The great debate over iodine in wound care continues: a review of the literature

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Abstract

The use of iodine in wound management can be traced back hundreds of years and yet continues to divide and create debate amongst today's clinicians. Is there a place for this agent in either infected or non-infected wounds? The body of evidence and pharmacopeia of iodine-based products available can prove daunting. This review outlines the properties of iodine-based products and seeks to examine the relevant clinical studies in an attempt to provide an evidence-based structure to facilitate the choice of iodine-based product. The authors reviewed both animal and human studies. Over 50 studies have been conducted on the use of iodine in wound care. Analysis of the literature reveals that there does appear to be a place for iodine in wound management, particularly in the presence of infection. However, the literature highlights iodine may cause harm, therefore a sound knowledge of the factors that contribute to the activity of iodine and its potential for cytotoxicity is required for its judicious use.

Introduction

In the absence of evidence-based clinical practice guidelines, the use of antiseptics, in particular iodine-based products, continues to promote a great deal of debate amongst clinicians. The term 'antiseptic' was first coined by Pringle in 1750 in his study of the effectiveness of mineral acids in preventing putrefaction in wounds on dead animals [1] and their use has grown ever since. Antiseptics are defined as "agents that destroy or hinder the growth of micro-organisms in or on living tissue" [2].

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Antiseptics have multiple targets and a broader spectrum of activity than antibiotics, which act selectively on a specific target [3]. *In vitro* experiments demonstrated that antiseptics cause disruption to collagen synthesis, were toxic to fibroblasts, impaired epithelial cell migration and inhibited the microcirculation [4]. Other studies demonstrated the toxicity of antiseptics on keratinocytes, leukocytes as well as pathogens [5-9]. It is in the shadow of this evidence that the debate was born. Clinicians today are faced with a myriad of antiseptics; this paper seeks to examine one – iodine.

The dispute over the use of iodine in wound care dates back to 1919 when Alexander Fleming delivered his lecture to the Royal College of Surgeons and subsequently published his study on the use of antiseptics in septic wounds [10]. He found that there was a lower incidence of gas gangrene in wounds treated with 2% iodine compared with carbolic acid in field hospitals during World War I. When Fleming discovered penicillin in 1929, the use of antiseptics decreased and during the late 1980s the routine use of antiseptics was questioned [11].

Iodine is a natural element of the halogen group which is also an essential nutrient in the body. It has been used throughout history in wound care for its antiseptic properties but modern clinicians have concerns regarding its use over fears of its systemic absorption, impact on metabolic function and wound healing. With the emergence of multi-resistant stains of organisms and a better understanding of the dynamics of wound healing, the use of topical iodine in wound care has taken a different profile. This paper outlines the properties of iodine-based products and reviews the relevant

research in this field. This will provide the clinician with an evidence-based framework to facilitate the choice of when it is appropriate to use iodine-based products in relation to wound care.

Iodine

Iodine has been used in wound care since the Greek age (4th century BC). Theophrastus, Aristotle's pupil, described the use of seaweeds and other plants enriched with iodine in relieving pain after sunburn wounds [12]. Wounded soldiers were first treated with plants enriched with iodine during Napoleon's Egyptian campaign [13]. Davis, in 1839, also reported using iodine for treating wounds during the American Civil War [14]. Despite being used for treatment of wounds for over a century, the natural element iodine was not discovered until 1811 by the Dijon chemist Bernard Courtois. The name came from the Greek word 'iodides' meaning 'violet coloured' because of the violet colours of its vapours [13].

Iodine is a dark non-metallic crystalline solid. The solubility of elementary iodine in water can be vastly increased by the addition of potassium iodide [12]. Aqueous or alcoholic solutions of iodine are toxic to tissue and cause skin discoloration, pain, irritation and inflammation. Aqueous solutions of iodine are also unstable in solution [15]. This resulted in the development of iodophors (iodine carriers or iodine-releasing agents), formulations which decreased the free available iodine. Iodophors are complexes of iodine and a solubilising carrier which acts as a reservoir of the active 'free' iodine [16]. The most widely used are povidone-iodine and cadexomer-iodine. Povidone-iodine was first introduced into Anglo-American countries in the 1960s [13] and cadexomer-iodine in the early 1980s.

Povidone-iodine or polyvinylpyrrolidone iodine complex (PVP-I) is a combination of molecular iodine and polyvinylpyrrolidone surfactant/iodine complex. It is a water-soluble complex with elemental iodine bound to a synthetic polymer 10% solution in water [17]. The bactericidal component is free iodine, approximately one part per million (1ppm) [18]. Even at low concentrations, the action of iodine is rapid, yet the exact mode of action remains unknown [15]. Iodine swiftly penetrates micro-organisms and attacks key protein groups (which are essential for bacteria survival – free sulphur amino acids cysteine and methionime), nucleotides and fatty acids; this results in bacteria cell death [16]. The antiviral activity is similar to that bacteria, although there is less known about the antiviral action of iodine [15]. Table 1 gives a summary of the antimicrobial spectrum of iodine.

Iodine formulations

- Povidone-iodine is available in a 7.5% concentration scrub with detergent for pre-operative and post-operative scrubbing and a germicidal wash, a 5% water-soluble first aid cream, and a 10% water-soluble ointment. The most commonly manufactured form is a 10% solution in water, for application as a paint, spray, or wet soak [18].
- Inadine consists of a knitted viscose fabric impregnated with a polyethylene glycol base containing 10% povidone-iodine equivalent to 1% available iodine.
- Cadexomer-iodine contains 0.9% iodine within a three dimensional starch lattice, formed into spherical microbeads and is available as a paste, powder and sheet.

Table 2 summarises iodine-based products from a pharmacological perspective.

Table 1. Antimicrobial spectrum of iodine (adapted [19]).

Gram-positive bacteria	Gram-negative bacteria	Fungi	Viruses
Bacillus subtilis	*Enterobacter aerogens*	*Aspergillus flavus*	Cytomegalovirus
Clostridium perfringens	*Escherichia coli*	*Candida albicans*	Influenza type A
Clostridium tetani	*Haemophilus vaginilis*	*Cryptococcus neoformans*	Polio type 1, Mahoney and Chat strains
Corynebacterium diptheriae	*Klebsiella pneumoniae*	*Epidermophyton floccosum*	*Herpes genitalis*
Diptheroids	*Proteus mirabilis*	*Nocardia asteroides*	Herpes simplex type 1
Diplococcus pneumoniae	*Pseudomonas aeruginosa*	**Protozoa and other organisms**	**Acid-fast bacteria**
Staphylococcus albus	*Pseudomonas pyocyanea*	*Entamoeba histoytica*	*Mycobacterium tuberculosis*
Staphylococcus aureus/ haemolytic	*Salmonella typhi*	*Trichomonas vaginalis*	
Streptococcus (b-haemolytic)	*Serratia marcesens*	*Treponema pallidum*	
Streptococcus faecalis	*Shigella dysenteriae*	*Chlamydia trachomatis*	
Streptococcus pyogenes	*Vibrio comma*	*Mycoplasma hominis*	
		Rabies	
		Rubella	
		Vaccinia	

Table 2. Outline of iodine-based dressing products.

Povidone-iodine (Inadine ™) – Johnson & Johnson	Cadexomer-iodine (Iodosorb ™) – Smith & Nephew
Composition	
• Polyvinylpyrrolidone – an iodophor (PVP-I), which increases the solubility of iodine and provides its sustained release • This is a chemically bound product • Inadine consists of a knitted viscose fabric impregnated with a polyethylene glycol (PEG) base containing 10% PVP-I equivalent to 1% available iodine	• Cadexomer-iodine – available in a pad, paste and powder, 50% w/w (equivalent available iodine 0.9%) • Composed of a three dimensional starch lattice formed into spherical microbeads • Iodine is released slowly with absorption of wound exudate as the beads take up fluid (requires the presence of wound exudate to maximise action)
Action	
• Antimicrobial.	• Antimicrobial • Highly absorbent (1gm – 6ml) • Facilitates desloughing
Pharmaco-kinetics	
• Systemically absorbed • Excreted in the urine	• Systemically absorbed • Excreted in the urine • Biodegradable by amylases normally present in wound fluid
Indications	
• As an antiseptic dressing for ulcerative wounds (e.g. heavily colonised and infected) where there is a small amount of exudate • Prevention of infection in minor burns and minor traumatic skin loss	• Chronic exuding (moderate to high) wounds including leg ulcers, pressure ulcers and diabetic ulcers, particularly when infection is present or suspected • Where slough, infection, or the risk of infection is an issue
Precautions	
• Treatment of kidney problems • Pregnant and breastfeeding women • Cases of Duhring's herpetiform dermatitis	• Severely impaired renal function • Past history of thyroid disorder (more susceptible to alterations in thyroid metabolism)
Contraindications	
• Known iodine hypersensitivity • Before and after use of radio-iodine	• Known or suspected iodine sensitivity • Hashimoto's thyroiditis and in cases of non-toxic nodular goitre • Children under 12 years of age • Pregnant and breastfeeding women
Adverse reactions	
• Contact allergy	• Contact allergy • Transient pain within first hour of application – may be described as 'stinging' or 'smarting'.
Dosage and administration	
• Not more than four dressings at any one time (i.e. 9.5 x 9.5 cm). • Frequency of dressing change	• Clean the wound – do not dry the surface. • Apply sufficient to cover the wound to a depth of 3mm (ung) • Frequency of change dependent on exudate, change when loss of colour. • May be daily initially, then 2-3 times/week. • A single application should not exceed 50gm • Not more than 150gm/week • Not more than 3/12 continuous treatments.
Interactions	
	• There is a potential interaction between lithium, sulphurazoles and the sulphonylureas so co-administration is not recommended.
Medical supervision	
• Suggested for any patient with thyroid disorders • In newborn babies and infants to the age of 6/12 • To treat ulcerative wounds, burns, or large injuries • If used for more than one week	

Clinical studies

In order to draw conclusions regarding the value of iodine-based products in wound care, the authors reviewed the results of both animal and human studies. Over 50 studies have been conducted on the use of iodine in wound care; studies that did not have an English translation were not included. Some studies examined the effect of povidone-iodine on infection and wound healing, whilst others examined only wound infection or wound healing. The results are summarised in Tables 3-6.

Human studies using povidone-iodine

Outcomes from human studies are contradictory. Connell [20] demonstrated a decrease in wound infection rates (11.9% to 6%) when povidone-iodine was eliminated from wound cleansing protocols on acute wounds requiring suturing in the emergency department. Gordon *et al.* [26] established an 18% rate of wound infection when povidone-iodine was used in a similar clinical setting. This group compared Betadine dry powder with Savlodil in 248 patients; however, statistical significance was not reached between the two groups. This could in part be due to the omission of any wound toilet procedure being carried prior to application of the antiseptic agents.

Conversely, Gravett *et al.* [28] and Stringer *et al.* [39] established that the use of povidone-iodine on patients prior to suturing lacerations reduced the incidence of wound infection. Their study compared 1% povidone-iodine scrubbing with normal saline irrigation with a control of the same treatment without scrubbing with povidone-iodine in 500 patients prior to suturing lacerations. Eleven became infected in the treatment group compared with 30 in the control ($p<0.01$).

When a dry dressing was compared with povidone-iodine dressing (Inadine™) on post-operative nail surgery, Denning [23] concluded that there was no significant difference in wound healing (2 sample t test $p=0.14$) or infection rates. There was no statistical difference in bacterial counts in a study by Lammers *et al.* [32] when comparing soaking contaminated traumatic wounds in either povidone-iodine, or normal saline versus no treatment. Povidone-iodine soaking was found not to be a successful alternative to wound cleaning and debridement. However, Sindlear & Mason [38] found there to be a decrease in wound infection rates when surgical wounds were irrigated with povidone-iodine post-operatively. The lack of effect in the previous study may be related to the study design rather that the antiseptic agent itself. Further, a study of 294 paediatric surgical wounds conducted by Viljanto [8] demonstrated that povidone-iodine did not impair wound healing rates and that a 1% povidone-iodine spray significantly decreased infection rates compared with a 5% povidone-iodine spray which increased infection rates.

Others have demonstrated that povidone-iodine increased bactericidal activity in lower concentrations [72]. Povidone-iodine was found to be no more effective than saline in reducing bacterial levels in infected pressure ulcers in a study by Kucan *et al.* [31]. The effect on wound healing was not studied. Lee *et al.* [33], by contrast, demonstrated a reduction in wound infection in pressure ulcers ($p<0.001$). Saydak [37] compared an absorbent dressing with povidone-iodine in pressure ulcers. Each patient had two wounds with similar co-morbidities, nutritional status and age, thereby serving as their own control. Although not a formal study, the use of human subjects serving as their own control provides significant information. The ulcers treated with povidone-iodine produced slower healing rates, although statistical significance was not found, possibly related to the small sample size.

When combining the use of a hydrocolloid dressing and povidone-iodine on clinically non-infected venous leg ulcers, Piérard-Franchimont *et al.* [35] found that the combination reduced bacterial clumps, neutrophilic vasculitis, and phagocytic infiltration and increased healing rates ($p<0.05$) in contrast to the hydrocolloid dressing alone. Fumal *et al.* [25] also established faster healing rates ($p<0.01$) and a positive reduction on the bacterial burden with povidone-iodine in a similar setting, when comparing three antiseptic agents on venous leg ulcers. Although there was not any improvement in wound healing rates, Daróczy [21] also concurred that the application of povidone-iodine reduced the number of bacterial colonies in chronic wounds.

The control of bacterial growth proved to be effective when Georgiade *et al.* [27] applied povidone-iodine ointment to 50 patients with burn wounds. There was, however, not a control group to draw a comparison. Knutson *et al.* [30] also studied burn victims and also concluded that there were improved healing rates and a reduction of bacteria when comparing povidone-iodine with granulated sugar. Two studies, Dekock *et al.* [22] and Hopf *et al.* [29], established that povidone-iodine was more effective than silver sulfadiazine in the treatment of burn wounds.

Although conflicting, the majority of human studies establish the efficacy of povidone-iodine in reducing the bacterial load in both acute and chronic wounds. There is a lack of evidence to determine if there is a positive or negative effect on wound healing.

Animal studies and povidone-iodine

Numerous animal studies have been performed examining the effect of povidone-iodine on wound healing rates and the bacterial burden in wounds. Most researchers provide

Table 3. Human and in vitro *studies using povidone-iodine.*

Author & year	Study	Results
Connell S (1991) [20]	Chart review of acute wounds requiring suturing in the emergency department (n=92)	Infection rates decreased from 11.9% to 6% with the elimination of povidone-iodine
Daróczy J (2002) [21]	Chronic ulcers (n=25). Cleaning the wound with PVP-1 solution and PVP-1 ointment placed in the ulcer	No significant improvement in wound size or depth. Reduced number of bacterial colonies within 4 weeks. Infection, satellite ulcer, erythema and oedema significantly improved after 6 weeks
DeKock *et al.* (1989) [22]	Human burn wounds (n=60) compares povidone-iodine to silver sulphadiazine	Fewer bacteria cultured in the povidone-iodine group. Statistical significance not calculated
Denning L (2003) [23]	123 procedures on 94 individuals: 76 procedures (n=58) dressed with a dry dressing; 47 (n=36) dressed with povidone-iodine	No significant difference in healing rates (2 sample t test p=0.14). Two people in the group without iodine developed a wound infection
Eming *et al.* (2006) [24]	Chronic venous leg ulcers (n=7). Effect of PVP-1 on metalloprotease, neutrophil elastase and plasmin activity in wound fluid	Inhibition of metalloprotease activity. Dose-dependent inhibition of neutrophil elastase activity. Less pronounced for plasmin activity
Fumal *et al.* (2002) [25]	Three groups of 17 patients with at least two similar chronic ulcers. Treatment with hydrocolloid dressings (control). One ulcer in each patient received applications of PVP-1, silver sulfadiazine or chlorhexidine digluconate	Modest improvement in healing rates at the sties receiving chlorhexidine digluconate or silver sulfadiazine. PVP-1 significantly increased healing rate (p<0.01)
Gordon *et al.* (1989) [26]	Contaminated wounds in emergency department requiring suturing (n=248). Compares betadine dry powder vs. savlodil	Infection rates 18% with povidone-iodine. No significant difference
Georgiade *et al.* (1973) [27]	50 patients with burns treated with betadine ointment	77% of wound cultures did not have bacterial growth after QID application vs. 42% and 33% for the BID/TID and QOD/QD application groups (p<0.001)
Gravett *et al.* (1987) [28]	500 patients prior to suturing lacerations treated with normal saline irrigation and 1% povidone-iodine and scrubbing vs. same treatment without scrubbing (control)	11 became infected in the treatment group 30 became infected in the control (p<0.01)
Hopf *et al.* (1991) [29]	Superficial wounds (n=25). Compares betadine cream vs. Silvadene cream vs. no treatment	Faster epithelization with betadine cream (p<0.01)
Knutson *et al.* (1981) [30]	Burns, chronic wounds (n=759). Treated with povidone-iodine and sugar (n=90), povidone-iodine ointment and sugar (n=515), standard treatment (n=154)	Decrease in infection. Increase in wound healing rates
Kucan *et al.* (1981) [31]	Compares povidone-iodine (n=15), vs. silver sulfadiazine (n=15), vs. saline (n=14) in pressure ulcers	Effect on wound healing not studied. Effect on infection – 60% of patients responded to treatment after 14 days vs. 60% and 90% at the saline and SSD groups
Lammers *et al.* (1982) [32]	Compared 33 acute wounds soaked in 1% povidone-iodine or normal saline vs. no treatment (control)	No difference in wound infection between the control and povidone-iodine groups. Normal saline group had increased bacterial counts (p<0.0001)

Lee *et al.* (1979)[33]	18 chronic wounds treated povidone-iodine 10%	67% were clinically cured, 33% showed improvement Two wounds continued to be infected (p<0.001)
Lineaweaver *et al.* (1985)[6]	*In vitro* comparison of 1% povidone-iodine, 0.5% sodium hypochlorite, 0.25% acetic acid, and 3% hydrogen peroxide on human cells and bacteria	At full strength all four agents killed 100% of fibroblasts. 0.25% acetic acid decreased bacterial survival, the other three agents were equally toxic
Lineaweaver *et al.* (1985)[5]	*In vitro* comparison of three topical antibiotics and four antiseptic agents (1% povidone-iodine, 0.25% acetic acid, 3% hydrogen peroxide, and 0.5% sodium hypochlorite) to assess their cytotoxicity to cultured human fibroblasts	All four were cytotoxic to fibroblasts
McKenna *et al.* (1991)[7]	0.005% sodium hypochlorite, 0.001% povidone-iodine, 0.0025% acetic acid, and 0.003% hydrogen peroxide tested for effectiveness against common wound isolates without compromising fibroblasts and leukocyte function	0.005% sodium hypochlorite effective topical antibacterial without inhibiting fibroblast activity. Bactericidal activity of the other agents was compromised at reduced levels that maintains fibroblast activity
McLure *et al.* (1992)[34]	*In vitro* comparing povidone-iodine 10% and chlorhexidine against 33 clinical isolates	Povidone-iodine significantly reduced the logarithmic reduction factors than chlorhexidine (p<0.001) at full and diluted strengths
Piérard-Franchimont *et al.* (2002)[35]	Treatment of hydrocolloid dressing alone or in combination with povidone-iodine in venous ulcers (n=30)	Increase in wound healing rates in povidone-iodine group in first 4 weeks (p<0.05). Decrease in infection (neutrophilic vasculitis, and bacterial clumps in povidone-iodine group, significance not calculated
Rodeheaver *et al.* (1982)[36]	*In vitro* testing comparing bactericidal activity of aqueous iodine, povidone-iodine antiseptic solution (Betadine), and povidone-iodine surgical scrub solution (Betadine), normal saline as control	Bactericidal activity of antiseptic solution was inferior to aqueous iodine. Aqueous iodine significantly potentiated infection, no therapeutic benefit compared with saline. Higher infection rates in the surgical scrub group compared with control
Saydak S (1990)[37]	Pressure ulcers (n=11), two ulcers per patient. Compares povidone-iodine with absorption dressing	Slower healing in the iodine group. No significant difference
Sindelar *et al.* (1979)[38]	Surgical wounds irrigated with either povidone-iodine (n=242) or saline (n=258)	Decrease in wound infection rates in the povidone-iodine group 2.9% vs. 15.1% (p<0.001)
Stringer *et al.* (1983)[39]	Acute wounds (n=80) cleansed with either hydrogen peroxide (n=20), normal saline (n=20), Savlon (n=20), or povidone-iodine (n=20)	Reduction of wound sepsis with the use of povidone-iodine (p<0.05)
Takahashi *et al.* (2002)[40]	Nine adults bacteriological evaluation of povidone-iodine under opsite dressing	Dressing changes can be avoided for at least 3 days postoperatively
Teepe *et al.* (1993)[9]	*In vitro* investigation of 35 antimicrobial and antiseptic agents on cultured human keratinocytes	Under certain conditions cultured epithelial cells may be exposed to clinical concentrations of 0.1% povidone-iodine
Vijanto *et al.* (1980)[8]	Surgical paediatric wounds (n=294) compares povidone-iodine 5%, povidone-iodine 1%, or saline (control)	No effect on wound healing in any group. Decrease in infection 2.6% with 1% povidone-iodine vs. 8.5% of the control group. Increase in infection 19% with 5% povidone-iodine vs. 8% of the control group

Table 4. Animal studies using povidone-iodine.

Author & year	Study	Results
Archer *et al.* (1990)[41]	Porcine model (n=3), four sites surgically incised treated with either, 0.8% povidone-iodine, semi-permeable film, or sugar paste	Impaired healing in the povidone-iodine group. Statistical significance not stated
Bennett *et al.* (2001)[42]	Porcine model, six wounds treated with either 5% mafenide acetate, 10% povidone with 1% free iodine, 0.25% sodium hypochlorite, 3% hydrogen peroxide, 0.25% acetic acid, and one untreated control	Re-epithelialisation not significantly influenced in any group. Mafenide acetate and sodium hypochlorite increased neodermal thickness ($p<0.05$), hydrogen peroxide and acetic acid inhibited neodermal formation ($p<0.001$. Apart from hydrogen peroxide all treatments increased fibroblast proliferation. Mafenide acetate and betadine enhanced angiogenesis ($p<0.05$)
Brennan *et al.* (1985)[4]	Rabbit ear model, compared normal saline as the control with eusol, povidone-iodine 5%, povidone-iodine 1%, hydrogen peroxide, chloramine T, and chlorhexidine gluconate 0.05%	All agents caused an adverse effect on granulation tissue. Eusol and chloramine T the formation of granulation tissue ceased.
Geronemus *et al.* (1979)[43]	Multiple wounds on domestic pigs treated with either Neosporin ointment, Furacin, silvadine cream, pharmadine (contains 9% to 12% free iodine), or no treatment	Neosporin significantly increased re-epithelialisation rates by 25%. Furacin retarded healing rates. Pharmadine did not affect the healing rate. Both Silvadene and its vehicle increased re-epithelialisation by 28% and 21% respectively
Gruber *et al.* (1975)[44]	Rat model multiple partial and full thickness wounds treated with 0.25% acetic acid, povidone-iodine, and 3% hydrogen peroxide, with a control of normal saline. Ten human donor sites half the donor site no treatment (control), the other half received one of the antiseptic agents	No effect on wound healing, 12.2 and 9.3 days mean healing time for betadine vs. 12.4 and 9.5 for saline in partial-thickness wounds in rats and humans; 19.2 vs. 19.5 in full-thickness wounds in rats, non-significant difference
Howell *et al.* (1993)[45]	Lacerations in a guinea pig model contaminated with *S. aureus* (n=48) vs. saline; cefazoline; no treatment	Effect on wound healing not studied. No effect on bacteria levels
Kashyap *et al.* (1995)[46]	Incision wounds (n=60) in mice randomly assigned to one of four (A-D) treatment groups. A and B received either povidone-ointment and ointment vehicle with no povidone-iodine. Group D no ointments (control), Group C received cortisone acetate	Povidone-iodine as well as steroid group had significantly reduced wound strength/no effect on collagen
Kjoselth *et al.* (1994)[47]	Full thickness wounds on mice. Comparing bacitacin, 0.25% sodium hypochlorite, 1% silver sulfadiazine, 8.5% mafenide acetate, 10% povidone-iodine, and control no treatment	Control wounds and wounds treated with silver sulfadiazine and mafenide acetate epithelialised faster ($p<0.01$). Povidone-iodine epithelialised the slowest
Malloy *et al.* (1993)[48]	Male rats (n=50), surgical incisions compares povidone-iodine with normal saline in clean wounds	Prolonged impairment of healing in povidone-iodine group ($p<0.05$)

Menton *et al.* (1994) [49]	120 wounds on 60 guinea pigs 3cm full thickness wounds Three treatment groups Betadine surgical scrub, Shur-Clens and DPS 89009 (pilot batch of SAF-Clens). Control wounds treated with saline	Betadine delayed epidermal and dermal healing vs. all groups. Increase tensile strength in betadine group at 21 days
Mertz *et al.* (1984) [50]	Partial thickness wounds (n=54) on 9 pigs. Compares 10% povidone-iodine with 70% alcohol, or control (sterile distilled water)	Decrease in bacteria (*S. aureus*) 5.94 log bacterial counts after 24 hours vs. 7.53 and 7.28 at the water and alcohol groups ($p<0.05$)
Mulliken *et al.* (1980) [51]	Incisional rat wounds (n=341). Hypothesis tested that 1% povidone-iodine inhibit the recovery of the tensile strength in healing wounds compared with ringer's solution	No effect on tensile strength (17.52 gm/mm^2 tensile strength after I week vs. 17.90 at the ringer's solution group; non-significant difference
Niedner *et al.* (1986) [52]	Full thickness wounds in guinea pigs (n=10 for each group). Effect on wound healing povidone-iodine 5 %, six other antiseptic agents vs. no treatment (control)	No effect on wound healing. Decrease of 19% of granulation tissue (non-significant difference)
Rodeheaver *et al.* (1982) [36]	Guinea pig model iodine vs. saline	Bacterial levels reduced (1.131 log reduction of bacteria 10 min after $p<0.001$; no effect 4 days after a single application; no effect on infection rate)
Severyns *et al.* (1991) [53]	Effect of wound irrigation fluids (povidone-iodine, chlorhexidine and saline) on rat femoral arteries and veins	Povidone-iodine toxic (marked difference of 10%) on histological assessment, damage to vascular endothelium and thrombosis, vs. saline, and chlorhexidine

information regarding the reason for the type of animal used in their study together with the location and types of tissue of the animal used for wounding, and clearly describe methods and products used in treating the wounds. Different types of animals show different healing responses. Loose-skinned animals (mice, rates, guinea pigs) heal through contraction, while the primary mode of healing in tight-skinned animals (pigs) is epithelisation; this resembles more closely the healing response in humans. Pigs are generally considered suitable for studying full thickness wound healing, since their epidermis, dermis and subcutaneous fat closely resemble that of humans [18]. None of the animal studies examine the effect of povidone-iodine in chronic wounds, as an animal equivalent does not exist [3].

Conflicting evidence was demonstrated in several studies in the experimental pig model [41-43, 50]. Povidone-iodine delayed wound healing and did not reduce bacterial growth in Archer *et al.*'s [41] study of full thickness pig wounds when compared with a film dressing and sugar paste. The results of their study supported detrimental and, in all probability, counter-productive treatment with povidone-iodine. The small sample size in this study warrants replication with larger numbers to gain any conclusion. Larger sample sizes comparing various antiseptic agents demonstrated that there was no significant difference in wound healing rates compared with the other antiseptic agents. These studies provide valuable information because of the similarity to human tissues.

The bactericidal properties of povidone-iodine solution and any potential therapeutic effect was studied by Rodeheaver *et al.* [36] in guinea pigs. The authors concluded that within the first 10 minutes of a single application of povidone-iodine there was a noteworthy decrease in the bacterial load; this effect, however, did not persist. There was also no significant difference in the bactericidal properties of povidone-iodine in comparison to cefazolin or normal saline in an investigation by Howell *et al.* [45] that examined contaminated 12 hour old lacerations in a guinea pig model. The authors did discuss that this may be due to the formation of a proteinaceous wound coagulum and that even parental antimicrobials are ineffective in preventing infection if administered 3 hours after wounding in animal models.

Menton *et al.* [49] and Niedner [52] did not examine the bactericidal properties in their research; they did, however, produce conflicting results in wound healing in experimental incision wounds on guinea pigs. Menton *et al.* [49] established that there was a decrease in wound healing rates but an increase in the tensile strength of wounds. However, Nieder *et al.* [52] demonstrated no difference in wound healing rates when povidone-iodine was used.

Table 5. Human and in vitro *studies using cadexomer-iodine.*

Author & year	Study	Results
Apelqvist *et al.* (1996)[54]	Diabetic foot ulcers (n=250, 12 treated with cadexomer-iodine, 13 with standard treatment	No difference in wound healing in either group
Danielsen *et al.* (1997)[55]	Venous leg ulcers (n=17) treated with cadexomer-iodine for the effectiveness in the treatment of *Pseudomonas aeruginosa*	Decrease in bacterial counts (65% of patients had negative *P. aeruginosa* cultures after 1 week
Floyer *et al.* (1988)[56]	Venous leg ulcers (n=30) treated with cadexomer-iodine to establish the effectiveness in wound healing, infection and sensitivity	Wound healing increased (15 out of 18 healed or reduced in size, 3 increased in size). Decrease in clinical signs of infection. 11 were withdrawn from the trial (pain n=8, increase in size n=4, new ulcers n=3, unrelated n=1). No allergies developed
Hansson (1998)[57]	Venous leg ulcers (n=153) treated with either cadexomer-iodine, hydrocolloid dressing, or paraffin gauze	Increase in wound healing (62% mean reduction of ulcer area vs. 41% and 24% in the hydrocolloid and paraffin gauze groups)
Harcup *et al.* (1986)[58]	Venous leg ulcers (n=72) cadexomer-iodine vs. standard treatment	Increase in wound healing. Ulcers reduced by 36% after 4 weeks of treatment vs. 10% in standard treatment (p<0.01%). Decrease in infection (p<0.05-p<0.001)
Hillstöm (1988)[59]	Venous leg ulcers treated with cadexomer-iodine (n=38) vs. standard treatment (n=36)	Increase in wound healing in cadexomer-iodine group, 34% reduction in ulcer size vs. 5%. Decrease in wound infection
Holloway *et al.* (1989)[60]	Venous leg ulcers treated with either cadexomer-iodine (n=38) or standard treatment of wet to dry dressings (n=37)	Increase in wound healing rates in cadexomer-iodine group (p<0.0025). No statistical significance on infection
Laundanska *et al.* (1988)[61]	Venous leg ulcers treated with cadexomer-iodine (n=30) vs. standard treatment cleaning with hydrogen peroxide and zinc paste dressing (n=30)	Increase in wound healing 74% mean reduction of size after 6 weeks vs. 54% in standard treatment (p<0.01)
Moberg *et al.* (1983)[62]	Decubitus ulcers (n=34) treated with cadexomer-iodine (18) vs. standard treatment; saline dressing, debriding agent or non-adhesive dressing (n=16)	Increase in wound healing in cadexomer-iodine group (76% decrease in ulcer size vs. 57%) (p< 0.05%)). Decrease in pain, pus and debris (p<0.005%)
Moss *et al.* (1987)[63]	Venous ulcers (n=21) treated with cadexomer-iodine vs. debrisan (n=21)	No significant difference in wound healing rates. Neither therapy significantly reduced colonisation
Ormiston *et al.* (1985)[64]	Venous leg ulcers (n=60), cadexomer-iodine (n=30) vs. standard treatment; gentian violet, and polymyxin-bacitracin ointment (n=30)	Increase in wound healing (0.89cm^2/wk ulcer healing vs. 0.46 in the standard treatment (p<0.0001). Non-significant effect on infection
Skog *et al.* (1983)[65]	Venous leg ulcers (n=74) cadexomer-iodine (n=36) vs. standard treatment at each centre (n=38)	Decrease in ulcer size 34% after 6 weeks treatment vs. 5% increase in size in standard treatment group. Decrease in infection in treatment group
Steele *et al.* (1986)[66]	Venous leg ulcer (n=38) cadexomer-iodine vs. standard treatment (n=36)	No difference in wound healing rates. No statistical significance at 1, 4, or 6 weeks
Stewart *et al.* (1987)[567]	Venous leg ulcer (n=46) cadexomer-iodine vs. Intrasite (n=49)	No statistical difference in wound healing rates
Travainen (1988)[68]	Venous ulcers (n=27) cadexomer-iodine (n=14) vs. dextranomer (n=13)	Increase in wound healing (64% healed vs. 50% of dextranomer group after 8 weeks of treatment). Non-significant effect on infection

Malloy & Brady [48] used a rat model (n=50) with two incised full thickness wounds each comparing normal saline wick to povidone-iodine wicks, and found that healing was delayed for 30 days in the povidone-iodine group compared to 15 days for the saline wick wounds. With a larger sample size (n=341), Mulliken *et al.* [51] compared povidone-iodine with Ringer's solution also in experimental incision wounds in rats. Their results demonstrated that brief irrigation with povidone-iodine solution does not affect factors important in the recovery of tensile strength during wound healing, such as fibroplasia and collagen cross-linking in the clean incised wound.

A marked difference of toxicity was established when Severyns *et al.* [53] compared irrigation of the femoral vessel in rats with saline, chlorhexidine or povidone-iodine. Irrigation with povidone-iodine caused the more damage to the vascular endothelium and thrombosis than the other agents tested. This supported the work of Brennan *et al.* [4] that, under experimental conditions, chlorhexidine was the safer agent to use as a wound irrigation fluid.

Two studies have been conducted using mice [46, 47], both demonstrating impaired wound healing with use of povidone-iodine. Clean lacerated experimental wounds in 60 mice were randomly assigned to one of four treatment groups (povidone-iodine, ointment vehicle, cortisone acetate or no treatment), in research by Kashyap *et al.* [46] designed to measure the effect of povidone-iodine on tensile strength. The groups treated with povidone-iodine and steroids had significantly reduced tensile strength in comparison to the other groups. Kjoseth *et al.'s* [47] results demonstrated earlier neovascularisation in the groups treated with povidone-iodine and silver sulfadiazine than with other antiseptic agents, (control, silver sulfadiazine, mafenide acetate, silver nitrate, bacitracin and povidone-iodine) in full thickness wounds on mice. However, epithelialisation was significantly slower with povidone-iodine than with any of the other agents tested.

Cadexomer-iodine

The majority of studies involving cadexomer-iodine are on human subjects. Three studies used the experimental porcine model. Mertz *et al.* [71] demonstrated that, unlike povidone-iodine, cadexomer-iodine applied daily in comparison to cadexomer ointment (the vehicle without iodine), or no treatment control, was able to accelerate the rate of epidermal

Table 6. Animal studies using cadexomer-iodine.

Author & year	Study	Results
Lamme *et al.* (1998) [69]	Full thickness pig wounds, treated with cadexomer-iodine (n=12), iodine with starch (n=120 or saline (n=12)	Increase in re-epithelialisation at 6 and 9 days in cadexomer-iodine group (p<0.05)
Mertz *et al.* (1999) [70]	Partial thickness pig wounds, inoculated with methicillin-resistant *S. aureus*. Assigned to three groups; air exposed untreated control, cadexomer (vehicle) dressing with starch no iodine, or cadexomer-iodine dressing	Cadexomer-iodine reduced the bacteria (p<0.004)
Mertz *et al.* (1994) [71]	Partial thickness pig wounds (n=120). Three treatment groups; cadexomer-iodine, air exposed, and ointment base control	Increase in epithelisation in the cadexomer-iodine group vs. controls (4.6 days vs. 4.9 and 4.7 days). Decrease in bacterial count in treatment group

migration and reduce the number of pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), in partial thickness wounds in pigs inoculated with MRSA and other pathogens. The author replicated this study in 1999 [70], inoculating the partial thickness pig wounds with MRSA only. The effect of wound healing was not examined in this study. Again, the results demonstrated the effectiveness of cadexomer-iodine in preventing proliferation of MRSA. Epidermal regeneration and epithelisation was also increased in full thickness pig wounds in research conducted by Lamme *et al.* [69]. This group compared cadexomer-iodine with normal saline – 12 pigs were allocated to each group, statistical significance was reached (p<0.05).

Human clinical studies using cadexomer-iodine in chronic wounds such as diabetic foot ulcers, venous leg ulcers or pressure ulcers have demonstrated a positive effect on wound healing. There was no difference in outcomes when comparing cadexomer-iodine with gentamicin solution, streptodornase/streptokinase or saline gauze in diabetic foot ulcers [54]. The study was small, with 12 patients treated with cadexomer-iodine and 12 treated with standard treatment (as outlined). The weekly costs were lower in the treatment group. Perhaps the outcomes would have been different by comparing silver impregnated dressing which were not available at the time of the study.

A randomised study of the treatment of pressure ulcers was undertaken by Moberg *et al.* [62]. This group compared cadexomer-iodine (n=16) to patients receiving standard treatment (n=18) which comprised of saline, enzyme-based or non-adhesive dressings. There was a considerable reduction in pus, debris and pain of the ulcers in the cadexomer-iodine group as well as accelerated wound healing. The ulcers were reduced by 76% versus 57% after 8 weeks of treatment in the cadexomer-iodine group. Only one of the standard treatment group healed compared with six in the cadexomer-iodine group.

Thirteen human studies with an English translation have been conducted comparing the clinical outcomes of cadexomer-iodine with other dressing modalities in the treatment of venous leg ulcers. Danielson *et al.* [55] examined the effects of cadexomer-iodine in venous leg ulcers colonised with *Pseudomonas aeruginosa*. The sample size was small, with only 19 patients entered into the study, and there was not a control group. Negative cultures were found in 65% and 75% of patients after 1 and 12 weeks of treatment respectively. The median ulcer area reduction obtained at 12 weeks was 32.9%. All patients had a short stretch bandaging system in place.

Two separate studies [57, 67] examined the effects of cadexomer-iodine and wound healing rates with conflicting results. Hansson [57] conducted a randomised, multi-centre trial comparing cadexomer-iodine (n=56) with either a hydrocolloid dressing (n=48) or paraffin gauze (n=49) as an adjunct to compression therapy. There was a mean reduction in ulcer size of 62% versus 42% and 24% in the hydrocolloid and paraffin gauze groups. Statistically significant difference in wound healing rates was not reached by Stewart & Leaper [67] when comparing cadexomer-iodine (n=49) with Intrasite gel (n=46) in chronic leg ulcers. The ulcers studied were of various aetiology, including venous, arterial, traumatic, diabetic and mixed/other, with the majority (n=42) being venous. Compression bandaging was not used in patients with venous leg ulcers; this may account for the lack of difference in healing rates in either of these groups.

Of the remaining 10 studies examining the effects of cadexomer-iodine in patients with venous leg ulcers, eight recorded an improvement in wound healing rates and

infection [56, 58-61, 64, 65, 68], whilst the remaining two did not find this to be the case [63, 66]. Moss *et al.* [63] compared cadexomer-iodine with dextranomer in 42 patients. The patients were observed for 6 weeks on standard outpatient therapy, and then randomly allocated to either agent, after which time ulcers not responding to treatment could be changed to the other treatment. At the end of the study there was no significant reduction in wound size or bacterial colonisation in either group. The authors do not clearly indicate if appropriate compression bandaging was in place, as this would also impact on wound healing rates. Steele *et al.* [66] recruited their patients from general practice and compared multiple standard therapies with cadexomer-iodine in 57 patients. There was no difference in healing rates. This group did not examine the effect on bacteria.

The most commonly quoted study demonstrating the effectiveness of cadexomer-iodine is by Skog *et al.* [65], a multi-centre study of 93 patients with recalcitrant venous leg ulcers. Patients were randomised to either cadexomer-iodine or one of various standard therapies (enzyme preparations, dextranomer, fucidic acid, trypure powder, polymix or silver nitrate) combined with compression bandaging. After 6 weeks of treatment with cadexomer-iodine, there was a 34% decrease in ulcer size compared with 5% in the other treatment groups. In the standard treatment group there was no effect on infection in 18 patients. However, in 16 out of 23 patients in the cadexomer-iodine group, infection cleared. Overall, in this study, there was a reduction of pain, removal of pus and debris, removal of exudate, stimulation of granulation and reduction of surrounding erythema in the group randomised to cadexomer-iodine. Similarly designed studies [56, 58-61, 64, 68] have also concluded that cadexomer-iodine has a positive effect on wound healing, reducing the bacterial load and decreasing infections.

Discussion

Evaluation of the results of numerous *in vivo* studies demonstrate overwhelmingly that there is enough evidence to support the use of cadexomer-iodine in the chronic wound environment. There is a lack of evidence to suggest that cadexomer-iodine would have a negative impact on wound healing and infection; on the contrary, wound-healing rates are improved. There are no studies demonstrating the effectiveness of cadexomer-iodine in acute wounds. However, with the correct set of circumstances such as infection, slough and exudate, one would expect this to transpire in acute

wounds, although there does need to be further study in this area to substantiate this.

In the presence of infection, the application of povidone-iodine proves to be effective at reducing bacteria numbers and decreasing wound infections. There is not enough evidence to support that wound healing is delayed in an infected wound and there are no human clinical studies to support the use of povidone-iodine in non-infected wounds. In view of this, in the absence of infection, povidone-iodine should be used with caution. As illustrated in the animal and *in vitro* model, povidone-iodine impairs collagen synthesis, has a toxic effect on fibroblasts and keratinocytes, and impairs epithelial cell migration, therefore potentially having a detrimental effect on the healing process in non-infected human wounds. Steen [73] conducted a review of the literature to determine the effects of povidone-iodine in burn victims. He concluded that povidone-iodine should be used with caution on granulating or recently incised surgical tissue.

When selecting povidone-iodine in wound care, a holistic approach needs to be taken and the systemic affects needs to be considered. Shetty & Duthie [74] describe a case of an elderly gentleman treated with povidone-iodine soaks to his multiple pressure sores. He had no goitre and normal radio-iodine uptake in his thyroid gland; however, he developed thyrotoxicosis caused by increased serum iodine availability. Fatal iodine toxicity was reported by D'Auria *et al.* [75], when a povidone-iodine solution was used as a continuous post-operative wound irrigation after hip debridement. Within 10 hours the patient died; serum total iodine concentrations were 1000 times the normal level. Burks [76] provides other examples of systemic iodine toxicity.

Conclusion

Iodine has been shown to be an effective antiseptic; however, the use of iodine in wound management remains a contentious issue for clinicians amidst concerns for its efficacy and impact on wound healing. A review of the literature reveals that there is a place for povidone-iodine in wound care in the presence of infection. Although there was evidence that demonstrated wound healing was delayed, the majority of studies illustrated that it did not impact on wound healing in the presence of wound infection. Cadexomer-iodine has a positive impact on healing in the chronic wound environment.

As there are no human studies examining the effects of povidone-iodine in the non-infected acute wound, one should use povidone-iodine with extreme caution, particularly those healing by secondary intention, such as wounds that have been surgically debrided, or split skin grafts in the absence of clinical signs of infection due to the detrimental cytotoxic effects on tissue. As illustrated, the systemic effects must always be considered.

References

1. Scanlon E & Stubbs N. To use or not to use? The debate on the use of antiseptics in wound care. Br J Community Nursing (Wound Care Supp) 2002; 8-20.
2. White RJ, Cutting K & Kingsley A. Topical antimicrobials in the control of wound bioburden: part 1. Ostomy Wound Manage 2006; **52(8)**:26-58.
3. Drosou A, Falabella A & Kirsner RS. Antiseptics on wounds: an area of controversy. Wounds 2003; **15(5)**:149-166.
4. Brennan SS & Leaper DJ. The effect of antiseptics on the healing wound: a study using the rabbit ear model. Br J Surg 1985; **72(10)**:780-782.
5. Lineaweaver WL, Howard R, Soucy D *et al.* Topical antimicrobial toxicity. Arch Surg 1985; **120**:267-270.
6. Lineaweaver WL, McMorris S, Soucy D *et al.* Cellular and bacterial toxicities of topical antimicrobials. Plast Reconst Surg 1985; **75**:394.
7. McKenna PJ, Lehr GS, Leist P *et al.* Antiseptic effectiveness with fibroblast preservation. Ann Plast Surg 1991; **27**:265-8.
8. Viljanto J. Disinfection of surgical wounds without inhibition of normal wound healing. Arch Surg 1980; **115**:253.
9. Teepe RGC, Koebrugge ES, M. LCWG *et al.* Cytotoxic effects of topical antimicrobial and antiseptic agents on human keratinocytes *in vitro*. J Trauma 1993; **35**:8-19.
10. Fleming A. The action of chemical and physiological antiseptics in a septic wound. Br J Surg 1919; **7**:99-129.
11. Rodeheaver G. Controversies in topical wound management. Wounds 1989; **1**:19-27.
12. Selvaggi G, Monstrey K, Van Landuyt K *et al.* The role of iodine in antisepsis and wound management: a reappraisal. Acta Chir Belg 2003; **103**:241-247.
13. Fleischer W & Reimer K. Povidone-iodine in antisepsis: state of art. Dermatol 1997; **195(Suppl 2)**:3-9.
14. Gershenfeld L. Povidone-iodine as a topical antiseptic. Am J Surg 1957; **94**:938-939.
15. McDonnell G & Russell AD. Antiseptics and disinfectants: activity, action and resistance. Clin Microbiol Rev 1999; **12(1)**:147-179.
16. Gottardi W. Iodine and iodine compounds. In: Block SS (Ed). Disinfection, Sterilization and Preservation (4th ed). Philadelphia: PA, 1991, p.152-166.
17. Khan NM. Antiseptics, iodine, povidone-iodine and traumatic wound cleansing. J Tissue Viability 2006; **16(4)**:6-10.
18. Kramer SA. Effect of povidone-iodine on wound healing: a review. J Vasc Nurs 1999; **17**:17-23.
19. Zamora JL. Chemical and microbiological characteristics and toxicity to povidone-iodine solutions. Am J Surg 1986; **151**:400-406.
20. Connell S. A two-part quality assurance project addressing infection rates of wounds sutured in the emergency department. J Emerg Nurs 1991; **17**:212-4.
21. Daróczy J. Antiseptic efficacy of local disinfecting povidone-iodine (betadine) therapy in chronic wounds of lymphedematous patients. Dermatol 2002; **204(suppl 1)**:75-78.
22. DeKock M, Van der merwe AE & Swarts C. A comparative study of povidone-iodine cream and silver sulfadiazine in the topical treatment of burns. Wounds 1989; **1**:65-71.
23. Denning L. The effect iodine has on post-phenolised nail surgery wounds. Br J Pod 2003; **6(4)**:96-99.
24. Eming SA, Simola-Hess S, Kurschat P *et al.* A novel property of povidone-iodine: inhibition of excessive protease levels in chronic non-healing wounds. J Invest Dermatol 2006; **126**:2731-2733.
25. Fumal I, Braham C, Paquet P *et al.* The beneficial toxicity paradox of antimicrobials in leg ulcer healing impaired by a polymicrobial flora: a proof-of-concept study. Dermatol 2002; **204(suppl 1)**:70-74.
26. Gordon MWG, Aikman L, Little K *et al.* Prevention of wound infection in the accident and emergency department: does povidone-iodine dry powder spray reduce infection rates? Br J Accident Emerg Med 1989; **1989(4)**:11-13.

27. Georgiade NG, William A & Harris MA. Open and closed treatment of burns with povidone-iodine. Plast Reconst Surg 1973; **52(6)**:640-644.
28. Gravett A, Sterner S, Clinton JE *et al.* A trial of povidone-iodine in the prevention of infection in sutured lacerations. Ann Emerg Med 1987; **16(2)**:167-171.
29. Hopf K, Grady R, Stahl-Bayl C *et al.* The effect of betadine cream vs silvadene cream on reepitheliazation in uninfected experimental wounds. Proceed Am Burn Assoc 1991; **23**:166.
30. Knutson RA, Merbitz LA, Creekmore A *et al.* Use of sugar and povidone-iodine to enhance wound healing: five years experience. Southern Med J 1981; **74(11)**:1329-1335.
31. Kucan JO, Robson MC, Heggers JP *et al.* Comparison of silver sulfadiazine, povidone-iodine and physiologic saline in the treatment of chronic pressure ulcers. J Am Geriatr Soc 1981; **29(5)**:232-235.
32. Lammers RL, Fourre M, Vallaham ML *et al.* Effect of povidone-iodine and saline soaking on bacterial counts in acute, traumatic, contaminated wounds. Ann Emerg Med 1990; **19(6)**:709-714.
33. Lee BY, Frieda S, Trainor P *et al.* Topical application of povidone-iodine in the management of decubitis and stasis ulcers. J Am Ger Soc 1979; **27**:302-306.
34. McLure AR & Gordon J. *In-vitro* evaluation of povidone-iodine and chlorhexidine against methicillin-resistant *Staphylococcus aureus.* J Hosp Infect 1992; **21**:291-299.
35. Piérard-Franchimont C, Paquet P, Arrese JE *et al.* Healing rate and bacterial necrotizing vasculitis in venous leg ulcers. Dermatol 1997; **194**:383-387.
36. Rodeheaver G, Bellamy W, Kody M *et al.* Bactericidal activity and toxicity of iodine-containing solutions in wounds. Arch Surg 1982; **117**:181-186.
37. Saydak SJ. A pilot test of two methods for the treatment of pressure ulcers. J Enterostomal Ther 1990; **17**:139-142.
38. Sindelar WF & Mason R. Irrigation of subcutaneous tissue with povidone-iodine solution for prevention of surgical wound infections. Surg Gynecol Obstet 1979; **148**:227-231.
39. Stringer MD, Lawrence JC & Lilly HA. Antiseptics and the casualty wounds. J Hosp Infect 1983; **4**:410-413.
40. Takahashi K, Muratani T, Saito M *et al.* Evaluation of the disinfective efficacy of povidone-iodine with the use of transparent film dressing opsite wound. Dermatol 2002; **204(Suppl 1)**:59-62.
41. Archer HG, Barnett S, Irving S *et al.* A controlled model of moist healing: comparison between semi-permeable film, antiseptics and sugar paste. J Exp Pathol 1990; **71**:155-70.
42. Bennett LL, Rosenblum RS, Perlov C *et al.* An *in vivo* comparison of topical agents on wound repair. Plast Reconst Surg 2001; **108(3)**:675-685.
43. Geronemus RG, Mertz PM & Eaglstein WH. The effects of topical antimicrobial agents. Arch Dermatol 1979; **115**:1311-14.
44. Gruber RP, Vistnes L & Pardoe R. The effect of commonly used antiseptics on wound healing. Plast Reconst Surg 1975; **55(4)**:472-476.
45. Howell JM, Stair TO, Howell AW *et al.* The effect of scrubbing and irrigation with normal saline, povidone-iodine, and cefazolin on wound bacterial counts in a guinea pig model. Am J Emerg Med 1993; **1993(11)**:134-138.
46. Kashyap A, Beezhold D, Wiseman J *et al.* Effect of povidone-iodine dermatologic ointment on wound healing. Am Surg 1995; **61(6)**:486-491.
47. Kjoseth D, Frank JM, NBarker JH *et al.* Comparison of the effects of commonly used wound agents on epithelization and neovascularization. J Am Coll Surg 1994; **179**:305-312.
48. Malloy RG & Brady MP. A modified technique of delayed primary closure using povidone-iodine wick: influence on wound healing in an experimental model. Irish J Med Sci 1993; **162**:297-300.
49. Menton DN & Brown M. The effects of commercial wound cleansers in cutaneous wound healing in guinea pigs. Wounds: Compend Clin Res Pract 1994; **6(1)**:21-27.
50. Mertz PM, Alvarez OM, Smerbeck RV *et al.* A new *in vivo* model for the evaluation of topical antiseptics on superficial wounds. Arch Dermatol 1984; **120**:58-62.
51. Mulliken JB, Healey NA & Glowacki J. Povidone-iodine and tensile strength of wounds in rats. J Trauma 1980; **20(4)**:323-324.
52. Niedner R & Schöpf E. Inhibition of wound healing by antiseptics. Br J Dermatol 1986; **115(Suppl 31)**:41-44.
53. Severyns AM, Lejeune A, Rocoux G *et al.* Non-toxic antiseptic irrigation with chlorhexidine in experimental revascularization in the rat. J Hosp Infect 1991; **17**:197-206.
54. Apelqvist J & Tennvall RG. Cavity foot ulcers in diabetic patients: a comparative study of cadexomer-iodine ointment and standard treatment. Acta Derm Venereol 1996; **76**:231-235.
55. Danieslen L, Cherry GW, Harding K *et al.* Cadexomer-iodine in ulcers colonised by *Pseudomonas aeruginosa*. J Wound Care 1997; **6(4)**:169-172.
56. Floyer C & Wilkinson JD. Treatment of venous leg ulcers with cadexomer-iodine with particular reference to iodine sensitivity. Acta Chir Scand 1988; **544(Suppl)**:60-61.
57. Hansson C. The effects of cadexomer-iodine paste in the treatment of venous leg ulcers compared with hydrocolloid dressing and paraffin gauze dressing. Int J Dermatol 1998; **37**:390-396.
58. Harcup JW & Saul PA. A study of the effect of cadexomer-iodine in the treatment of venous leg ulcers. Br J Clin Pract 1986; **40**:360-4.
59. Hillström L. Iodosorb compared to standard treatment in chronic venous leg ulcers: a multicentre study. Acta Chir Scand 1988; **544**:53-56.
60. Holloway AG, Johansen KJ, Barnes RW *et al.* Multicenter trial of cadexomer-iodine to treat venous stasis ulcer. West J Med 1989; **151**:35-38.
61. Laudanska H & Gustavson B. In-patients treatment of chronic varicose venous ulcers: a randomised trial of cadexomer-iodine versus standard dressing. J Int Med Res 1988; **16**:428-435.
62. Moberg S, Hoffman L, Grennert M-L *et al.* A randomized trial of cadexomer-iodine in decubitus ulcers. J Am Ger Soc 1983; **31(8)**:462-465.
63. Moss C, Taylor AEM & Shuster S. Comparison of cadexomer-iodine and dextranomer for chronic venous ulcers. Clin Exp Dermatol 1987; **12**:413-418.
64. Ormiston CM, Seymor MTJ, Venn GE *et al.* Controlled trial of iodosorb in chronic venous ulcers. Br Med J 1985; **291**:308-310.
65. Skog E, Arnesjö B, Troëng T *et al.* A randomized trial comparing cadexomer-iodine and standard treatment in the out-patient management of chronic venous ulcers. Br J Dermatol 1983; **109**:77-83.
66. Steele K, Irwin G & Dowds N. Cadexomer-iodine in the management of venous leg ulcers in general practice. Practitioner 1986; **230**:63-68.
67. Stewart AJ & Leaper DJ. treatment of chronic leg ulcers in the community: a comparative trial of Scherisorb and Iodosorb. Phlebol 1987; **2**:115-121.
68. Tarvainen K. Cadexomer-iodine (iodosorb) compared with dextranomer (Debrisan) in the treatment of chronic leg ulcers. Acta Chir Scand 1988; **544(Supp)**:57-59.
69. Lamme EN, Gustanfsson TO & Middelkoop E. Cadexomer-iodine ointment shows stimulation of epidermal regeneration in experimental full thickness wounds. Arch Dermatol Res 1998; **290**:18-24.
70. Mertz PM, Oliveira-Gandia MF & Davis SC. The evaluation of a cadexomer-iodine wound dressing on methicillin resistant *Staphylococcus aureus* (MRSA) in acute wounds. Dermatol Surg 1999; **25(2)**:89-92.
71. Mertz PM, Davis SC, Brewer LD *et al.* Can antimicrobials be effective without impairing wound healing? The evaluation of a cadexomer-iodine ointment. Wounds: Compend Clin Res Pract 1994; **6(6)**:184-192.
72. Berkelman RL, Holland BW & Anderson RL. Increased bactericidal activity of dilute preparations of povidone-iodine solutions. J Clin Microbiol 1982; **15**:635-639.
73. Steen M. Review of the use of povidone-iodine (PVP-I) in the treatment of burns. Postgrad Med J 1993; **69(Suppl 3)**:S84-S92.
74. Shetty KR & Duthie EH. Thyrotoxicosis induced by topical iodine application. Arch Inter Med 1990; **150**:2400-2401.
75. D'Auria J, Lipson S & Garfiel JM. Fatal iodine toxicity following surgical debridement of a hip wound: a case report. J Trauma 1990; **30**:353-355.
76. Burks RI. Povidone-iodine solution in wound treatment. Phys Ther 1998; **78**:212-218.