く皮膚科>

- 1) The wound/burn guidelines: Guidelines for the management of burns
- 2The Wound/Burn Guidelines Committee
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- 4The Journal of Dermatology
- ⑤第43巻9号 P989-1010, 2016

Topical Treatments: Topical Agents CQ21: What Topical Agents should be used for the Treatment of Second-Degree Burns?

Remarks on recommendation: For the initial treatment of second-degree burns, ointments with oleaginous bases such as petrolatum, zinc oxide and dimethyl isopropylazulene are recommended as an option (C1).

For second-degree burns, trafermin, tretinoin tocopherol, bucladesine sodium and prostaglandin E1 are recommended (B).

Lysozyme hydrochloride, aluminum chlorohydroxy allantoinate (Alcloxa) and so forth are recommended as an option (C1).

For chronic ulcers accompanied by necrotic tissue resulting from DDB, the use of bromelain ointment, cadexomer iodine, dextranomer and silver sulfadiazine is recommended as an option for the removal of necrotic tissue (C1).

Recommendation level: B and C1.

Comments:

- For chronic ulcers caused by burns, topical agents should be selected for wound bed
 preparation based on the TIME concept or moist wound healing. It is also important to
 appropriately select not only the principal agent but also the base according to the condition of
 the wound surface. The following topical treatments are recommended by the Guidelines for
 the Management of Pressure Ulcers as topical agents appropriate for wound bed preparation,
 but the topical agents used for T (removal of necrotic tissue) and M (maintenance of the moist
 environment) in burns are the same:
 - T (removal of necrotic tissue): Cadexomer iodine, silver sulfadiazine, dextranomer, bromelain ointment.
 - I (control/elimination of infection): Cadexomer iodine, silver sulfadiazine.
 - M (maintenance of the moist environment): When effusion is excessive, cadexomer iodine, dextranomer and bucladesine sodium; when effusion is deficient, aluminum chlorohydroxy allantoinate, ointments containing antibiotics (antibacterial agents), tretinoin tocopherol, prostaglandin E1, lysozyme hydrochloride and ointments with a oil base such as petrolatum.
 - E (management of wound edges): No recommendable topical agents.

- Concerning the use of oil-based ointments for second-degree burns, there is only an expert opinion,[138] and the evidence level is VI. There is one RCT showing the effectiveness of trafermin for the treatment of second-degree burns, [139] and the evidence level is II. Regarding tretinoin tocopherol, there is one double-blind RCT comparing it with bendazac in patients with various skin ulcers including those caused by burns[140] and one non-blinded RCT comparing it with lysozyme hydrochloride,[141] and the evidence level is II. However, no details such as the depth of the burns are provided. Concerning bucladesine sodium, there is one double-blind RCT each comparing it with the base and lysozyme hydrochloride in patients with various skin ulcers including those caused by burns,[142, 143] and the evidence level is II. However, no detailed description concerning the burns is provided. As for prostaglandin E1, there is a non-blinded RCT comparing it with lysozyme hydrochloride in patients with various skin ulcers including those due to burns,[144] and the evidence level is II, but no detailed information including the depth is provided about the burns, and the number of patients is small. However, as tretinoin tocopherol, bucladesine sodium and prostaglandin E1 are rated similarly to trafermin in the Guidelines for the Management of Pressure Ulcers, which are similar chronic skin lesions, the recommendation levels of these topical agents were determined similarly to trafermin on the basis of consensus of the committee. Concerning lysozyme hydrochloride, there is one RCT comparing it with bendazac in patients with various skin ulcers including those due to burns[145] and one case series study in patients with ulcers due to burns,[146] and the evidence level is II and V, respectively. However, the recommendation level of the former was set at C1 because of the lack of detailed description about the burns. Regarding aluminum chlorohydroxy allantoinate, there is a double-blind RCT comparing it with the base in 62 patients with skin ulcers including those due to burns, erosion, eczema and dermatitis,[147] but the recommendation level was set at C1, because there was no detailed description or evaluation about the burns.
- In second-degree burns, damage of the dermis is partial, and the selection of topical agents in consideration of not only the antibacterial action but also wound healing is necessary. The principle of topical treatment for wounds in general converges on protecting the wound surface and maintaining a moist environment.[148] However, as it is difficult to accurately determine the depth of burns early after injury, and as burns ranging from first-degree burns to DDB are often mixed, topical agents to be used are difficult to specify. Therefore, oil-based ointments may be used in the stage of initial treatment, but topical agents appropriate for the condition of the wound surface must be selected as it becomes clear.
- Ointments containing antibiotics (antibacterial agents) are oil-based ointments. While they may
 be used for the protection of the wound surface and maintenance of the moist environment,
 their use should be restricted to a short period, because their long-time use may invite the
 development of resistant bacteria.
- Akita et al. performed an RCT by randomizing 102 adults with second-degree burns into trafermin and non-trafermin groups.[139] As a result, they reported that the time until cure was significantly shorter in the trafermin group and that the elasticity and hardness scores of the scar and moisture-retaining ability were all significantly higher in the trafermin group compared with a control group consisting of 51 healthy volunteers. Komuro et al. evaluated 32 patients (including children) with second-degree burns conservatively treated using trafermin, comparing those administrated the drug within 3 days and after 4 days or more after injury, and reported that the mean number of days until epithelialization and cumulative cure rate were both statistically superior in the group treated within 3 days.[149] Fujiwara et al. evaluated 20 patients with fresh second-degree burns in whom treatment was initiated within 48 h after injury by comparing those treated with trafermin and those treated with white petrolatum alone and reported that the number of days until epithelialization was significantly shorter in the trafermin

group.[150] Also, Shiozawa *et al*. performed a case—control study comparing 171 patients with DDB (including infants and children) treated with trafermin and 53 historical controls conservatively treated without trafermin[151] and reported that patients who showed hypertrophic scarring were significantly fewer in the trafermin group.

- Trafermin is a spray type liquid preparation, and it must be used with some topical agents or
 dressing material to maintain a moist environment for burns. Recently, there have been reports
 of the concomitant use of artificial dermis and intra-bulla injection,[152, 153] but no established
 method has been proposed concerning the selection of the topical agents or dressing materials
 to be used with these treatments.
- A double-blind RCT comparing tretinoin tocopherol and bendazac has been performed in 152 patients with various skin ulcers including 44 with ulcers due to burns by the L-300 Clinical Trial Group.[140] While there is no mention of the depth of burns or time after injury, granulation 1 week after the application of the test drugs was reported to be significantly better in the tretinoin tocopherol group. There is also a unblended RCT comparing tretinoin tocopherol and lysozyme hydrochloride in 217 patients with various skin ulcers including 36 with ulcers due to burns, but no detailed description is provided concerning the depth of burns or time after injury, and no significant difference was reported to be observed in the ulcers due to burns between the two groups.[141]
- Shinmura et al. performed double-blind RCT comparing bucladesine sodium and the base in 150 patients with pressure ulcers/skin ulcers including 20 with ulcers due to burns and comparing bucladesine sodium and lysozyme hydrochloride in 275 patients with pressure ulcers/skin ulcers including 40 with ulcers due to burns.[142, 143] According to these reports, bucladesine sodium was significantly superior in the ulcer area reduction rate, granulation and epithelialization, but no detailed information is provided concerning the depth of burns or time after injury. There is, however, a report that the blood concentration of bucladesine sodium increased and remained elevated for a period after its topical application,[154] so attention to the general condition including the blood pressure, urine volume and blood glucose level is necessary when it is topically applied to a wide area.
- Imamura et al. performed a non-blinded RCT comparing prostaglandin E1 and lysozyme hydrochloride in 171 patients with pressure ulcer/skin ulcer including 26 with ulcers due to burns.[144] According to their report, there is no detailed mention of the depth of burns or time after injury, but the efficacy rate in ulcers due to burns was significantly higher in the prostaglandin E1 topical application group. On the other hand, no significant difference was observed in the ulcer area reduction rate between the two groups.
- Kawakami et al. performed a case series study using lysozyme hydrochloride in 28 patients with SDB and 40 with DDB.[146] In this study, the improvement of all second-degree burns was greater in the lysozyme hydrochloride group, but granulation was suggested to become excessive, and epithelialization to be delayed, in patients with old (topical application initiated ≥5 days after injury) DDB.
- Konjiki carried out a double-blind RCT comparing aluminum chlorohydroxy allantoinate and the
 base in 62 patients with skin ulcers including those due to burns, erosion, eczema or
 dermatitis,[147] and reported that the efficacy rate in all patients was significantly higher in the
 true drug group, but the number of patients with each disorder was small, and no statistical
 evaluation of individual disorders including burn was performed.
- If ulcers accompanied by necrotic tissue have developed as a result of DDB, topical agents should be selected from the above after surgical debridement. If the general condition is poor, or if the necrotic tissue is thin, and surgical debridement cannot be performed, topical

application of bromelain, silver sulfadiazine, cadexomer iodine or dextranomer for the removal of necrotic tissue should be considered (see CQ23).

References

- 138 Kamiya T, Ono I. A practical concept of topical therapy in burn wound (moist wound care). MB Derma 2008; 146: 21–28. (evidence level VI).
- Akita S, Akino K, Imaizumi T, Hirano A. Basic fibroblast growth factor accelerates and improves second-degree burn wound healing. Wound Rep Reg 2008; 16: 635–641. (evidence level II).
 - CrossRef | Web of Science® Times Cited: 38
- Clinical Research Group for L-300. Clinical evaluation of L-300 ointment in the treatment of skin ulcers controlled comparative study by using Bendazac ointment as a control. *J Clin Therap Med*, 1991; 7: 437–456. (evidence level II).
- 141 Clinical Research Group for L-300. Clinical evaluation of L-300 ointment in the treatment of skin ulcers controlled comparative study by using Lysozyme chloride ointment. *J Clin Therap Med*, 1991; 7: 645–665. (evidence level II).
- Niimura M, Yamamoto K, Kishimoto S et al. Clinical evaluation of DT-5621 in patients with chronic skin ulcer – multicenter, placebo-controlled double blind study. *Jpn Pharmacol Ther* 1990; 18: 245–258. (evidence level II).
- Niimura M, Ishibashi Y, Imamura S et al. Clinical study of Dibutyryl cyclic AMP ointment (DT-5621) in chronic skin ulcers – well-controlled comparative study with Lysozyme ointment. J Clin Therap Med 1991; 7: 677–692. (evidence level II).
- 144 Imamura S, Sagami S, Ishibashi Y et al. Clinical study of prostaglandin E1 ointment (G-511 ointment) in chronic skin ulcers – well-controlled comparative study with Lysozyme chloride ointment. J Clin Therap Med 1994; 10: 127–147. (evidence level II).
- Study Group for KH-101. Clinical evaluation of KH-101 ointment (Reflap ointment) in skin ulcers new analysis of well controlled comparative study. *Nishinihon Derma*, 1986; 48: 553–562. (evidence level II). CrossRef
- 146 Kawakami S, Tsukada S, Nanba K *et al* . The effect of Lysozyme ointment for the treatment of dermal burn wounds. *J J Burn Inj* 1989; **15**: 109–117. (evidence level V).
- 147 Konjiki S. Clinical evaluation of Alkisa ointment in the treatment of skin disease double blind controlled study. *Jpn Pharmacol Ther* 1977; **5**: 172–176. (evidence level VI).
- 148 Hinman CD, Maibach H. Effect of air exposure and occlusion on experimental human skin wounds. *Nature* 1963; 200: 377–378.
 - CrossRef | PubMed | CAS | Web of Science® Times Cited: 309 | ADS
- 149 Komuro A, Kishibe M, Yamamoto Y *et al* . Treatment for second-degree burn wounds using Trafermin (Fiblast® spray). *J J Burn Inj* 2009; **35**: 27–39. (evidence level III).
- 150 Fujiwara O, Soejima K, Nozaki M et al . Treatment of acute second degree burn wound with bFGF. J J Burn

- 151 Shiozawa K, Mukae N, Nishimura G. Inhibition of hypertrophic scars by administration of basic fibroblast growth factor. *Jpn J Plast Surg* 2009; **52**: 543–549. (evidence level IVb).
- 152 Mitsukawa N, Suse T, Karube D *et al* . Clinical study of treatment skin defects using a combination of artificial dermis and bFGF preparation. *Jpn J Plast Surg* 2009; **52**: 517–527.
- Kurokawa M, Morooka H, Jinno C. Treatment for partial thickness burns with Intra-bleb bFGF infusion therapy and hydrogel covering therapy following bFGF spray. *J J Burn Inj* 2009; **35**: 21–26.
- 154 Ito Y, Aoyama H, Yokoo K *et al* . Absorption of Bucladesine sodium ointment from burn wounds. *J J Burn Inj* 1998; **24**: 13–21.

CQ22: Is Silver Sulfadiazine Useful for the Treatment of Extensive Third-Degree Burns?

Remarks on recommendation: Silver sulfadiazine is recommended for the treatment of extensive thirddegree burns.

Recommendation level: B.

Comments:

- Concerning the topical use of silver sulfadiazine for the treatment of third-degree burns, there are two non-randomized comparative trials,[155, 156] and the evidence level is III. The primary objective of topical agents for extensive third-degree burns is to prevent infection from the wound surface until surgical debridement. Silver sulfadiazine is widely used in Japan and abroad for the treatment of burns, and there are multiple reports indicating an excellent antibacterial action. Also, as it is convenient for application to a wide area because of the emulsion base, its recommendation level was set at B.
- Pegg et al. performed a non-randomized comparative trial in patients with burns of various degrees by treating 314 with silver sulfadiazine, 156 with maphenide (unmarketed in Japan), and 175 historical controls with gentamycin sulfate and so forth,[155] and reported that the mortality rate, positive rate of bacterial cultures, and detection rates of P. aeruginosa, staphylococci, Proteus and Candida were significantly reduced in the silver sulfadiazine group compared with the control and maphenide groups. In Japan, Oyama et al. carried out a non-randomized comparative trial evaluating the effects of silver sulfadiazine and gentamycin sulfate in 31 patients with moderate to severe burns according to Artz's criteria,[156] and reported that silver sulfadiazine was markedly effective against Klebsiella, Serratias, other Gram-negative bacteria and Candida.
- Ono et al. evaluated the minimum inhibitory concentrations (MIC) of various antibacterial agents against P. aeruginosa, because its detection rate increases with time among bacteria isolated from burns. As no strain resistant to silver sulfadiazine or maphenide was observed, they recommended them as topical antibacterial agents for burns.[157] Also, Yura et al. performed resistance-acquisition and bactericidal studies using silver sulfadiazine against P. aeruginosa and reported infrequent development of resistance and a satisfactory bactericidal action of the drug.[158] On the other hand, there have been reports of infections resistant to silver preparations including silver sulfadiazine.[159] According to the report by Li et al.,[160] bacteria are shown to acquire resistance to silver in the presence of silver at a low

concentration, and Atiyeh *et al*. suggested the necessity to maintain an appropriate silver concentration at the wound, because resistance to silver develops at concentrations near the MIC but not at a sufficient concentration.[161] Also, in extensive burns with a large amount of exudates, silver sulfadiazine is reported to be inactivated with a marked decrease in its effect. [162] Therefore, repeated applications should be considered under such circumstances.

- Because an emulsion base is used in silver sulfadiazine preparations, they have high tissue permeability and are expected to produce a debriding effect by promoting autolysis of necrotic tissue (see CQ23).
- As adverse effects of silver sulfadiazine, leukocytopenia, methemoglobinemia, silver
 deposition, allergic reaction to sulfonamides and so forth have been reported. Sufficient
 attention to these adverse effects is considered necessary, particularly when silver sulfadiazine
 is topically applied to extensive burns. However, leukocytopenia is also occasionally observed
 in the use of other drugs, and there is the opinion that it should not be regarded as a side-effect
 specific to silver sulfadiazine.[163] There is also the opinion that the use of silver sulfadiazine
 should be avoided as much as possible for wounds showing active proliferation of epidermal
 keratinized cells such as donor site wounds and SDB, because the cytotoxicity of silver delays
 wound healing.[161]

References

Pegg SP, Ramsay K, Meldrum L, Laundy M. Clinical comparison of maphenide and silver sulfadiazine. Scand J Plast Reconstr Surg 1979; **13**: 95–101. (evidence level III).

```
CrossRef | PubMed | CAS | Web of Science® Times Cited: 13
```

- Ohyama K. Clinical comparison of silver sulfadiazine cream (T-107) and Gentamycin ointment in burn wound. *J J Burn Inj* 1980; **6**: 87–96. (evidence level III).
- Ono I, Ohura T, Manabe M *et al* . Topical therapy on burned patients comparison with silver sulfadiazine cream and other ointment. *J J Burn Inj* 1982; **8**: 3–12. (evidence level VI).
- 158 Yura J, Andoh M, Ishikawa S. Clinical evaluation of silver sulfadiazine (T107) in decubitus, chronic skin ulcers comparison with placebo by a double blind method. *Chemotherapy* 1984; **32**: 208–222.
- Heggers JP, Robson MC. The emergence of silver sulphadiazine-resistant *Pseudomonas aeruginosa*. Burns 1979; 5: 184–187.

```
CrossRef | Web of Science® Times Cited: 18
```

160 Li XZ, Nikaido H, Williams KE. Silver-resistant mutants of Escherichia coli display active efflux of Ag+ and are deficient in Silver Sulfadiazine. J Bacteriol 1997; 179: 6127–6132. (evidence level VI).

```
PubMed | Web of Science® Times Cited: 121
```

161 Atiyeh BS, Costagliola M, Hayek SN, Dibo SA. Effect of silver on burn wound infection control and healing review of the literature. *Burns* 2007; **33**: 139–148. (evidence level V).

```
CrossRef | PubMed | Web of Science® Times Cited: 404
```

Hoffmann S. Silver sulfadiadine: an antibacterial agent for topical use in burns. Scand J Plast Reconstr Surg 1984; 18: 119–126. (evidence level V). 163 Frederick W. The side effect of silver sulphadiazine. *J Burn Care Res* 2009; **30**: 464–470. (evidence level V).

CrossRef | PubMed | Web of Science® Times Cited: 38

CQ23: What Topical Agents should be used to Remove Necrotic Tissue from Small Third-Degree Burns?

Remarks on recommendation: As topical agents aimed to remove necrotic tissue from small third-degree burns, bromelain, cadexomer iodine, dextranomer and silver sulfadiazine are recommended as an option. Recommendation level: C1.

Comments:

- Concerning bromelain, there is one RCT evaluating its debriding effect on third-degree burns,
 [164] and the evidence level is II. However, as its effect was similar to those of other drugs and attenuated in dried wounds, the recommendation level was set at C1.
- Regarding dextranomer and cadexomer iodine, there are non-randomized comparative trials in
 patients with various skin ulcers including ulcers due to burns,[165, 166] and a case series
 study,[167] and the evidence level is III and V, respectively. In these reports, the response rate
 with the debriding effect included was high, but burns were not focused, and the number of
 patients was small. Both of these drugs are indicated for wounds rich in effusion, and caution is
 needed in their use for wounds deficient in effusion, because they may cause drying of the
 wound surface and delay wound healing.[168]
- For silver sulfadiazine, there is no report evaluating the debriding effect except for expert
 opinions about pressure ulcers,[166, 167] and the evidence level is VI. However, there has
 been rich experience in the clinical use of silver sulfadiazine, and it is also expected to have a
 preventive effect against infection (see CQ22).
- As for the ointment containing calf blood extract, there is one RCT indicating its usefulness for the treatment of third-degree burns,[169] and the evidence level is II. However, as this preparation was manufactured and approved in 1963 and has recently been used rarely, it was excluded from the evaluation for recommendation.
- Regarding the debriding effect of fradiomycin sulfate/crystalline trypsin, there are only expert opinions, and the evidence level is VI. As this preparation was also manufactured and approved in 1962 and has recently been used rarely, it was excluded from the evaluation for recommendation.
- Anzai et al. performed an RCT using bromelain and placebo prepared by mixing inactivated bromelain with the same base in 33 patients with deep second-degree or third-degree burns (7–10 days after injury).[164] They separated the wound of each patient into halves, applied the true drug or placebo topically to each half, and compared the degree of lysis of necrotic tissue, hemorrhage and pain, reporting that the true drug showed a significantly greater debriding effect in third-degree burns. There are many other case reports indicating the usefulness of bromelain. Ogawa et al. evaluated the debriding effect of bromelain in ulcer patients including 28 with ulcers due to burns and reported that a response rate of 86% was obtained in ulcers due to burns.[170] In using bromelain, attention to pain, which occurs

frequently, is necessary. Also, as highly water-absorbing macrogol is used as the base, its debriding effect is attenuated when effusion or the moisture of the wound surface is reduced. [168]

Silver sulfadiazine is considered to produce a wound surface cleaning effect as its emulsion
base with high water content causes softening and lysis of necrotic tissue due to its permeation
characteristics.[171] However, there are a few points that need attention in its use: it may
cause edema on the wound surface in wounds rich in effusion, its effect is attenuated when it is
used with povidone iodine, and its concomitant use with other drugs, particularly topical
cutaneous enzyme preparations, should be avoided.[165]

References

- Anzai T, Tomizawa T, Muramatsu T et al. Effect of Bromelain ointment in necrotic tissue. Jpn J Plast Surg 1972; 15: 456–462. (evidence level II).
- 165 Asada Y, Higashida T, Odaka T *et al* . Clinical efficacy of NI-009 in various cutaneous ulcers (phase III study). *J Clin Therap Med* 1990; **6**: 101–117. (evidence level V).
- Japanese Society of Pressure Ulcers "Pressure Ulcer Prevention and Control Guideline" Development Committee. *Removal of Necrotic Tissue for N to n.* 2009; 107–113. (evidence level VI).
- 167 Tachibana T, Miyachi Y. Conservative treatment by drug. Jpn J Plast Surg 2003; 46: 459–470. (evidence level II).
- 168 Study Group for SK-P-9701. Clinical study results of SK-P-9701 (Dextranomer paste) in various cutaneous ulcers. *J Clin Therap Med*, 2000; **16**: 1419–1437. (evidence level III).
- 169 Suetsugu T, Yashiro A, Yamasaki R *et al* . Clinical efficacy of Solcoseryl ointment in burn. *The Clinical Report* 1975; **9**: 2433–2452. (evidence level II).
- 170 Ogawa Y, Kurooka S, Katakami S *et al*. The evaluation of the effect of Bromelain ointment on the debridement of eschar of burn, decubitus and various wound. *J New Rem Clin* 1999; **48**: 69–77. (evidence level V).
- 171 Kukita A, Ohura T, Aoki T *et al* . Clinical evaluation of NI-009 on various cutaneous ulcers comparative study with Elase®-C ointment. *J Clin Therap Med* 1990; **6**: 817–848.

CQ24: Are Topical Steroid Preparations Useful for the Treatment of First-Degree Burns and SDB?

Remarks on recommendation: The use of topical steroid preparations is recommended as an option in expectation of their anti-inflammatory effects.

Recommendation level: C1.

Comments:

 There are only expert opinions concerning the usefulness of topical steroid preparations for the treatment of burns,[172-174] and the evidence level is VI. On the other hand, there are three RCT (including double-blind trials) suggesting that topical steroid preparations showed no antiinflammatory effect on the skin that has sustained physical damage including burn.[175-177] However, we noted that expert opinions suggesting the usefulness of topical steroid preparations for the treatment of first- or second-degree burns are predominant and that topical steroid preparations have been used widely for the treatment of burns in Japan.

- Yamanaka et al. recommend the use of a very strong or even stronger topical steroid preparation for first-degree burns for a short period from immediately after injury to rapidly repair damaged tissue and control inflammation.[172] Takuma et al. recommend the use of topical steroid preparations for areas of first-degree burns with marked reddening/pain.[173] Hitoshi et al. reported that the use of topical steroid preparation should be restricted to the first 2 days after injury in first- or second-degree burns, because they delay wound healing and suppress epithelialization while they are very effective for suppressing reddening and edema and mitigating pain in the acute period.[174]
- Pederson et al. however, performed a double-blind RCT by artificially creating first-degree burns or SDB in healthy volunteers and compared the anti-inflammatory effect between clobetasol propionate and placebo according to the severity of pain and erythema and reported no significant difference between the two groups.[175] Faurschou et al.[176] examined the effects of an topical steroid preparation on sun burn (ultraviolet B irradiation) in 20 healthy volunteers but observed no clinical usefulness when it was applied after irradiation.
- Also, Matsumura et al. carried out a double-blind trial concerning the effects of betamethasone valerate/gentamycin sulfate on fresh second-degree burns using gentamycin sulfate as a control drug.[177] According to this study, no difference was observed in the alleviation of swelling or pain between the two groups, and betamethasone valerate/gentamycin sulfate promoted epithelialization until 2 days from the beginning of their use but suppressed it after 4 days or more. They also treated one group by using gentamycin sulfate after topical application of betamethasone valerate/gentamycin sulfate for 3 days but another group by using gentamycin sulfate alone from the beginning and observed no significant difference in the comprehensive evaluation of objective findings, number of days until completion of epithelialization or overall pharmacological effect.

References

- 172 Yamanaka K, Mizutani H. Princple of initial treatment in burn wound. *MB Derma* 2008; **146**: 16–20. (evidence level VI).
- 173 Taguma K, Sasaki J. 9 Treatment and topical therapy, BURN index of initial treatment and topical therapy antibacterial chemotherapy in burn. *Med J*, 2008; 129–156. (evidence level VI).
- 174 Todoroki T, Okano Y, Moriuchi H. From daily inquiry adrenal corticosteroid. *J Pract Pharm* 1988; **39**: 1085–1093. (evidence level VI).
- 175 Pedersen JL, Moiniche S, Kehlet H. Topical glucocorticoid has no antinociceptive or anti-inflammatory effect in thermal injury. *Br J Anaesth* 1994; **72**: 379–382.
 - CrossRef | PubMed | CAS | Web of Science® Times Cited: 18
- 176 Faurschou A, Wulf HC. Topical corticosteroids in the treatment of acute sunburn a randomized, double-blind clinical trial. *Arch Dermatol* 2008; **144**: 620–624.
 - CrossRef | PubMed | Web of Science® Times Cited: 5

177 Muramatsu T, Sekiguchi T. The clinical use of corticosteroid ointment for acute second degree burn. Jpn J Plast Surg 1972; 15: 318.

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- ⑤58巻10号 P1529-1532、2016

ジアフェニルスルホンが有効であった水疱性類天疱瘡の1例

森岡理恵子* 堀内 賢二* 中山 宏文**

要約

水疱性類天疱瘡の治療は、ステロイド全身投与が中心である。しかし、ステロイドの長期投与により感染症・高血圧・糖尿病・胃潰瘍・骨粗鬆症による易骨折などの副作用が生じることがある。今回われわれは、糖尿病、脂質異常症を合併した水疱性類天疱瘡にジアフェニルスルホン単独で有効であった症例を経験した。ジアフェニルスルホンは溶血性貧血、メトヘモグロビン血症、薬疹、DDS症候群などさまざまな副作用があるが、それらに注意すればステロイド内服が難しい症例で治療の選択肢のひとつになり得ると考える。

Key words: 水疱性類天疱瘡, ジアフェニルスルホン

I. はじめに

水疱性類天疱瘡の治療はステロイド全身投与が中心である。しかし、ステロイド投与による感染症・高血圧・糖尿病・胃潰瘍・骨粗鬆症などの副作用のため同剤が使用しにくい場合もある¹⁾。今回われわれは、糖尿病、脂質異常症を合併した水疱性類天疱瘡にジアフェニルスルホンが有効であった症例を経験したので報告する。

Ⅱ. 症 例

患 者 71歳,女性

主 訴 躯幹・四肢の紅斑, びらん

家族歴 特記事項なし。

既往歷 糖尿病, 脂質異常症

現病歴 初診1年前より躯幹・四肢に痒みを 伴う紅斑,水疱が出現。市販の外用剤を使用し たが改善しなかった。初診1カ月前より口内炎 が出現。近医皮膚科を受診し,自己免疫性水疱 症を疑われ当院を紹介受診した。

初診時現症 上顎の歯肉部,軟口蓋に1cm 大までのびらんが1つずつみられた。右前胸部 に3cm大の紅斑,びらんがあり,頸部・躯幹・ 四肢に2cm大までの紅斑,びらん,色素沈着 が散在していた(図1-a,b)。

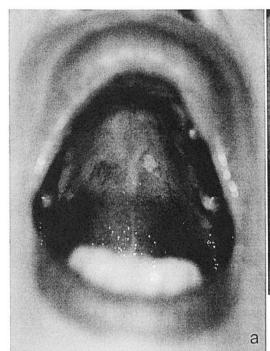
臨床検査所見 <u>K 5.6 mEq/l</u> の増加以外は血 算, 血液生化学に異常なし。<u>抗 BP180 抗体 79.3</u> U/ml と増加。抗 Dsg1 抗体, 抗 Dsg3 抗体陰性。

病理組織学的所見 右前胸部:表皮基底層に 液状変性、表皮真皮間に裂隙があり、有棘層に 軽度の海綿状態がみられた。また、真皮表層お よび中層の血管周囲および間質にリンパ球が中 等度浸潤しており、好酸球も散在していた(図2)。 蛍光抗体直接法陰性。

治療および経過(図3) 臨床所見,検査所見 より水疱性類天疱瘡と診断し,ミノサイクリン

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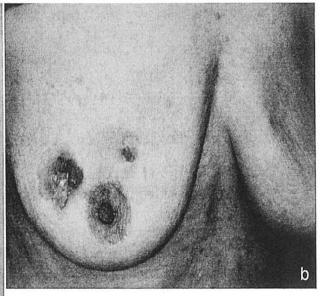


図1 初診時臨床像 a, b:口腔内にびらんあり。躯幹・四肢に紅斑, びらん が散在していた。

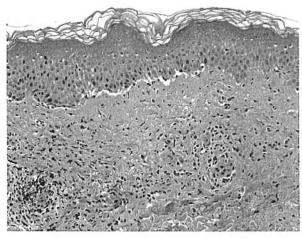


図2 病理組織像:表皮基底層の液状変性と表皮 真皮間の裂隙があり,真皮上層の血管周囲 および間質にリンパ球が中等度浸潤,好酸 球が散在していた。

塩酸塩(ミノマイシン®)200 mg/日内服を開始。内服開始後胃痛が出現したためレバミピド(ムコスタ®)200 mg/日内服を追加。皮疹が改善しないため、初診1カ月後よりジアフェニルスルホン(レクチゾール®)50 mg/日内服を追加。その1カ月後に口腔内病変以外の皮疹はほぼ消失し、抗 BP180 抗体も低下した。初診3カ月後に皮膚の色素沈着が出現したため、ミノサ

イクリン塩酸塩の内服を中止した。その後も口腔内病変は一進一退であったが、それ以外の皮疹は出現せず、抗 BP180 抗体は低下を続け、経過良好である。

Ⅲ.考察

自験例は口腔内病変もあったため瘢痕性類天 疱瘡も鑑別にあがるが、躯幹・四肢に紅斑やび らんが散在していたことから水疱性類天疱瘡と 診断した。蛍光抗体直接法は陰性であったが、 水疱性類天疱瘡における蛍光抗体直接法の陰性 率は3.3%²⁾、6.4%³⁾との報告がある。皮膚生検 をする際、水疱部では表皮基底膜部が損傷を受 け、蛍光抗体直接法が偽陰性になる場合がある¹⁾。自験例でも病理組織所見で表皮真皮間に 裂隙がみられ、基底膜部が損傷されたため蛍光 抗体直接法が偽陰性となった可能性がある。

水疱性類天疱瘡の治療はステロイド全身投与が中心である。しかし、ステロイドの長期投与により感染症・高血圧・糖尿病・胃潰瘍・骨粗 鬆症による易骨折などの副作用が生じることがある¹⁾。特に高齢者では全身の諸臓器の機能低

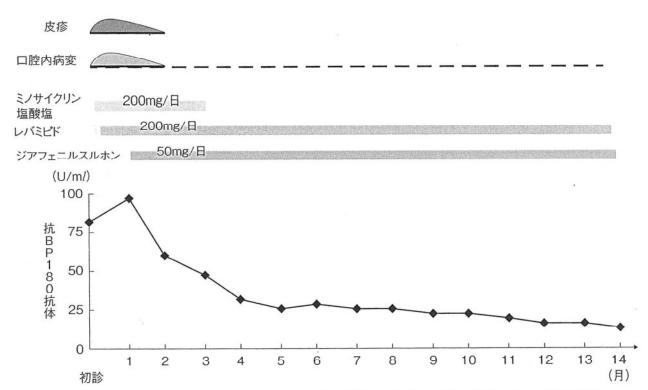


図3 治療および経過図: ジアフェニルスルホン内服開始1カ月後に口腔内病変以外の皮疹は消失し, 抗 BP180 抗体は低下を続けた。

下があるため、極力副作用が生じないよう有効 で安全な治療が望まれる。水疱性類天疱瘡の非 ステロイド療法には、テトラサイクリン塩酸 塩・ニコチン酸アミド併用療法, ミノサイクリ ン塩酸塩・ニコチン酸アミド併用療法、マクロ ライド系抗菌薬, ジアフェニルスルホンがあ る⁴⁾。ミノサイクリン塩酸塩・ニコチン酸アミ ド併用療法はテトラサイクリン塩酸塩・ニコチ ン酸アミド併用療法より有効性が高いとする報 告5)もあるが、10%に薬剤性間質性肺炎を認め た報告⁶⁾⁷⁾や、これにより死亡した報告⁸⁾もある ことから注意が必要である。マクロライド系抗 菌薬はエリスロマイシン⁹⁾とロキシスロマイシ v^{10} が有効であった報告があり、テトラサイク リン塩酸塩やミノサイクリン塩酸塩が使用でき ない症例や薬疹歴のある症例が適応となる。

自験例では、まずミノサイクリン塩酸塩内服を行ったが皮疹の改善はみられず、抗 BP180 抗体も低下しなかった。その後、糖尿病、脂質異常症で治療中であり、皮疹が軽度であったため

ステロイド内服治療は選択せず,ジアフェニルスルホン内服を行った。経過中皮膚の色素沈着が出現し、ミノサイクリン塩酸塩の副作用と考え同剤を中止した。ミノサイクリン塩酸塩の内服中止後も皮疹の再燃はなく,抗 BP180 抗体が低下傾向であることからジアフェニルスルホンは有効と考える。

ジアフェニルスルホンはダプソンにより発見された化合物で、抗菌作用が注目され開発された。近年では水疱症、血管炎、慢性円板状エリテマトーデスなどに有効とされている¹¹⁾。作用機序は好中球のインテグリンを介した走化性因子依存性接着能の抑制、シグナル伝達、呼吸活性化、分泌などの機能抑制などがある¹²⁾¹³⁾。副作用としては溶血性貧血、メトヘモグロビン血症、肝炎などがあり、発熱、紅斑丘疹型・剥脱性皮膚型の皮疹、肝機能障害、リンパ節腫脹などを示す DDS 症候群にも注意が必要である¹⁴⁾¹⁵⁾。メトヘモグロビン血症、溶血性貧血、DDS 症候群は用量依存性の副作用であるた

表 1 水疱性類天疱瘡をジアフェニルスルホン単独で治療した症例

報告者/報告年	年齢/性別	粘膜疹	抗 BP180 抗体 初診時(index)	治療反応性
加藤ら ¹⁷⁾ /1983	3/女	あり	記載なし	25 mg/日で著効, 4カ月で中止
藤岡ら ¹⁸⁾ /1985	3/男	あり	記載なし	25 mg/日で有効
Tamura ら ¹⁹⁾ /2005	14/女	なし	60.7	75 mg/日で著効,2カ月で中止

め¹¹⁾,少量から開始し血液検査をしながら徐々に増量していくことが必要である。

水疱性類天疱瘡に対するジアフェニルスルホ ンの治療では、成人で1日50~100 mgで使用 されることが多く、限局性水疱性類天疱瘡や小 水疱性類天疱瘡といった亜型の症例に有効であ ることが知られている1)。また、事前にステロ イドが投与されていた水疱性類天疱瘡の症例に 対して、ジアフェニルスルホンを併用すること でステロイドが減量または中止でき, 再発を抑 制できたという報告¹⁶⁾がある。しかし、本邦で 水疱性類天疱瘡にジアフェニルスルホン単独で 治療された報告は少ない (表 1)17)~19)。これら はすべて小児例であり、ステロイドには成長遅 延などのさまざまな副作用があるため、小児で はステロイド以外の治療が選択されたものと思 われる。自験例は高齢者であったが、ジアフェ ニルスルホン単独で有効であった。ジアフェニ ルスルホンはさまざまな副作用に注意すれば高 齢者にも使用可能であり、ステロイド内服が難 しい症例で治療の選択肢のひとつになり得ると 考える。

本論文の要旨は日皮学会第137回広島地方会にて報告した。 (2015年12月16日受理)

文 献

- 1) 橋本 隆:最新皮膚科学大系,6巻,1版,玉置邦彦 ほか編,中山書店,2002,98-103頁
- 2) 松尾淑江ほか:臨皮, 68:915-919, 2014
- 3) 金井塚生世ほか: 臨皮, 47:145-148, 1993
- 4) 名嘉眞武国ほか: Derma., 190:94-99, 2012
- 5) 阿部俊文:日皮会誌, 111:2093-2099, 2001
- 6) 橋本 隆:皮膚臨床, 37:1063-1066, 1995
- 7) Kawahara Y et al: Eur J Dermatol, 6: 427-429, 1996
- 8) 原 弘之ほか:日皮会誌, 107:1168, 1997
- 9) FOX BJ et al: J Am Acad Dermatol, 7:504-510, 1982
- 10) 小野文武,名嘉眞武国:医のあゆみ,**218**:957-961, 2006
- 11) 川久保洋:皮膚臨床, 49:1239-1242, 2007
- 12) Booth SA et al: J Invest Dermatol, 98:135-140, 1992
- 13) Debol SM et al : I Leukoc Biol. 62 : 827-836, 1997
- 14) 加倉井真樹ほか: Derma., 137:61-65, 2008
- 15) 荒川晶子ほか:西日皮, 70:377-380, 2008
- 16) Schmidt E et al: Cutis, 76: 205-209, 2005
- 17) 加藤直子ほか:皮膚臨床, 25:1263-1266, 1983
- 18) 藤岡 彰ほか: 臨皮, 39:1023-1028, 1985
- 19) Tamura A et al : I Dermatol, 32: 809-812, 2005