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POVIDONE IODINE SKIN ABSORPTION: AN EX-VIVO STUDY

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HIGHLIGHTS

- Povidone iodine hand-scrub solutions, which are considered safe antiseptics, contain large amounts of iodine that can be absorbed by skin.
- Iodine can be absorbed through intact skin in time dependent manner.
- In professional use the repetitive contact with PI, also as soap, can cause iodine skin permeation that must be considered when the washing procedures are repeated more than 20 times a day.

ABSTRACT
Povidone iodine is a water-soluble complex used to disinfect the skin surface and it exerts prolonged germicidal action against a broad spectrum of germs. Indeed, it is often applied on burned skin, large wounds, deep tissues or mucosa. Notably some surgical hand-scrub solutions, which are considered safe antiseptics, contain large amounts of iodine that can be absorbed by skin. The aim of present study was to study the skin absorption of iodine after the application on the skin of povidone-iodine solution, used by health care workers during surgical procedure. We use Franz diffusion static cells with human skin. After 24 h from the beginning of our measurement the iodine concentration in the receiving compartment was11.59 ± 6.3 μg/cm^2. The medium flux calculated was 0.73 ± 0.33 μg/cm^2/h with a lag time of 8.9 ± 1.5 h. These in vitro results confirmed that povidone iodine could pass through the skin in a relevant amount that can explain the clinical findings in burned or surgically treated patients. In professional use the repetitive contact with povidone iodine, also as soap, can cause iodine skin permeation that must be considered when the washing procedures are repeated more than 20 times a day.

Introduction

Povidone iodine (PI) is a water soluble complex used to disinfect the skin surface and it exerts prolonged germicidal action against a broad spectrum of germs as gram-positive and gram-negative bacteria, including antibiotic resistant organism, as well as fungi, viruses, protozoa and yeasts (Furudate et al., 1997). The bactericidal action of iodine-based disinfectants is caused by free molecular iodine. Because of its excellent penetration and its poor reactivity with protein constituents(it reacts under the conditions prevailing at disinfection only with S–H functions) iodine easily enters the skin where it forms a solid solution. In the case of Lugol's solution (strong iodine solution) this produces a dark brown staining which cannot be removed by washing with soap and water or by moistening with reducing material. It decreases only very slowly and in the case of strong iodine loads can be observed even after 12 h. The decrease in the absorbed iodine has two causes: one part diffuses into deeper skin layers where it is reduced to iodide and produces an increase of serum-iodide, while the other part diffuses back out of the skin (Gottardi, 1995).
One of the most important external uses of iodine is as disinfectant in skin soaps. Notably some surgical hand-scrub solutions, which are considered to be safe antiseptics, contain large amounts of iodine and are commonly used as broad-spectrum disinfectants (Erdogan et al., 2013). The most studies which reported the effect of iodine disinfectant are limited to patients only, but there is also an occupational exposure to be considered. With regard to transcutaneous iodine

absorption in healthy adults, only a few studies or cases have been reported (Erdogan et al., 2013). Some of the occupations that involve iodine exposure are those in operating rooms where hand scrubbing is done with iodine-containing solutions (Erdogan et al., 2013). Besides a wide use for skin antisepsis, PI is also employed internally. Indeed, it is often applied on burned skin, large wounds, deep tissues or mucosa (Lakhal et al., 2011). In patients where the burned injury spread over 25% of the skin surface with deep second- and third- degree burns, the serum total iodine levels have been reported to markedly increase to 4500–48,000 mcg/dl and possible systemic complications due to elevated free iodine levels have been reported (Aiba et al., 1999).
The amount of absorption is higher in cases of skin damage or the presence of thinner skin, therefore this effect was noted in infants (Erdogan et al., 2013; Findik et al., 2010). In animal experiments, transcutaneous absorption of PI through healthy skin has also been examined using radioisotope I125 (Furudate et al., 1997).
In individuals with dysregulation of the thyroid follicular cell, excess iodine exposure can induce thyroid dysfunction, which might be transient or permanent (Leung and Braverman, 2014).
The aim of our study was to calculate the skin absorption of iodine after the application on the skin of povidone-iodine solution used by health care workers during surgical procedures. We use the protocol defined during the European project EDETOX (Evaluations and predictions of DErmal 102 absorption of TOXic chemicals), a three-year research program (2001–2004) founded by European Union (EDETOX, 2000) and used to test the skin permeation of chemicals and metals (Filon et al., 2006).

Materials and methods

Chemicals

All chemicals were analytical grade. Urea, disodium hydrogen phosphate, potassium dihydrogen phosphate, hydrogen peroxide (30% v/v) were purchased from Carlo Erba (Milan, Italy); lactic acid (90%) from Acros Organics (Geel, Belgium); sodium chloride, ammonium hydroxide (25% w/v), nitric acid (>69% v/v) from Sigma–Aldrich (Milan, Italy).
The povidone-iodine solution (10%) used in the experiments is a stable chemical complex of polyvinylpyrrolidone (povidone, PVP) and elemental iodine (Esoform Jod 75, that contains 10% (7.5 g) of polyvinylpyrrolidone–iodine with 0.75% of active iodine; Esoform S.P.A. Laboratorio Chimico Farmaceutico, Via del Lavoro 10, Rovigo, Italy).
Water reagent grade was produced with a Millipore purification pack system (milliQ water). The physiological solution used as receptor fluid was freshly prepared by dissolving 9 g of NaCl, 2.38 g of Na_2HPO_4 and 0.19 g of KH_2PO_4 into 1 l of milliQ water (final pH 7.35). The synthetic sweat solution used as donor fluid consisted of 0.5% sodium chloride, 0.1% urea and 0.1% lactic acid in milliQ water; pH 4.5 was adjusted with ammonia.

Preparation of skin membranes

Human abdominal full thickness skin was obtained as surgical waste after the authorization of the local Ethical Committee and it was used for the absorption experiments immediately after the surgical operations. Prior to freezing, the subcutaneous fat was removed and the hair shaved with a razor. All the pieces of full thickness skin were stored in freezer at -25 o C for a period up to, but not exceeding, two months. It has been shown that this method of storage does not damage the skin since no difference in permeability was observed between fresh and frozen segments of the same skin in a separate series of experiments (Franz, 1975).
From each skin specimen, 4 x 4 cm^2 pieces were cut and mounted separately on the diffusion cells, that were previously washed the first time with freshly prepared aqua regia, the second time with diluted nitric acid, and rinsed three times with milliQ water.

Skin integrity was tested before and after each experiment using electrical conductibility by means of a conductometer (Metrohm, 660, Metrohm AG Oberdorfstr. 68 CH-9100 Herisau) operating at 300 Hz and connected to two stainless steel electrodes (Fasano et al., 2002). The conductibility data in mS were converted into KΩ cm^{-2}. Cells with a resistance lower than 3.95 ± 0.27 KΩ cm^{-2} were considered to be damaged and rejected as suggested by Davies et al. (2004).

In vitro diffusion system

Percutaneous absorption studies were performed using static diffusion cells following the Franz method (Franz, 1975). The receptor compartment had a mean volume of 14.0 ml and was maintained at 32 ^{o}C by means of circulation of thermostated water in the jacket surrounding the cell. This temperature value was chosen in order to reproduce the hand physiological temperature at normal conditions. The solution in each cell was continuously stirred using a Teflon coated magnetic stirrer.
Each piece of skin was clamped between the donor and the receptor compartment; the mean exposed skin area was 3.29 cm^2 and the average membranes thickness was 0.9 mm. For each experiment, the skin of 2 different donors, male and female, with a range of age from 50 to 70 years was used.

The experiment

The experiments were carried out as follows:
Experiment 1: at time 0, the exposure chambers of 6 Franz diffusion cells were filled with 1.0 ml of synthetic sweat and 2.0 ml of the povidone-iodine solution (10%) providing an amount of 0.606 g cm^{-2} of iodine in order to ensure an infinite dose. At selected intervals (2, 4, 6, 8, 12, 20 and 24 h) 1.5 ml of the dermal bathing solution was removed and collected for the analyses. Each receptor sample was immediately replaced with an equal volume of fresh made physiological solution. At 24 h, the dermal bathing solutions were removed and stored in the freezer, the donor solutions were collected in order to verify the iodine concentration in the donor phase.

Experiment 2: experiment 1 was repeated miming the hand washing protocol used by nurses and medical doctors during surgery in Trieste Hospitals: each donor chamber has been filled with 1.0 ml of the povidone-iodine solution (10%) and the skin has been carefully washed with a cotton balls for two minutes. After that, the skin surface has been rinsed three time with 2.0 ml of physiological solution. The washing operation has been repeated twice. At selected intervals (1, 2, 4, 6, 8, 12, 20 and 24 h) 1.5 ml of the dermal bathing solution was removed and collected for the analyses. Each receptor sample was immediately replaced with an equal volume of fresh made physiological solution. At 24 h, the dermal bathing solutions were removed and stored in the freezer, the donor solutions were collected in order to verify the iodine concentration in the donor phase.

Blanks: for each experiment, one cell was added as blank. The blank cells were treated as the other cells with the exception that no povidone-iodine solution (10%) has been introduced to the exposure chamber, but only synthetic sweat.
As the equipment used was static, there is no relationship between the cells tested, hence each of them represents an independent evaluation.

Analytical measurements

ICP-MS 7500 CE Agilent Technologies Inc., Santa Clara, CA, USA instrument (with integrated autosampler) was used to determinate the total iodine concentration in the receiver phases. A

five-point standard curve was used for ICP-MS measurements (0, 0.1,1,10, and 100 $\mu g/l^{-1}$, ion mass 127 u.m.a.). The limit of detection of iodine was 0.002 $\mu g/l^{-1}$ and the precision of the measurements as repeatability (RSD%) for the analysis was always <2%.

Data analysis

Iodine concentration data ($\mu g/cm^{-3}$) in the receptor solution were converted to the total amount that penetrated ($\mu g/cm^{-2}$), with a correction for dilution due to sample removal.
Data analysis was performed using the statistical software SPSS for Windows (version 15.0). Data are reported as mean ± standard deviation (SD). The difference between independent data was assessed by means of the Mann–Whitney and Kruskal–Wallis tests. A p value of <0.05 was considered as the limit of statistical significance.

Results

Estimation of free-iodine concentration by iodine permeation assay through the skin

As we assumed the concentration of iodine in the acceptor compartment increased linearly over time in proportion to contact time between iodine and the intact skin in the donor compartment (Table 1). The slope of the graph reflects the permeability speed of free-iodine (Fig. 1). After 24 h from the beginning of our measurement the concentration in the acceptor compartment was 11.59 ± 6.3 $\mu g/cm^2$, the total amount of iodine diffusing out during this period is proportional to the total iodine absorbed by the bloodstream. The medium flux calculated was 0.73 ± 0.33 $\mu g/cm^2/h$ and the lag time was 8.9 ± 1.5 h.

Residual effect of skin iodine

Even though the first two test tubes were marked as blank, we measured an increased concentration of free iodine in the acceptor compartment due to the presence of iodine into the skin and in synthetic sweat used in the donor phase. Fig. 2 shows the increase in the concentration of iodine in the course of the first approximately 8 h until it reaches the plateau.

Influence of contact time

Iodine concentration in the receiving phases after the washing protocol is reported in Table 2. After one hour we find an increase of iodine content that decreased over time reaching the same values of control cells (Fig. 2).
Fig. 2 shows that iodine flux is dependent on contact time (experiments with operating room protocol). The influence of contact time on free iodine flux was evaluated by applying the commercial preparation (Esoform) for 2 min and measuring the concentration of free-iodine in the receptor compartment by one-hour intervals.
The obtained results clearly show that also PI that has been washed out after its application is absorbed into the bloodstream during the first hour.

Discussion

Our study on percutaneous absorption of iodine shows a significant permeation of iodine through the skin that is time of contact dependent. Our experimental data confirmed for the first time in vitro what has been reported in other clinical studies on patients who underwent surgical procedures or burned. In a previous clinical investigation by Dela Cruz et al. (1987), it was underlined that the reports of iodine absorption from topical povidone iodine solution suggest that the absorption is

enhanced when the compound is applied to denuded skin, mucosal surface with high absorptive capacity or extensive areas of intact skin. The evidence for iodine absorption of most of these studies includes documented serum iodine concentration and thyroid function abnormalities. Kovacikova et al. (2005) investigated thyroid function and ioduria in infants after cardiac surgery with primary sternal closure compared with delayed sternal closure (DSC) and the exposure to povidone iodine for sternal wound protection. The patients with DSC display more profound thyroid suppression in the immediate postoperative period. The use of PI adhesive drapes with single iodine mediastinal irrigation in patients with DSC is associated with significant iodine absorption but no significant thyroid dysfunction. Also Mitchell et al. (1991) established a fourfold concentration rise of total plasma iodine (range 160– 1.440%) after PI skin preparation of infants undergoing closed cardiac or thoracic procedures (covering 20–30% of body surface by povidone iodine). PI applications to surgical wounds of neonates with giant omphalocele were studied by Whitehouse et al. (2010) who concluded that topical PI promotes escharification and epithelialisation and may cause transient TSH elevation especially in the early phase of treatment.

PI gel is a widely used topical microbial agent in cases of burn injured patients. The free iodine is released at a slow rate from this complex at the treated site, where it acts as a bactericidal and fungicidal agent, especially in longer protracted cases (Aiba et al., 1999). A possibly collateral effect of this therapy is the excessive iodine systemic absorption. In fact, Edna and Bernard (1985) found that an increase of 1% iodine in the treated area contributed to an increase of 30 mcg iodine per 100 ml of serum.

In the patients with a normal renal function, the serum iodine level continues to rise until the discontinuation of drug administration. More than 1 week is required for the serum iodine level to return to normal after the last iodine application (Steen, 1993).

Below in 2006 underlined that 0.3–4.5% of the iodine of the PI is absorbed through the skin, depending on the concentration and the size of the area to which it is applied. Miller et al. (1985) reported that topical application of tincture or PI to the skin of rats was found to be as effective as oral administration of potassium iodine in blocking thyroid uptake of parenterally administrated iodine-131. Gosset et al. (2008) used PI for cavity clearance in a 62-years-old patient with post-pneumonectomic empyema after an operation for non-small cell lung cancer. They reported in 2008 that the patient suffered from thyrotoxicosis as a result of the therapy and the patient should be monitored during management (Gosset et al., 2008). Moreover, the iodine used during cataract surgery is absorbed by the body and that the use of PI is contraindicated in patients with thyroid pathology (Below et al., 2006).

In previous studies, it was also shown that PI use in preoperative preparations made for vaginal disinfection (daily vaginal douche and mouthwash) was associated with increased serum and urine iodine levels (Tomoda et al., 2005; Vorherr et al., 1980; Nobukuni and Kawahara, 2002; Ader et al., 1988).

Furudate et al. (1997) investigated the ^{125}I uptake competing with iodine absorption by the thyroid gland following povidone iodine skin application in mice and rats and the PI application group showed a significant decreased uptake of ^{125}I (Furudate et al., 1997).

Our study confirmed that PI solution can permeate the intact skin in time dependent matter and permitted us to define a flux and lag time that can be used to predict iodine absorption into bloodstream considering the exposed area of the skin. These values are surely higher when applied on impaired skin or on mucosa or on the skin of young babies.

To increase the knowledge on iodine skin absorption, we repeated our experiment considering the washing protocol used by health care professional during their work in operating rooms in Trieste Hospitals. These workers must wash their hand using PI solution for 2 min, than they rinse hands using water and they repeat the PI application and the rinsing. This procedure is repeated many times during the day (20–30 times). The obtained results clearly show that also PI that has been washed out after its application is absorbed into the bloodstream during the first hour. It can be concluded that the greatest part of PI is absorbed into the bloodstream after the washing of hands in

the course of the first hours following the contact. It is already demonstrated that a washing procedure can enhance skin permeation due probably to the action of soap and water that can alter skin surface (Filon et al., 2006).
In the occupational field there are two clinical studies that confirmed our results by urinary iodine concentration in vivo. The first study was conducted with a limited number of nonsurgical ward nurses, who had to use PI products for hand washing and gargling several times a day in Japan (Nobukuni and Kawahara, 2002). Although it was demonstrated that the serum levels of iodine did not significantly increase in the group using PI, the mean serum-free thyroxine levels were slightly, but not significantly, higher compared to the controls. However, this study include only small group of nurses, and the mucosal or cutaneous exposure time to the PI products were short. The second study investigated the effect of hand scrubbing with iodine-containing solutions on urinary iodine concentrations of the operating room staff. Erdogan et al. (2013) demonstrated that the operating room staff can have significantly higher levels of urinary iodine concentration (UICs) compared with the staff from nonsurgical units, probably due to high exposure time and also the operating rooms staff might be exposed to more gaseous forms of iodine because of the large number of people using hand scrubs within the same time-frame and it is the same scrubbing sinks, in addition to the topical, preoperatively applied PI on patients in the operating room. In nearly 40% of the staff using solely the iodine-containing scrub solution, urinary iodine concentrations were >300 mcg/l. According to World Health Organization a median urinary iodine level >300 mcg/l indicates excessive iodine intake for a surveyed population and can be associated with adverse health consequences (Erdogan et al., 2013). Anyway the in vitro design of our study deserve some limitations:

1. When assessing the results obtained in vitro it is necessary to consider the difference between the artificial character of the experimental studies conducted in vitro and reality; because the extrapolation to "real-world" events is an imperfect art (Filon et al., 2006).
2. Absorption of a topical substance through the skin is most notably influenced by concentration, contact duration, frequency, and exposed area. The interplay between these factors, along with skin biology and physiochemical properties of the penetrant, can lead to enhanced percutaneous penetration (Blickenstaff et al., 2014).
3. Furthermore, we have to consider that in the first part of our experimental study we applied the infinite dose in the donor compartment and we demonstrated that the iodine concentration in the receptor compartment increased linearly over time in proportion to contact time between iodine and the intact skin in the donor compartment. This situation could be similar in cases of wide use of PI during surgical procedures and as a topical antiseptic of skin, mucosa, wound or deep tissues (Tomoda et al., 2005; Paul et al., 1988; Zafer et al., 1992).
4. Nevertheless, it is also necessary to take into consideration that during the surgical hand washing the operating room staff cover about 9% of the total body surface (20 cm2) with iodine containing solutions and scrub it with it. One application to the skin of PI solution can cause the absorption of 232 mcg of iodine each time (11.6 mcg/cm^2 x 20 cm^2) in 24 h, while one application with rinsing of PI solution can cause the absorption of 2 mcg of iodine in 1 h for each washing procedure (0.10 mcg/ cm^2 x 20 cm^2). Considering that one worker washes hands and forearms for more than 20 times a days the total amount of iodine that can permeate the skin is 40 mcg per day.
5. In the field of occupational medicine we also have to consider the workers that can suffer from dermatitis or other skin pathologies. It was already demonstrated that damaged skin has a higher permeation rate to xenobiotics (Filon et al., 2006).

Conclusion

Our study demonstrated in vitro that iodine can be absorbed through the skin when PI antiseptic is used in a time and area exposed dependent manner. Iodine is present in different preparations

including soap, solutions, surgical scrub used by health care professionals. The repetitive use of surgical hand antiseptics containing iodine among the operating-room staff may cause excessive iodine exposure by transcutaneous absorption, recently demonstrated in a clinical study with urinary iodine assessment (Erdogan et al., 2013) and the increase of iodine serum concentration can cause thyroid dysfunction (Dela Cruz et al., 1987; Philippou et al., 1992; Jubiz et al., 1977; Sternthal et al., 1980; Vagenakis et al., 1974).

In accordance with previous data a long term use of PI can present a risk for iodine excess-inducing thyroid disorders for both patients and medical workers (Nobukuni and Kawahara, 2002; Linder et al., 1997; Ader et al., 1988; Bürgi, 2010).

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Table 1
Iodine content in receiving phases in blank and treated cells (µg/cm2).

Time (h)	Blank	Blank	Cell A	Cell B	Cell C	Cell D	Cell E
0	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
2	0.0242	0.0236	0.0417	0.0475	0.1460	0.0515	0.0610
4	0.0308	0.0212	0.1211	0.1474	0.3574	0.1813	0.1988
6	0.0620	0.0325	0.2499	0.3393	0.6939	0.4657	0.5052
8	0.0841	0.0684	0.4074	0.5758	2.6428	0.8727	0.9445
12	0.0836	0.1075	1.0750	0.9458	6.9176	2.4070	2.4243
20	0.0984	0.1405	3.3009	4.2358	16.6837	8.2156	7.7759
24	0.1141	0.1665	6.0536	6.7368	21.8045	12.1363	11.2264

Table 2
Iodine concentration in receiving cells after the washing protocol (µg/cm2).

Time (h)	Cell I	Cell L	Cell M	Cell N
0	0.0000	0.0000	0.0000	0.0000
1	0.1397	0.1192	0.0941	0.0605
2	0.0925	0.0752	0.0605	0.0454
4	0.0850	0.0879	0.0634	0.0533
6	0.1029	0.0883	0.0734	0.0533
8	0.0958	0.0970	0.0654	0.0606
12	0.1168	0.1032	0.1011	0.0908
20	0.1311	0.1199	0.1078	0.1049
24	0.1443	0.1279	0.1239	0.1122

Fig. 1. Skin absorption profiles of iodine through intact skin, compared to blank cells.

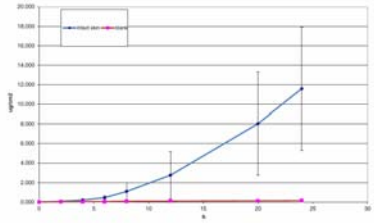
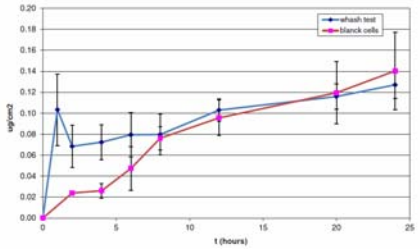
Fig. 2. Skin absorption of iodine in cell washed compared to blank cells.