controls
Gravett A, et al. <i>Ann Emerg Med</i> 1987; 16(2): 167–71	Topical 1% povidone-iodine vs normal saline	A prospective, randomised study (n=500)	Traumatic lacerations	PVP-I solution (1%) reduced the incidence of wound infection. Of 201 in the PV-I group, 11 became infected compared with 30 of 194 control wounds
Knutson RA, et al. <i>South Med J</i> 1981; 74(11): 1329–35	Povidone-iodine and granulated sugar mixture used to treat patients over a 56-month period	Five-year prospective study (n= 605)	Wounds, burns, ulcers	The authors concluded that this combination 'rapidly' increased the rate of wound healing, reduced the requirement for skin grafting and antibiotics and lowered hospital costs.

antiseptic dressing when the intention is to suppress biofilm formation or prevent recontamination²³.

Recent evidence suggests that sustained release iodine may penetrate biofilms more effectively than silver or polyhexamethylene biguanide (PHMB)²⁵.

Can patients build up bacterial resistance to iodine?

Despite 170 years of prolonged and extensive use of iodine in medicine and wound care, iodine-resistant microbial strains are exceptionally rare.

The validity of the one documented case of resistance to iodine products²⁶ has been questioned and the methodology of the study criticised²¹.

When is iodine indicated?

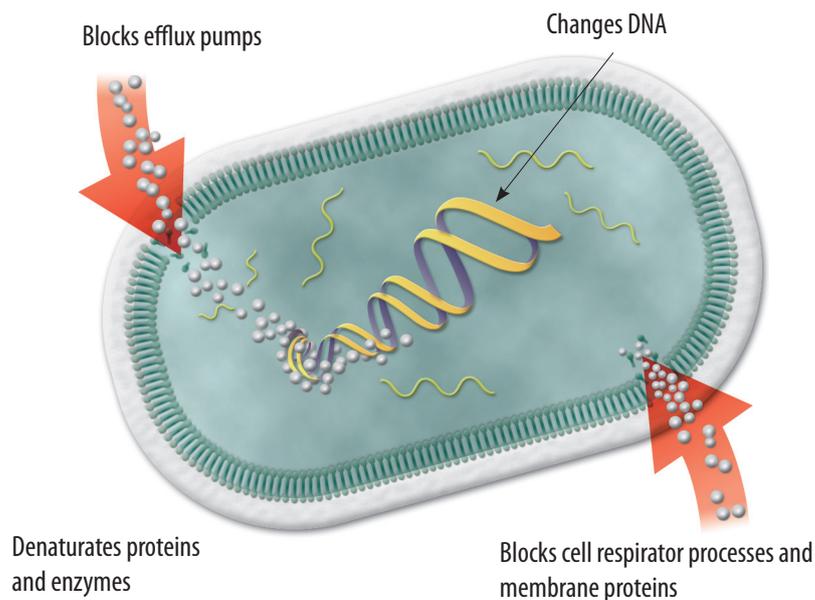
An international consensus document on managing wound infection²⁷, recommends the use of antiseptic dressings as being part of an overall management plan in the following circumstances:

- to prevent wound infection or recurrence of infection in patients at greatly increased risk of infection
- to treat localised infection
- to treat spreading infection when healing is delayed

Slow release iodine dressings have been used to treat a range of wound types where infection is present or suspected.

These include pressure ulcers, venous leg ulcers, diabetic foot ulcers, minor burns and superficial skin-loss injuries^{24,28}.

Figure 1 The antimicrobial action of iodine



When are iodine dressings contraindicated?

Iodine dressings must be used under medical supervision in patients with thyroid diseases, known or suspected iodine sensitivity, in pregnant or breastfeeding women or in newborn babies and up to the age of six months⁸.

Long-term use of PVP-I has been loosely associated with mild hyperthyroidism²⁹ and long-term use is not recommended for patients with impaired thyroid function. However, a number of studies have monitored thyroid function during PVP-I clinical trials and have reported that it remains unchanged³⁰⁻³².

To avoid toxicity or the hypothetical risk of thyroid-related complications, iodine products should be used with caution in children, in those with large burn areas, and where prolonged treatment of large open wounds is required. The use of iodine dressings should also be avoided

before and after the use of radio-iodine diagnostic tests (until permanent healing).

Reports of systemic effects following short-term PVP-I treatment are extremely rare. Iodine absorption has been found to be dependent on the size of the wound and the duration of treatment³³. Hunt *et al*³¹ also discovered a relationship between wound area and iodine levels in serum and urine following the treatment of burn wounds with PVP-I, but it was proposed that renal function was a factor in the determination of this. Iodine should, therefore be avoided in patients with significant renal disease.

How to apply iodine dressings

The method of application depends on the mode of delivery. Dressings should be applied directly to the surface of the wound and covered using a secondary dressing as appropriate. All dressings should be applied according to the manufacturer's instructions for use.

Why does iodine stain the skin brown?

The skin is sometimes stained brown after treatment with iodine products. This is because of the effects of the tri-iodide ion and, to a lesser extent, free molecular iodine⁸.

However, any staining that may occur is harmless and will quickly fade.

Why does the application of iodine sometimes sting?

Iodine-based products can be associated with a transient burning or stinging sensation immediately after they are applied to open wounds. However, this is not harmful³⁴. The stinging probably relates to the osmotic loads delivered by higher concentrations of iodine in some preparations.

The prevalence of allergic reactions to the topical application of iodine varies considerably (between 0.7% and 41%), depending on which study is reviewed.

For example, in a dermatological study by Juhász³⁵ involving 50 patients, no cases of sensitisation to PVP-I after patch-testing were recorded.

How frequently should dressings be changed

The slow release of the iodine in these preparations allows the wound to remain in continuous contact with the antiseptic, whereas with a single exposure to a product such as PVP-I the iodine is soon broken down^{36,37}. It is important to remember that even with modern iodine dressings (eg Inadine, Iodosorb and Iodoflex), which provide a slow release of iodine, this is only for a relatively short time and frequent dressing changes are required to constantly replenish the supply of antiseptic to the wound. It is assumed that once the dressing has lost its 'colour' the antiseptic effect has been lost and the dressing should be changed.

In heavily exuding wounds, dressings may need to be changed daily. With appropriate moisture balance iodine dressings can be applied 1–3 times per week.

When should treatment be discontinued?

Medical supervision should be sought if using iodine for more than one week.

Treatment should be re-evaluated regularly and discontinued when the signs of infection resolve and the wound is healing.

If the wound does not improve after 10-14 days, the patient and the wound should be re-evaluated and an alternative antiseptic dressing regimen or systemic treatment with an antibiotic considered²⁷.

What are the economic arguments for iodine?

Povidone iodine dressings and irrigating solutions are relatively inexpensive compared to other antimicrobial therapies. Dressings that lose their colour (eg Inadine) may be more cost-effective in that they provide an indicator of how frequently dressings should be changed⁸.

Iodine and the future

Iodine-containing dressings may be developed that combine the antimicrobial effect of iodine with autolytic debridement, moisture balance and active therapies to optimise wound healing.

Summary

Although it has been speculated that iodine delays healing and is cytotoxic, there is substantial evidence to suggest that the commonly-used low concentration, slow release iodophors improve healing rates and are effective as highly potent antimicrobials with a broad spectrum of activity, including antibiotic-resistant strains such as MRSA. It is unfortunate that the concerns about iodine are based on studies that are so varied in method and design that it is difficult to draw reliable comparisons and conclusions. The reputation of iodine wound products, used as antimicrobials, suffered as a result of these studies but it is now widely accepted that slow-releasing iodophor antimicrobials are safe and have minimal detrimental impact on wound healing.

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Healthcare practitioners are advised to consult the package inserts for any iodine-based products before applying the dressing to a wound.

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