Hydrofluoric Acid Dermal Burns

An Assessment of Treatment Efficacy Using an Experimental Pig Model

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There currently exist various opinions concerning the best therapy for managing hydrogen fluoride (HF) dermal burns. Previously reported animal studies designed to evaluate the efficacy of certain therapies are not completely convincing. Studies initially were conducted to develop a reliable animal model for assessing efficacy of treatment. Evaluation of several animal species, dosing regimens (HF concentrations, exposure periods), and application techniques showed that the most consistent and reproducible dermal lesions were produced with 38% HF applied to the skin of anesthetized pigs for exposures of 9, 12, or 15 minutes using Hill Top Chamber® patches. Using this model, the efficacy of six clinically applicable treatments was assessed by subjectively scoring and statistically analyzing photographic and histopathological data obtained from treated and untreated control lesions. Photographic data analysis ranked treatments with respect to effectiveness as follows: iced Zephiran and 10% calcium acetate soaks—highly effective; 2.5% calcium gluconate gel, 5.0% calcium gluconate injection and iced Hyamine soaks—effective; 10% calcium gluconate injection—ineffective. Histopathological data analysis showed the topical treatments (2.5% calcium gluconate gel, iced Hyamine, or iced Zephiran soaks) to be most effective in reducing superficial epidermal damage, and the 5% calcium gluconate injection or 10% calcium acetate soaks to be beneficial to deeper tissues of the dermis and subdermis. Injection of 10% calcium gluconate was ineffective. This study suggests that the anesthetized pig model has good applicability for assessing efficacy of HF dermal burn therapies. In addition, it indicates that further experimentation with 10% calcium acetate soaks is warranted.

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Hydrogen fluoride (HF), one of the strongest inorganic acids, is capable of causing serious and progressively destructive skin burns in humans. HF produces injury to the skin that is directly related to the acid's concentration, its release of free hydrogen ions, and its duration of contact. In addition, fluoride ions penetrate the epidermis, dermis, and subcutaneous tissues causing liquefaction necrosis.[1] It is the effect of fluoride ions that makes HF injuries very difficult to treat. The injury is thought to be caused by the binding of fluoride ions with tissue calcium and magnesium cations to form insoluble salts, which are believed to interfere with cellular metabolism, inducing cellular death and necrosis.[2,3]

Initial clinical treatment of HF burns is similar to that of other chemical burns. The affected skin is immediately washed with copious amounts of water while removing contaminated clothing to prevent further contact with the acid. After these procedures, specialized medical treatment must be administered to prevent serious injury, disability, or even death. The therapies currently used by clinicians to manage HF dermal burns are diversified but have a common goal: to bind the fluoride ion and/or alter its reactivity with tissue to prevent deep-tissue destruction and systemic absorption. When blistering occurs, it is necessary to drain and debride affected areas before continuing with treatment. Skin grafting and/or excision of damaged tissues may be necessary when patients are inadequately treated.

Most literature regarding treatment of HF dermal burns is based on anecdotal clinical experiences. Recommendations made for treatment vary,

and there remains a lack of agreement among clinicians as to which treatment is the most effective for management of HF dermal burns. There are proponents of calcium gluconate infiltration of the HF affected area,[4–6] especially for treatment of the most severe fluoride burns.[5,6] Others have reported that aqueous or alcohol soaks with high-molecular-weight quaternary ammonium compounds, such as Hyamine® 1622 (benzethonium chloride) or Zephiran® (benzalkonium chloride), are effective therapies when applied for at least 4 hours.[7–10] The use of ice-cold saturated magnesium sulfate soaks also has been suggested.[10] Topical treatment with a 2.5% Ca gluconate gel over a period of several days has been reported as effective.[11,12] More recently, intra-arterial calcium infusion methods have been used and reported to successfully aid healing of digits exposed to HF.[13,14]

The treatment chosen for such serious chemical injury should be the best possible and should have a sound experimental basis for its effectiveness. Several investigations comparing effectiveness of various treatments[5,15–19] using rats or guinea pigs have produced, in some cases, conflicting results, which create uncertainty as to which treatment may be most effective.

In designing the present study, the most common current methods of treating HF burns were selected: iced quaternary amine soaks, topical calcium gluconate gel, and the injections of 5% and 10% calcium gluconate. In addition, because of recent personal communication between the authors and a physician from Industrias Quimicas de Mexico, Mexico,[20] calcium acetate also was tested.

The anesthetized pig model used in the present investigation was developed from extensive preliminary research[21] designed to identify a reliable animal model for inducing reproducible HF dermal burns that would be suitable for assessing the efficacy of treatments. Those studies evaluated the effects of various concentrations of aqueous HF at several exposure times in three species (rat, rabbit, and pig). The best reproducibility for inducing characteristic HF dermal burns was achieved with the pig using aqueous 38% HF at contact times of 9, 12, and 15 minutes. The pig was also considered a good model because it provided a large experimental surface area and its skin permeability properties[22,23] were most similar to those of the human. The research also evaluated the effect that various epicutaneous patch systems would have on reproducing consistent reactions on clipped and depilated pig skin. The most consistent reactions were produced on depilated skin using 25 mm Hill Top Chambers.®

Methods

Chemicals

Aqueous HF (38%) was supplied by Allied-Signal Inc. (Geismar, La). A commerical preparation of calcium gluconate gel (2.5% wt/vol; H-F Antidote Gel) was obtained from Industrial Pharmaceutical Service Ltd (Altrincham, United Kingdom). Calcium gluconate for injection (10% wt/vol) was obtained from Parke-Davis, Division of Warner-Lambert Co (Morris Plains, NJ). Zephiran® chloride (benzalkonium chloride concentrate, 17% wt/vol) was obtained from Winthrop-Breon Laboratories (New York, NY) and formulated at WIL Research Laboratories as a 1:750 dilution in sterile water (USP). Hyamine® 1622 (benzethonium chloride) was purchased from Lonza Inc (Fairlawn, NJ) and formulated at WIL Research Laboratories as a 1:500 dilution in sterile water. Calcium acetate was purchased from Fisher Scientific Co (Fairlawn, NJ) and formulated at WIL Research Laboratories Inc. as a 1:10 dilution in sterile water.

Animals

Twenty-four male adolescent white pigs, weighing 7.6 to 9.9 kg, were purchased from Oberholtzer Farms (Ashland, Ohio) and quarantined for at least 7 days. Animals were housed individually in stainless steel flush cages with grate bottoms in an environmentally controlled room having a 12-hour light/dark photoperiod cycle. Air handling units provided approximately 10 fresh air changes per hour. Buckeye Porkmaker® pig food was provided on schedule. Water was available ad libitum.

Animal Preparation

Approximately 24 hours before HF exposure, the hair on the back of each animal was clipped with an Oster electric small animal clipper equipped with a No. 40 (surgical) blade. The remaining hair stubble on the dorsal surface was removed with a depilatory (Neet® Lotion Hair Remover, Whitehall Laboratories, Inc, NY).

Just before HF exposure, each pig was anesthetized to allow dosing and treatment to be conducted in a safe, precise, controlled, and humane manner.[24] Atropine sulfate (0.04 mg/kg) and fentanyl-droperidol [INNOVAR VET®] (68.5 μL/kg) were administered by intramuscular injection (IM). With onset of sedation (10 to 15 minutes), ketamine HCl was administered yIM at a dose level of 11 mg/kg to induce anesthesia. Surgical anesthesia was attained in 5 to 10 minutes and lasted approximately 30 to 45 minutes. Maintenance of surgical anesthesia was achieved with supplemental IM administration of ketamine and/or fentanyl-droperidol at dose levels ranging between 2.2 to 6.6 mg/kg and 17 to 41 μL/kg, respectively.

HF Exposure

All animals were exposed to HF similarly. Six dermal sites (three on each side of and parallel to the spinal column) were each topically exposed to a volume of 0.4 mL of 38% wt/vol HF contained under a 25 mm Hill Top Chamber® patch. Two patches at a time (one on each side of the back) were applied at 3-minute intervals and kept in place for a period of either 9, 12, or 15 minutes. This application procedure allowed the removal of all patches from each animal at the same time.

Treatment

Immediately after exposure, all six dermal sites on each animal were

rinsed with running, temperature controlled (21.5 to 24°C) tap water for exactly 1.5 minutes at a rate of approximately 7.2 to 9.8 L/min. Uniform rinsing of all sites was achieved by administering the water with a hose fitted with a spray head. Treatment of HF-exposed sites was initiated 2 minutes after completion of the water rinse. Each treatment was administered to a group of four pigs. In each treatment group, dermal lesions on the right side of two pigs received treatment, those on the left side remained untreated (controls), and dermal lesions on the left side of the other two pigs received treatment while those on the right side served as untreated controls. These treatments were evaluated:

Calcium Gluconate Gel. The gel was gently massaged over the HF-exposed dermal sites for 1 minute, every 15 minutes, for 4 hours. A double layer of surgical gloves was used to avoid contact with any residual HF.

Iced Aqueous Zephiran® Soaks. Chilled Zephiran solution, maintained at a temperature of approximately 35°F in a water bath containing ice cubes, was applied to compresses (consisting of three layers of 2 × 2 inch sterile gauze patches) covering the HF-exposed dermal sites. The compresses remained in place for 3 hours, and fresh iced Zephiran solution was administered to them every 3 minutes using a large volume syringe.

Iced Aqueous Hyamine® 1622 Soaks. Chilled Hyamine solution, maintained at a temperature of approximately 35°F in a water bath containing ice cubes, was applied to compresses covering the HF-exposed dermal sites every 3 minutes for 3 hours, as described for the Zephiran soaks.

Calcium Acetate Soaks. Room temperature calcium acetate solution was applied to compresses covering the HF-exposed dermal sites every 3 minutes for 3 hours, as described for the Zephiran soaks.

5% Calcium Gluconate Injection. Sterile 5% calcium gluconate injection solution was injected beneath, around, and into each HF-exposed dermal site using a 1 cc tuberculin syringe with a No. 30 gauge needle. The volume injected did not exceed 0.5 mL per sq cm of affected skin surface.

10% Calcium Gluconate Injection. The same procedure described for the 5% calcium gluconate injection was used.

Gross Examination and Photography

Untreated control and treated dermal lesions were observed, described, and photographed 30 minutes; 4 hours; 1, 2, 4, 7, 10, 14, 18, and 21 days after exposure.

Subjective Assessment of Lesions Using Photographs

Using 35 mm slides projected at the same size scale, the appearance (size and severity) of each untreated dermal lesion produced by 38% HF for each specific exposure period (either 9, 12, or 15 minutes) was subjectively and simultaneously compared with each treated dermal lesion on the contralateral side of the same pig by a panel of five investigators. A consensus score for each lesion, indicative of treatment effectiveness, was assigned by the panel to each comparison at intervals of 1, 7, 14, and 21 days after initiation of the treatments. Positive scores were assigned when the treated lesion appeared either slightly (+1), moderately (+2), or substantially (+3) smaller and/or less severe than the untreated control lesion. Negative scores were assigned when the treated lesion appeared either slightly (−1), moderately (−2), or substantially (−3) larger and/or more severe than the untreated control lesion. A score of zero (0) was assigned when the treated site was comparable in appearance to the untreated control site.

Pathology

Immediately after sacrifice on day 21, full-thickness skin (including epidermis, dermis, and subdermis) was excised from the treated and untreated control sites and preserved in 10% neutral buffered formalin. Standard paraffin embedded, hematoxylin/eosin stained sections were examined microscopically by a veterinary pathologist.

The degree of microscopic injury to the skin was evaluated: (a) The pathologist assigned a Severity Grade of 1 to 4 (minimal to severe) to each histopathological finding. Because some histopathological findings were thought to represent a greater degree of injury than others, each was assigned a Weighted Significance Value (Table 1). (b) For each histopathological finding a lesion score (LS) was calculated as: LS = severity grade × weighted significance value. (c) For both the treated and untreated sites of each treatment group (n = 4), a pathological score (PS) was calculated for each layer of skin by summing the lesion scores for all histopathological findings occurring in that layer:

$$PS = LS_1 + LS_2 + \ldots LS_n$$

Where n represents the number of histopathological findings in a layer of skin.

Originally it was assumed that marked differences in the dermal lesions produced by exposure to HF for 9, 12, and 15 minutes would be easily determined histopathologically. However, the variability of histopathological data within the treatment groups was large, and the group sizes were relatively small. Therefore, the PS for the 9, 12, and 15 minutes HF exposure periods were summed to obtain a larger population for statistical analysis. The effectiveness of each treatment was then evaluated: (a) To evaluate the effectiveness of each treatment for each layer of skin, a relative comparative pathology score (CPS) was determined by dividing the PS of the treated skin layer by the PS of the untreated skin layer.

$$\text{CPS} = \frac{\text{PS of the treated skin layer}}{\text{PS of the untreated skin layer}}$$

Therefore, the greater the CPS, the *less* effective the treatment. A relative efficacy score (RES) for each treatment, representing the percentage of improvement of treated versus untreated sites, was then calculated for

TABLE 1
Weighted Significance Values Assigned to Histopathological Findings and Depth of Injury Weight Factors Assigned to the Layers of Skin

Layer of Skin	Histopathological Finding*	Weighted Significance Value†	Depth of Injury Weight Factor‡
Epidermis	Hyperkeratosis	4.0	1
	Inflammation, suppurative	6.0	
Dermis	Inflammation, suppurative	2.4	
	Necrosis, dermis	3.3	2
	Necrosis, connective tissue	4.3	
Subdermis	Acute hemorrhage	1.0	
	Mineralization	2.0	
	Chronic inflammation	2.0	3
	Fibroplasia	2.0	
	Necrosis, adipose tissue	3.0	

* The severity of each histopathological finding was graded by a veterinary pathologist: 1 = minimal, 2 = mild, 3 = moderate, 4 = severe.

† Weighted significance values were assigned to the histopathological findings so that the total value for each layer of skin equaled 10.

‡ Depth of injury weight factors were used for calculation of the total relative comparative pathology score (CPS_{tot}) to emphasize the significance of deeper tissue damage.

each layer of skin:

$$RES = (1.0 - CPS) \times 100.$$

(b) To evaluate the effectiveness of each treatment for the entire skin, PSs for each layer of skin were totaled. These Pathological Scores were then multiplied by a weight factor (1, 2, and 3 for the epidermis, dermis, and subdermis, respectively) because it was believed deeper tissue damage represented more significant injury than did superficial damage (Table 1). A total relative comparative pathology score (CPS_{tot}) was then calculated as follows:

$$CPS_{tot} = \frac{(1 \times PS_e) + (2 \times PS_d) + (3 \times PS_s) \text{ of treated site}}{(1 \times PS_e) + (2 \times PS_d) + (3 \times PS_s) \text{ of untreated site}}$$

where e = epidermis, d = dermis, and s = subdermis. A total relative efficacy score (RES_{tot}) for each treatment, representing the percentage improvement of treated versus untreated sites, was calculated:

$$RES_{tot} = (1.0 - CPS_{tot}) \times 100.$$

Statistical Analysis

Data were analyzed parametrically using ANOVA and Duncan's multiple range test.

Results

Photographic Data

Results of the subjective assessment of lesions using photographs are graphically represented in Figure 1. The topical iced Zephiran soaks appeared to be the most effective treatment for skin exposed to HF for the shortest duration (9 minutes), and the topical 10% calcium acetate soaks appeared to be the most effective treatment for skin exposed to HF for the longest duration (15 minutes). The least effective treatment for skin exposed to HF for longer durations (12 and 15 minutes) was clearly the 10% calcium gluconate injection.

The variability within treatment groups was large, therefore, statistical significance between treatments was not often detected. To obtain a larger population for statistical analyses, data for exposure periods 9, 12, and 15 minutes and data for days 1, 7, 14, and 21 were combined. As presented in Table 2, both the topical iced Zephiran soaks and the 10% calcium acetate soaks were significantly more effective than the other four treatments evaluated. This analysis also showed that the 2.5% calcium gluconate gel, 5% calcium gluconate injection, and iced Hyamine soaks were significantly better than the 10% calcium gluconate injection treatment.

Histopathological Data

Results of the histopathological examination of day 21 skin lesions are

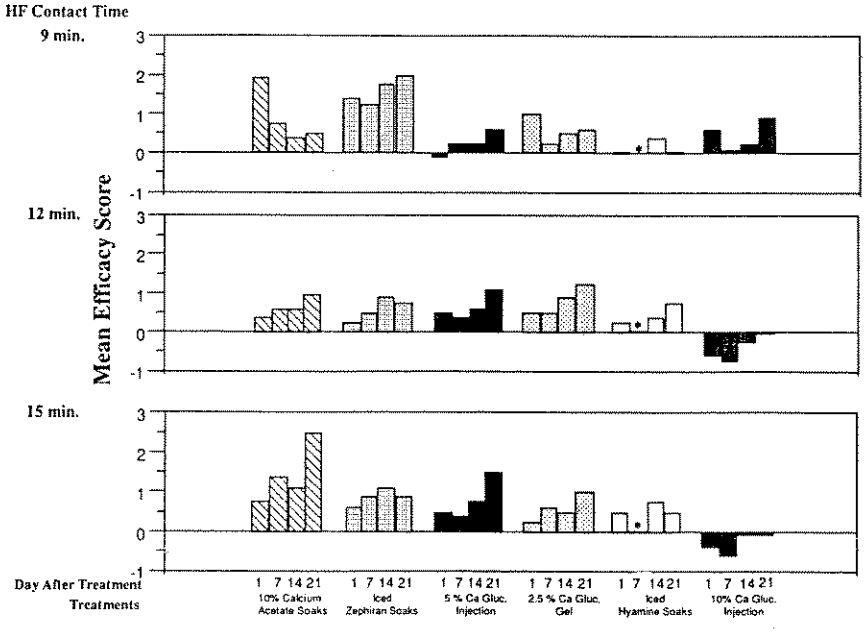

Fig. 1. Mean efficacy scores (n = 4) for hydrogen fluoride-exposed skin receiving various treatments. Dermal lesions were evaluated subjectively by comparing the visual appearance of untreated control sites with that of contralateral treated sites using 35 mm slides projected at the same size scale. Efficacy scores were assigned based on differences in size and severity. Positive scores (+1, +2, or +3) indicated that the treated lesion appeared either slightly, moderately, or substantially smaller and/or less severe than did the untreated control lesion. Higher scores represent greater efficacy. * = photo data were not available.

TABLE 2
Analysis of Subjective Photographic Data: Treatment Ranking Based on Effectiveness to Reduce Dermal Damage after Hydrogen Fluoride Exposure

Treatment*	Mean Efficacy Scores†	Effectiveness
A		
Iced Zephiran soaks	1.02	Highly effective
10% Ca acetate soaks	0.99	
B		
2.5% Ca gluconate gel	0.66	Effective
5% Ca gluconate injection	0.58	
Iced Hyamine soaks	0.39	
C		
10% Ca gluconate injection	−0.07	Ineffective

* Treatment groups A, B, and C were statistically different ($P < .10$).
† N = 12, with the exception of the iced Hyamine soaks, where N = 9.

tate soaks, iced Zephiran soaks, 5% calcium gluconate injection, and calcium gluconate gel to be the most effective treatments in this study. The iced Hyamine soaks were effective to a lesser degree, and the 10% calcium gluconate injection treatment was shown to be ineffective.

Discussion

Findings of this study were compared in two ways: first by the multiple analyses of photographic data on days 1, 7, 14, and 21, and second by analysis of histopathological data after termination of the study on day 21 when the animals were killed and dermographically represented in Figure 2. Photomicrographs of representative lesions are shown in Figure 3. When possible, a distinction was made between dermal necrosis (full thickness necrosis) and dermal connective tissue necrosis (necrosis of individual fibers). In the epidermal layer, iced Zephiran and Hyamine soaks and 2.5% calcium gluconate gel were most effective, with iced Zephiran having the highest efficacy score. A negative epidermal response resulted from injection of both 5 and 10% calcium gluconate and from topical application of the 10% calcium acetate soaks. The 5 and 10% calcium gluconate injections were significantly ($\alpha = 0.1$) less effective than were all other treatments.

All treatments were approximately equally effective in the dermis, with the exception of a negative response to 10% calcium gluconate injection, which was statistically different from all others.

In the subdermis, the 10% calcium acetate soaks, 5% calcium gluconate injection, 2.5% calcium gluconate gel, and iced Zephiran soaks produced similar responses and were significantly ($\alpha = 0.1$) more effective than were either the iced Hyamine soaks or the 10% calcium gluconate injection.

As presented in Figure 4, when the importance of the three layers of skin was considered in relationship to depth of injury by assigning greater weight to deeper injury, statistical analysis showed the 10% calcium ace-

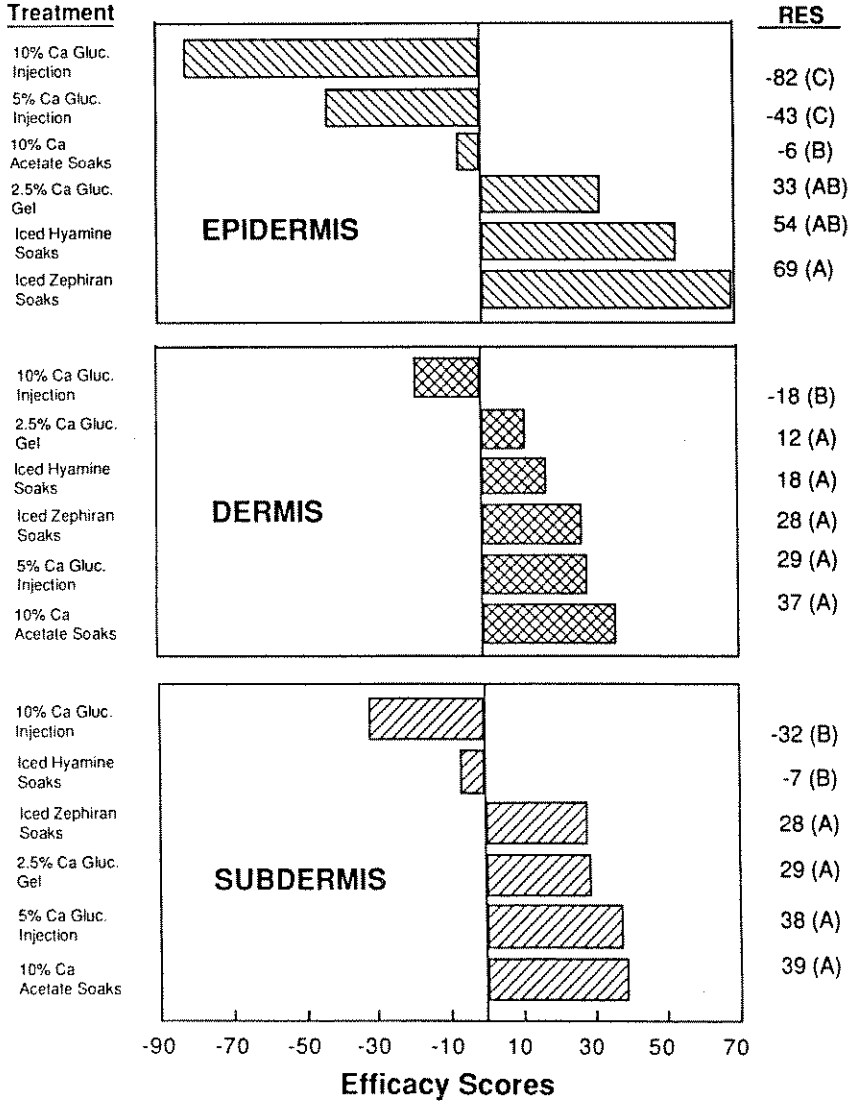

Fig. 2. For each layer of skin evaluated, a relative efficacy score (RES) for each treatment was calculated. The greater the RES, the more efficacious the treatment was considered. The control value is taken as zero. Means with the same letter are not significantly different ($\alpha = 0.1$).

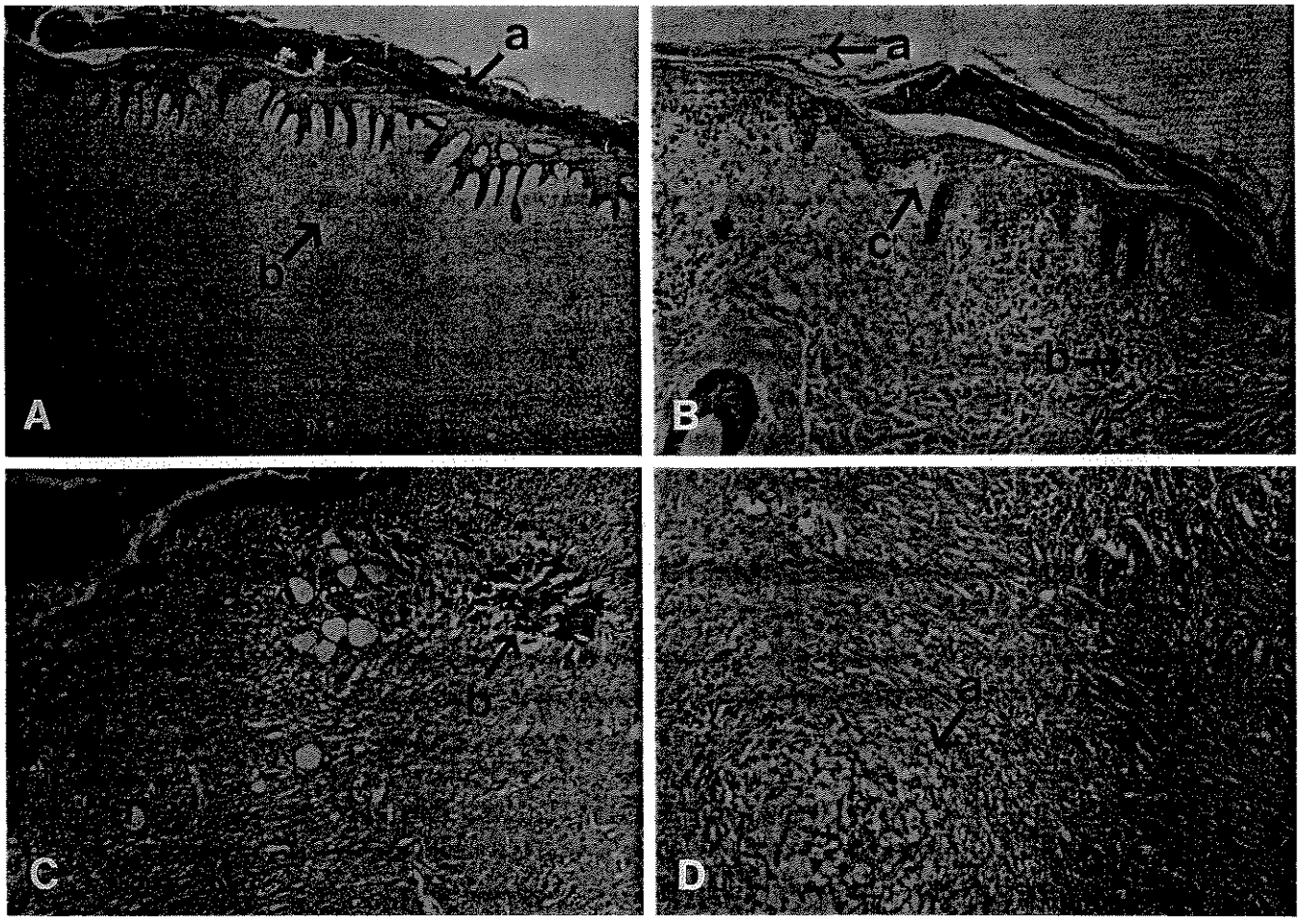

Fig. 3. Representative skin lesions induced by exposure to 38% (wt/vol) aqueous hydrogen fluoride for a 15 min period. A: a = epidermal inflammation, suppurative; b = dermal connective tissue necrosis and fibroplasia, 2.5×. B: a = epidermal hyperkeratosis; b = subdermal chronic inflammation; c = dermal connective tissue necrosis (individual collagen fibers), 10×. C: a = subdermal acute hemorrhage; b = subdermal mineralization, 10×. D: a = subdermal adipose tissue necrosis, 10×.

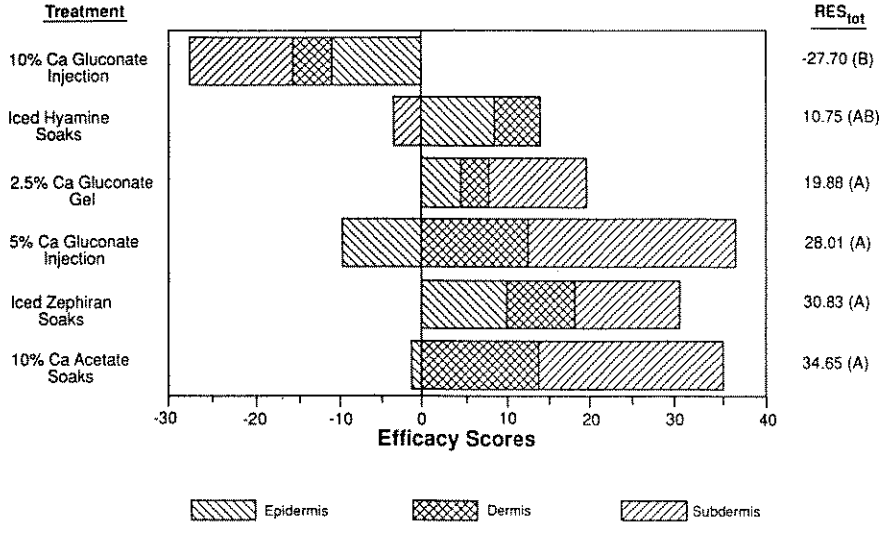

Fig. 4. When the skin was evaluated as a whole, a total relative efficacy score (ie, relative to untreated control − RES_{tot}) was calculated for each treatment. The bars representing the RES_{tot} are subdivided to reflect the contribution of each layer of skin. The greater the RES_{tot}, the more efficacious the treatment was considered. Means with the same letter are not significantly different ($\alpha = 0.1$).

mal tissues were evaluated histopathologically. The histopathological data were further divided to assess treatment efficacy for the three layers of skin (epidermis, dermis, and subdermis). A composite analysis of the three layers was also done. These analyses demonstrated moderate agreement of the results from the photographic data and the histopathologic data.

The results from the photographic data, presented in Figure 1, were assessed separately for the 9-, 12-, and 15-minute HF contact sites. In addition, the analysis was done on days 1, 7, 14, and 21. For the 9-minute HF contact sites, which were perhaps equivalent to mild HF burns in humans, 10% calcium acetate soaks and iced Zephiran soaks were most effective a day after treatment, with calcium gluconate gel being somewhat

less effective. As the 9-minute HF exposure sites progressed to day 21, it was apparent that the most effective form of treatment, based on photographic information, was the iced Zephiran soaks. For the 12-minute HF contact sites, a great deal of variation was observed. However, the 10% calcium gluconate injection showed consistently a negative effect, which was most prominent at 7 days. The 2.5% calcium gluconate gel was the most effective treatment, with 5% injection of calcium gluconate and 10% calcium acetate soaks only slightly less effective. Moderately good results were obtained with both the iced Zephiran and Hyamine soaks. For the deeper burns, those resulting from a 15-minute exposure to HF, the most effective treatment at all the observation periods was 10% calcium acetate with 5% calcium gluconate injection, 2.5% calcium gluconate gel, and iced Zephiran soaks being somewhat less effective. Inasmuch as 10% calcium acetate soaks were more effective for lesions caused by longer exposures to HF, this suggested this treatment was protective of deeper tissues.

The histopathological data, representing the 21-day results, were evaluated by two approaches. The results were initially described by evaluating the three layers of skin separately and then cumulatively. When the skin layers were assessed separately, the topical treatments such as iced Zephiran and Hyamine soaks or 2.5% calcium gluconate gel appeared to be the most effective in reducing epidermal tissue damage. In the dermis, the 10% calcium acetate soaks, 5% calcium gluconate injection, and the iced Zephiran soaks appeared more effective than did the iced Hyamine soaks and 2.5% calcium gluconate gel, although statistical significance ($\alpha = 0.1$) was not demonstrated between any of the five treatments. The most effective treatments for the deepest subdermal layer were 10% calcium acetate soaks, 5% calcium gluconate injection, 2.5% calcium gluconate gel, and iced Zephiran soaks. These results for 10% calcium acetate soaks further support the conclusion from the photographic evaluation that this treatment is effective in the deeper tissues.

It is not surprising that the 5% calcium gluconate injection, which reaches the deeper layers of skin, was ineffective in the epidermis. The loss of efficacy of iced Hyamine soaks in the deeper tissues indicates that Hyamine's primary effect is limited to the upper layer of skin. The iced Zephiran soaks and 2.5% calcium gluconate gel were effective in all three layers of skin, although these were clearly most effective in the epidermis. In each layer of skin, the 10% calcium gluconate injection produced a negative response and thus appeared to be an ineffective treatment.

An evaluation of the overall effect of each treatment indicated that the 10% calcium acetate soak was the most effective treatment. The next most effective treatment was the iced Zephiran soaks. The other methods of treatment, 2.5% calcium gluconate gel and iced Hyamine soaks, were somewhat less effective. The 10% calcium gluconate injection was completely ineffective.

Although it is always difficult to relate results of animal experiments with human experience, it is our belief that the model studied offers a reasonable correlation in most parameters with human burns. Most treatments provided a definite improvement in the healing of the lesions both from the visual and the histopathological aspects. However, 10% calcium gluconate injection appeared to have a negative effect on the pig's skin; indeed, during preliminary probe studies, it was noted that control sites not exposed to HF but injected with 10% calcium gluconate showed some damage to the skin. This possibly accounts for the lack of efficacy of the 10% calcium gluconate injection treatment, at least in the skin of pigs.

As a result of this study, it is our belief that 10% calcium gluconate injection should not be used in treating human burns. However, 5% calcium gluconate appears to be an appropriate concentration for treating dermal HF burns. It is further apparent that the use of quarternary amine soaks, and particularly Zephiran, is an effective method of treating HF dermal burns. Iced Zephiran soaks appear to provide a positive response in all layers of the skin.

The 2.5% calcium gluconate gel, although less effective than the soaks, also appears to be an effective method of treating HF dermal burns. It is particularly more effective for the protection of the epidermis. This may indicate that its most effective role is in treating dilute HF burns or more superficial burns. An interesting finding was noted relative to the 10% calcium acetate soaks that were used at room temperature. This appeared to be a very effective method of treating HF dermal burns. However, because of a lack of clinical experience, further study is needed in this area.

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