

FEATURE

Comparative evaluation of the active eye and skin chemical splash decontamination solutions Diphoterine and Hexafluorine with water and other rinsing solutions: Effects on burn severity and healing

By **Laurence Mathieu, François Burgher, Joël Blomet**

More than thirty million inorganic and organic substances are registered by the Chemical Abstract Service (CAS).¹ About 600,000 are commonly used in industry and several thousand new molecules are created each year as the result of research. More than 25,000 irritant and corrosive chemicals have been identified as having the potential to cause burns.² In Europe, 104,031 commercial chemical substances have been recognized and numbered under the European Inventory of Existing Commercial Chemical Substances

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¹Prevor Laboratory is the manufacturer of Diphoterine and Hexafluorine active eye/skin decontamination solutions.

(EINECS; 100,204 substances) and the European List of Notified Chemical Substances (ELINCS; 3,827 substances) Information Systems. Among these products, 1,230 chemical substances are identified as irritant or corrosive with Xi and C risk sentences, which means that they can respectively induce reversible or non-reversible damage to human tissues.

Chemical burns are the result of a chemical reaction between a corrosive or irritant molecule and one or more biochemical components of the skin or eye.³ The severity of a chemical burn depends mainly on the nature and concentration of the chemical, the chemical energy involved, and the duration of contact. Chemicals which result in "burns" are corrosives and irritants: acids, bases, oxidizing agents, reducing agents, chelating agents, and solvents. The severity of the chemical burn also depends on physical factors such as pressure or temperature, the anatomical body area, the total body surface area (TBSA) involved, and whether the exposed tissues were healthy or previously injured. The effectiveness of emergency decontamination and first aid care influences both the appearance and development of chemical burns and, consequently, the significance of the sequelae.

It is well known that early decontamination of a chemical splash makes it possible to decrease the severity of the

potential burn. Historically, water was the usual decontamination method. This was a great advance in limiting the severity of chemical burn lesions. However, progress was limited by two factors:

- the intervention time (the period of time between exposure and intervention, and thus the length of chemical contact),
- the high concentration of the major corrosive agents.

The very short recommended intervention time period for water decontamination, about 10 s, is difficult to actually carry out at the time of the accident and is thus a source of worsening of the lesions.

The ANSI Z358.1-1998 Emergency Eyewash and Shower Equipment Standard uses the term "flushing fluid" for eyewashes, defined as "potable water, preserved water, preserved buffered saline solution, or other medically acceptable solution manufactured and labeled in accordance with acceptable government regulations" ("potable water" is defined as "water that is suitable for drinking," although no pH is specified). Such "potable water" is, however, commonly used for eye and skin decontamination of chemical splashes because of its ready availability, low cost, and because it is "traditional."

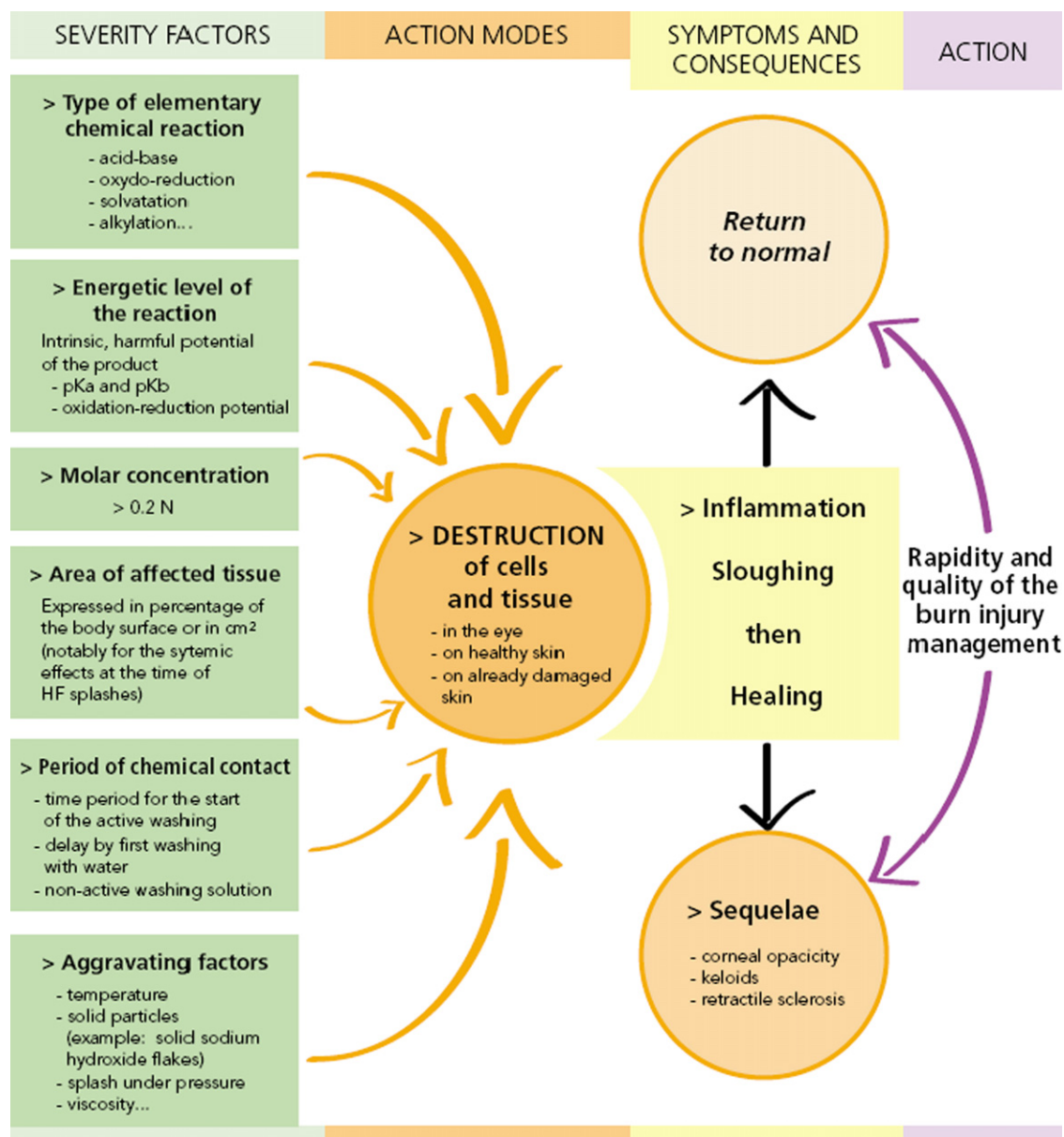


Figure 1. Chemical burns and aggravating factors.

Study and elucidation of the chemical burn mechanism (Figure 1) has led PREVOR Laboratory to create solutions for “active rinsing,” which can be considered as improvements on water rinsing. A water-soluble, amphoteric molecule named Diphoterine, with multiple binding sites capable of reacting with corrosives and irritants and preventing or decreasing their action on the tissues, was added to the effects of mechanical rinsing and passive dilution provided by water decontamination.

This active rinsing solution is also hypertonic, which means it is able to stop corrosives or irritants from penetrating into the tissues by establishing an osmotic gradient. Diphoterine has been registered as a medical device in Europe, Canada, Brazil, and Australia. The purpose of active rinsing with solutions such as Diphoterine is to prevent or decrease the development and sequelae of chemical burns.

As with water, the purpose of using Diphoterine rapidly is to attempt to prevent chemical burns. The more

rapidly Diphoterine is used, the shorter the contact with the chemical will be. The risk of a chemical burn occurring will thus be minimized.

Figure 2 represents the in vitro efficacy of rinsing on the corrosive substance with a simple dosage of 1 mL of 1N sodium hydroxide and hydrochloric acid by adding an increasing volume of rinsing solutions, tap water, or Diphoterine. This simple in vitro experiment illustrates the chemical activity of a decontamination solution on irritants and corrosives, exclusive of

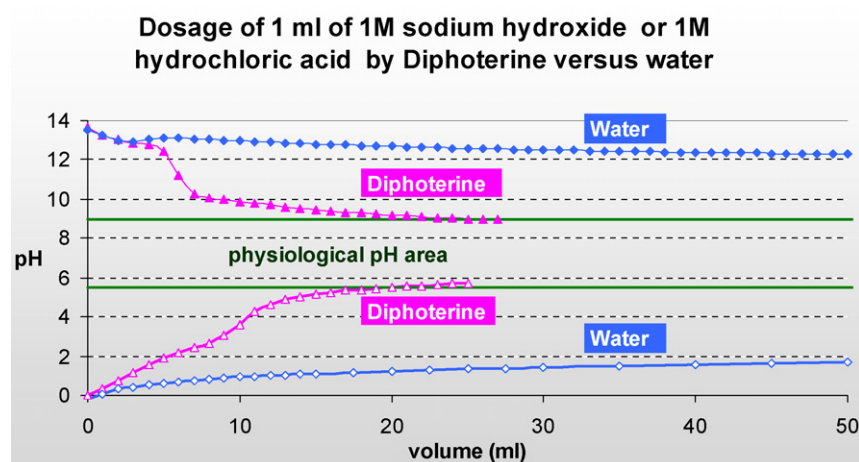


Figure 2. In vitro effectiveness of Diphoterine on sodium hydroxide and hydrochloric acid.

physical effects such as mechanical rinsing or osmotic pressure. With approximately 20 mL, Diphoterine, as an amphoteric compound, has bound both the base and the acid and reacted with it, returning the pH to a physiological state (between 5.5 and 9). Water only dilutes the corrosive agent and the pH remains higher than 12 for the bases and less than 2 for the acids after 50 mL of water have been added.

Diphoterine's effectiveness has been compared to that of water and normal saline solution on an experimental as well as on a clinical level. The analysis of these data concerning chemical decontamination is based on three levels of scientific evidence.

Table 1. Diphoterine toxicological testing

Test	Results	References
Ocular irritation	Non-irritating	Test no. 133/4, in rabbits, Safepharm Laboratories Limited, UK, 1987
In vitro evaluation of the eye irritation potential of a medical device	No cytotoxic or irritating potential in the eye after a short (10 min) or prolonged (24 hr) time of contact	Test no. REL/032/05/IRRO/ELB, on human fibroblast cultures, test Integra, Italy, 2005
Cutaneous irritation	Non-irritating	Test no. 2005-024, in vitro, Dermal Irritation test method, Integra, Italy, 2005
Ocular irritation of a residue of a rinsing of an acid with Diphoterine	Non-irritating	Test no. 6463 TAL, in rabbits, hydrochloric acid, International Center of Toxicology, France, 1990
Ocular irritation of a residue of a rinsing of a base with Diphoterine	Non-irritant	Test no. 6462 TAL, in rabbits, sodium hydroxide, International Center of Toxicology, France, 1990
Oral toxicity	Oral LD ₅₀ > 2,000 mg/kg; non-toxic, no deaths, normal evolution of weight, no abnormality at necropsy	Test no. 6564 TAR, in rats, International Center of Toxicology, France, 1990
Acute dermal toxicity	Acute dermal LD ₅₀ > 2,000 mg/kg; non-toxic, no deaths, no signs of systemic toxicity or dermal irritation, normal evolution of weight, no abnormality at necropsy	Test no. 133/9, in rats, Safepharm Laboratories Limited, UK, 1988
Sensitization	Non-sensitizing	Test no. 20030418ST, Magnusson and Kligman method, in Guinea pigs, OECD 406, CERB, France, 2003
Mutagenesis	Non-mutagenic; negative Ames test	Test no. 29023 MMT, Bacterial reverse mutation Test on <i>Salmonella typhimurium</i> TA 1535, TA 1537, TA98, TA 100, and TA 102, <i>Escherichia coli</i> WP2 uvrA, International Centre of Toxicology, France, 2005
Cytotoxicity	Non-cytotoxic	Test no. REL/003/06/IRRC/ELB, ISO 10993-5 standard, Integra, Italy, 2006
Anti-inflammatory potential	Not anti-inflammatory; no cytotoxic or irritant effects observed on a 3D human epidermis model	Test no. REL/011/06/FUNZ/ELB, MTT in vitro tests + pro-irritation potential IL-1 α , Integra, Italy, 2006

MANAGEMENT OF CHEMICAL SPLASHES: CONVERGENT CLINICAL DATA

In spite of the difficulties of performing studies on first aid in the workplace and the inevitable limitations related to the interpretation of the results, much of the data collected on human subjects provide convergent elements.

In the literature, most of the clinical data coming from industry are case reports or small case series. One of the reasons for this is the fact that it is both ethically and technically difficult to set up a clinical study and to collect data. This also depends on the regulations and the choice of protocols. But perhaps the most important difficulty is the lack of harmonization in collecting detailed and evaluable cases involving chemical agents, decontamination methods, treatment, and outcomes such as sequelae, lost work time, etc., sometimes with no specific classification for accidents due to chemical burns.

Many accounts of Diphoterine use, with or without comparison with water rinsing, have been provided by companies that use this product.⁴ Generally transmitted by occupational medicine physicians, these reports can be criticized individually, either for problems of methodology or interpretation. However, when all of these several hundred cases of Diphoterine use are combined, the coherence of the whole reveals some certainties about its effectiveness:

- no deleterious effects⁵ (Table 1); it does not contain phosphates,
- less pain,
- no after-effects,

Table 2. Effectiveness of different decontamination solutions on splashes due to bases

Rinsing Solution	Diphoterine	Acetic Acid	Water
No secondary care ^a	100% ± 15	0% ± 15	0% ± 15
Simple secondary care	0% ± 15	80% ± 15	25% ± 15
Medical secondary care	0% ± 15	20% ± 15	75% ± 15
Number of days of work loss	0.18% ± 0.4	2.91% ± 4.3	8% ± 8.12

^a Secondary care: care required other than initial decontamination.

Table 3. Evaluation of water vs. Diphoterine rinsing at Atofina (Total Petrochemicals), France

Rinsing	Water	Diphoterine	<i>p</i>
With lost work time	7 (3.4%)	0	<0.05
Without lost work time	198	170	
No need for secondary care	68 (52%)	88 (33%)	<0.05
Need for secondary care	137	82	

- absence of or only a small amount of secondary care (treatment required other than initial decontamination),
- absence of or only a few days of lost work time.

The French National Institute of Research and Safety (INRS) decided to independently verify the effectiveness of the various chemical splash decontamination methods, including Diphoterine. For that purpose, an investigation⁶ was carried out with the help of company physicians in France. Seventy-three companies and more than 60 accidents were evaluated. This study shows Diphoterine's action on a varied sample of chemicals, and indicates that Diphoterine, when used according to the recommended protocol, was always at least as effective as water. The continuation of this investigation⁷ showed that the Diphoterine results, in a total of 145 chemical splash cases studied, were superior to

those of water for concentrated bases. In a study carried out by the Martinswerk company in Germany,⁴ the superiority of Diphoterine rinsing on bases, both in terms of effectiveness and rinsing safety, appeared to be confirmed in spite the small size of the case series (Table 2). The number of lost days following water rinsing and the high standard deviation illustrate this.

No secondary care was necessary with Diphoterine rinsing. There was a significant difference ($p < 0.05$) between Diphoterine and water concerning the need of secondary care.

Another study⁴ involved 375 splashes of concentrated acrylic acid (AA), the acrylate family (ethyl, methyl, or butyl), concentrated sulfuric acid (H₂SO₄ 98% or Oleum), sodium hydroxide (NaOH) with a maximum concentration of 22% (5.5 M), and dimethylaminoethylacrylate (ADAME). ADAME was differentiated from other acrylates due to the seriousness of the burns it

Table 4. Reported cases decontaminated with Diphoterine: No sequelae

Year	Cases	Firm/Country	Exposure	Body Surface Area
1999	1	Knoll AG, Germany	96% sulfuric acid	Cheek
1998	1	Giesecke & Debrient, Germany	100% nitric acid	Hand
1995	1	Metaleurop, Germany	96% sulfuric acid	Face + neck
1994	1	Stockhausen, Germany	100% acrylic acid	Leg
1993	1	Mewa, Germany	50% soda ^{a,b}	Forearm
1991	1	Alusuisse, France	Soda ^a flakes	Left eye
1991	2	Orgachim, France	98% sulfuric acid	Face + neck + shoulders; face + neck + shoulders + legs

^a Soda = sodium hydroxide.

^b Cream ointment for the first exposure.

causes, especially in the eyes. The observed criteria were lost work time and requirement for secondary care. The results are summarized in Table 3 and are significantly in favor of Diphoterine.

For individual cases (Table 4), the reports are also very significant with no sequelae, no need of secondary care, and no lost work time. Consider also two cases of large TBSA cutaneous splashes of concentrated sulfuric acid with equal concentrations (95%): one rinsed with water developed serious sequelae and had six months of lost work time; while the other rinsed with Diphoterine had neither sequelae nor lost work time.⁸

EXPERIMENTAL IN VIVO DATA WHICH CONFIRM THE CLINICAL RESULTS

When a chemical burn does occur, its development is determined by two phenomena:

- the cleaning phase (inflammation, destruction), which is increased in cases of chemical burns,
- the repairing phase (healing), which is decreased.

In vivo experimental studies have confirmed that when the development of a chemical burn is stopped, the healing of the injured tissues is carried out in better conditions. Cavallini and Casati⁹ and Cavallini et al.¹⁰ compared the effectiveness of rinsing with Diphoterine to rinsing with normal saline solution on a concentrated cutaneous hydrochloric acid burn in the rat. Diphoterine stopped the development of the chemical burn, which had the following consequences:

- better healing of the skin (size of the lesion after seven days: Diphoterine, 4 mm; normal saline solution, 6 mm; no rinsing, 12 mm),
- a significant reduction of pain (as indicated by Substance P in the first 48 hr, $p < 0.05$; and β -endorphin after seven days, $p < 0.05$),
- a reduction of inflammation (IL-6 at 48 hr, $p < 0.01$; after and seven days, $p < 0.05$).

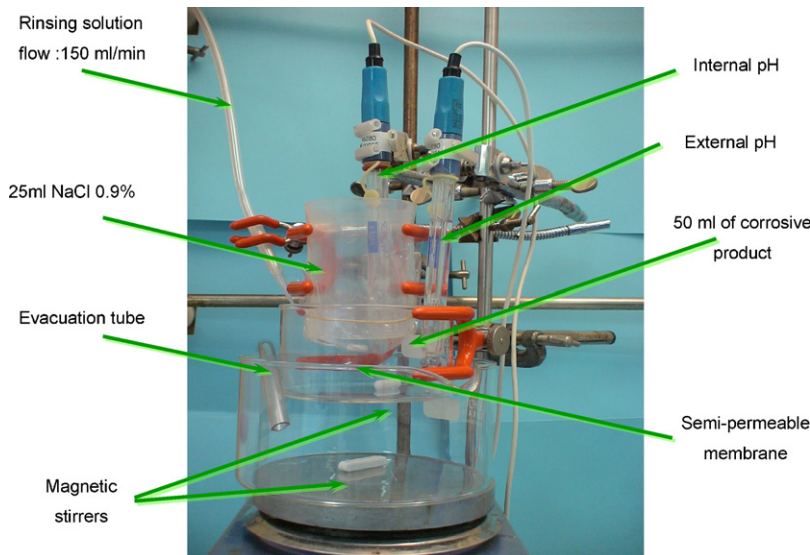


Figure 3. In vitro model for evaluation of corrosive and irritant potential and effectiveness of decontamination.

Gérard et al.¹¹ studied a 15.3% ammonia ocular burn in rabbits. This study has permitted an understanding of the chemical burn mechanism and has showed the relevance of delayed treatment of such an ocular burn. This experimental burn model was then tested in order to compare the effectiveness of Diphoterine versus normal saline solution.¹² After rinsing with Diphoterine there is:

- an absence of stromal edema, while it was observed after rinsing with saline solution or when there is no rinsing,
- a return towards normal of the pH, which was not observed after rinsing with saline solution or when there was no rinsing.

The presence of stromal edema, resulting from inflammation due to the burn and the hypotonic effect of rinsing, is known to be an aggravating factor in the development of chemical burns.¹³

EXPERIMENTAL DATA IN VITRO WHICH EXPLAIN THE CLINICAL RESULTS

PREVOR Laboratory has developed an in vitro model¹⁴ (Figure 3) in order to evaluate the irritant and corrosive potential of chemical agents and the effectiveness of decontamination. A semi-permeable membrane mimics the cornea or the surface of the skin. Two pH probes measure the evolution

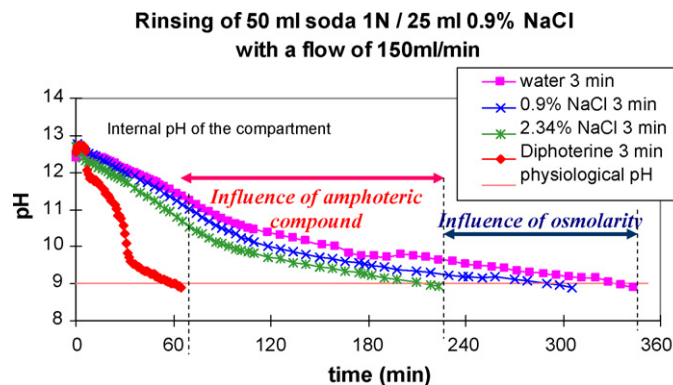


Figure 4. Influence of osmotic pressure and amphoteric properties on rinsing effectiveness.

of the pH at the surface of the surrogate tissues and in the surrogate tissues.

In Figure 4, the influence of the osmotic pressure of rinsing solutions and the improvement brought by an active solution with amphoteric properties such as Diphoterine are shown. The test was performed on 1 mL of 1N sodium hydroxide, and the rinsing solutions were water, normal saline solution, hypertonic saline solution, and Diphoterine.

MANAGEMENT OF CHEMICAL BURNS

A recent study published by Merle et al.¹⁵ shows the usefulness of using Diphoterine even in cases of delayed rinsing, in the initial hours following an accident. The study compares, for equivalent grades of ocular burns, the differences which occur after rinsing with Diphoterine versus rinsing with saline solution before treatment of a base burn. The evaluation of the severity of the burn was carried out after rinsing with saline solution or Diphoterine. This study shows a significant reduction in the amount of time needed for the re-epithelialization of the cornea with Diphoterine rinsing (Table 5) (ocular burn classification is shown in Table 6).

Gérard et al.¹⁶ have published a case of a severe ocular chemical burn (Grade IV) which shows the benefit of delayed rinsing with Diphoterine and describes the associated secondary treatment, principally aimed at reducing inflammation, infection, and pain. The case evolved towards progressive re-epithelialization in less than 21 days, with complete, stable healing in 180 days. No surgical treatment was necessary in this case.

MANAGEMENT OF HYDROFLUORIC ACID BURNS

All chemists, toxicologists, safety managers and company doctors, as well as workers, know how significant burns caused by hydrofluoric acid (HF) can be. Even though it is a weak acid ($pK_a = 3.2$), it can induce more severe

Table 5. Results of a clinical study in Martinique of ocular burns due to bases

Re-epithelialization Time in Days	Diphoterine	Saline Solution	<i>p</i> -value
Grade I	1.9 ± 1	11.1 ± 1.4	$p < 10^{-7}$
Grade II	5.6 ± 4.9	10 ± 9.2	$p < 0.02$
Grade III	20 ± 14.1	45.2 ± 23	0.21 NS

No cases of Grade IV ocular burns decontaminated with Diphoterine.

Table 6. Ocular chemical burn classification (Roper-Hall)

Grade	Initial Clinical Examination
1	Epithelial ulcer, no limbal ischemia
2	Corneal edema ischemia < 1/3 of the limbal circumference
3	Complete corneal ulcer > 1/3 and ischemia > 1/2 of the limbal circumference
4	Opaque cornea with non-visible iris ischemia > 1/2 of the limbal circumference

damage than all other strong acids. This is due to its "double hazard," corrosive because of the acidic (H^+) ions and toxic because of the fluoride (F^-) ions that can bind calcium and magnesium. As HF is not completely dissociated, it induces evolving burns (such as is the case with bases), but also systemic effects depending on the anatomical site, the TBSA exposed, and the HF concentration (Table 7).

In the management of HF splashes, immediate and prolonged water rinsing was the first improvement. Nevertheless, water rinsing has its limitations, especially with high concentrations of HF, where systemic effects have developed and sometimes led to fatal consequences. Mayer and Gross¹⁸ published a case of a 10% TBSA exposure rinsed immediately with water which had a fatal outcome. Different treatments, following water rinsing, have

been evaluated, first by topical applications on the skin, and then by intravenous or subcutaneous injection: topical treatments such as calcium gluconate¹⁹ gave improved results on skin while no real proof of efficacy could be obtained in the eye, even if 1% calcium gluconate as a primary irrigation or as eye drops seemed to improve the evolution of the burn.²⁰ These treatments limit the evolution of the burn while binding fluoride ions but have only a slight effect on the H^+ ions. The acidic part of HF is thought to create the superficial damage on the tissue leading to an increased penetration of fluoride ions. Afterwards, several topical applications or injections are often necessary, depending on whether or not the patient feels any pain.

The protocol of water rinsing + calcium gluconate first showed some limitations with highly concentrated

Table 7. HF burns with a high risk of developing lethal electrolyte imbalances, after Dunser et al.¹⁷

Route	% Body Surface	HF Concentration
Burn by contact	1	Anhydrous
Burn by contact	5	>70%
Burn by contact	7	50–70%
Burn by contact	10	20–50%
Burn by contact	20	<20%
Prolonged exposure or long delay to treatment	Minor HF burns	
Ingestion of HF		>5%
Inhalation of HF		>5%

Table 8. Five case reports of emergency decontamination²⁵

Number of Cases	Splashed by	Affected Body Surface	Type of Rinsing	Consequences/Results
1	HF/HCl bath	Total immersion	Hexafluorine on the body Ocular rinsing with water	→Slight burns on the abdomen and the back →Serious burn of the left eye
1	70% HF vapor	Right cheek	Hexafluorine	Slight painless erythema. Application the next day of calcium gluconate gel, no lost work time
1	38% HF	One eye	Hexafluorine	No burns, no lost work time
2	5% HF	Body	Hexafluorine	No burns, no lost work time

Table 9. Series of 11 cases at The Mannesmann Plant (Germany)²⁶

Splash	40% HF	6% HF/15% HNO ₃	40%HF (Skin)	6% HF/HNO ₃ 15% (Skin)
Number of cases	1	1	5	5
% Affected area	One eye ^a	One eye	0.2–1–4.5–4.5–16.5 ^a	0.2–2.25–4–4.5–10.5
First rinsing (at the site of the accident)	Hexafluorine	Hexafluorine	Hexafluorine	Hexafluorine
Second rinsing (at the infirmary)	Hexafluorine	Hexafluorine	Hexafluorine	Hexafluorine
Results	No sequelae, no further care required, no lost work time			

^a Ocular and cutaneous splash with 40% HF.

exposures. Tepperman²¹ published a case report of a 2.5% TBSA exposure to 100% HF that was fatal. Another case report²² with a ratio of 8% TBSA surface to 70% HF was also fatal.

However, more recently, Dunser et al.¹⁷ have reported improved management of a patient with a 70% HF splash on 30% TBSA who was immediately rinsed with water at the workplace for 10 min and then had intravenous, intra-arterial, subcuta-

neous, and topical applications of calcium gluconate, as well as fluid and analgesic treatment. The patient was also treated surgically with debridement and artificial skin wound coverage. This patient was treated for sepsis and deterioration of pulmonary function. Only after three months was he free of complaints.

Other cutaneous treatments such as iced benzalkonium salts have been successfully evaluated in order to replace

calcium gluconate topical gels, but only experimental data are available.²³

If treatments can be improved, initial decontamination should also be improved. Water rinsing is only passive, with a mechanical effect of irrigation at the surface of the tissue inducing dilution of the corrosive agent.²⁴ Adding chemical and physical properties to water itself should preserve the mechanical effect and preserve its non-toxic and polyvalent properties.

Table 10. A series of 16 cases at Outokumpu (Avesta, Various Sites, Sweden)²⁷

Number of Cases	Splashed With	Affected Body Surface	Length of Contact	Work Loss
2	70% HF	Left forearm – oral cavity	<1 min	0–1
1	HF (concentration unknown)	One eye	<1 min	0
2	HF/HNO ₃ pH = 1	One eye	<1 min	0–0
1	HF/HNO ₃ pH = 1 ^a	One eye	3–5 min	3
1	HF/HNO ₃ pH = 1	Two eyes	<1 min	0
1	HF/HNO ₃ pH = 1	One thigh	<1 min	0
2	HF/HNO ₃ pH = 1	Two thighs	1–1.5 hr	2–2
1	HF/HNO ₃ pH = 1 ^a	Face	3–5 min	3
2	HF/HNO ₃ pH = 1	Face + oral cavity – forehead	<1 min	1–1
3	HF/HNO ₃ pH = 1	Forearm-arm – arm + hand – two elbows	<1 min	0–0–1
1	HF/HNO ₃ pH = 1	Wrists	2 hr	0
Decontamination	Rinsing with Hexafluorine			
Results	Immediate analgesic effect, no sequelae. In 75% of cases including two splashes with 70% HF, no additional care was required and the average lost work time was less than one day ($\sigma = 1.1$)			

^a HF/HNO₃/H₂SO₄ pH = 1 represents the same ocular and cutaneous splash.

The solution named Hexafluorine has been specifically created for decontaminating hydrofluoric acid and fluoride ions in an acidic environment. It has been designed to preserve the properties of water, and supplements them by adding chelation of fluoride ions and neutralization of acidic ions, without creating any significant exothermic reaction. It is also hypertonic, which means it is able to stop the HF from penetrating the eye or the skin by creating an osmotic gradient. It is not irritating to the eyes and skin, non-toxic (oral LD₅₀ > 2,000 mg/kg in rats), and is non-sensitizing.

Several cases, decontaminated at the workplace with Hexafluorine, have been published (Tables 8–10), showing that the development of the burn was avoided or minimized. A standard treatment such as calcium gluconate was applied when clinically necessary.

Among the 32 case reports of Hexafluorine decontamination, and using Dunser's table (Table 7), 5 accidents could have presented lethal risk but no sign of systemic effect was observed when decontamination with Hexafluorine was performed immediately and treatment was applied with calcium gluconate, if needed. No surgical treatment or long hospitalization was necessary in these cases.

CONCLUSION

It is necessary to rinse a chemical agent as soon as possible at the site of the accident, in order to prevent or minimize the inflammatory phenomena which are established very early as a result of cutaneous or ocular chemical burns. Decreasing the length of contact time with strong corrosives

is the key point in the management of chemical splashes and one of the main factors needed for a return to normal status, as well as for improvement of the quality of wound healing. When no or not enough tap water is available, it is vital to have an efficient means of decontamination. Optimal and reproducible effectiveness can be achieved with active rinsing, such as with Diphoterine or Hexafluorine (HF splashes) in portable containers. For the management of chemical burns caused by prolonged contact with chemicals, decontamination is necessary in order to first stop the action of the chemical agent and then the evolution of the burn, by implementing a treatment adapted to the burn severity.

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