

Review Article

Skin occlusion and irritant and allergic contact dermatitis: an overview

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Occlusion, widely used to enhance percutaneous absorption of drugs, also increases penetration of other chemicals and antigens, and hence may exacerbate irritant and allergic contact dermatitis. This overview summarizes the adverse effects of occlusion.

Key words: enhancer; irritant contact dermatitis; occlusion, percutaneous absorption-penetration; stratum corneum; transdermal therapeutic systems; transepidermal water loss.. © Munksgaard, 2001.

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Skin occlusion enhances stratum corneum hydration and often, but not always, increases percutaneous absorption (1–4). On the other hand, it compromises skin barrier function by impairing passive transepidermal water loss (TEWL) at the application site, and hence aggravates the irritant effect of applied compounds (2, 4–7).

Transdermal therapeutic systems (TTS) are typically occlusive patches placed on the skin surface for 1–7 days while delivering drugs into the systemic circulation (5) and have been extensively investigated because of potential advantages over traditional oral or other administration routes (7–13). However, local reactions (i.e., irritation and/or sensitization) have been become obstacles to the design and application of TTS in the clinical situation (7–13). This overview summarizes the effects on contact dermatitis of occlusion.

Skin and Effects of Occlusion

Skin envelops the body surface as a flexible shield, acting as a 2-way barrier, minimizing loss of water, electrolytes, and other body constituents, and decreasing the entry of noxious substances from the external environment. Stratum corneum is the principle barrier and normally contains 10–20% water (14). Skin barrier function may be perturbed by physical, chemical, therapeutic and patholog-

ical factors; even changes in environmental humidity may also induce pathophysiologic alterations (15). Increasing stratum corneum hydration can progressively reduce its barrier efficiency (1–5, 16, 17).

Occlusion is created by covering tape, gloves, impermeable dressings or transdermal devices (5). In addition, certain topical vehicles such as those containing fats and oils (petrolatum, paraffin, etc.) may be occlusive (6, 18). Moisturizer/emollients may functionally be occlusive. Most studies demonstrated a duration of moisture of minutes to hours. Loden (19) provided extensive documentation in this area.

Passive TEWL can be completely blocked by occlusion (5). The consequence is to increase stratum corneum hydration, thereby swelling the corneocytes, and promoting the uptake of water into intercellular lipid domains (2, 4, 20). Occlusion alters many factors that may influence percutaneous absorption: (i) altering the partitioning between the surface chemical and the skin due to the increasing presence of water content of stratum corneum from a normal range of 10–20% up to 50% (2, 4); (ii) swelling the corneocytes and possibly altering the intercellular lipid phase organization (2, 4, 20); (iii) increasing the skin surface temperature from a normal range of 32°C to 37°C (2, 4); (iv) increasing blood flow (2, 4); (v) preventing the accidental

wiping or evaporation (volatile compound) of the applied compound, in essence maintaining a higher applied dose (21); (vi) serving as a reservoir of the drug for penetration as a result of hydration (21). Initially, a drug enters the stratum corneum under occlusive conditions. After dressing removal and stratum corneum dehydration, the movement of drug slows and the stratum corneum becomes a reservoir (21). However, occlusion does not enhance penetration of all chemicals (1–4). Skin hydration increased penetration of lipid-soluble, non-polar molecules but had less effect on polar molecules (1, 3). The absorption of more lipophilic steroids was enhanced by occlusion in man but the most water-soluble were not (1). In addition, physicochemical properties (such as volatility, partition coefficient, and aqueous solubility), anatomic site, and vehicle may also influence the effect of occlusion on absorption (1–4, 22, 23).

In fact, the effects of occlusion are complex and may produce profound changes: occlusion can alter epidermal lipids, DNA synthesis, epidermal turnover, microbial flora, pH, epidermal morphology, sweat glands, Langerhans cells stresses, wound healing, etc. (5, 6, 15, 24–28).

Data on Occlusion and its Local Reactions

Bucks et al. (2, 4) observed that about 1/3 of normal, healthy, male volunteers experienced plastic chamber occlusion-induced irritation following contact with TTS for periods greater than 24 h; however, they did not show any irritation when using the nonocclusive patch system on the same volunteers following identical contact periods with the same penetrant.

Hurkmans et al. (29) documented irritation produced by TTS during long-term (5-day) application in man. Different types of TTS were applied to the back of male volunteers for 120 h, and sweat accumulation and bacterial growth were studied. Hydrogel discs of systems had less skin irritation but intense bacterial growth was observed when compared to other systems. They concluded that water accumulation is a major cause of skin irritation under TTS during long-term application, and that bacteria and/or yeasts apparently play only a minor rôle; in addition, the incorporation of hydrogels in the TTS may reduce skin irritation by absorbing water.

Nieboer et al. (30) investigated the effects of occlusion with TTS on Langerhans cell and skin irritation. 25 health volunteers were divided into 5 groups of 5 volunteers, and were occluded with a placebo TTS and a silver-patch test for 5 time periods (6 h, 1, 2, 4 and 7 days). Irritation was judged on morphology, histopathologic and immu-

nofluorescence findings, and changes in the Langerhans cell systems. They noted that occlusion with their systems provoked only slight or no skin irritation.

Van der Valk & Maibach (31) utilized a post-application occlusion human model to assess if occlusion increases the irritant response of the skin to repeated short-term sodium lauryl sulfate (SLS) exposure in 10 healthy subjects. In an open application procedure, the volar side of the forearm was treated by repeated application of SLS. 1 test site on either arm was exposed for 5 consecutive days and 1 adjacent skin site was exposed on alternate days. After the open exposure, the skin was either left open or occluded with plastic wrap. Skin irritancy was measured by means of visual grading and TEWL measurements. The occluded skin sites showed a significant increase in visual grading and TEWL values (both every-day and alternate-day schedules) when compared to unoccluded sites. They indicated that post-exposure occlusive treatment markedly enhanced irritant response.

Bircher et al. (32) evaluated the adverse skin reactions to nicotine in a TTS in 14 volunteers with a history of former adverse skin reactions to this device. Individual components of TTS were tested for immediate- and delayed-type reactions. 9 subjects developed mild irritant erythematous reactions due to occlusion (reacting to both the adhesive and matrix layers) and 5 individuals had positive allergic patch test reactions to nicotine base. The optimal test agent and concentration for elucidating the adverse skin reaction was an aqueous solution of 10% nicotine base. They suggested that nicotine should be added to the expanding list of TTS which may elicit contact dermatitis.

Emtestam & Ollmar (33) measured the electrical impedance index in human skin after occlusion, in 5 anatomical regions and in mild irritant contact dermatitis. The volunteers were divided into 3 groups. In the occlusion group with 11 subjects, the test sites were occluded on the back for 24 h using empty aluminum chambers and chambers with water, physiological saline, a paper disc or 0.002% of SLS. In the normal skin group of 10 subjects, electrical impedance was measured at 5 body sites for 5 consecutive days. In the long-term study group of 3 subjects, daily measurements for 1 month were performed on normal skin and skin following the application of 2% SLS. They observed that the irritation index based on electrical skin impedance gives little day-to-day variation at 1 and the same test site, in comparison to the variations between different test sites on the same subject and the interindividual variations observed. Occlusion did not affect readings taken 24 h or

later after removal, but increased variance for readings taken 1 h after removal.

Matsumura et al. (25) investigated the effect of occlusion on the skin in man. The flexor sides of both upper arms were covered with column-shaped polyethylene foam closed chambers. The tops of the chambers were sealed by plastic films with various levels of water vapor permeability to control moisture in each chamber. After 24 h of application, morphological changes on the surface of occluded skin were observed using a nitrocellulose-replica method. The number of deepened skin furrows on the skin surface was increased by lower water vapor permeability of the film, as well as increasing temperature and humidity on the test day. This result suggested that simple occlusion with water vapor permeability below 30 g/m²h can induce morphological alternations on the skin surface, and implied that prolonged exposure by simple occlusion may act as a primary irritant.

Kligman (5) studied hydration dermatitis in man; 1 week of an impermeable plastic film did not injure the skin; 2 weeks were moderately harmful to some but not all subjects; 3 weeks regularly induced hydration dermatitis. Hydration dermatitis was independent of race, sex, and age. He examined the potential role of microorganisms in developing hydration dermatitis by using antibiotic solutions immediately following occlusion with plastic wrapping. Results showed that the microorganisms clearly had no impact. In addition, they noticed that some hydrogels did not appreciably hydrate or macerate the surface by visual inspection when left in place for 1 week. But some TTS may indeed provoke a dermatitis when applied 2× weekly to the same site. From a histologic study, they demonstrated marked cytotoxicity to Langerhans cells, melanocytes and keratinocytes.

Graves et al. (34) assessed the detrimental effect of occlusive glove patches in man. 4 test sites were assigned on both forearms of each subject. On day 1, 2 sites were occluded with a glove patch for 4 h and 8 h, respectively; the 3rd site was left unoccluded as a control. On day 2, the 4th site was covered with a transparent dressing (without glove patch) for 8 h as an active control. The effects on the skin barrier were evaluated by percorneal permeability, TEWL, skin surface roughness and skin surface compliance. Results showed that percorneal permeability, TEWL, and compliance parameters were significantly increased after occlusion for 4 and 8 h, and skin surface roughness was significantly reduced in terms of roughness parameters Ra and Rz by 4 and 8 h occlusion. They concluded that the glove patches caused a temporary impairment in barrier function and suggested the repeated occlusion by gloves may have a cumulative effect.

Wilhelm (35) investigated the effects of surfactants on stratum corneum (SC) hydration in 9 human subjects: a series of sodium alkyl sulfates were applied to the volar forearm using occlusive plastic chambers for 24 h. SC hydration was evaluated by measurements of electrical capacitance (CAP) at 30 min after removal of the patches and thereafter at daily intervals for 7 days. All alkyl sulfates, with the exception of sodium lauryl sulfate, resulted in a temporary decrease in SC hydration 1 h after patch removal. At day 2, SC hydration levels of surfactant-treated skin were not significantly different from controls. Thereafter, a 2nd decrease in CAP value was observed with lowest hydration at day 7.

Wood et al. (28) observed the impacts of occlusion on epidermal cytokines in essential fatty acid-deficient and normal mice. They noted that occlusion lowers cytokine mRNA levels in essential fatty acid-deficient and normal mouse epidermis, but not after acute barrier disruption.

Welzel et al. (36, 37) evaluated the effect of occlusive treatments on repair of the human skin permeability barrier under controlled experimental conditions. Barrier perturbation was induced either by application of SLS or by repeated tape stripping. This was followed by treatment with occlusive and semipermeable dressings, partly after pre-treatment with petrolatum. Repair of water barrier function was evaluated by daily measurements of TEWL for 1 week. SLS irritation and tape stripping led to a 6× increase in TEWL as a sign of severe water barrier perturbation, followed by a stepwise decrease over the following days. They indicated that occlusion did not significantly delay barrier repair as measured by TEWL.

Ramsing & Agner (38, 39) evaluated the effect of glove occlusion on normal and compromised human skin by non-invasive methods in 2 studies (A and B). Each subject wore an occlusive glove on one hand, while the other hand served as control. Hypoallergenic non-latex gloves were used. In study A, 20 volunteers wore a glove on normal skin 6 h/day for 3 days; in study B, 20 wore a glove on SLS-compromised skin 6 h/day for 3 days. Skin barrier function was evaluated by measurement of TEWL, skin hydration by electrical capacitance and inflammation by erythema index. Glove occlusion on normal skin for short-term exposure (6 h/day for 3 days) did not significantly change the water barrier function, but caused a significantly negative effect on SLS-compromised skin for the same period.

They also evaluated the effect of long-term glove occlusion on normal skin (6 h/day for 14 days) in 2 studies (A and B) (39). In addition, the effect of a cotton glove worn under the occlusive glove was also determined. In study A, 19 volunteers wore

an occlusive glove on normal skin 6 h/day for 14 days on one hand only, while the other hand served as control. In study B, 18 volunteers wore occlusive gloves on both hands on normal skin. A cotton glove was worn under the occlusive glove on one hand while other hand utilized the glove only. This long-term using glove occlusion on normal skin (6 h/day for 14 days) caused a significant negative effect on skin barrier function, as measured by TEWL, which was prevented by the cotton glove. They concluded that occlusion may be an additional factor in the pathogenesis of cumulative irritant contact dermatitis.

Fluhr et al. (40) evaluated the barrier damage

by prolonged occlusion in man. 5 sites were assigned on the volar forearm: 4 were occluded by a plastic chamber and 1 site served as a control on day 0, and then occlusion was removed at site 1 after 24 h, at site 2 after 48 h, at site 3 after 72 h and at site 4 after 96 h. 2 h after occlusion removal, TEWL and skin hydration were measured and a sorption-desorption test performed. TEWL increased, reaching a plateau on day 2. Hydration and water holding capacity did not show significant changes. They concluded that occlusion induced barrier damage without skin dryness.

Brief data on local reactions caused by occlusive conditions are shown in Table 1.

Table 1. Brief data of local reactions caused by occlusive conditions

Occlusive conditions	Local reactions	Refs.
TTS for greater than 24 h	1/3 of volunteers experienced plastic chamber occlusion-induced irritation.	(2, 4)
a serial TTS for 5 days	hydrogel discs of systems had less skin irritation when compared to other systems.	(29)
TTS and a silver-patch test for 5 time periods: 6 h, 1, 2, 4 and 7 days.	occlusion with their systems provokes only slight or no skin irritation.	(30)
post-application occlusion on SLS-induced compromised skin	post-exposure occlusive treatment markedly enhanced irritant response.	(31)
nicotine TTS and its device	9 of 14 subjects developed mild irritant erythematous reactions due to occlusion (reacted to both adhesive and matrix layers).	(32)
aluminum chambers and chambers with water, physiological saline, a paper disc or 0.002% of SLS for 24 h	occlusion did not affect readings of electrical skin impedance taken 24 h or later after removal, but increased variance for readings taken 1 h after removal.	(33)
polyethylene foam closed chambers for 24 h	the number of deepened skin furrows on the skin surface was increased by lower water vapor permeability of the film, as well as increasing temperature and humidity on the test day	(25)
impermeable plastic films for 1, 2, and 3 weeks and various TTS	1 week of an impermeable plastic film did not injure the skin; 2 weeks were moderately harmful to some but not all subjects; 3 weeks regularly induced hydration dermatitis. Some hydrogels did not appreciably hydrate or macerate the surface by visual inspection when left in place for 1 week. But some TTS may indeed provoke a dermatitis when applied twice weekly to the same site	(5)
glove patch for 4 and 8 h, and empty dressing; HN as an indicator	percorneal permeability, TEWL, compliance parameter were significantly increased after occlusion 4 and 8 h, and skin surface roughness was significantly reduced in terms of roughness parameters Ra and Rz by 4 and 8 h occlusion	(34)
plastic chambers with a series of sodium alkyl sulfates for 24 h.	all alkyl sulfates, with the exception of sodium lauryl sulfate, resulted in a temporary decrease in SC hydration 1 h after patch removal. At day 2, SC hydration levels of surfactant-treated skin were not significantly different from controls. Thereafter, a 2nd decrease in capacitance value was observed with lowest hydration at day 7	(35)
occlusion on essential fatty acid-deficient and normal mouse for 8, 24 and 48 h	occlusion lowers cytokine mRNA levels in essential fatty acid-deficient and normal mouse epidermis, but not after acute barrier disruption	(28)
different occlusive and semipermeable dressings for 23 and 46 h on irritation and tape stripped skins	occlusion did not significantly delay barrier repair	(36, 37)
short-term (6 h/day for 3 days) gloves on normal skin and gloves on SLS-compromised skin	glove occlusion on normal skin for short-term exposure did not significantly change the water barrier function but caused a significantly negative effect on SLS-compromised skin for the same period	(38)
long-term (6 h/day for 14 days) gloves on normal skin and a cotton glove worn under the occlusive glove	this long-term glove occlusion on normal skin caused a significantly negative effect on skin barrier function, as measured by TEWL, which was prevented by the cotton glove	(39)
plastic chambers at 24, 48, 72 and 96 h	significant progressive increase under occlusion, reaching a plateau on day 2. Hydration and water-holding capacity did not show significant changes	(40)

Conclusions

Most of the studies referred to in this overview related to occlusive effects on normal skin. Data on compromised skin is unfortunately limited (28, 31, 36–38). As noted above, occlusion alone may produce cytological damage to the skin that has been termed hydration dermatitis by Kligman (5). With application of chemicals/drugs under occlusive conditions, it can increase penetration of chemicals and antigens into the skin and thus also increase dermatitis (5, 6). These side-effects should be considered whenever applying occlusion in clinical situations. However, such reactions can be minimized by approaches such as immunosuppressive agents, antioxidants, local anesthetics, and other anti-irritant technologies (41). Application of optimal hydrocolloid patches that absorb water in both liquid and vapor form can also decrease the irritant reaction (26, 42, 43). Topical corticosteroids are another alternative but their role in the suppression of TTS-induced dermatitis needs to be better defined, especially for patients who require continued treatment with long-term application of such devices (7). Hopefully, more efficacious and realistic approaches to abrogating contact dermatitis will be developed.

The most important findings are emphasized as follows.

- (i) Occlusion decreases skin barrier function.
- (ii) Occlusion increases irritant and allergic contact dermatitis, in particular on compromised skin.
- (iii) Optimal design, like hydrogel, can reduce such dermatitis.
- (iv) Occlusion does not significantly delay barrier repair in man.

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