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A comparison of the irritant and allergenic properties of antiseptics

Over recent years, interest in the use of antiseptics has been reinforced as these molecules are not concerned by the problem of bacterial resistance. Whereas the *in vitro* efficacy of antiseptics has been well-studied, much less is known regarding their irritant and allergenic properties. This review provides an update on the comparative irritant and allergenic properties of commonly-used antiseptics in medicine nowadays. All antiseptics have irritant properties, especially when they are misused. Povidone-iodine has an excellent profile in terms of allergenicity. Allergic contact dermatitis is uncommon but is often misdiagnosed by practitioners, who confuse allergy and irritation. Chlorhexidine has been incriminated in some cases of allergic contact dermatitis; it is considered a relatively weak allergen, although it may rarely cause immunological contact urticaria and even life-threatening anaphylaxis. Octenidine is considered a safe and efficient antiseptic when used for superficial skin infections, however, aseptic tissue necrosis and chronic inflammation have been reported following irrigation of penetrating hand wounds. Polihexanide is an uncommon contact allergen as regards irritant and/or allergic contact dermatitis but cases of anaphylaxis have been reported. Considering the data available comparing the irritant and allergenic properties of major antiseptics currently in use, it should be acknowledged that all antiseptics may induce cutaneous side-effects. The present article reviews the most recent safety data that can guide consumers' choice.

Key words: adaptive immunity, chlorhexidine, hexamidinediisethionate, innate immunity, octenidine, polyhexanide, povidone-iodine, quaternary ammonium compounds, silver dressings, triclosan

For many years, topical antibiotics have been considered the treatment of choice of superficial skin bacterial infections and/or infected wounds. More recently, *Staphylococcus aureus* has become a major health problem worldwide. Multi-drug resistant strains are endemic in hospitals (MRSA). Moreover, there is now a rapid emergence of community-associated methicillin-resistant *S. aureus* (CA-MRSA). The resistance of these strains to antibiotics has been emphasized. Neomycin and bacitracin, known for their allergenic properties, are less used in Europe, in contrast to the United States and/or African countries. Two topical antibiotics are frequently used in European countries : sodium fusidate (Fucidin®) and mupirocine (Bactroban®). Resistance to sodium fusidate has been documented [1] and its allergenic properties identified. In this study, a clear link between prescription of the antibiotic and an increase in bacterial resistance was demonstrated. The use of mupirocine (exceptionally allergenic) is limited to well-defined indications, such as nasal carriage of *S. aureus,* but resistance has been indicated [2]. But the most important message is the increased resistance of *S. aureus* to topical antibiotics and this leads to a reinforced interest in antiseptics, which are not concerned by the problem of bacterial resistance.

Antiseptics are well studied regarding *in vitro* efficacy but less regarding irritancy and allergenic properties. Therefore, this article is exclusively focused on the comparative irritant and allergenic properties of the most important antiseptics used nowadays.

Irritant and allergic contact dermatitis: a new perspective

A new approach to common side effects consecutive to applied chemicals onto the skin is now developing. Classically, in previous years, the two main side effects, irritation and contact allergy, were considered entirely separate entities. Times have changed, due to a better understanding of the processes involved in the two types of reaction.

Irritant contact dermatitis is the prototype of innate immunity. The pathways of inflammatory cascades include a vast repertoire of cells, as well as different cytokines and chemokines.

Activation of innate immunity is necessary for the development of allergic contact dermatitis (ACD). The latter is therefore linked with the activation of T effector lymphocytes, specifically sensitized to allergens (adaptive immunity). This view has been clearly demonstrated [3-5]. In other words, most chemicals in direct contact with the skin are potentially irritant; their irritancy is related, not only to their chemical nature, but also to several environmental factors : concentration, vehicle, occlusion, temperature or altered skin (mechanical trauma, ulcerations, eczematous lesions, etc.). These considerations apply directly to antiseptics, which share irritant and, rarely, allergenic properties.

The practical implication of the new concept for the clinician is : if the patch test remains the "gold standard" for diagnosing allergic contact dermatitis, it has to be interpreted more cautiously, in particular in cases of weak (questionable : ± ?) reactions, to avoid a misinterpretation of the conclusion (irritation *versus* allergy). Its pertinence has to be reinforced by additional tests, such as the open test, semi-open test [6] and ROAT test [7]. More sophisticated laboratory investigations have been developed [3, 5]. They represent the only scientific way to differentiate irritant from allergic contact reactions, by unquestionably trapping the antigen-specific T lymphocytes in relation to a defined allergen. But at the present time, these techniques are inaccessible to the clinician.

Antiseptics and disinfectants

The terms "antiseptics" and "disinfectants" are often used as synonyms in the current literature, even in well-documented textbooks of dermatology. In fact, the definitions are quite important :

Antiseptics are substances that inhibit the growth and development of microorganisms (without necessarily killing them) in living tissues. Their indications are varied, such as the cleansing of preoperative skin, the cleansing of acute and chronic wounds and also in the treatment of superficial skin infections.

Disinfectants refer, by definition, to substances designed to destroy pathogens in the environment (e.g. on work surfaces or operating materials). They are very diversified, with different chemical structures. Classical examples are: bleach (chlorinated water, "eau de Javel"), formaldehyde, glutaraldehyde, glyoxal and quaternary ammonium compounds. It is noteworthy that the latter are used both as antiseptics and as disinfectants.

The antiseptics taken into consideration in this review are the ones that are commonly used in medical care nowadays. The landscape of antiseptics has evolved in recent years. The four antiseptics most frequently used nowadays are: povidone-iodine, chlorhexidine, octenidine and polyhexanide. Other antiseptics are silver based dressings, quaternary ammonium compounds, hexamidine diisethionate and triclosan. Although all antiseptics share a well-defined irritant profile, some are more allergenic

than others. Dermatochemistry can, to some extent, explain these discrepancies [8]. Mercury compounds are out of course.

The comparative irritant properties of antiseptics

There are several reports on the cytotoxicity of antiseptics but it is important to compare them under identical test conditions. The cytotoxicity of PVP-I, chlorhexidine digluconate (Chex), octenidine dihydrochloride (Oct) and polyhexamethyl enebiguanide (polihexanide, PHMD) was compared on CHO-K1 cells. PVP-I was more than 20 times better tolerated by L929 cells than Chex, Oct and PHMD [9].

Another investigation analyzing the stratum corneum tolerance of PVP-I 10%, PVP-I 7.5% and chlorhexidine showed that PVP-I 10% is less aggressive to the stratum corneum than PVP-I 7.5% and chlorhexidine [10]. In a comparison between PVP-I, benzalkonium chloride, chlorhexidine gluconate and alkyldiaminoethylglycine hydrochloride, PVP-I had a weaker skin irritancy *versus* the other antiseptics [11]. Recently, seventeen burn wound dressings, ointments and creams showed that the most cytotoxic products included those containing silver or chlorhexidine [12].

All these studies are *in vitro* studies and need to be confirmed clinically. An *in vivo* comparison of leg ulcers treated by PVP-I, silver sulfadiazine and chlorhexidine indicated that the densities in microvessels and dendrocytes (no dendrocytoclasis) were higher in PVP-I-assigned lesions than those receiving silver sulfadiazine or chlorhexidine digluconate, resulting in better wound healing with PVP-I compared to the other antimicrobials [13, 14]. 70% ethanol, Softasept®, Octenisept® (octenidine) and Lavasept® (polihexanide) were compared, octenidine had the least impact on microcirculatory parameters [15]. A study assessing the tissue compatibilities of Dibromol® (bromchlorophene, isopropyl alcohol, sodium 3.5-dibromo-4-hydroxybenzenesulphonate), Kodan® (propanol), Jodobac® (PVP-I), Octenisept® (octenidine), 0.2% Lavasept® (polihexanide) hydrogen peroxide, 0.5% chlorhexidine digluconate and 60% 2-propanol found that the most severe tissue toxicity was induced by 0.5% chlorhexidine digluconate and by propanol. Irritation values were determined for Dibromol®, Octenisept® and 60% 2-propanol but moderate vascular injuries were caused by PVP-I. Lavasept® and hydrogen peroxide showed no tissue toxicity [16].

Röhner *et al.* [17] studied polihexanide and hydrogen peroxide and showed that both solutions induced significant cell death of human chondrocytes after a short incubation time. It has been demonstrated that chlorhexidine induced cytotoxicity and genotoxicity on macrophages *in vitro* [18]. A very particular side effect of octenidine, which does not primarily concern superficial skin infections, has been recently described [19]. It refers to aseptic tissue necrosis and chronic inflammation after irrigation of penetrating hand wounds using Octenisept®. Penetrating hand wounds are common and these are managed by thorough

debridement. However, stab wounds without evidence of divided structures are often treated with irrigation using antiseptic substances, antibiotic therapy and immobilization. Octenisept® was considered suitable, due to its broad spectrum of antiseptic efficacy, but, within a few months, four patients presented severe tissue necrosis. Repeated surgery and debridement were required in all patients. Wound healing was prolonged and the patients had persisting oedema. The conclusion of the authors was that penetrating hand wounds must not be irrigated with Octenisept® [19]. It has not been decided whether this side effect was associated (or not) to the combined presence of octenidine and phenoxyethanol but it has to be emphasized that it has never been related to phenoxyethanol when used alone [20].

Similarly, a long-lasting cutaneous side effect after inappropriate use of Octenisept® solution has been described. Following the lavage of an abscess in the inguinal region, a painful erythematous infiltration mimicking cellulitis persisted for several months. Octenisept® shows considerable tissue toxicity *in vivo,* including – but not restricted to – blood vessel damage. Deterioration of endothelial cells followed by oedema and continued tissue damage can be seen histologically [21].

Some studies have also focused on the cytotoxicity of antiseptics on human chondrocytes. Müller and Kramer analyzed PVP-I 10%, polihexanide 0.005% and 0.01% (PHMD) and octenidine 0.005% and 0.01% (Octenisept®), showing a toxic effect with octenidine and polihexanide 0.01%, whereas PVP-I and polihexanide 0.005% were both well tolerated, povidone iodine stimulating chondrocytes *in vitro* [9]. But further studies are needed to confirm, or not, this current opinion.

Silver-based dressings have an irritant potential, due to their cytotoxic effect on fibroblasts and keratinocytes, with a significant delay of re-epithelialization. Therefore, caution should be exercised in using these dressings in clean superficial wounds, superficial burns and also when cultured cells are being applied to wounds [23].

The comparative allergenic properties of antiseptics [24]

Povidone-iodine (Polyvinylpyrrolidone-iodine; PVP-iodine)

For several years now, povidone-iodine (PVP-I) has replaced other iodine compounds, such as iodoform or iodine tincture. Iodoform was considered a very strong irritant and/or contact allergen as early as in 1911, by Bruno Bloch in Zürich. It was introduced in the first standard series of patch tests.

Iodine tincture (10% free iodine) is also a prominent irritant and/or allergen. Extensively used in cattle for treating ringworm, it provoked severe reactions. It was even worse when farmers, infected by cattle, applied it on their skin, leading to bullous reactions. PVP-I is an iodophor, with a sustained release system that reduces the irritancy of iodine. It is used as a topical antiseptic, on a very large scale throughout the world, under several trade names (the most common is Betadine®). A 10% PVP-I solution contains 1% available iodine but free-iodine is at 0.1% concentration. It is well demonstrated nowadays that skin exposure causes irritant rather than allergic contact dermatitis. It has been advocated not to use PVP-I on damaged skin (e.g., eczematous lesions of atopic dermatitis, perilesional irritated skin encountered in various types of wounds or stomas). This statement has indeed to be moderated; it is agreed that PVP-I should not be applied on eczematous lesions of atopic dermatitis. Moreover, it has been shown that PVP-I could be used advantageously for the treatment of superficial skin infections [25].

Rare cases of allergic contact dermatitis to PVP-I have been reported in the literature. An epidemic of occupational allergic contact dermatitis of the hands has been reported in a pig slaughterhouse [26]. Slaughterers worked bare-handed and suffered from frequent cuts. They washed their hands many times daily with a PVP-I solution. Other cases have been reported [27-29]. The results of patch tests to PVP-I (10% pet, i.e., 1% free-iodine), considered positive in the literature, can in some cases be false positives, due to an irritation to PVP-I (under occlusion). In a well-documented study [30], 500 consecutive patients were patch tested with PVP-I. Fourteen had a positive patch test (2.8%). In a second step, the 14 patients were tested again, in a different way: the PVP-I aqueous solution was applied twice daily (without occlusion) at the flexor aspect of the forearm (5 × 5 cm) over 7 days, i.e., 14 open applications (ROAT test) [7]. At day 7, only 2 patients had a positive ROAT test and 12 had a negative ROAT test. This meant that only 2 out of 500 patients were allergic to PVP-I (prevalence: 0.4%).

Patch testing [30] reflects the difficulties encountered in practice. Several options have been proposed: 5-10% water; 5-10% pet.; 0.5% alcohol. In the above-mentioned study [30], the problem was partially solved.

PVP-I is not mentioned at all in the series of patch tests proposed by the different companies involved in dermato-allergology, even in the leg ulcers series (Chemotechnique®, Trolab®, Brial®), contrary to chlorhexidine. Immediate immunological reactions to PVP-I (either urticarial or anaphylactic) are considered exceptional. This is not surprising. In the 1960s, PVP was used extensively in intravenous and/or subcutaneous injections, either as a plasma substitute or as a support of some drugs, particularly in the treatment of diabetes insipidus. That use resulted in a specific entity: thesaurismosis of PVP in many tissues, including the skin, due to a lack of enzyme degradation, but it never involved an immunological process [31].

Chlorhexidine

Chlorhexidine is a synthetic biguanide used as an antiseptic and disinfectant, available in different forms (diacetate, dihydrochloride and digluconate). The use of chlorhexidine as an antiseptic has increased in recent years at the expense of quaternary ammonium compounds. Chlorhexidine is used clinically for disinfection of the hands and operation sites, in the treatment of burns (despite its potential irritancy) and scalds, in urology and gynecology, and by dentists in the treatment of caries and periodontitis. It can be considered irritant, when concentrations are high, depending on each individual use.

Allergic contact dermatitis to chlorhexidine has been well known since the first publication by Calnan in 1962 [32]. Large studies show a sensitization rate of 2%, mainly after repeated applications. It is generally considered a rather common event in terms of relevance [33]. In most cases, the reaction is limited to the site of application but it can eventually extend to other areas of the skin. Exceptionally, it causes photosensitivity, or even a fixed drug eruption. The diagnosis is confirmed by patch testing and/or photo-patch testing. Patch test concentration : 0.5% in water.

Chlorhexidine is listed in allergen catalogues in the leg ulcer series [34]. It should be kept in mind that the differential diagnosis with irritant reactions is important, in particular when chlorhexidine is used under occlusion.

Occupationally-related allergic contact dermatitis cases have also been reported [35, 36]. Contact (immunological) urticaria and anaphylactic reactions to chlorhexidine are well-documented [37]. This is a problem of great concern, even if the number of reported cases is rather low. Its importance is emphasized in a special chapter devoted specifically to those reactions to chlorhexidine, in the classic Marzulli and Maibach's *Textbook of Dermatotoxicology* [38]. Anaphylactic, life-threatening reactions are quoted in detail in this review paper. They occur under different circumstances: - application to damaged skin surfaces, such as wounds, burns and dermabrasions; vein puncture; application on mucous membranes; intra-urethral instillation of urethral jelly prior to cystoscopy; chlorhexidine-containing lubricant applied intravaginally prior to gynecological examination; chlorhexidine-impregnated medical devices. In a recent paper, anaesthesiologists emphasized that, in a series of 344 patients who experienced perioperative anaphylaxis, 7% could be incriminated to chlorhexidine [39]. The responsibility of chlorhexidine in the occurrence of those immediate- type reactions, either urticarial or anaphylactic, can be proved by prick testing.

The U.S. Food and Drug Administration has issued an alert concerning hypersensitivity reactions to chlorhexidine-impregnated medical devices. Useful additional information is available in an alert paper from Switzerland [40]. This is therefore considered a new occupational hazard. Urticaria, angioedema and anaphylaxis have been reported in health care workers [41]. Increased awareness and easier access to chlorhexidine-specific IgE serological testing should facilitate the early diagnosis of affected health care workers, avoiding inappropriate investigations and thus reducing the risk of potentially severe allergic reactions in the future. Chlorhexidine-specific IgE serological testing is highly recommended.

Octenidine

Octenidine is a cationic antibacterial of the bis-pyramidine class [22]. It is present in Octanilin® solution and Octenilin® gel at a concentration of 0.05%. It is also available at a higher concentration (0.10%) as Octenisept® (octenidine and phenoxyethanol). The fields of application are: moisturizing of chronic wounds and burns, facilitation of the mechanical debridement of wounds and burns and prevention of bacterial infections [42].

Skin side effects include irritation and allergic contact dermatitis [43]. Health care personnel have to be aware nowadays of this potential hazard if preventive measures are

not taken when treating wounds and burns. Patch testing: 0.1% in water is recommended. Due to its more recent introduction in medical use, its potential for allergenicity has not been defined with certainty. Further reports are needed.

Polyhexanide

Polyhexanide (polyhexamethylenebiguanide or PHMB) is available as a solution, a gel and in certain dressings. It belongs to the family of cationic biguanides. The range of antimicrobial dressings offers dressings containing PHMB with a low concentration of 0.2%. For instance, Suprasorb® + PHMB is a swab of large cellulose fibers arranged in a broad-woven matrix impregnated with 0.3% PHMB. A chemical composition close to that of PHMB is found in Prontosan®, which is available as a gel or a solution. It contains polyhexamide at a concentration of 0.1%, used as a preservative [44, 45]. It is used particularly in the treatment of venous leg ulcers and/or pressure wounds. It is claimed that, in orthopaedic surgery, polyhexanide promotes apoptosis of human chondrocytes *in vitro*, which may indicate the use of polyhexanide in septic joint surgery.

As far as skin side effects are concerned, polyhexanide is considered an uncommon contact allergen in terms of irritant and/or allergic contact dermatitis [46]. Nevertheless, in the future, health care personnel should be aware of the potential risk of occupational disease. In other terms, when a new chemical to be applied on the skin is introduced, it usually takes some time to evaluate its implication in events of irritation and allergenicity. Cases of severe anaphylaxis have been reported [47, 48]. This is not surprising, since polyhexanide is a polymer of chlorhexidine. When this particular event occurs, the tool of investigation for confirming the diagnosis is prick testing, monitored with great caution to avoid systemic symptoms (see chlorhexidine). But, on the whole, polyhexanide may be considered a safe and effective biocide [49]. Patch testing with 2.5 and/or 5% in water is recommended.

Other antiseptics

Silver dressings

The increasing use of silver in health care, particularly in health care dressings, is controversial [50, 51]. Information about the potential allergenic properties of silver dressings is still missing, but silver is not considered a contact allergen [53].

Quaternary ammonium compounds

Quaternary ammonium compounds are a vast family of cationic detergents and are mainly used nowadays as disinfectants. Their use as antiseptics is still important, e.g. in topical antiseptics for burns, ointments, and mouth-and hand washes.They are irritant, for instance even as dilute as 0.1% under occlusion, and their allergenic properties do exist, although they are not so frequent and are masked by their strong irritancy. All of them have been incriminated in the occurrence of occupational dermatitis (irritant and/or allergic) in people at risk [53].

Table 1. A comparison of the allergenic properties of major antiseptics in current use.

Antiseptics	Allergic contact dermatitis	Urticarial and/or anaphylactic reactions	Others
Chlorhexidine	Common	Well documented	Not reported
Octenidine	Rare	Not documented	Aseptic tissue necrosis
Polyhexanide	Rare	Severe reactions documented	Not reported
Povidone-iodine	Rare	Exceptional	Not reported

Benzalkonium chloride is the most widely used quaternary ammonium compound. Its irritation potential is mentioned extensively in all the textbooks of environmental dermatology. Allergic contact dermatitis of the hands has been reported in many occupations, particularly in medical personnel from exposure to instruments soaked in it. It has also provoked airborne reactions [54]. Patch testing with benzalkonium chloride is a difficult issue (0.1% in water). When positive, skin reactions are often weak or questionable. As emphasized by the North American Contact Dermatitis Group, caution should be used when interpreting results and a ROAT test is very often advisable. Patch testing: 0.1% in water.

Hexamidine diisethionate

Despite its limited antiseptic activity, hexamidine is still used extensively in some countries. It is known to induce papulo-vesicular and diffuse allergic contact dermatitis [55, 56]. Some lesions are purpuric, mimicking leukocyclastic vasculitis [57]. Patch testing with 0.15% (pet) is recommended.

Triclosan

Triclosan, an antimicrobial agent of the family of diphenylether derivative, is mainly used today in personal care products. In the past, it was also used in topical drugs, due to its antifungal activity [58]. We conducted a prospective study about the potential allergenicity of triclosan [59], using the maximization test according to Magnusson and Kligman [60] in humans and guinea pigs, a test whose value has since been questioned. We concluded to a low allergenic potential but this view was contradicted by the daily use of triclosan [61]. Allergic reactions have been reported. Its use is currently being revised. A case of immunological contact urticaria was recently reported [62]. Patch testing with 2% (pet) is recommended.

Mercury compounds

These should be withdrawn from our daily clinical practice. They have been used for decades but are now completely abandoned because of their toxicological and/or allergenic properties. More potent and safer antiseptics have advantageously replaced them [52].

Conclusions (*table 1*)

All antiseptics have irritant properties, mainly when they are misused, i.e. on an eczematous skin, under inadequate occlusion or at too high concentrations.

- Povidone-iodine has an excellent profile in terms of allergenicity. In other words, allergic contact dermatitis is uncommon but it is often misdiagnosed by practitioners, who confuse allergy with irritation. In our view, contact urticaria and anaphylaxis are exceptional, if existing at all.
- Chlorhexidine has occasionally been incriminated in cases of allergic contact dermatitis but is nevertheless considered a relatively rare and weak allergen. On the other hand, it is very troublesome for the dermatologist because it can cause immunological contact urticaria and even life-threatening anaphylaxis. Caution is advised when considering its use. PVP-I is therefore preferred to chlorhexidine, in terms of allergenicity.
- Octenidine is considered a safe and efficient antiseptic (very few cases of irritant and/or allergic contact dermatitis have been reported) when used for treating superficial skin infections. However, a particular side effect has been reported after irrigation of penetrating hand wounds, i.e. aseptic tissue necrosis and chronic inflammation, lasting for weeks or even months.
- Polyhexanide is considered an uncommon contact allergen referring to irritant and/or allergic contact dermatitis. Cases of anaphylaxis have been reported, which is not surprising, since polyhexanide is a polymer of chlorhexidine.
- Taking into account all the data available comparing the irritant and allergenic properties of major antiseptics in current use, we can consider PVP-I as the safest antiseptic in terms of irritancy and allergic profile. ■

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