Cadexomer iodine: A fresh look at an old gem

Brett DW

Keywords Cadexomer iodine, mode of action, inflammation, clinical evidence, desloughing.

For referencing Brett DW. Cadexomer iodine: A fresh look at an old gem. WP&R Journal 2019; 27(1):42-48.

DOI https://doi.org/10.33235/wpr.27.1.42-48

ABSTRACT

Iodine-based preparations have been used for almost two centuries in the prevention of surgical site and other wound infections, but they can be toxic to tissue. Cadexomer iodine is an iodophor, which provides controlled release of iodine without cytotoxic effects. Cadexomer iodine is a long-established topical antimicrobial, which is used in the treatment of a variety of wounds. Its therapeutic efficacy is supported by a large body of clinical evidence. Moreover, ongoing research continues to reveal new insights into the mode of action of cadexomer iodine, and suggests new therapeutic applications. In addition, new clinical evidence/reviews in the form of Cochrane Reviews reveals comparisons to a wide range of topically applied wound care therapies.

INTRODUCTION

Iodine is a trace element of the halogen group and a component of thyroxin, a hormone produced by the thyroid gland, and it is required for physical and mental development[1]. Iodine is found in the form of iodides in seaweed and kelp. Iodine has been widely used in industry, the arts and health domains, but owes its discovery to a serendipitous accident in 1811, which involved the manufacture of gunpowder. Saltpetre (potassium nitrate) is a component of gunpowder and requires potassium carbonate, which is extracted from wood or seaweed ash, during the manufacturing process. French chemist, Barnard Courtois, was a saltpetre manufacturer who in 1811, when adding sulphuric acid to seaweed ash to aid extraction of sodium and potassium salts, added too much acid to the suspension. A violet vapour arose from the suspension and condensed to form crystals. These were analysed by Courtois who postulated that he had discovered a new element. Although Courtois did not publish his findings, he gave some of the crystals to colleagues, amongst them Gay-Lussac who named the new element 'iode' from the Greek *ioeides*, which means 'violet'[2].

David W Brett
BS, BS, MS
Science & Technology Manager
Smith & Nephew Wound Management Division
Fort Worth, TX, USA
Email dave.brett@smith-nephew.com

Since then, iodine-based preparations have been widely used for an assortment of ailments and from the mid-19th century have been used in the prevention of surgical site and other wound infections. During the mid-20th century, iodophors were adopted in concentrations that allowed a controlled release of iodine without its negative side effects, such as pain, irritation and staining. The two most common iodophors in current usage are povidone iodine (PVP-1) and cadexomer iodine[3].

IODINE FORMULATIONS

Molecular iodine quickly passes through the cell wall of microorganisms and reacts with N-H, S-H and phenolic groups of amino acids, resulting in disruption of protein structure. In doing so, metabolic enzymes are rendered inoperable and cellular respiration is brought to a standstill. As a result, the microbe is unable to metabolise nutrients and cannot survive. Iodine also interacts with C=C bonds in unsaturated fatty acids, thereby disrupting the cell membrane. In this case, the cell lyses and the microbe perishes[4]. Numerous clinical trials using cadexomer iodine preparations have shown that this form of topical iodine is an effective antimicrobial agent and is useful in wound debridement, stimulation of granulation tissue and overall wound healing[5]. Cadexomer iodine has shown rapid antimicrobial activity *in vitro*, outperforming nearly all antimicrobial silver dressings currently on the market[6]. This shouldn't come as surprise as the majority of silver dressings currently in use release very low levels of silver (many in the 1 ppm range). It has been demonstrated that the antimicrobial activity of silver is dose-dependent, thus higher levels of silver typically result in a higher level of antimicrobial activity. It is safe to assume that iodine is dose-dependent as well. In comparing the lowest level of iodine in use today (cadexomer iodine) versus the lowest levels of silver, we see a huge discrepancy. Cadexomer iodine delivers iodine at 0.9% (9,000 ppm) compared to low-dose silver dressings delivering in the range of 1 ppm. This difference in dose may account for the differences in antimicrobial activity between cadexomer iodine and many of the silver dressings currently in use.

Although it is an effective antimicrobial, molecular iodine can be toxic to tissue. Povidone iodine and cadexomer iodine are iodine formulations that have been developed to regulate iodine availability and eliminate or reduce toxicity within the

wound bed. Povidone-iodine is a stable chemical complex of iodine plus polyvinylpyrrolidone (PVP), containing 9–12% of iodine on a dry weight basis. Povidone iodine is completely soluble in water and other liquids, while it releases iodine in a fashion controlled by the hydrogel composition it is loaded into. It is effective against a wide range of bacteria, fungi, and spores, and rapidly inactivates cytoplasmic structures[7].

There have been reports that povidone iodine can be toxic to granulocytes and monocytes, even at low concentrations[8], resulting in decreased chemotaxis[9]. It has also been shown that dilute solutions of povidone iodine (0.1% and 1.0%) can be toxic to human fibroblasts[10], although there is partial recovery if the exposure is limited. However, there is some conflicting evidence as other literature states that povidone iodine lacks cytotoxicity *in vivo*[3,11].

CADEXOMER IODINE (MoA)

The cadexomer matrix is a chemically modified starch which consists of a helical polysaccharide backbone to which carboxymethyl groups have been added. This network is fashioned into hollow microspheres of 0.1–0.3 mm in diameter with multiple holes in their outer shell. Iodine is physically trapped within the centre of the bead at a concentration of 0.9%[12].

Fluid absorption

As the polysaccharide molecule has an abundance of hydrogen and hydroxide moieties, there is a great deal of hydrogen bonding that occurs in the presence of water, creating a gel. This allows the polysaccharide to absorb wound fluid, up to six times its weight.

Iodine release

When the gel is allowed to swell in wound fluid a portion of the iodine is dissolved as “free iodine” into the surrounding media. If cadexomer iodine is placed within an iodine-free fluid environment, iodine is released until equilibrium is achieved. Once the iodine in the surrounding media has been depleted, more will be released from the cadexomer matrix until the equilibrium is re-established. As a result, the iodine will be released when it is needed by the wound. Cadexomer iodine can also modulate wound pH, via an ion exchange mechanism. In the creation of the cadexomer matrix, carboxymethyl groups are added to the polysaccharide backbone. The carboxylic acid portion allows for a release of protons and a subsequent lowering of the wound fluid pH. This pH modulation has two interesting outcomes: enhancement of the antimicrobial activity of iodine and a unique anti-inflammatory property (which will be discussed in detail later in this review). By lowering the pH of the wound fluid the antimicrobial activity of iodine is enhanced. In an acidic environment, acid-catalysed hydrolysis between iodine and water converts iodine into two of its bactericidal forms, molecular iodine (I_2) and hypoiodous acid (HOI)[13]. In addition to enhancing the antimicrobial activity of iodine, a low pH also inhibits proliferation of bacteria. Before cadexomer iodine is hydrated, there is no release of iodine. The initial release will occur only when water (wound fluid) is present. Once iodine release is initiated, there is an interesting mechanism of sustained iodine at a specific concentration for a prolonged period of time. Historically, there are two noted mechanisms of release. One mechanism of achieving sustained release is by using a matrix through which the active agent can diffuse (diffusion-control release). However, this only allows a very slow initial release, which may only result in bacteriostatic activity. Another mechanism is to use matrix material through which the agents do not diffuse (to any extent), but are loosely dissolving (dissolution-control release). However, these two mechanisms do not account for the release characteristics observed with cadexomer iodine. Iodine is a small molecule with a high diffusion coefficient. The swollen cadexomer matrix gel is dilute and open when compared to other matrices previously described. In addition, the cadexomer matrix “beads” are very small and the diffusion distances are very short. Consequently, the diffusion of iodine through the swollen cadexomer gel is likely to occur very fast and cannot explain the sustained release that is observed. The explanation is that the assumption of a “sink condition” (which is necessary in diffusion-control and dissolution-control release) does not apply in the case of cadexomer iodine. Rather, a state of equilibrium is established at which there is no net diffusion of iodine out of the “beads”[14]. This state of equilibrium allows for a constant level of iodine available in the wound to kill pathogens at all times. As iodine is consumed in the process, the equilibrium shifts to provide additional free iodine. The iodine will remain at this bactericidal, yet non-cytotoxic level until all of the iodine has been consumed. Elemental iodine is not water-soluble and may be cytotoxic *in vivo* and, as a result, its use has largely been abandoned. Attempts to make iodine more water-soluble resulted in the creation of povidone-iodine (iodine plus polyvinylpyrrolidone). This improved preparation was also able to release iodine more slowly. However, it was not until the creation of cadexomer iodine that iodine was truly water-soluble, able to be released continuously at the wound site, while absorbing exudate and assisting in the debriding process[5].

Desloughing

The cadexomer matrix is particularly well known for its wound cleaning and desloughing properties. The polysaccharide (cadexomer) molecule has an abundance of hydrogen and hydroxide moieties, which allow for a great deal of hydrogen bonding with wound exudate to create a gel. This hygroscopic (readily taking up and retaining moisture) action of the cadexomer matrix allows debris within a wound to be removed with the exudate as it is drawn into the matrix[15]. Numerous clinical trials using cadexomer iodine preparations have shown that this form of topical iodine is useful in wound ‘cleansing’. Other papers describe wound debridement or, more appropriately, ‘desloughing’ of a wound. Desloughing is defined as the removal of loose, fibrous non-viable tissue. The clinical evidence ranges from case studies

to multi-centre randomised controlled trials (RCTs) and meta-analysis. Other papers make specific reference to a debriding or desloughing action[5,16-18]. Troeng[43] performed a multi-centre, randomised, blinded, controlled study with 72 patients over a six-week period to assess the action of cadexomer iodine. Criteria evaluated included ulcer closure, exudate absorption, removal of pus and debris, reduction of bacterial counts and management of oedema and odour. After six weeks, patients in the standard treatment group showed no change in ulcer size. The cadexomer iodine group demonstrated a significant reduction in ulcer size after one week. A significant difference in increase of granulation was evident at six weeks. Pain steadily decreased for both groups. The most dramatic difference between the treatments was in removal of pus and debris. Harcup[19] performed a multi-centre, randomised, optional crossover trial (which allows patients to change treatment at the mid-point of the trial) involving 72 patients with exuding chronic venous ulcers of the lower legs. Patients were evaluated using cadexomer iodine or standard treatment. Standard treatment consisted mostly of support bandaging or stocking and a dry dressing. At week 4, cadexomer iodine produced significant improvement over standard therapy for all criteria measured: ulcer size ($p < 0.01$), oedema ($p < 0.05$), erythema ($p < 0.05$), exudates ($p < 0.001$), odour ($p < 0.01$), pus and debris ($p < 0.05$) and pain ($p < 0.005$). Holloway[20] performed a crossover study designed to judge the efficacy of cadexomer iodine, in accelerating the healing of venous stasis ulcers in 75 patients were prospectively, randomly assigned to receive either cadexomer iodine or standard treatment. The control treatment consisted of standard saline wet-to-dry compressive dressing. The patients improved with either treatment: ulcers closed more than twice as rapidly using cadexomer iodine (n=38) as with standard therapy (n=37) (p=0.0025). Ulcers treated with cadexomer iodine showed trends towards less pain, exudate, pus, and debris and a more rapid development of granulation tissue. Twelve patients crossed over from control treatment to the use of cadexomer iodine because of failure to heal, but no patients switched to control therapy from the use of cadexomer iodine (p=0.01). Ormiston[21] performed a randomised comparison of cadexomer iodine and standard treatment in venous leg ulcers (VLUs). In this 54-patient study, it was concluded that ulcers treated with cadexomer iodine showed significantly more rapid desloughing and closure than those treated with standard dressings. This is reflected in faster reduction in bacterial colonisation and in early pain relief. Skog[16] performed a randomised trial on 93 patients with chronic infected venous wounds comparing cadexomer iodine with a variety of standard ulcer treatments over a six-week period. Fifty per cent of the patients received cadexomer iodine, while the other 50% received one of a variety of standard treatments, including dextranomer, fusidic acid, trypane powder and silver nitrate. The direct measurement of ulcer size by tracing and planimetry showed a significant reduction in ulcer size in the cadexomer iodine group, a decrease that continued during the next five weeks. After six weeks of treatment, ulcer size in the cadexomer iodine group was reduced by 34%, while in the standard group it increased by 5%. In both treatment groups there was a significant debriding effect on the ulcers, but this was significantly greater in the cadexomer iodine group ($p < 0.005$). Clearly there is clinical evidence of a 'debriding' or 'desloughing' property of cadexomer iodine. However, this should not be confused with other modalities of debridement (such as enzymatic or mechanical). The MoA of debridement of cadexomer iodine is autolytic debridement. It is important that the clinician use the appropriate method of debridement based upon co-morbidity, care setting, wound characteristics and the end goal. From the literature we see that cadexomer iodine offers the clinician another option for removing pus, debris and slough, given the proper wound conditions (that is, wet/sloughy).

INFLAMMATION

Wound healing depends upon cell-to-cell interactions which are regulated by messenger molecules know as cytokines, growth factors and chemokines. The first cells to arrive on the scene are neutrophils and macrophages. Neutrophils are phagocytic cells that can kill a variety of pathogens. In addition, neutrophils are also a source of pro-inflammatory cytokines that serve as some of the earliest signals, thus activating local fibroblasts and keratinocytes. Macrophages originate from circulating monocytes, which migrate to the wound where the local environment causes them to differentiate into macrophages. Chronic wounds are characterised by an apparent conversion from a healing to a chronic inflammatory response[22]. The inflammatory infiltrate within chronic wound tissue is composed primarily of blood-derived lymphocytes and macrophages with additional neutrophils being found in infected tissue[23]. Macrophages predominate numerically and studies have demonstrated that they play a crucial role in the regulation of wound healing[24]. T-lymphocytes form a significant portion of inflammatory leucocytes in chronic wounds and interact with cytokines, growth factors and chemokines in the modulation of the healing process[23]. All chronic wounds seem to be plagued by non-resolving inflammation[25-28]. Under normal acute wound healing conditions, the signals that promote inflammatory activity largely dissipate within a few days of injury. When pro-inflammatory signals continue to be produced, a chronic inflammatory state is established and wound healing does not proceed. In many cases, sub-clinical bacterial contamination of wound tissue is thought to elicit the inflammatory response and prevent wound closer[29]. The first leucocytes on the scene secrete certain signalling molecules that encourage further inflammatory activity within the wound[30]. These signalling molecules include certain pro-inflammatory cytokines, such as TNF-α, IL-1β, IL15 1α and IL-6. Under normal acute wound conditions, levels of these cytokines briefly rise to promote a brief period of inflammation, and then subside as wound healing progresses[29]. These cytokines help to raise local tissue temperatures, promote inflammatory cell recruitment (neutrophils and macrophages) and stimulate cellular

production of various proteinases and cytokines[31]. It is clear that the primary obstacle to closure for the chronic wound is an inflammatory phase past which the wound is unable to move. There are two ways one might hypothesise about this situation. One hypothesis focuses on a pro-inflammatory response that is out of control due to various factors such as local tissue ischaemia, bioburden, necrotic tissue, repeated trauma, and so on. In this case there is an over-stimulation of the wound, elevated numbers of inflammatory cells are called to the wound site, then over-stimulated. As a result, these cells produce elevated levels of pro-inflammatory cytokines, which ultimately results in fibroblasts and other cells releasing elevated levels of protease, which, in turn, degrade key structural components (such as collagen) of the extracellular matrix (ECM). Without a functional ECM, granulation tissue is not formed. As a result, the dermal tissue is not functional and keratinocytes are unable to move across the dermal tissue and close the wound. Thus, the wound remains open and chronic. A second hypothesis focuses on the lack of activity of the biochemical players responsible for a proinflammatory response. In this case, cells such as macrophages are present, but in a non-functioning state. Regardless of the hypothesis one chooses to adopt, the result is the same, the wound is not able to progress past the inflammatory phase of healing and thus does not close. In the case of an out-of-control pro-inflammatory response, the logical therapy might be one of anti-inflammatory activity. In the case of non-functioning macrophages, the logical therapy might be one of encouraging macrophages to become active again. There are likely numerous therapies that might be of a benefit in both cases, though research is limited in this area. The following is a discussion of one such therapy for which there is a great deal of *in vitro* and clinical support. We will see how cadexomer iodine seems to play both a pro- and anti-inflammatory role. Though this concept may seem paradoxical at first glance, the benefits of this technology have been borne out in the clinical evidence with use on chronic wounds for over four decades. With numerous studies involving VLUs, PUs, DUs and thousands of patients, cadexomer iodine has been proven to promote wound closure in chronic wounds[5].

Anti-inflammatory property

In an *in vitro* study by Greener[32], the anti-inflammatory activity of the cadexomer matrix portion of the cadexomer iodine technology was investigated. In this study there was no iodine present. As previously mentioned, an elevated level of protease activity in chronic wounds delays the healing process. Proteases have therefore been deemed a good target for chronic wound therapy. In this study, the enzyme activity profile of four key wound proteases (elastase, cathepsin G, plasmin and 7 kDa gelatinase) was assessed in the pH range 2 to 11. Before and after treatment with the cadexomer matrix, the pH and protease activity of a range of chronic wound fluids (pressure ulcers — PUs, mixed aetiology leg ulcers and diabetic foot ulcers — DUs) were measured using a flatbed pH probe and a matrix damage model (*in situ* zymographic film), respectively. All four proteases displayed maximum enzyme activity in the pH range 7 to 8. However, enzyme activity of each protease dropped dramatically when pH was reduced below pH 7. In the 31 chronic wound fluids tested, the pH was reduced from (on average) pH 8.1 to pH 5.0 in response to treatment with the cadexomer matrix. This cadexomer matrix appears capable of adjusting the pH of chronic wound fluids from a pH range of maximum protease activity to a pH range of minimum protease activity. In 11 chronic wound fluids tested, the cadexomer matrix effectively protected against matrix damage by excess protease activity in this model. *In vitro* data suggests that this cadexomer matrix modulates wound fluid pH. (An acidic pH is achieved via the release of protons from the carboxymethyl groups of the cadexomer matrix as discussed previously in this review.) It is expected that this same modulation of the pH may occur *in vivo* as well. In the wound, we might expect to see a reduction in enzymatic activity of proteases such as matrixmetalloprotienases in the chronic wound and protection of newly formed ECM, potentially allowing ultimately for re-epithelialisation of the wound[32].

Pro-inflammatory property

Iodine also aids in intracellular killing of organisms by phagocytes. When iodine is converted to iodide it is taken up by leukocytes. Once activated, these cells exhibit respiratory burst behaviour where ingested bacteria are killed via the formation of reactive oxygen species (free radicals). The enzyme, myeloperoxidase, is involved in this process and needs to interact with a halide such as iodide, chloride or bromide for maximum effects. Cadexomer iodine also has a pro-oxidant effect via the release of iodine into the wound. The iodine enters the microbial cells and reduces the glutathione and NAD(P)H. This allows the hydrogen peroxide levels to increase, ultimately resulting in an increase in fibroblast proliferation. Chemokines, cytokines and growth factors interact in a dynamic fashion during wound healing[22]. One key cellular component involved in healing is the generation of an inflammatory response, resulting in the influx of mononuclear leukocytes, particularly macrophages to the wound site[33]. This influx is dependent upon cytokine generation Luckacs[34] and macrophages are themselves a rich source of cytokines[35]. Therefore, a therapy which helps to regulate cell function so the cells present at the wound site might be manipulated to modulate their cytokine profile *in situ* may be of a benefit clinically. Cadexomer iodine may be an appropriate therapy in this respect. As the cadexomer hydrates in the moist wound environment, iodine is released to exert an antimicrobial effect. However, it appears that the iodine may be able to interact with specific cell types in the wound. Iodine is bioactive in that it has been shown to be an essential co-factor in neutrophil Clark[36] and macrophage Nathan[37] cytocidal activity generated via a myeloperoxidase hydrogen peroxide pathway initiated as a consequence of phagocytosis. Moore[23] set out to determine if cadexomer iodine might modify the healing process by interacting with macrophages to modulate cytokine production, thus

indirectly influencing the projection of chronic wounds. To do so, the researchers used human histolytic lymphoma cell line U937 (macrophage) in their study. The macrophages were co-cultured with cadexomer iodine, cadexomer iodine-conditioned media or elemental iodine. They were then activated with bacterial lipopolysaccharide (LPS) from *Escherichia coli*. The resulting pro-inflammatory response was determined by measuring the concentration of TNF-α and IL-6 (two well studied pro-inflammatory cytokines) in the culture medium after 24 hours. In addition, 6 mm punch biopsies were taken from the beds of chronic leg ulcers then subjected to immunohistologic analysis. The results indicated that cadexomer iodine induced a threefold increase of TNF-α production by the macrophages. It was noted that without the co-stimulatory effect of LPS, cadexomer iodine did not induce TNF-α secretion. However, co-culturing with cadexomer iodine enhanced TNF-α even at sub-stimulatory levels of LPS. To determine the effects of cadexomer iodine on the secretion of IL-6 from macrophages, the concentration of IL-6 was monitored in culture supernatants where enhanced levels of TNF-α had been demonstrated after cadexomer iodine co-culture. LPS enhanced IL-6 secretion, but no additional effect could be demonstrated in the presence of cadexomer iodine. In fact co-culturing macrophages with cadexomer iodine actually reduced the production of IL-6 by >60%, but did not inhibit it completely. Granulation tissue in chronic leg ulcers contains large numbers of macrophages. In biopsies taken from non-infected wounds the majority of these macrophages did not contain TNF-α. Evidence exists indicating that cadexomer iodine may enhance the projection of chronic wounds by a mechanism additional to its antimicrobial effects. For example, in a clinical study by Holloway[20], it was demonstrated that significant wound re-epithelialisation was demonstrated in the cadexomer iodine group, even though only 42% of the wounds were infected. Macrophages are a rich source of cytokines and growth factors that may be instrumental in regulating healing[35]. Paradoxically, chronic wound tissue is heavily infiltrated with macrophages and to a lesser extent T-lymphocytes. The cytokine profile of macrophages is modulated upon activation and it is possible that within chronic wounds macrophages are either not active or inappropriately activated (senescent). In the majority of chronic leg ulcers the macrophages distal to vessels are non-activated. A possible mechanism of action of iodine may be to activate inactive macrophages within the chronic wound and thus modulate macrophage cytokine production. Where iodine seems to enhance the production of TNF-α, it seems to decrease the production of IL-6. It has been shown that IL-6 down regulates the production of TNF-α by U937 cells and human monocytes in response to LPS *in vitro* and also *in vivo*[38]. Thus IL-6 acts as the negative arm of the feedback loop meant to ensure control of this aspect of the pro-inflammatory response. An interesting take-away from this study was the finding that iodine's effect on TNF-α production was manifested only at a concentration of LPS that was sub-stimulatory to the macrophage. A chronic wound that is not clinically infected is still likely to be colonised with low to moderate levels of bacteria. As a result, low to moderate levels of LPS would exist in the wound, resulting in a sub-stimulatory level of LPS. In the absence of an appropriate level of stimulus for the cytokine network, macrophages will remain non-activated. This concept is supported by the fact that the majority of macrophages in chronic wound tissue are negative for TNF-α with only cells close to the vessels being positive for TNF-α. Thus, interaction with iodine may, in fact, help to activate these "stalled" macrophages to release TNF-α, with this effect being optimised with a down-regulation of IL-6 production. The generation of an inflammatory response within chronic wound tissue may re-initiate the healing process. TNF-α could be considered an ideal molecule for this role. In fact, an intradermal injection of TNF-α to human volunteers generated an infiltrate of macrophages and T helper cells and also induced expression of endothelial cell and keratinocyte adhesion molecules[39]. The possibility of delivering iodine to non-activated macrophages within chronic wounds may induce TNF-α activity and, as a consequence, a fresh influx of macrophages and T-helper cells, which play a critical role in the modulation wound progression[22].

CLINICAL USE

Cadexomer iodine has a rich history of clinical use. Moberg[40] performed a randomised trial of cadexomer Iodine in decubitus ulcers. In this 34-patient comparative study it was found that cadexomer iodine showed debriding action, accelerated healing and superiority in reducing pain compared to standard treatment. Skog[16] performed a randomised multicentre trial of 93 patients, comparing cadexomer iodine to standard treatment of chronic venous ulcers. The study showed reduction in pain, pus, exudate, erythema, bacterial count and stimulation of granulation. Cadexomer iodine increased rate of healing of infected ulcers. During the six-week trial, ulcers treated with cadexomer iodine reduced significantly in size. Ormiston[41] performed a controlled trial of cadexomer iodine in chronic venous ulcers. In this 61-patient comparative trial the epithelium of ulcers treated with cadexomer iodine grew faster ($p<0.001$) compared to that of ulcers receiving standard treatment. It was noted that ulcers treated with cadexomer iodine healed nearly twice as quickly during the first 12 weeks of the study. Hansson[42] performed a randomised controlled clinical trial comparing the effects of cadexomer iodine paste in the treatment of VLUs compared with hydrocolloid dressing and paraffin gauze dressings. In this 12-week RCT involving 153 patients, cadexomer iodine showed faster wound closure and was an efficient, cost-effective alternative to hydrocolloid and paraffin gauze dressings. Troëng[43] performed a randomised multi-centre trial comparing the efficacy of cadexomer iodine and standard treatment on chronic venous ulcers. In this trial, 72 patients with VLUs present for at least three months. The trial concluded that the use of cadexomer iodine was associated with more rapid wound closure and 'cleansing' of ulcers and that the removal of organisms relates to

more rapid re-epithelialisation. Danielsen[44] performed a trial evaluating cadexomer iodine in ulcers colonised by *Pseudomonas aeruginosa*. In this study, the researchers concluded that cadexomer Iodine might be the treatment of choice for VLU colonised with *P. aeruginosa*. Ormiston[21] performed a randomised comparison of cadexomer iodine and standard treatment in VLUs. In this 54-patient study it was concluded that ulcers treated with cadexomer iodine showed significantly more rapid desloughing and closure than those treated with standard dressings. This is reflected in faster reduction in bacterial colonisation and in early pain relief. Steele[45] performed a trial of cadexomer iodine in the management of VLUs. In this 57-patient clinical study the main advantages identified for chronic suffers of leg ulcers was the ability of the cadexomer iodine to reduce pain, odour, and accelerate wound closure. Holloway[20] performed a multi-centre trial of cadexomer iodine for the treatment of venous stasis ulcers. In this 75-patient prospective, randomised clinical trial the mean ulcer closure rate was more than twice as great using cadexomer iodine as with standard therapy of wet-to-dry dressing with saline-soaked gauze pads and elastic compression bandage. Ulcers treated with cadexomer iodine showed trends toward less pain, exudate, pus and debris, and a more rapid development of granulation tissue. In addition to the aforementioned clinical trials, there are few very interesting reviews of the clinical literature. Falanga[5] found that cadexomer iodine has been shown to accelerate ulcer debridement and healing. Sundberg[18] performed a retrospective analysis of the clinical literature. In this retrospective review of cadexomer iodine the authors consider the efficacy, safety, biological action and cost-effectiveness. They found that since 1982 a published body of evidence containing almost 10,000 patients supports the efficacy and safety of cadexomer iodine in treating a variety of ulcer types and burns, including sloughy, and sloughy and infected ("dirty") wounds. These studies showed cadexomer iodine to be as effective as or more effective than standard treatments, using both subjective and objective measures of wound closure. Their review concludes that the now extensive literature base supports the effective and economical use of cadexomer iodine in a variety of chronic wounds. Gilchrist[46] cites evidence of efficacy in critically colonised wounds. He concludes that many of the concerns about iodine are based on toxicity of older formulations containing elemental iodine, or arise from *in vitro* studies, which may not be relevant to *in vivo* situations. Newer preparations appear to have useful antimicrobial properties and may be effective for the debridement and treatment of a variety of wounds. Lastly, at the time of this publication there are four Cochrane Reviews reviewing clinical evidence of a wide range of topical applications. From these meta-analyses, we see a consistent message of efficacy of cadexomer iodine. When compared to a wide range of topical therapies the authors state, "in terms of topical preparations, there is some evidence to support the use of cadexomer iodine and evidence to suggest that Cadexomer Iodine generates higher wound closure results than standard care"[47-50].

CONCLUSION

This review has addressed a variety of aspects of cadexomer iodine such as mode of action, release rates, antimicrobial activity, desloughing ability, clinical efficacy, cytotoxicity, and so on. Most importantly, from this review it was found that unlike many wound care technologies, there exists an ample body of high-quality clinical evidence in support of cadexomer iodine; as described in over 75 clinical trials (11 RCTs) involving VLUs, PUs, DUs spanning over 40 years involving over 14,000 subjects. It is hoped that this review will provide clinically relevant (and clinically proven) insights into iodine and specifically cadexomer iodine. As a result, the clinician will have a broader understanding and another tool to prepare the wound bed for wound closure.

CONFLICT OF INTEREST

The author is an employee of Smith & Nephew, Inc. So, in this sense Smith & Nephew, Inc. supports this paper.

FUNDING

Smith & Nephew, Inc. provided funding for this paper.

ETHICS

As this a review paper, an IRB was not necessary.

REFERENCES

1. Cavalieri R. Iodine metabolism and thyroid physiology: current concepts. Thyroid 1997;7(2):177–181.
2. Abrahams GE. The history of iodine in medicine part 1: From discovery to essentiality [Internet]. The Original Internist: 2006. Available from: http://www.optimox.com/iodine-study-14
3. Sibbald RG, Leaper DJ, Queen D. Iodine made easy. Wounds Int 2011;(2)2:1–3.
4. Cooper RA. Iodine revisited. Int Wound J 2007;4:124–137.
5. Falanga V. Iodine-Containing Pharmaceuticals: A Reappraisal. Proceedings of the 6th European Conference on Advances in Wound Management. Macmillan Magazines Ltd. (Eds). London, UK, 1997; 1-3.
6. Brett D. Comparison of the antimicrobial activity of a slow release cadexomer iodine antimicrobial dressing to various silver based antimicrobial dressings. Proceedings of The Symposium on Advanced Wound Care; August 1-4; San Antonio (TX): 2006:(52)8.
7. Misra A. Use of gauze soaked in povidone iodine for dressing acute open wounds. J Plast Reconstr Surg 2003;111:2015–6.
8. van den Broek PJ, Buys LF, van Furth R. Interaction of povidone-iodine compounds, phagocytic cells, and microorganisms. Antimicrob Agents Chemother 1982;22:593–7.
9. Connolly JC, Gilmore OJ. A study of povidone iodine on polymorphonuclear leucocyte chemotaxis. Br J Exp Pathol 1979;60:662–6.
10. Balin AK, Pratt L. Dilute povidone-iodine solutions inhibit human skin fibroblast growth. Dermatol Surg 2002;28:210–4.
11. Fumal I, Braham C, Paquet P, Piérard-Franchimont C, Piérard GE. The beneficial toxicity paradox of antimicrobials in leg ulcer healing impaired by a polymicrobial flora; a proof-of-concept study. Dermatology 2002;204(Suppl 1):70S–74S.
12. Gustavson B. Cadexomer iodine. In: Fox JA & Fischer H (Eds). Cadexomer Iodine. Stuttgart: Schattauer Verlag; 1983:35–41.

13. Gottardi W. The influence of the chemical behavior of iodine on the germicidal action of disinfectant solutions containing iodine. J Hosp Inf 1985;(Suppl 6):1–11.
14. Westrin B. Iodine release from Cadexomer Iodine products. Perstorp (SW): Perstorp Pharma, Department of Chemistry & Pharmacy; 1996. 7 p. Report No.: 95076.
15. Jacobsson S, Rothman U, Arturson G, Ganrot K, Haeger K, Juhlin I. A new principle for the cleansing of infected wounds. Scand J Plast Reconstr Surg 1976;10:65–67.
16. Skog E, Arnesjo S, Troeng T. A randomized trial comparing cadexomer iodine and standard treatment in the out-patient management of chronic venous ulcers. Br J Derm 1983;109:77–83.
17. Jones V, Milton T. When and how to use iodine dressings. Nurs Times 2000;96(45):2–3.
18. Sundberg J, Meller R. A retrospective review of the use of cadexomer iodine in the treatment of chronic wounds. Wounds 1997;9(3):68–86.
19. Harcup JW, Saul PA. A study of the effect of cadexomer iodine in the treatment of venous leg ulcers. Br J Clin Practice 1986;40:360–4.
20. Holloway GA, Johansen KH, Barnes RW, Pierce GE. Multicenter trial of cadexomer iodine to treat venous stasis ulcer. West J Med 1989;151:35–38.
21. Ormiston MCM, Seymour MTJ, Venn GE, Cohen RI, Fox JA. A randomized comparison of cadexomer iodine and a standard treatment in out-patients with chronic venous ulcers. In: Fox JA & Fischer H (Eds). Cadexomer Iodine 1983;63–69.
22. Moore K. Cell biology of chronic wounds: the role of inflammation. J Wound Care 1999;8(7):345–348.
23. Moore K, Ruge F, Harding KG. T-lymphocytes and the lack of activated macrophages in wound margin biopsies from chronic leg ulcers. Br J Dermatol 1997;137:188–194.
24. Liebovich SJ, Ross R. The Role of the macrophage in wound repair: a study with hydrocortisone and anti-macrophage serum. Am J Path 1975;78:71–100.
25. Herrick SE, Sloan P, McGurk M, Freak L, McCollum CN, Ferguson MW. Sequential changes in histologic pattern and extracellular matrix deposition during the healing of chronic venous leg ulcers. Am J Pathol 1992;141(5):1085–1095.
26. Phillips TJ, Palko MJ, Bhawan J. Histologic evaluation of chronic human wounds treated with hydrocolloids and nonhydrocolloid dressings. Acad Dermatol 1994;30(1):61–64.
27. Yager DR, Nwomwh BC. The proteolytic environment of chronic wounds. Wound Repair Regen 1999;7(6):433–441.
28. Argen MS, Eaglstein WH, Ferguson MW. Causes and effects of the chronic inflammation in the venous leg ulcers. Acta Derm Venereol Suppl (Stockh) 2000;210:3–17.
29. Hart J. Inflammation II: its role in the healing of chronic wounds. J Wound Care 2002;11(7):245–249.
30. Fahey TJ, Sherry B, Tracey KJ. Cytokine production in a model of wound healing: the appearance of MIP-1, MIP-2, Cachectin/TNF and IL-1. Cytokine 1990;2(2):92–99.
31. Lee RH, Efron DT, Tantry U. Inhibition of tumor necrosis factor-α attenuates wound breaking strength in tars. Wound Repair Regen 2000;8:547–553.
32. Greener B. Absorption of chronic wound fluid by a unique cadexomer polysaccharide lowers the pH of the fluid and may indirectly inhibit the activity of proteolytic enzymes. Poster presentation from The Wound Healing Society 16th Annual Meeting & Exhibition; May 14–17, Scottsdale (AZ): 2006.
33. Dyson M, Young SR, Pendle CL, Webster DF, Lang SM. Comparison of the effects of moist and dry conditions on dermal repair. J. Invest. Dermat 1998;9:435–439.
34. Luckacs NW, Strieter RM, Elner V, Evanoff HL, Burdick MD, Kunkei SL. Production of chemokines, interleukin-8 and monocyte chemo attractant protein-1 during monocyte endothelial cell interactions. Blood 1995;86:2767–2773.
35. Nathan CF. Secretory products of macrophages. J Clin Invest 1987;79:319–326.
36. Clark RA, Klebanoff SJ. Neutrophil-mediated tumor cell cytotoxicity: role of the peroxidase system. J Invest Dermat 1975;141:1442–1447.
37. Nathan CF, Brukner LH, Silverstein SC, Cohn ZA. Intracellular cytolysis by activated macrophages and granulocytes. pharmacologic triggering of effector cells and the release of hydrogen peroxide. J Exp Med 1979;149:84–99.
38. Aderka D, Jumming L, Vilcek J. IL-6 inhibits lipopolysaccharide-induced tumor necrosis factor production in cultured human monocytes U937 cells and in mice. J Immunol 1989;143:3517–3523.
39. Groves RW, Allen MH, Ross EL, Barker JNW, MacDonald DM. TNF∞ is proinflammatory in normal humans skin and modulates cutaneous adhesion molecule expression. Br J Dermatol 1995;132:345–352.
40. Moberg S, Hoffman L, Grennert ML, Holst A. A Randomized trial of cadexomer iodine in decubitus ulcers. J Am Geriatrics Sac 1983;31:462–465.
41. Ormiston MC, Seymour MT, Venn GE, Cohen RI, Fox J. A controlled trial of Iodosorb in chronic venous ulcers. BMJ 1985;291:308–310.
42. 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.
43. Troeng T, Skog E, Arnesjo B, Gjores JE, Bergljung L, Gundersen J. A randomized multi-centre trial to compare the efficacy of cadexomer iodine and standard treatment in the management of chronic venous ulcers in outpatients. In: Fox JA, Fischer H (Eds). Cadexomer Iodine. Stuttgart: Schattauer Verlag; 1983:43–50.
44. Danielsen L, Cherry GW, Harding K, Rollman O. Cadexomer iodine in ulcers colonised by *Pseudomonas aeruginosa*. J Wound Care 1997;6(4):169–172.
45. Steele K, Irwin G, Dowds N. Cadexomer iodine in the management of venous leg ulcers in general practice. The Practitioner 1986;230:63–68.
46. Gilchrist B. Should iodine be reconsidered in wound management? J Wound Care 1997;6(3):148–150.
47. O'Meara S, Al-Kurdi D, Ovington LG. Antibiotics and antiseptics for venous leg ulcers (Review). Cochrane Libr 2008;1:1–52.
48. O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG, Martyn-St James M, Richardson R. Antibiotics and antiseptics for venous leg ulcers (Review). Cochrane Collaboration in Cochrane Libr 2010;10:1–100.
49. O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG, Martyn-St James M, Richardson R. Antibiotics and antiseptics for venous leg ulcers (Review). Cochrane Libr 2013;12:1–194.
50. O'Meara S, Al-Kurdi D, Ologun Y, Ovington LG, Martyn-St James M, Richardson R. Antibiotics and antiseptics for venous leg ulcers (Review). Cochrane Libr 2014;1:1–194.