

Iodine revisited

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ABSTRACT

Iodine is an antiseptic that has been used in wound care for more than 150 years. Traditional formulations of iodine had serious limitations that were reduced in later products. Much has been written about iodine and opinions on its clinical efficacy are divided. There have been reviews of the chemical properties of iodine, its antimicrobial activity, human physiology, cytotoxicity and its clinical effectiveness, but few have addressed all these aspects. With the recent development of iodine-containing wound care products and the continued publication of laboratory and clinical studies, it seems timely to reassess the evidence relating to the effectiveness of iodine for treating wounds. This literature review attempts to provide an appropriate chemical and physiological background of the characteristics of iodine in order to provide a sound basis for understanding the available microbiological and clinical data. It will show that understanding the factors that contribute to the activity and potential cytotoxicity of iodine are important in evaluating the clinical evidence. Although definitive studies are needed, the sustained delivery of low doses of free iodine offers the potential to inhibit a broad range of microbial species without selecting for resistant strains or inducing cytotoxic effects.

Key words: Antimicrobial activity • Antiseptic • Cytotoxicity • Iodine • Resistance

Key Points

- Iodine is a chemical element, which occurs naturally as iodide salts in seaweeds, fish, shellfish and seawater
- it is believed that molecular iodine (I_2) has the highest antimicrobial potential
- pH significantly influences the position of dynamic equilibria and therefore also iodine concentration; maximal bactericidal activity occurs when the forms of iodine without bactericidal activity are minimised

THE CHEMISTRY OF IODINE

Iodine is a chemical element, with the chemical symbol I. It occurs naturally as iodide salts in seaweeds, fish, shellfish and also in seawater. Elemental iodine (I_2) was first isolated in 1811. At room temperature it is a dark purple, lustrous, crystalline solid. On heating it melts to form liquid at 113.5°C and boils to a pinkish purple vapour at 184.4°C, but can sublime to vapour directly from the solid, depending on conditions. Its name is derived from the Greek word 'iodēs' for violet.

Iodine is the least reactive halogen (other halogens are fluorine, chlorine and bromine). It has an atomic number of 53 and an atomic mass of 126.904. Iodine dissolves readily in ethanol or ether to produce brown solutions, or in chloroform or benzene as violet solutions. It is sparingly soluble in water (0.33 g/l, 1.2 mM, at 25°C) giving a yellowish brown solution (1). Solubility of elemental iodine increases in the presence of iodide ions, such as potassium

iodide, where iodine reacts to form tri-iodide ions. Aqueous solutions of iodine are not stable and, depending on conditions, many different species may be present. Of these, it is believed that molecular iodine (I_2) has the highest antimicrobial potential. Stability is influenced by pH and activity diminishes with increased alkalinity and storage time (1). To be able to clearly understand how iodine behaves chemically, its reactions in water have been summarised (Table 1) (2). The seven principal iodine species found in aqueous solution are I_2 , HOI, OI^- , H_2OI^+ , I_3^- , I^- and IO_3^- , of which only hydrated iodine (I_2), hypoiodous acid (HOI) and iodine cation (H_2OI^+) possess bactericidal activity. At physiologically compatible pH and low concentrations, the only species of importance are I^- , I_2 and I_3^- (3). As H^+ features in four of the above reactions, pH significantly influences the position of dynamic equilibria and therefore also iodine concentration; maximal bactericidal activity occurs when the forms of iodine without bactericidal activity are minimised (2).

THE DEVELOPMENT OF IODINE PRODUCTS FOR WOUND CARE

One of the first antiseptic preparations of iodine was Lugol's solution (1). This tincture of iodine was an aqueous solution of iodine and

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Table 1 Potential reactions of molecular iodine (I_2) in water (2)

Category	Reaction	Type of reaction
I	$I_2 + H_2O \leftrightarrow HOI + H^+ + I^-$	Hydrolysis
II	$HOI \leftrightarrow OI^- + H^+$	Dissociation
III	$HOI + H^+ \leftrightarrow H_2OI^+$	Protonation
IV	$I_2 + I^- \leftrightarrow I_3^-$	Complex formation
V	$3HOI \leftrightarrow IO_3^- + 2I^- + 3H^+$	Disproportionation

potassium iodide in ethanol that was used as an antiseptic to treat wounds by Davies in 1839 (4). Subsequently it was used extensively throughout the American Civil War and both Louis Pasteur and Robert Koch are reported to have independently evaluated it (4). It continued to be used professionally and domestically until the 1950s, but it caused acute pain and irritation on application, as well as distinctive staining.

To overcome these clinical limitations, iodophores (or iodine carriers) were developed. Four types of carriers have been used: polyoxymers iodophores, cationic surfactant iodophores, non ionic surfactant iodophores and polyvinyl-pyrrolidone iodophores (otherwise known as polyvinyl-pyrrolidone-iodine, povidone iodine or PVP-I). In most of these agents, iodine is carried in aggregates (or micelles) of detergent which act as reservoirs of iodine. On dilution, these micelles slowly disperse to release free elemental iodine in aqueous solution, so that the concentration of the active agent gradually increases without reaching the undesirable concentrations associated with former products. This free iodine is known as available iodine and the activity of the iodophore is related to the amount of iodine released. Equations to calculate the equilibrium concentration of free iodine released into water from iodine solubilised in surfactants have been derived (5) and titration against sodium thiosulphate with starch indicator allows the concentration of free iodine to be determined experimentally.

In the most common iodophore in clinical use (PVP-I), iodine is chemically bound as triiodide to the surfactant povidone. It was introduced into clinical use in 1956 (6) and it is available as a solution, aerosol spray, ointment, cream or wound dressing. Concentrations vary in different PVP-I preparations, with available iodine ranging between 9.0% and 12% (w/v)

(7). It is important to realise that formulations of PVP-I are not identical and that many studies fail to note the precise chemical composition of povidone iodine preparations used. This point was emphasised in a study designed to assess the antibacterial activity of PVP-I where the formulations of PVP-I solution and PVP-I scrub were defined (Table 2), and surfactants were identified (8).

In 1981, cadexomer iodine was developed as another means of delivering 'safe' iodine. It consists of beads of starch containing 0.9% (w/w) iodine. It is available as a powder, ointment and wound dressing. In the wound it readily absorbs fluids to form a gel and as the strands of starch polymer separate on swelling, free iodine in aqueous solution is slowly released (9).

A new generation of iodine products has been developed more recently. In an enzyme-based iodine disinfectant, horseradish peroxidase effects the conversion of iodine from sodium iodide by generating hydrogen peroxide from calcium peroxide (10). An enzyme-mediated system is also used in OxyzymeTM and IodozymeTM wound dressings, where glucose oxidase generates hydrogen peroxide using atmospheric oxygen. The hydrogen peroxide, in turn produces oxygen and free iodine (11). An advantage of these products is that inactivated iodide, the reduced form of iodine, can be re-activated by oxidation with further hydrogen peroxide, so that the overall level of iodine/iodide present in the product can be relatively low. In Repithel[®], polyvinyl-pyrrolidone-iodine liposomes containing 3% iodine are prepared in a hydrogel (12). Recently a paste comprised of 70% sugar and 30% PVP-I (U-PASTTM) has been developed that is claimed to stimulate wound healing by modulating the activity of keratinocytes and fibroblasts (13).

ANTIMICROBIAL ACTIVITY OF IODINE

Iodine has been used extensively as an antiseptic. It has a broad spectrum of antimicrobial activity, rapidly inhibiting bacteria, yeasts, moulds, protozoa and viruses (1,8,14). Enveloped viruses are more susceptible to iodine than non enveloped viruses, probably because of binding of iodine to the lipid component of the envelope. Endospore-forming bacteria generally are less susceptible to antiseptics than non sporing bacteria; however, iodine is an effective sporicidal agent. Inhibition of

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Key Points

- iodine has been used extensively as an antiseptic and has a broad spectrum of antimicrobial activity, rapidly inhibiting bacteria, yeasts, moulds, protozoa and viruses
- iodine is an effective sporicidal agent
- unlike antibiotics where inhibitory effects tend to be localised to a specific cellular location, antiseptics have generalised effects by simultaneously affecting multiple sites in microbial cells
- most of the data demonstrating antimicrobial efficacy have been derived from suspensions of microbial cells tested *in vitro*

Table 2 Typical povidone iodine formulations (8)

Product	Components in the formulation	Concentrations
PVP-I aqueous solution	PVP-I	1% available iodine
	Glycerol	1% (v/v)
	Nonyl phenoxy polyoxyethylene ethanol*	0.25% (v/v)
	Buffer, disodium phosphate/citric acid	Remainder
PVP-I scrub	PVP-I	0.75% available iodine
	Lauric acid diethanolamine condensate*	4% (w/v)
	Ammonium alkyl phenoxy polyoxyethylene glycol sulphonate*	25% (v/v)
	Sodium hydroxide and hydrochloric acid to adjust pH to 4-6	
	Water	Remainder

PVP-I, polyvinyl-pyrrolidone-iodine.

*Surfactants.

mycobacteria has also been reported. Methicillin-resistant staphylococci and methicillin-sensitive staphylococci have been shown to be equally susceptible to iodine (15,16). As little as 0.1 fg (236 000 molecules) of iodine can destroy one bacterial cell (15).

Inhibition of biofilms of *Pseudomonas aeruginosa* and *Burkholderia cepacia* cultivated on Teflon chips has been showed after 10 minutes exposure to PVP-I (0.2%), whereas 60 minutes in contact with chlorhexidine gluconate (0.2%), alkylidiaminoethyleneglycine hydrochloride (0.2%) and benzalkonium chloride (0.2%) had no effect (17). Biofilms have been implicated in chronic wounds and are associated with infections linked to indwelling medical devices (18). They are notoriously difficult to treat because of their reduced susceptibility to antimicrobial agents; iodine seems to offer some potential in limiting biofilms.

MODE OF ACTION OF IODINE

Surprisingly little has been published about its mode of action, but molecular iodine (I₂) is the active agent. At low concentrations, its activity can be affected by organic matter (19). Unlike antibiotics where inhibitory effects tend to be localised to a specific cellular location, antiseptics have generalised effects by simultaneously affecting multiple sites in microbial cells. Binding of iodine to proteins leads to their denaturation in several ways: oxidation of S-H bonds in amino acids such as cysteine and methionine, and the prevention of hydrogen bonding by reacting with N-H groups in arginine, histidine and lysine or the phenolic group of tyrosine. These changes affect the structure and function of both enzymes and

structural proteins and therefore have extensive deleterious effects on microbial function. Furthermore, membrane structure is compromised by the reaction of iodine with C=C bonds in fatty acids, and hydrogen bonding in nucleic acids is prevented by iodine binding to nucleotides such as adenine, cytosine and guanine. Hence, changes in cell walls, membranes and cytoplasm result in rapid death following exposure to iodine (1). Structural effects of PVP-I on microbial cells were investigated by electron microscopy and biochemical analysis (20). Rapid partitioning of cytoplasm, coagulation of nuclear material and loss of enzyme activity were found. Cells did not appear to show complete disruption, but pore formation in cell walls led to leakage of selected cellular materials (20).

THE QUALITY OF THE IN VITRO EVIDENCE OF THE ANTIMICROBIAL ACTIVITY OF IODINE

Most of the data demonstrating antimicrobial efficacy have been derived from suspensions of microbial cells tested *in vitro*. Activity of antimicrobial agents is always influenced by pH, temperature, concentration, contact time, presence of organic matter, electrolytes, microbial strains and the neutralisers used. Experimental conditions, therefore, influence laboratory observations. Despite the publication of numerous studies, critical evaluation of reported data is hampered by incomplete descriptions of methodology and inadequate specification of the formulation of iodine that was used (1).

Disinfectants and antiseptics have been routinely evaluated in the laboratory since the

early 20th century by various methods, but the need to rationalise protocols to provide suitable tests that mimicked the environments in which specific agents were destined to be used has been recognised. In Europe, a range of standardised methods for the laboratory evaluation of antimicrobial agents has gradually been developed since 1995. Initially suspension tests to establish efficacy against bacteria or fungi became available (known as phase 1 tests). In phase 2/step 1 tests, antimicrobial activity in the presence of interfering substances is assayed to determine whether an agent can achieve a 10^5 log reduction of selected test organisms in a given contact time. Phase 2/step 2 tests aim to simulate in vivo conditions before phase 3 tests (clinical trials) are attempted. A complete range of tests is not yet available. Suggested organic challenges for antiseptics that will be used in the oral cavity, on mucous membranes, or on wounds for either prophylactic or therapeutic use have been evaluated with selected antiseptics. A mixture of 4.5% albumin, 4.5% sheep blood and 1% mucin was found to be the most difficult organic challenge and only povidone iodine, octenidine and chlorhexidine retained activity (21). The performance of inhibitory agents in vivo is always less than predicted from laboratory data because in vivo conditions are never faithfully recreated in vitro. Once standardised tests for evaluating antiseptics that are destined to be used on wounds become available, comparisons between agents will become easier. Although the design of laboratory tests can be criticised, there can be little doubt that iodine is a rapid cidal agent.

RESISTANCE TO IODINE

One of the most remarkable features of iodine as an antiseptic is the lack of selection of resistant strains. Only one report of iodine resistance has been published (22). In this report, 10 cultures of methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from different patients were tested against four antiseptics and resistance to PVP-I and sodium hypochlorite together with reduced susceptibility to chlorhexidine acetate and chlorhexidine gluconate was found. However, the experimental conditions used in this study have been criticised because nutrient broth was used which contained components that would have inacti-

vated iodine (15). Another study failed to detect povidone iodine resistance in MRSA (23). Attempts to train bacteria to become resistant to povidone iodine by repeated exposure in the laboratory have failed (24), as have attempts to detect iodine resistance in bacteria isolated from nosocomial infections (25,26). In one study (25), 504 isolates recovered from 12 French hospitals were tested under differing laboratory conditions and inconsistent results were seen. Using a micro-method, 18 strains appeared to be resistant to PVP-I, but none were resistant when a standardised method was adopted (25). The other study was conducted in Italy with 379 isolates recovered from surgical wound infections during a six-year period and no significant variation in susceptibility to antiseptics (including PVP-I) was detected (26). Attempts to show resistance to povidone iodine (0.01%) in coagulase-negative staphylococci isolated from continuous ambulatory peritoneal dialysis patients following long-term prophylactic use of antiseptics at device insertion sites have also failed (27). The consensus is, therefore, that iodine-resistant strains of micro-organisms have not yet emerged. Yet reports of resistance to other antiseptics have been accumulating since the early 1950s (Table 3) and include resistance to quaternary ammonium compounds, chlorhexidine and triclosan in enteric bacteria, pseudomonads and staphylococci (6).

THE PHYSIOLOGY OF IODINE

For humans, iodine is an essential trace element that is acquired by eating fish, shellfish and seaweed. The normal daily iodine requirement for adults is between 100 and 200 μg (28). Iodine is absorbed from the blood and concentrated in the thyroid gland where it is used to produce the two thyroid hormones, thyroxine and triiodothyronine, which are important in regulating metabolism. Inadequate iodine intake leads to endemic goiter, endemic cretinism and increased child mortality (29). In developed countries, iodisation of salt (supplementation of sodium chloride with traces of iodide or iodate salts) is an effective strategy in preventing dietary iodine deficiency, because iodised salt is used extensively in processed foods.

Multiple adverse effects are associated with excess iodine including mental depression,

Key Points

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- once standardised tests for evaluating antiseptics that are destined to be used on wounds become available, comparisons between agents will become easier
- one of the most remarkable features of iodine as an antiseptic is the lack of selection of resistant strains

Key Points

- decisions about the choice of a topical antimicrobial intervention by practitioners depend on judgements of safety, effectiveness and appropriateness
- internationally recognised standardised methods, such as ISO 10993, are used for the evaluation of medical devices
- two broad categories of wound care product can be identified: those that contribute to healing and those that contribute to aspects of wound care other than healing

Table 3 Acquired resistance to antiseptics used in wound care

Agent	First clinical use	Resistance	Organisms
Honey	Antiquity	ND	ND
Silver	19th century	1970s	<i>Pseudomonas aeruginosa</i> Enterobacteriaceae
Iodine	1839	ND*	ND*
Hydrogen peroxide	1887	ND	ND
Quaternary ammonium compounds	1993	1951	<i>Ps. aeruginosa</i>
Chlorhexidine	1954	1967	<i>Proteus mirabilis</i>
		1990s	Staphylococci
Triclosan	1970s	1998	<i>Ps. aeruginosa</i>

ND, not detected.

*There was a single report of resistance for MRSA in 1985 but of questionable methodology (21).

nervousness, insomnia, myxoedema, hypothyroidism, hyperthyroidism, hypersensitivity and skin reactions (28,30,31). Acute poisoning by ingestion can be fatal (30). Fluctuations in dietary iodine levels, however, are overcome by an autoregulatory mechanism in the thyroid that is known as the Wolff–Chaikoff effect. Although the mechanism of this protective response is not fully understood, it comes into effect when excess iodine levels are ingested. Rather than converting the excess iodine into excess thyroid hormones, the first step in their biosynthetic pathway (oxidation of iodine by organic binding) is temporarily inhibited. Iodine is expelled from the thyroid, removed by the kidneys and excreted in urine. Escape from the Wolff–Chaikoff effect normally ensues after 48 hours, when iodine levels have normalised. Pathological changes arise when autoregulation is defective, for example in the foetus and neonates, and in Hashimoto's thyroiditis, Grave's hyperthyroidism or cystic fibrosis (29). Renal dysfunction in diabetic patients with advanced nephropathy has been linked to non autoimmune primary hypothyroidism (32). Here, elevated serum iodine levels were thought to have resulted from a prolonged Wolff–Chaikoff effect that caused iodine to be expelled from the thyroid, but impaired renal function prevented efficient excretion.

The behaviour of iodine-based antiseptics on skin was investigated by Gottardi in 1995. Using Lugol's iodine solution and PVP-I, uptake (absorption) of free iodine by intact skin was followed by a reversal of the absorption process (or back diffusion). The dynamics of this flux depended on the concentration of free

iodine in the preparation applied, contact time and the thickness of the treated area (33).

THE SUITABILITY OF IODINE AS A TOPICAL AGENT IN THE MANAGEMENT OF WOUNDS

Decisions about the choice of a topical antimicrobial intervention by practitioners depend on judgements of safety, effectiveness and appropriateness. The way in which those attributes are assessed depends to a certain extent on the methods used. It should be remembered that proprietary wound care products satisfy criteria set by regulatory bodies before being licensed. Often, however, these supporting data never reach the public domain and comparisons between products by potential users have to be made from evidence generated by clinical researchers. Historically evaluations of safety and clinical efficacy used a variety of diverse tests. Now internationally recognised standardised methods, such as ISO 10993, are used for the evaluation of medical devices. ISO 10993 is comprised of 18 parts: parts 1–12 concern biological testing and 13–18 chemical characterisations. Similarly European legislation was laid down to ensure the safety of medical devices (90/385/EEC and 93/42/EEC) and essentially the tests have been harmonised with ISO 10933. Two broad categories of wound care product can be identified: those that contribute to healing and those that contribute to aspects of wound care other than healing. The biological evaluation of medical devices includes tests for genotoxicity, carcinogenicity and reproductive toxicity (ISO 10993 part 4), in vitro cytotoxicity (part 5), irritation and sensitisation (part 10) and systemic toxicity

(part 11). A comprehensive evaluation strategy for a topical antimicrobial solution determines antimicrobial activity of the agent using monolayer cell cultures of each of the cell types that occur in the target tissue (human or mouse fibroblasts, keratinocytes and polymorphonuclear leukocytes). The effect of an agent on processes pertinent to wound healing is tested (i.e. cell migration, angiogenesis, synthesis of extracellular matrix components and wound closure) using three-dimensional models. Finally, *in vivo* studies on animal models are performed and clinical evidence was collected from humans.

SAFETY OF IODINE: EVIDENCE FROM IN VITRO CYTOTOXICITY STUDIES

Although antiseptics in general have a reputation as cytotoxic agents, the evidence to support that assumption for iodine is not overwhelming because both negative and positive reports have been published. By exposing granulocytes and monocytes to a range of concentration of three preparations of PVP-I, it was demonstrated that the concentrations used clinically (0.1–20% v/v) were toxic. In the presence of lower concentrations (0.005% v/v), viability and phagocytic activity were retained after 60 minutes, as well as antibacterial activity (34). This study indicated that toxicity was related to PVP-I concentration and suggested that dilute solutions may be clinically effective. However, growth of human adult skin fibroblasts and foetal lung fibroblasts was progressively retarded by 0.01% and 0.025% PVP-I and completely inhibited at higher concentrations, which suggested that even dilute solutions of PVP-I were toxic (35). Cytotoxicity of 1% PVP-I towards human fibroblasts obtained from newborn foreskins has also been published (36); similarly, negative effects of diluted PVP-I solutions (and a range of other topical antimicrobial agents) against human fibroblasts and keratinocytes were reported (37). A toxicity index for 20 skin and wound cleansers has been derived using human infant fibroblasts and keratinocytes (38). Using the viability of cells exposed to saline as a baseline (no toxicity), the viability of cells exposed to a series of dilutions of cleansers was determined. The dilution factor of test solution that did not affect viability was deduced to be the toxicity index. Hence, highly toxic agents

would require high dilution (high toxicity index) before inhibition (viability) of cells was prevented, but non toxic agents (low toxicity index) required less dilution. In this study, 10% povidone, PVP-I surgical scrub and hydrogen peroxide (3%) were all 100 times less toxic than household bath soaps but 1000 times more toxic than saline (38).

Most investigations into cytotoxicity have used cells directly involved in wound repair, but the effect of topical antimicrobial agents on human neutrophils isolated from blood was tested in an attempt to discover whether host defence cell function was affected. PVP-I solutions at or below clinically relevant concentrations did inhibit respiratory burst (39). Any loss of this important function would impact on the killing of ingested micro-organisms within these cells, and so was considered to undermine antiseptic potential.

Not all reports confirm cytotoxic effects of iodine *in vitro*. Exposing human fibroblasts to a range of concentrations of cadexomer iodine *in vitro* showed that viability and collagen synthesis were unaffected at 0.45%, which was thought to illustrate its lack of toxicity *in vivo* (40). Two studies have suggested potentially beneficial effects of iodine on wound healing. The human macrophage cell line U937 exposed to 0.25% cadexomer iodine (Iodosorb) was stimulated to secrete proinflammatory cytokines (tumour necrosis factor- α or TNF- α) in response to 0.00225% iodine (41). Macrophages stained in biopsies taken from chronic wounds are negative for TNF- α , therefore a role for iodine in stimulating the activation of macrophages in non healing wounds was postulated by these researchers. Cadexomer iodine formulations might also promote healing by modulating the redox environment. Investigation into the pro- and antioxidant activities of cadexomer iodine, its constituents and of excipients present in commercial preparations showed some interesting effects on L929 mouse fibroblasts and mouse macrophages (42). The modified starch in cadexomer iodine was found by two assays to lack free radical scavenging antioxidant activity and did not generate hydrogen peroxide through auto-oxidation. Cadexomer iodine (0.05–2% w/v) enhanced proliferation in the fibroblasts, while Iodosorb powder (1–2% w/v) and iodine alone (0.009–0.018% w/v) inhibited superoxide generation in stimulated macrophages. Iodine was

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postulated to cause these effects by the oxidation of intracellular reducing agents, such as reduced nicotinamide adenine dinucleotide phosphate (NAD(P)H) and glutathione. A further antioxidant effect (singlet oxygen scavenging) was attributed to excipients (42). Although not made in a chronic wound, these observations indicate that iodine can influence the formation of free radicals derived from oxygen, and so modulate the function of cells involved in healing. An inference is that oxygen influences the function of iodine *in vivo*.

It can be argued that cells in culture do not behave as cells *in vivo*, because their susceptibility is reduced in the absence of homeostatic mechanisms. Fibroblasts, for example, are protected by the upper layers of the skin *in vivo*. To overcome some of these criticisms, three-dimensional collagen lattices seeded with human fibroblasts were developed as wound-healing models (43). The immortalized mouse fibroblast cell line L929 has been used extensively for cytotoxicity testing. Yet immortalized cells and cell lines derived from human explants may not accurately represent a chronic wound. Hence, a fibroblast gel contraction model using equine fibroblasts collected from granulation tissue in a slow healing wound was used to test several topical iodine antiseptics. The results indicated that prolonged treatment with iodine might be detrimental to wound healing (44).

SAFETY OF IODINE: EVIDENCE FROM IN VIVO ANIMAL MODELS

Irrigation of guinea pig wounds with iodine antiseptics was found to be effective in preventing wound infection (45). Of four antiseptics applied to clean wounds created in white domestic pigs, PVP-I was not found to affect the rate of healing (46). The clinical use of antiseptics was profoundly influenced by two studies that were published in 1985 in which animal models were used to evaluate the toxicity of antiseptics (36,47). Using incisions on the backs of rats, irrigation with solutions of 1% PVP-I, 0.25% acetic acid, 0.5% sodium hypochlorite or 3% hydrogen peroxide showed retarded epithelialisation and reduced wound strength (36). A rabbit ear chamber (47) allowed the effect of antiseptics (EUSOL, PVP-I 1% and 5%, hydrogen peroxide 10 vol, Chloramine T 1%

and chlorhexidine 0.05%) to be determined on granulation tissue. Direct microscopic observation showed that blood flow was markedly affected (particularly by EUSOL and Chloramine T, where empty capillaries did not recover in 10 days). In these studies, all the antiseptics tested showed adverse effects in comparison to saline; recommendations to restrict the use of antiseptics were made. Some practitioners interpreted these findings as a warning not to use antiseptics in wounds (28). The anionic detergent present in PVP-I surgical scrub has been implicated in increased inflammation in guinea pigs (48). Another indication that a specific surfactant might contribute to toxicity came from cytotoxic effects of three PVP-I formulations on guinea pig wounds. Polyoxyethylene nonylphenyl ether was reported to be 100 times more toxic than sodium polyoxyethylene lauryl ether sulphate (49).

Efficacy of cadexomer iodine was showed on partial thickness wounds in pigs challenged with MRSA (50). Positive effects of cadexomer iodine on epidermal regeneration during healing in full thickness, non infected wounds in the pig have also been reported (51).

SAFETY OF IODINE: EVIDENCE OF ADVERSE EFFECTS FROM TREATED PATIENTS

In relation to wounds, comments on the safety of iodine seem largely to concern povidone iodine not cadexomer iodine, but once again conflicting evidence exists. Reports of systemic effects following short-term use of PVP-I are rare. Fatalities have been attributed to topical use of PVP-I in two burns patients (52) and following surgical debridement of a hip wound (53). Mediastral irrigation with PVP-I has been reported to result in acute renal failure (54) and seizures (55). Elevated serum iodine has been linked to renal impairment and hyperchloremic acidosis following the use of PVP-I (56,57), and it has been suggested that long-term topical treatment with PVP-I on 40 neurological in-patients caused mild thyroid dysfunction (58). Investigations into the extent of iodine absorption through wounds do not yield conclusive evidence of adverse systemic effects. Iodine levels were monitored in the blood and urine of 33 burns patients and undesirable thyroid or renal effects were not detected (59). Likewise, changes in the levels of

thyroid hormones of 10 patients with extensive third-degree burns that were treated with PVP-I were not found (60), and the use of PVP-I in 18 paediatric cardiac patients did not lead to altered thyroid function (61). Serum and urine iodine levels after topical application of PVP-I were deduced to be related to the size of a burn and renal function, but effects on thyroid function were not found (62). Increased levels of serum iodide in burns patients relate not only to the size of the affected area but also to the length of treatment (63). Although serum iodide levels can be expected to return to normal following cessation of treatment with PVP-I, patients with existing thyroid disease, pregnant women, nursing mothers and infants were considered unsuitable candidates for long-term topical application of povidone-iodine (63). Adverse effects noted in case reports may have been associated with underlying pathologies, rather than iodine alone because some patients had multiple aetiologies (63). Recommendations that iodophores should be used in neither patients with renal damage nor those with extensive burns (52,62) are sensible.

Allergic reactions to iodine have also been reported, with prevalence reports ranging from 0.7% to 41% (63). A high prevalence of sensitisation to topical agents in leg ulcer patients prompted a French group to analyse published studies and to review their own patients (64). Patch testing in three groups of patients with the European series of standards and an additional series of potential allergens pertinent to leg ulcers showed that Balsam of Peru, fragrance mix and nickel sulphate had sensitisation rates above 10%, whereas PVP-I as Betadine[®] had lower rates than neomycin or Cetavlon[®], but not chlorhexidine digluconate or Flamazine[®] (64). In Hungary, the successful use of Betadine[®] with dermatology patients over many years was reported (65); to determine whether any patients had been sensitised to PVP-I, 50 were challenged by patch testing and no sensitisation was found.

Doubts about the validity of positive patch tests where PVP-I (10% solutions in petrolatum, i.e. 1% free iodine) are tested under occlusion caused Lachapelle to test 500 consecutive patients with conventional patch tests (66). Only 14 positive patients were found; each of them was retested in a repeated open application test where PVP-I dermal solution was applied to the open forearm twice daily

for 7 days. Two of these tests were positive, thus a prevalence rate of 0.4% with true allergic contact dermatitis to PVP-I was deduced. It has been suggested that PVP-I containing detergents caused cytotoxicity and sensitisation in wounds but not intact skin (67). Testing panels must always include components contributing to the manufacture of modern dressings. Fears that manufacturers fail to declare all ingredients in their formulations may confound sensitivity testing (68). It must also be remembered that sensitisation may occur before treatment regimes commence and that allergen tests reflect not only health care experiences. Reports of iodine allergy may, therefore, be exaggerated.

EVIDENCE OF THE EFFICACY OF IODINE FROM CLINICAL STUDIES

The role of iodine in wound care is predominantly an antimicrobial agent. Solutions, sprays and scrubs have been used to irrigate contaminated trauma wounds, and prophylactically to reduce skin flora immediately before and sometimes after surgery. Iodine-containing ointments, creams and dressings are intended to prevent ingress of pathogens into wounds, to act as a barrier to cross-infection, and to prevent the progression from localized to overt infection. Infection interrupts healing and extends the time to wound closure therefore preventing infection prevents the extension of the healing period. A correlation between decrease in bacterial load and the rate of wound healing was established with the topical application of furazolidone to 56 pressure sores and stasis ulcers in 47 alcoholic or neuropsychiatric patients (69). This principle provides the rationale for the use of topical antimicrobial agents in wounds, yet few studies monitor the quantitative effects of topical agents on microbial flora. The efficacy of five antiseptic solutions and four antimicrobial creams in eradicating coagulase-negative staphylococci from the stratum corneum was investigated in one study, though (70). Four of the agents contained iodine (solutions of 10% PVP-I, 2% aqueous iodine, 2% tincture of iodine and iodophore ointment were used). All nine agents successfully eradicated the bacteria from surface layers, but only 2% iodine, mupirocin and a triple antibiotic ointment removed bacteria

Key Points

- adverse effects noted in case reports may have been associated with underlying pathologies, rather than iodine alone because some patients had multiple aetiologies
- fears that manufacturers fail to declare all ingredients in their formulations may confound sensitivity testing
- reports of iodine allergy may, therefore, be exaggerated
- the role of iodine in wound care is predominantly an antimicrobial agent
- iodine-containing ointments, creams and dressings are intended to prevent ingress of pathogens into wounds, to act as a barrier to cross-infection, and to prevent the progression from localized to overt infection

Key Points

- cadexomer iodine has been shown to enhance healing rates in chronic wounds, particularly venous leg ulcers; it has been shown to be an efficient, cost-effective and safe alternative to hydrocolloid dressing and paraffin gauze dressing for the treatment of chronic leg ulcers

from within the layers of the skin. Repopulation by resident flora occurred within 24 hours following use of 2% iodine and iodophore; PVP-I and tincture were not tested (70). Hence, the temporary nature of antimicrobial effects was illustrated.

Much of the data on the effectiveness of iodine have been generated from randomised controlled trials (RCTs) in surgical patients, and therefore relates to acute wounds. It is neither conclusive nor consistent. Preoperative antibiotics were found to be superior to PVP-I in preventing postoperative wound infections following abdominal surgery (71). Considering the high levels of contamination possible in this situation, it is plausible that systemic rather than localized antimicrobial intervention is required. However, in appendectomies bacterial contamination depends on the inflammation associated with the appendix and can be mild or slight. Viljanto (72) investigated the efficacy of PVP-I in paediatric patients with appendicitis who did not have either peritonitis or periappendicular abscesses. In these moderately contaminated wounds, a 5% PVP-I solution containing excipients (glycerol, citrate phosphate buffer, polyoxyethylated nonylphenol) affected healing more than 1% PVP-I without excipients (72). Intraperitoneal irrigation with 0.1% PVP-I solution was compared with saline in a prospective randomised clinical trial with 168 consecutive laparotomy patients and significantly fewer intra-abdominal abscesses were seen with PVP-I. Increased serum iodine levels were noted 24 hours after irrigation, but normal levels were regained within 72 hours and no changes in thyroxine were seen (73). Povidone iodine was found to be a safe and effective way to prevent postoperative wound infection following gastrointestinal surgery (74), but less convincing data were generated in another study (75).

The benefits of PVP-I in the treatment of traumatic wounds have been investigated. In a prospective RCT of 500 consecutive patients attending an emergency department with lacerations requiring sutures, a 60-second irrigation with 1% PVP-I and scrubbing gave rise to less wound infection than saline without scrubbing (76). The effect of soaking traumatic wounds in either 1% PVP-I or saline, or no soaking showed no statistically significant difference between numbers of bacteria in PVP-I-treated wounds and controls (77).

Healing rates in patients following toenail surgery by matrix phenolisation were compared in an RCT using either medicated honey dressings or PVP-I impregnated dressings. Statistically significantly accelerated healing rates were found with iodine compared with honey in patients with total nail avulsion, but not in partial avulsion (78).

Disinfection of skin at incision sites before surgery has a long history, but a review of the effectiveness of preoperative antiseptics in preventing postoperative wound infections after clean surgery concluded that there was insufficient data to draw firm conclusions (79).

Fewer clinical studies on the efficacy of iodine in chronic wounds have been performed. Quantitative bacteriology was used in a prospective RCT of the topical treatment of pressure sores with 40 patients. Silver sulphadiazine was more effective in reducing bacterial load than PVP-I or saline, but the numbers of patients were low (80). Burns and chronic ulcers treated over 5 years with granulated sugar and PVP-I or PVP-I alone had reduced the need for grafting and antibiotics (81). Cadexomer iodine has been shown to enhance healing rates in chronic wounds, particularly venous leg ulcers (82–84). It has been shown to be an efficient, cost-effective and safe alternative to hydrocolloid dressing and paraffin gauze dressing for the treatment of chronic leg ulcers (84).

The continued debate on the deleterious effects elicited by both micro-organisms and antiseptics on human cells intimately involved in the healing process motivated an investigation into the efficacy of iodine using histological and inflammatory markers. In 15 female patients with at least two chronic ulcers, either hydrocolloid dressing alone or hydrocolloid dressing with daily application of PVP-I solution were used in each of the two wounds and biopsies were collected after 4 weeks of treatment. Size of ulcer reduced faster in wounds with hydrocolloid and PVP-I, together with the observation of fewer bacteria and less pronounced inflammatory effects. Reduction in bacteria-related inflammation was thought to promote the enhanced healing rate (85). In a further study by this group, the effect on healing in chronic leg ulcers of three antiseptics (PVP-I, silver sulfadiazine and chlorhexidine digluconate) was investigated. Compared with controls, PVP-I significantly increased healing

rate and reduced time to healing. All the antiseptics caused decreased bacterial density in biopsies collected from the treated wounds with concordant-abated vasculitic changes. Only PVP-I, however, did not significantly reduce the density of dendrocytes and fibroblasts, therefore selective, moderate cytotoxicity in vivo was argued to result in a paradoxically beneficial outcome (86).

A novel property attributed to povidone-iodine that supports its use in chronic non healing wounds is its ability to reduce protease activity. Depending on concentration, PVP-I has been shown by zymography to inhibit metalloprotease activity in samples of wound fluid obtained from non healing wounds and to reduce neutrophil elastase and plasmin activity (87).

Although antimicrobial interventions have long been used on chronic wounds, a systematic review of antimicrobial agents commonly used in the management of chronic wounds concluded that there were insufficient clinical data to recommend any agent (88).

CLINICAL USE OF IODINE TODAY

Advice on using iodine-based wound care products can be found in the British National Formulary. Newer formulations of iodine have not yet become widely integrated into local formularies and clinical data are limited to date. Povidone iodine is mainly used in skin disinfection and in acute wounds, such as contaminated traumatic wounds or surgical incisions; cadexomer iodine is more commonly used in chronic wounds. Both are used prophylactically, and can be used to limit localized infection. Another reason for using iodine might be in non healing wounds where other limiting influences have been addressed, because underlying subclinical infection might impede healing. Neither PVP-I nor cadexomer iodine should be used repeatedly over long periods in wounds that remain unchanged. Both offer benefits in terms of cleansing and debridement and can be used with compression therapy and pressure relief (89). Cadexomer iodine dressings have considerable absorptive characteristics (82), but highly exudating wounds will elute PVP-I from impregnated dressings (90). An evaluation of clinical evidence indicated that many antiseptics including cadexomer iodine and PVP-I do

not impede healing, and that cadexomer iodine promotes healing (91). Where a specific wound product has been showed to offer no clinical advantage over comparable products, relative costs become important and cadexomer iodine has been shown to be cost-effective in relation to other topical agents (92).

EVALUATING INFORMATION ABOUT THE EFFICACY OF IODINE

In caring for wounds, practitioners have to consider many factors in deriving an effective therapeutic strategy that provides optimum conditions to support rapid healing (93). Undoubtedly systemic antibiotics are indicated in cases of overt wound infection (94), and all antimicrobial agents must be used sparingly to avoid the selection of resistant strains. Whereas iodine used to be considered to be inappropriate for wound care (95,96), attitudes are changing as a result of the analysis of accumulated data.

The effects of PVP-I on healing have been reviewed (97). Solution, scrubs, ointment and cream were considered in animal and human studies and it was concluded that PVP-I did not have a deleterious effect on wound healing (97). A report of a consensus meeting on the use of iodine in wound care that was organized by the European Tissue Repair Society was largely supportive of iodine (98). It was deduced that slow-release formulations that generate low concentrations of iodine in a wound were effective and non toxic.

Reviews of animal and clinical data indicate that despite reported cytotoxicity, common antiseptics (particularly those containing iodine) do not appear to impede healing (90,91,99–101), especially when used appropriately (99). Although PVP-I has been judged to be relatively safe for small acute wounds, caution is evident in relation to use in more extensive and chronic wounds (100). Iodine has been described as one of the most powerful antiseptics available (28). A review of 22 clinical studies using PVP-I and 13 studies using cadexomer iodine evaluated effects on wound healing and re-epithelialisation, as well as efficacy in reducing bacterial loads and the incidence of infection (91). For PVP-I-negative effects on wound healing were not found, and cadexomer iodine accelerated healing. The authors concluded that 'In the majority of clinical trials, antiseptics appear to be safe and

Key Points

- newer formulations of iodine have not yet become widely integrated into local formularies and clinical data are limited to date
- neither PVP-I nor cadexomer iodine should be used repeatedly over long periods in wounds that remain unchanged
- an evaluation of clinical evidence indicated that many antiseptics including cadexomer iodine and PVP-I do not impede healing, and that cadexomer iodine promotes healing
- cadexomer iodine has been shown to be cost-effective in relation to other topical agents
- iodine used to be considered inappropriate for wound care but attitudes are changing as a result of the analysis of accumulated data
- a report of a consensus meeting on the use of iodine in wound care that was organized by the European Tissue Repair Society was largely supportive of iodine
- it showed that slow-release formulations that generate low concentrations of iodine in a wound were effective and non toxic

Key Points

- the authors concluded that 'In the majority of clinical trials, antiseptics appear to be safe and were not found to negatively influence wound healing'
- increased understanding of the factors that influence the activity of iodine (e.g. pH, oxygen, free iodine concentration) together with those that contribute to cytotoxicity (e.g. presence of surfactants) will allow the development of better products
- formulations that deliver a low, sustained dose of iodine have the potential to provide effective antimicrobial activity without significant cytotoxicity
- perhaps its greatest strength, after over 150 years of use in humans, is that there is no evidence that bacteria have found a way of developing resistance

were not found to negatively influence wound healing' (91).

An evaluation of the evidence for PVP-I contained in 41 studies together with another 14 literature sources used for background reading has recently been published (101). A hierarchy of experimental studies, descriptive studies and expert evidence was derived using defined criteria in order to judge the quality of evidence. Overall 49% of articles did not support the use of PVP-I, whereas 71% of the 'better' quality articles did support PVP-I (101).

THE FUTURE FOR IODINE

A recurring theme in the analysis of the evidence for any wound care treatment seems to be the paucity of good quality data, the poor design of studies and the low numbers of patients treated. Yet many dressings have gained acceptance without objective evidence (102,103). Definitive clinical studies (RCTs) are essential to substantiate claims of efficacy of iodine. However, increased understanding of the factors that influence the activity of iodine (e.g. pH, oxygen, free iodine concentration) together with those that contribute to cytotoxicity (e.g. presence of surfactants) will allow the development of better products. Formulations that deliver a low, sustained dose of iodine have the potential to provide effective antimicrobial activity without significant cytotoxicity.

CONCLUSION

Iodine should no longer be regarded as an old-fashioned antiseptic. Formulations of iodine in earlier wound care products had serious limitations, but newer formulations have reduced those disadvantages. By the sustained delivery of free iodine at concentrations that retain antimicrobial activity without cytotoxicity for mammalian cells, it is possible to reduce microbial load and to modulate host cells to elicit responses that stimulate healing. When used appropriately, iodine seems to offer potential as an effective, broad-spectrum antimicrobial agent that can promote healing. Perhaps its greatest strength, after over 150 years of use in humans, is that there is no evidence that bacteria have found a way of developing resistance.

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