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Enhancing drugs absorption through third-degree burn wound eschar

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ARTICLE INFO

Article history:
Accepted 24 July 2007

Keywords:
Burn wound
Third-degree burn eschar
Permeation
Penetration enhancers
Antimicrobials

ABSTRACT

Antimicrobial therapy remains the most important method of wound infection treatment. Systemically administered antimicrobials may not achieve therapeutic levels in wound. On the other hand, some topically applied antimicrobials cannot penetrate eschar well enough. Therefore, an attempt has been made here to increase permeation of topically applied drugs through eschar using the so-called skin penetration enhancers.

To perform this investigation, effects of different potential penetration enhancers on permeation of chlorhexidine, silver sulfadiazine and nitroglycerin through human third-degree burn eschar was evaluated.

Results showed that water, glycerin, saline, sodium lauryl sulphate (SDS) and ethanol tend to reduce permeation of chlorhexidine through burn eschar. But, water, glycerin, hexane:ethanol and ethyl acetate:ethanol were able to increase permeation of silver sulfadiazine significantly by about 1.2–1.8 times, while saline, SDS and dimethyl sulfoxide were not able to change its permeation. Glycine showed 2.7 times enhancement toward permeation of nitroglycerin, followed by water, hexane:ethanol mixture, saline and SDS with enhancement ratios of 1.8–2.3. Urea, ethanol and citral were not able to increase permeation of nitroglycerin through eschar. This study shows that permeation of drugs through burn eschar can be improved by penetration enhancement including hydration; the effect depends on the nature of the penetrant.

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1. Introduction

Sepsis is the leading cause of morbidity and mortality in burn patients [1–4]. An ample variety of microorganisms may colonize the burn wound, proliferate on and within the eschar, progress in depth and initiate a systemic infection. Prevention and treatment of burn wound infection includes proper wound dressing [5], surgical debridement and systemic and topical antimicrobial therapy [6,7], of which the latest is the subject of the present investigation.

Third-degree burn wound eschar is avascular and frequently several millimeters distant from patient microvasculature. Therefore, systemically administered antimicrobial agents may not achieve therapeutic levels by diffusion to the wound, where microbial numbers are usually very high [6–8]. It has been shown that some chemicals including anesthetics can improve dermal perfusion in burn [9,10], but this approach does not seem able to alleviate this problem completely. In addition, systemic antibiotics can lead to the development of drug-resistant respiratory and urinary tract infections [11].

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0305-4179/$34.00 © 2007 Elsevier Ltd and ISBI. All rights reserved.
doi:10.1016/j.burns.2007.07.018

Therefore, topical antimicrobial therapy remains the most important method of wound infection treatment [7,8,12,13].

To act properly, topical antimicrobial agents should be able to penetrate the wound eschar in therapeutic amounts. Unfortunately, we have several reports indicating that some antimicrobial agents used topically in wound treatment, including silver sulfadiazine, cannot penetrate into eschar well enough to provide therapeutic levels [14,15].

Water and other chemicals, the so-called penetration enhancers, are available and were used over decades for increasing permeation of drugs through the intact skin and its models [16–18]. It has been shown in our laboratories that controlled hydration of eschar can increase permeation of silver sulfadiazine, as studied ex-vivo using diffusion cells [19]. We have decided here to apply the same strategy to increase eschar permeation of three model drugs using different classes of penetration enhancers and hydratants.

2. Materials and methods

2.1. Chemicals

Ethyl acetate (99%), glycerin (90%), NaCl (99.5%), *n*-hexane (>95%), glycine (USP grade), methanol (99.8%), urea (BP grade), dimethyl sulfoxide (DMSO) and sodium dodecyl sulphate (SDS, 99%) were purchased from Merck (Germany). Ethanol (96%) was provided by Bidestan (Iran). Nitroglycerin (glyceryl trinitrate, GTN) was received as 10% mixture in lactose from Soha Pharmaceutical Company (Iran). Chlorhexidine gluconate aqueous solution (20%) was received as a gift from Share-Darou Co. (Iran). The 1% silver sulfadiazine cream (Sobhan-Darou Pharmaceutical Co., Iran), available on the market, was purchased from local drugstore. Citral, as 20% in propylene glycol, was purchased from du Crocq (The Netherlands).

Nitroglycerin was extracted from its mixture by first dissolving the lactose in water, separation of nitroglycerin and further purification by ether. A 0.5 mg ml^{-1} aqueous solution was used for permeation studies. All other chemicals, reagents and microbial media were of pharmaceutical grade and were used as received.

2.2. Eschar

Third-degree burn eschar, separated at the time of surgical debridemant (2–3 weeks post-burn) from abdominal and leg regions of burned patients were obtained from Motahari Burn Center (Tehran, Iran).

2.3. Diffusion cells

Homemade Franz-type diffusion cells with effective surface area of 5 cm^2, designed by Dr. Hamid Reza Moghimi and made by Ashke Shisheh (Tehran, Iran), were used in this study. These cells comprise of donor and receptor chambers.

2.4. Methods

Two different methods, antimicrobial studies and diffusion cell permeation studies, were employed to evaluate the ability of penetration enhancers to increase permeation of model drugs through eschar. Microbial studies are closer to real situations, but it cannot provide pharmacokinetic data (e.g. permeation flux), which can be measured by diffusion cell permeation studies. The methods are discussed below in detail.

2.4.1. Antimicrobial effect study

Staphylococcus aureus, which is one of the most common infectious agents of burn wounds and shows a high degree of resistance to antimicrobial regimens, was used for this study. The ATCC 25923 type of this organism was used and was grown in tryptic soy broth (Merck, Germany) and plated onto Muller–Hinton agar (Oxoid, UK). Eschar disks (d = 15 mm) were cut from whole-thickness eschar using a stainless steel punch. The disks were then pretreated with the enhancers for 4 h by placing them in a plate containing the enhancers as solutions or mixtures, as described below. Dry disks (without enhancer treatment) were considered as the control condition. Water, saline (0.9%), glycerin aqueous solution (10%, v/v), DMSO aqueous solution (60%, v/v), SDS aqueous solution (1 mg ml^{-1}), ethanol aqueous solution (50%, v/v), ethyl acetate:ethanol mixture (1:1, v/v) and *n*-hexane:ethanol mixture (1:1, v/v) were used as potential penetration enhancers in this part of the study.

The pretreated disks were then placed on the staphylococcus cultured media and a stainless-steel ring was put on top of each disk. Model antimicrobial agents, 3 drops of chlorhexidine and 0.4 g of silver sulfadiazine cream, were then applied to the eschar samples and plates were incubated at 37 °C. After about 24 h incubation, the diameter of non-growing area of each disk was measured. Enhancement ratios were calculated by dividing the diameter of non-growing area in the enhancer-treated samples by the diameter of non-growing area in non-treated samples (dry control).

2.4.2. Diffuse cell permeation studies

Nitroglycerin, which shows good permeability through intact skin, was used as a model lipophilic agent for these studies. Eschar samples were sandwiched between donor and receptor chambers of diffusion cells, while the epidermal side faced the donor compartment. The receptor chamber was then filled with 30 ml receptor phase (distilled water) and the donor chamber with 10 ml water or enhancer solutions. The donor chamber was kept empty in control samples (called dry eschar in here). The system was then stored at room temperature for 24 h to allow enhancer-treatment and skin equilibration with the receptor phase.

Water, saline (0.9%), glycine aqueous solution (100 mg ml^{-1}), SDS aqueous solution (1 mg ml^{-1}), urea aqueous solution (10%, w/v), ethanol aqueous solution (50%, v/v), *n*-hexane:ethanol mixture (1:1, v/v) and citral solution in propylene glycol (20%, w/w) were used as potential penetration enhancers in this part of study.

After enhancer-treatment and equilibration, the contents of both donor and receptor chambers were removed. The receptor chamber was washed twice and then filled with 30 ml fresh receptor phase. A 5 ml of drug solution (0.5 mg ml^{-1} nitroglycerin aqueous solution) or its control solvent was

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