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Critical evaluation of cadexomer-iodine ointment and povidone-iodine sugar ointment☆

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ABSTRACT

Topical iodine forms are used for infected and necrotic pressure ulcers. Despite antimicrobial advantages several potential disadvantages were observed with controversial results. To clarify the controversy, the reactivity of povidone-iodine (PI) sugar ointment and cadexomer-iodine (CI) ointment toward biological components was investigated. L-Tyrosine as a component of proteins and egg lecithin as a component of lipid membranes were reacted with forms of iodine. Furthermore, water absorption abilities of ointments were investigated. The reactions of PI sugar ointment and CI ointment with L-tyrosine were reversely dependent on iodine concentrations. CI ointment reacted with lecithin in an iodine concentration dependent manner, while PI sugar ointment reacted with lecithin in an iodine concentration independent steady manner. However, at the clinically relevant iodine concentration (0.1, w/v%) PI sugar ointment reacted efficiently with L-tyrosine and less efficiently with lecithin, while CI ointment reacted efficiently with lecithin and less efficiently with L-tyrosine. Water absorption rate constant was 29.9 mg/cm^2/min$^{0.5}$ for PI sugar ointment and 15.3 for CI ointment. Water absorption capacity per weight over 24 h was 76% for PI sugar ointment and 26% for CI ointment. These results suggest that PI sugar ointment and CI ointment have different characteristics for iodine reactivity and water absorption.

1. Introduction

For more than a century iodine has been regarded as one of the most efficacious antiseptics to reduce infectious complications and topical iodine forms have been used for wound treatment. The simplest form of iodine is Lugol's solution, which has irritating and caustic properties. The iodine complexes such as povidone-iodine (PI) and cadexomer-iodine (CI) are exploited to conquer the disadvantage (Fig. 1). PI is a complex of triiodide and polyvinylpyrrolidone, and a paste consisting of 70% sugar and 3% PI is commercially available in Japan (U-PASTA^{TM}, Kowa, Nagoya, Japan). The paste dissolved in wound exudates releases triiodide keeping the equilibrium between triiodide and PI complex. CI is a hydrophilic modified-starch polymer bead where molecules of iodine are immobilized. In Europe, North America and Japan a macrogol ointment consisting of CI is available (Bianchi, 2001) (Cadex^{TM}Ointment, Smith & Nephew, Tokyo, Japan). Upon application the polymer beads in CI are swollen by wound exudates and gradually release incorporated iodine (Lamme et al., 1998; Zhou et al., 2002).

These ointments are recommended by the Japanese Society of Pressure Ulcers to treat the pressure ulcers carrying an infection or a necrotic tissue (Ohura, 2005). Though the iodine contained in these ointments has different chemical structures, the effects of these ointments are assumed to be equivalent. Despite the antimicrobial advantages obtained through its use, several potential disadvantages were observed in its clinical application for wound treatment with different and controversial results, so that practitioners are concerned with forms of iodine (Balin and Pratt, 2002; Oliveira and Santos, 2007).

In this study the equivalence of PI and CI was evaluated by conducting the reaction of these ointments toward L-tyrosine as a component of proteins and toward egg lecithin as a component of lipid membranes, and toward wound exudates. In pressure ulcer treatment appropriately controlling the moist environment is vitally important for promoting healing processes (Ohura, 2005). Ointment base could exhibit different water-absorbing properties and potentially affect the healing processes of pressure ulcers. Thus, the water absorption properties of these ointments

Abbreviations: CI, Cadexomer-iodine; PI, Povidone-iodine; PBS, Phosphate buffered saline.

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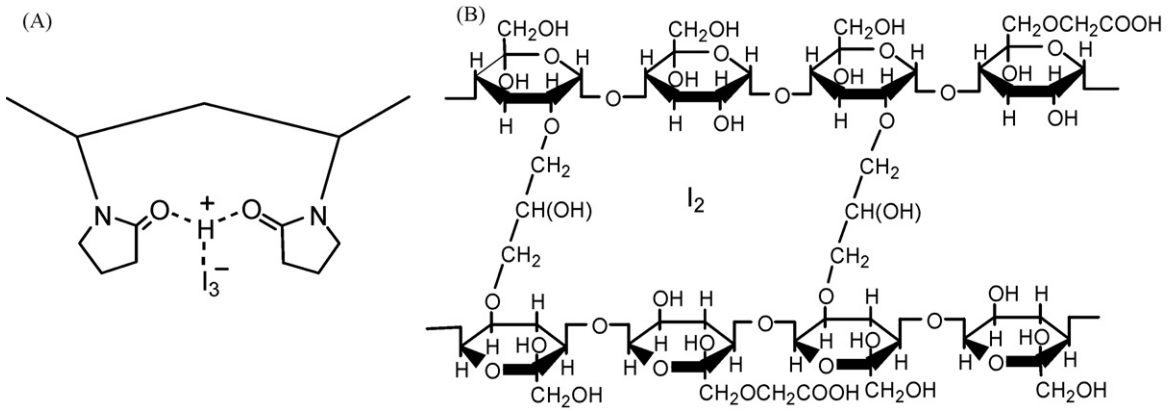

Fig. 1. The structures of povidone-iodine (PI) (A) and cadexomer-iodine (CI) (B).

were investigated to evaluate the influence on moist wound environment.

2. Materials and methods

2.1. Materials

L-Tyrosine was obtained from Wako Pure Chemical Co., Ltd. (Osaka, Japan). Egg lecithin (Coatsome NC-20) was obtained from NOF (Tokyo, Japan). U-PASTA™ was from Kowa Co., Ltd. (Nagoya, Japan). Cadex™ ointment was from Smith & Nephew Wound Management Corporation (Tokyo, Japan). By vacuum technique wound exudates were collected at Hekinan Municipal Hospital (Hekinan, Japan) from five wound parts of three patients who had been hospitalized for the treatment of pressure ulcers. The study was approved by the institutional ethical committee and the procedures were in accordance with the institutional guidelines and the principles of Declaration of Helsinki. Silicon film (thickness 0.10 mm) was from AS ONE Corporation (Osaka, Japan). Sodium iodide, sodium thiosulfate and seamless cellulose tubing as cellulose membrane were from Wako. Potassium iodide was from Nacalai Tesque, Inc. (Kyoto, Japan). Starch was from Kenei Pharmaceutical Co., Ltd. (Osaka, Japan). The phosphate buffered saline (PBS) was prepared by Mg/Ca ion free Dulbecco's prescription.

2.2. Methods

2.2.1. Assessment of the concentration of free-iodine in the aqueous solution

Apparent permeability of iodine has been found to depend on the activity of iodine in aqueous solution (Takikawa et al., 1978). For measurement of permeability of iodine through silicon membrane with a thickness of 0.1 mm, a permeation cell commercially available was employed. The permeation cell consisted of two compartments with a membrane between them. The area of membrane for permeation was 4.91 cm^2. Each compartment was agitated by a magnetic stirring bar. Twenty-five milliliters of a test solution and 10% NaI solution were placed in the donor and the receptor compartments, respectively. A water jacket of the permeation cell was maintained at 30 °C. One milliliter of samples was pipetted from the receptor solution, and assayed spectrophotometerically at 352 nm employing a spectrophotometer.

2.2.2. Reactivity of iodine toward L-tyrosine, lecithin and wound exudates

The L-tyrosine solution was prepared by dissolving the weight quantities with PBS at the concentration of 10 mM. The lecithin solution (10 mM) was prepared as a suspension of lipid particles. In brief, lecithin was dissolved in chloroform and evaporated to thin lipid film on the wall of a round flask. PBS was added to the flask with ultrasonication to obtain the suspension of lipid particles. The solutions of iodine forms were prepared by dissolving the weight quantities with PBS. After diluting the iodine solution to specified concentrations 2 mL of the L-tyrosine, lecithin or wound exudates solution was added to 18 mL of an iodine solution. The mixture solution was stood in water bath at 30 °C. The time of mixing was taken as time 0: 2 mL of the solution was pipetted into 1 mL of 1% potassium iodide–0.5% starch solution. The available iodine in the solution was titrated with 0.01 M thiosulfate solution. Every reaction was run for at least three times and means of amount of iodine consumption were calculated.

2.2.3. Measurement of water absorption rate using Franz diffusion cell

The ointment sample (1.2 g) was applied to the cellulose membrane mounted on the Franz diffusion cell (Kawashima et al., 1993) and 20 mL of PBS was introduced to the bellower cell. A water jacket of the permeation cell was maintained at 30 °C. After every 15 min or 30 min the water level in the branch tube attached to the cell was checked and PBS was added to the cell form the edge of the branch tube by a syringe until the water level reached its original level. The weight change of the syringe by adding the medium was applied to the amount of absorbed water. Every test was run for at least three times and the means of the amount of water absorbed were calculated.

2.2.4. Measurement of water absorption capacity using agarose gel

The water absorption capacities were determined using the test method based upon British Standard Institute Test methods (2002) for primary wound dressings. In brief samples (1.5 g) were placed onto the surface of 10 g plugs of agar (2% prepared in PBS) and contained within the barrel of 50 mL syringes, from which the nozzle ends have been removed to form smooth-sided cylinders. Once the test materials were in place, the open ends of the cylinders were sealed with an impermeable cover. The sealed syringes were incubated for 24 h at 25 °C and the test materials were gently removed from the plugs and the cylinders were then re-weighed. Every test was run for at least three times and the percentage change in weight of each sample was calculated.

2.3. Data analysis

All experiments were conducted in triplicate at least. Data are expressed as means ± S.D.s. In experiments using wound exudates, each of the initial reaction rates of PI sugar ointment treated group

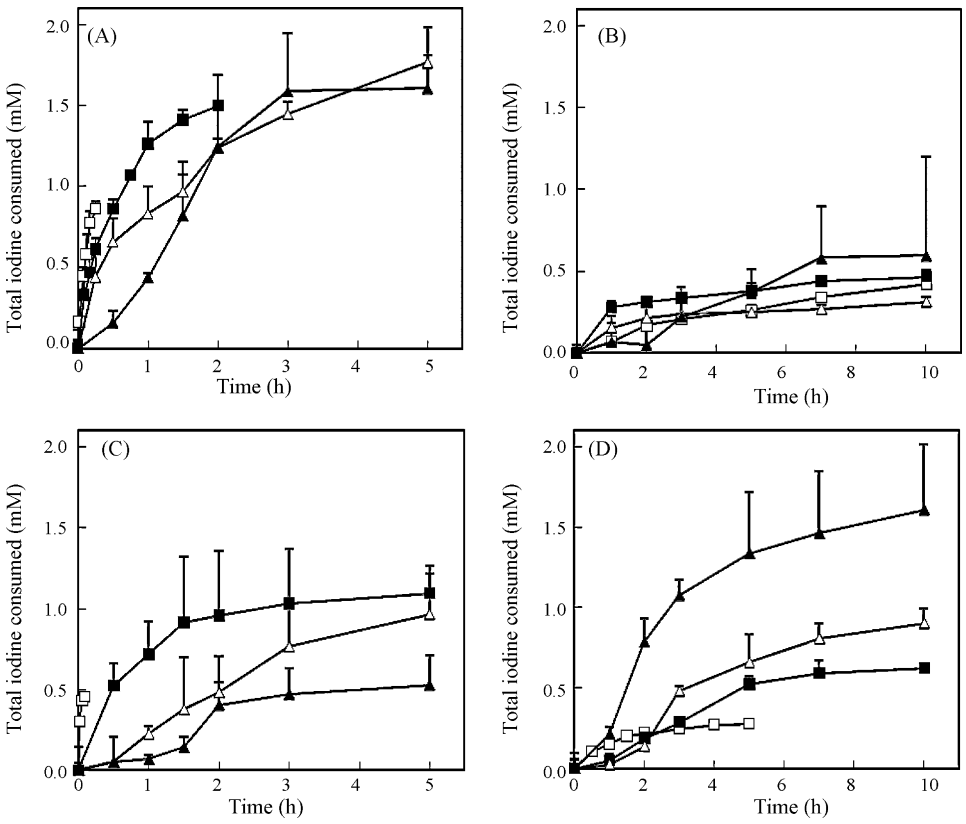

Fig. 2. (A) Reaction of PI sugar ointment with L-tyrosine. The elapsed time was plotted on the *X* axis and the concentration of the total iodine consumed was plotted on the *Y* axis. The initial iodine concentration was 0.02 (open square), 0.04 (closed square), 0.06 (open triangle), and 0.1 (closed triangle) w/v%. Results are expressed as means ± S.D. ($n = 3$). (B) Reaction of PI sugar ointment with lecithin. The elapsed time was plotted on the *X* axis and the concentration of the total iodine consumed was plotted on the *Y* axis. The initial iodine concentration was 0.02 (open square), 0.04 (closed square), 0.06 (open triangle) and 0.1 (closed triangle) w/v%. Results are expressed as means ± S.D. ($n = 3$). (C) Reaction of CI ointment with L-tyrosine. The elapsed time was plotted on the *X* axis and the concentration of the total iodine consumed was plotted on the *Y* axis. The initial iodine concentration was 0.01 (open square), 0.03 (closed square), 0.06 (open triangle), and 0.1 (closed triangle) w/v%. Results are expressed as means ± S.D. ($n = 3$). (D) Reaction of CI ointment with lecithin. The elapsed time was plotted on the *X* axis and the concentration of the total iodine consumed was plotted on the *Y* axis. The initial iodine concentration was 0.01 (open square), 0.03 (closed square), 0.06 (open triangle), and 0.1 (closed triangle) w/v%. Results are expressed as means ± S.D. ($n = 3$).

and of CI ointment treated group was obtained from a slope of the regression line calculated by least squares method. In experiments of water absorption, water absorption rate constants were obtained from a slop of the regression line in the same manner.

3. Results

3.1. Chemical properties of iodine coordinated in forms

3.1.1. Iodination of L-tyrosine and lecithin by PI sugar ointment

When PI sugar ointment was used as an iodinating reagent of L-tyrosine, iodine was rapidly consumed at relatively low iodine concentration (Fig. 2A). The amount of iodine consumption reached approximately 2 mM as the reaction toward 1 mM L-tyrosine approached its completion. In contrast the rate of the iodine consumption for lecithin was slower than that for L-tyrosine. Total amount of the iodine consumption in 10 h of reaction did not reach 1 mM. Its rate showed less dependence on the iodine concentration (Fig. 2B).

3.1.2. Iodination of L-tyrosine and lecithin by CI ointment

When CI ointment was used as an iodinating reagent of L-tyrosine, the manner of iodine consumption was similar to that of PI sugar ointment (Fig. 2C). The rate of iodine consumption was slower than that in PI sugar ointment and only 1 mM of iodine was consumed as the reaction toward 1 mM L-tyrosine approached its completion. In contrast, the manner of the iodine consumption for lecithin was markedly different from that for L-tyrosine. Its rate increased depending on the iodine concentration (Fig. 2D). At 0.1 (w/v%) of iodine solution the amount of the iodine consumption appeared to reach approximately 2 mM as the reaction toward 1 mM lecithin approached its completion

3.1.3. Reactivity of PI sugar ointment and CI ointment toward wound exudates

The clinical characteristics of the wound exudates are shown in Table 1. PI sugar ointment or CI ointment was allowed to react with the wound exudates at the concentration of 0.1 (w/v%) iodine in PBS. Iodine in PI sugar ointment was consumed faster than that in CI ointment and reached completion of the reaction in 7 h (Fig. 3). Each of the initial reaction rates was obtained from a slope of the regression line in 3 h after time 0. The reaction rate of PI sugar ointment toward wound exudates was faster than that of CI ointment by 3.5-fold at the concentration of 0.1 (w/v%) iodine (Table 2).

3.1.4. Permeation patterns of free-iodine through the silicone membrane

Permeability of iodine through a silicone membrane was measured at 30 °C. As shown in Fig. 4 only free-iodine I_2 was assumed

Table 1
Clinical characteristic of the wound exudates.

Specific gravity	1.035 ± 0.003
Total protein (g/dL)	4.88 ± 0.64
Cell counts (μL^{-1})	18,000 ± 8,934

Each value represents the means ± S.D. of values from quadruplicate.

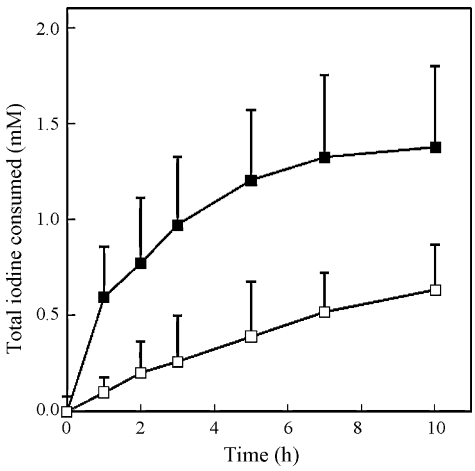

Fig. 3. Reaction of wound exudates with PI sugar ointment or CI ointment. The amount of iodine consumed when wound exudates reacted with PI sugar ointment (closed square) was larger than the amount of iodine consumed when wound exudates reacted with CI ointment (open square). The experiments were performed at the 0.1 (w/v%) iodine concentration. Results are expressed as means ± S.D. (n = 9).

Table 2
Observed initial reaction rate of PI sugar ointment and CI ointment toward wound exudates.

Formulation	Observed initial reaction rate (10^{-6} M/min)[a]
PI sugar ointment	5.13
CI ointment	1.45

[a] Value of a slope obtained from regression line at an initial phase of the reaction in Fig. 3.

to permeate the silicone membrane and reside in the receptor cell as iodine ion I_3^-. Iodine concentration in the receptor cell was calculated using molar absorbance coefficient (ε = 26,303). When free-iodine permeates through a silicone membrane from the donor cell to the receptor at the sink condition, the permeation rate is expressed by $dM/dt = DK/h\ SC$, where D is diffusivity in the membrane, K is partition coefficient between membrane and donor solution, h is thickness of membrane, S is area for the permeation, C is iodine concentration of donor cell. When apparent permeability is defined by $P = DK/h$, the amount of permeate iodine M is expressed by $M = PSCt$. Therefore, the amount of permeate iodine M is expressed by the primary linear expression of time and the slope of the graph is proportional to the iodine concentration in the donor cell. The slope calculated from the graph of permeation pattern of free-iodine through the silicone membrane of PI sugar ointment (Fig. 5) was 7.93 (10^{-10} mol/s) and that of CI ointment was 0.868 (10^{-10} mol/s). Under the condition tested the free-iodine concentration of CI ointment was 9.1-fold higher than the free-iodine concentration of PI sugar ointment.

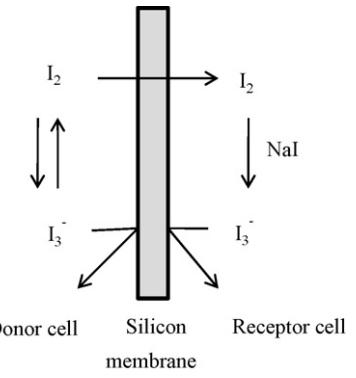

Fig. 4. Proposed model for permeation of free-iodine through the silicon membrane.

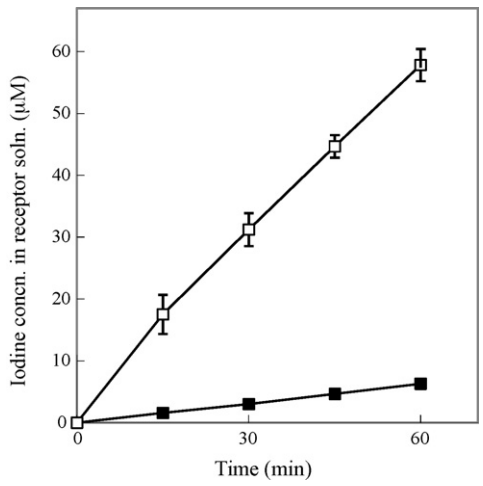

Fig. 5. Permeation patterns of free-iodine (initial total iodine concentration, 0.1%) through the silicone membrane at 30 °C. PI sugar ointment is expressed as closed square and CI ointment is expressed as open square. Results are expressed as means ± S.D. (n = 3).

3.2. Water absorption property of ointment base

3.2.1. Rate of water absorption of ointment base

Franz cell for evaluation of drug release from ointments or gels (Vlachou et al., 1992) was used for evaluating absorption ability of ointments in this study. Amount of water absorbed into PI sugar ointment increased in a time-dependent manner. After 1 h PI sugar ointment was almost completely dissolved. CI ointment absorbed water gradually and amount of water absorbed into CI ointment decreased in a time-dependent manner. Even after 2 h CI ointment retained the original form and continued to absorb water. Macrogol ointment used as the ointment base of CI ointment exhibited similar absorbance behaviors. Cumulative amount of water absorbed was plotted against the square root of time (Fig. 6) as previously described (Kawashima et al., 1993). Cumulative amount of water absorbed to CI ointment was well linearly related to the square root

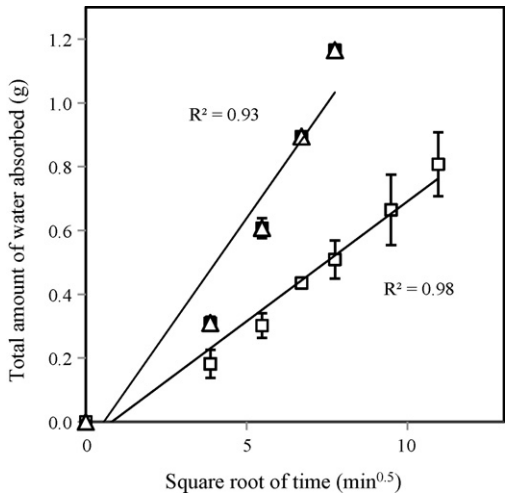

Fig. 6. Total amount of water absorbed into ointments. The square root of time was plotted on the X axis and the total amount of water absorbed was plotted on the Y axis. PI sugar ointment is expressed as closed square, CI ointment is expressed as open square and macrogol ointment is expressed as open triangle. Results are expressed as means ± S.D. (n = 3).

Table 3
Water absorption characteristics of ointments.

	Water absorption rate constant per unit area ($mg/cm^2/min^{0.5}$)[a]	Water absorption capacity per weight (%)[b]
PI sugar ointment	29.9	26 ± 2
CI ointment	15.3	76 ± 5
Macrogol ointment	29.9	57 ± 5

[a] Value of a slope obtained from the regression line in Fig. 6.
[b] Means ± S.D. of values from triplicate.

of time (R^2 = 0.98). Water absorption rate constant per unit area was calculated from the slope and 29.9, 15.3, and 29.9 $mg/cm^2/min^{0.5}$ for PI sugar ointment, CI ointment and macrogol ointment, respectively (Table 3).

3.2.2. Capacity of water absorption of ointment base

When PI sugar ointment was placed on agar, it dissolved almost completely within 1 h. The dissolved ointment was absorbed into the agar and absorbed water was at immeasurable level. Thus, as to PI sugar ointment and macrogol ointment 500 mg gauze patch was used to absorb the dissolved ointment. The water absorption capacity per weight over 24 h was 26 ± 2, 76 ± 5 and 57 ± 5 (%) for PI sugar ointment, CI ointment and macrogol ointment, respectively (Table 3).

4. Discussion

4.1. Reactive equivalence of iodine contained in PI sugar ointment and CI ointment

Triiodide can react with L-tyrosine as a protein component and with egg lecithin as a lipid membrane component (Li, 1942; Zanger and Rabinowitz, 1975). In this study the reactions of PI sugar ointment and CI ointment with L-tyrosine were reversely dependent on iodine concentrations. CI ointment reacted with lecithin in an iodine concentration dependent manner, while PI sugar ointment reacted with lecithin in an iodine concentration independent steady manner. The reaction of PI sugar ointment with L-tyrosine became the fastest and reached completion in 1 min at an iodine concentration of 0.01 (w/v%) (data not shown). Iodination was investigated toward other amino acids, with which iodine was supposed to react specifically on human albumin (Rosa et al., 1967). This iodine form completely reacted with L-cysteine within 1 min at higher iodine concentration of 0.01–0.1 (w/v%), but reacted hardly with L-histidine at high iodine concentration of 0.1 (w/v%) for as long as 10 h.

The optimal iodine concentration for antiseptic property was 0.01 (w/v%), suggesting that the reactivity of iodine with L-tyrosine is closely linked to antimicrobial activity. Free-iodine concentration is independent of total iodine concentration (Berkelman et al., 1982), suggesting that antimicrobial activity is dependent on free but not total iodine concentration. Because substantial portion of iodine is consumed when it is applied topically at low concentration (0.01, w/v%) to wounds, it is recommended to be used at 0.1 (w/v%). At this clinically relevant concentration PI sugar ointment reacted efficiently with L-tyrosine and less efficiently with lecithin, while CI ointment reacted efficiently with lecithin and less efficiently with L-tyrosine. The amount of iodine reacted with actual wound exudates in PI sugar ointment was twofold larger than the amount of iodine reacted with wound exudates in CI ointment, suggesting that for PI sugar ointment iodine is rapidly consumed by protein component and antiseptic effect is attenuated promptly. For CI ointment iodine could be gradually consumed by protein components and antiseptic effect may sustain longer. However, as the reactivity with lipid components may also sustain, CI ointment may be more cytotoxic.

The differences in reactivity at the same total iodine concentration with PI sugar ointment and CI ointment using L-tyrosine and lecithin could be due to the differences in free-iodine. Thus, free-iodine concentration of supernatant fluid of CI ointment measured by titration with 0.01 M thiosulfate solution was 1.2 mM. As to PI sugar ointment determining free-iodine concentration was difficult because supernatant fluid was not available. Therefore, free-iodine concentration was indirectly estimated using the measurement of permeability of iodine through silicon membrane (Takikawa et al., 1978). Free-iodine concentration dissolved from CI ointment was 9.1-fold higher that the value from PI sugar ointment and free-iodine concentration in PI sugar ointment was estimated to be 0.13 mM. These differences in free-iodine may be the major determinant of differences in reactivity of two different forms of iodine in PI sugar ointment and CI ointment.

4.2. Water absorption equivalence of PI sugar ointment and CI ointment

Measurement of water absorption rate using Franz diffusion cell revealed that cumulative amount of water absorption in PI sugar ointment or macrogol ointment was linearly related to time, suggesting that absorption capacity depends on the dissolution of the base ointment. In contrast, cumulative amount of water absorption in CI ointment was well linearly related to the square root of time, suggesting that the diffusion process of dissolved macrogol and water to macromolecular beads (cadexomer) was the rate-determining step. Furthermore, measurement of water absorption capacity using agarose gel revealed that the water absorption capacity per weight over 24 h for CI ointment was 2.9-fold higher than that for PI sugar ointment. The water absorption capacity per weight over 24 h for macrogol ointment exhibited the intermediate value. Measurement of water absorption rate using Franz diffusion cell also revealed that after 1-h PI sugar ointment was almost completely dissolved. Collectively, these results suggest that whether the base ointment retains its original form or is dissolved after water absorption plays a critical role in determining cumulative amount of water absorbed. When PI sugar ointment and CI ointment are clinically used for pressure ulcer, PI sugar ointment may exhibit transient low water absorption as the base ointment is dissolved, while CI ointment may exhibit sustained water absorption as the diffusion process of dissolved macrogol and water to macromolecular beads is the rate-determining step.

5. Conclusion

Form consisting of PI and CI enhances healing and reduces bacterial contamination in a wide variety of chronic wounds, burns and ulcers (Khan and Naqvi, 2006; Knutson et al., 1981; Nakao et al., 2006; Ohtani et al., 2007). Iodine is recommended for pressure ulcer with infection and necrosis. Despite the antimicrobial advantages obtained through its use, several potential disadvantages were observed in its clinical application with different and controversial results so that practitioners show some concerns for topical wound treatment with forms of iodine (Balin and Pratt, 2002; Oliveira and Santos, 2007).

The results in this study suggest that these apparently contradictory results are due to the differences of reactivity of two different forms of iodine in PI sugar ointment and CI ointment. Furthermore, water absorbing capacities of base ointments used in PI sugar ointment and CI ointment are different. Thus, use of these two ointments could lead to divergent results when they are used for pathogenetically similar pressure ulcers.

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