DIPHOTERINE® FOR EMERGENT EYE/SKIN CHEMICAL SPLASH DECONTAMINATION: A REVIEW

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Diphoterine® is an hypertonic, polyvalent, amphoteric compound developed in France as an eye skin chemical splash water-based decontamination solution. In vitro and in vivo, it decontaminates approximately 600 chemicals, including acids, alkalis, oxidizing and reducing agents, irritants, lacrimators, solvents, alkylating agents such as sulfur mustard, radionuclides ($^{238}$U, $^{137}$Cs, $^{90}$Sr/Y), and organophosphate pesticides. It has some antimicrobial activity. Its chemical bond energy for such agents is greater than that of tissue receptors. Its hypertonicity impedes chemical tissue penetration and may remove some amount of skin/cornea-absorbed toxicants that have not already bound to tissue receptors. Diphoterine® chemical reactions are not exothermic. In experimental animals, Diphoterine® and its acid/alkaline decontamination residues are not irritating to the eyes or skin. It is essentially nontoxic (LD$_{50}$’s $> 2000$ mg/kg by oral and dermal exposure routes in rodents). In human volunteers, Diphoterine® was not irritating in normal eyes. Diphoterine® has prevented or decreased severity of chemical eye/skin burns with 96% sulfuric acid, 100% acrylic acid, 50% acrylamide, solid sodium hydroxide flakes, and dimethylethylamine. In 2 European workplaces, Diphoterine® decontamination of acid and base chemical splashes was associated with significant decreases in lost work time and the need for additional burn treatment as compared with water lavage. In a German metallurgy facility, 24 workers exposed to weak or strong acids and bases had immediate Diphoterine® decontamination: no eye/skin burns developed and there was no necessity for further medical or surgical burn treatment. Three workers each had 1 lost workday; the other 21 workers had no lost work time. Diphoterine® is an active and efficacious decontamination product for eye/skin chemical splashes. It washes harmful chemicals off exposed tissues as well as neutralizing the substances. It can prevent eye/skin burns following chemical splashes and results in nearly immediate pain relief. Its early use prevents sequelae, the necessity for medical or surgical burn treatment, and lost work time. Diphoterine® is a safe and efficacious product for decontamination of eye/skin chemical splashes.
INTRODUCTION

Eye/skin chemical burns are a significant problem, both in industry and amongst the general public, but the actual prevalence is difficult to determine. Josset et al. noted that there were approximately 7,000 serious occupational injuries from chemical burns in France in 1984, and that about one-half of these involved the eyes. These chemical burns were responsible for approximately 120,000 lost work days and 250 cases of permanent disability.

In the U.S., national data on exposures reported to Poison Control Centers are maintained by the American Association of Poison Control Centers in its Toxic Exposure Surveillance System. However, this database covers only exposures reported to participating Poison Control Centers, covers all exposure routes, and includes data on exposure to consumer products, medications, biological-botanical toxins, etc., in addition to chemicals. Suicidal exposures and adverse medication reactions, as well as accidental or occupational exposures are included.

In the TESS database for 1998 (the most recent year available), there were a total of 2,241,082 human poison exposure cases, including 775 poisoning fatalities. Total dermal exposure cases were 198,247 (8.4%) and ocular exposure cases were 142,145 (6.0%). Of the 775 fatalities, 13 (1.5%) were from dermal exposure and only 2 (0.2%) were from ocular exposure. Of categories in the TESS database with the largest number of deaths, Alcohols were the 6th most common (56 deaths), Chemicals were the 7th most common (45 deaths), Gases and Fumes were the 8th most common (38 deaths), Hydrocarbons were the 13th most common (18 deaths), and Insecticides/Pesticides (including Rodenticides) were the 16th most common (16 deaths).

Reviewing Workers’ Compensation records from the U.S. State of West Virginia during a 1-year period from July 1, 1997 through June 30, 1998, Islam et al. found that eye burns (thermal
as well as chemical) had an incidence rate of 28.0/100,000 employees. There were a total of 183 ocular burn injuries which resulted in medical care reimbursement, payment for lost wages, or permanent partial disability benefits. Ocular chemical exposures in this group of workers were associated with burn injury, atopic conjunctivitis, and acute conjunctivitis. Chemical exposures accounted for 43.7% of ocular burn injuries (80/183), 67.3% of atopic conjunctivitis cases (136/202), and 29.3% of acute conjunctivitis cases (12/41), overall the most frequent cause of these conditions.

At least for decontamination of chemical eye splashes, it has been stated that: “The ideal flushing solution is a sterile, isotonic, preserved, physiologically balanced saline solution. At a minimum, flushing fluid should be clean and non-toxic.” However, such solutions provide only a passive decontamination by washing the chemical off the cornea and conjunctiva or skin. A better approach would be to combine this flushing activity with active decontamination of the involved chemical.

Diphoterine® is an eye/skin chemical splash decontamination solution produced by Laboratoire Prévor in France. It is a polyvalent, slightly hypertonic, amphoteric, water-soluble molecule which binds acids, bases, oxidizing agents, reducing agents, solvents, irritants, alkylating agents, and radionuclides. Its reactions with chemicals are not exothermic (do not release heat which could further damage injured tissues). The following is a review of published and unpublished studies of eye/skin chemical exposure decontamination with this compound.

**METHODS**

All available previously published and currently unpublished studies on the safety and efficacy of Diphoterine® as a decontamination solution for eye/skin chemical splashes were
reviewed. These included in vitro studies performed at Laboratoire Prévor and experimental animal studies of safety and efficacy performed by either commercial contract laboratories or independent academic researchers funded by the manufacturer.

Human studies reviewed included Diphoterine® use in decontaminating eye/skin chemical splashes in industrial settings performed by corporate health and safety departments or by the French Institut National de Recherche et de Sécurité (National Institute for Research and Safety). Other human studies reviewed were performed by independent investigators, some funded by the manufacturer and others not.

These experimental animal and human studies were carried out in accordance with all applicable guidelines and regulations on animal use and care and human subjects protections in the countries where they were performed.

When unpublished data are cited in this review, they are identified in the References section by the notation: (unpublished). More information on these studies in English or French may be obtained from: Laboratoire Prévor, Moulin de Verville, F-95 760, Valmondois, France; mail@prevor.com.

RESULTS

In vitro studies:

In vitro, Diphoterine® has been proven to neutralize approximately 600 chemical compounds, including acids, bases, oxidizing agents, reducing agents, solvents, irritants, alkylating agents (sulfur mustard), certain organophosphate pesticides, and radionuclides (Uranium-238, Cesium-137, and strontium/yttrium-90). The most recent list of specific chemical compounds tested can be obtained on the internet at: www.prevor.com (choose
“English” from the Home Page, choose “Documents” from the next page, then under Diphoterine® choose “Tested Products”). In vitro, Diphoterine® is more efficacious at returning IN hydrochloric acid or sodium hydroxide solutions to a physiological pH.8

**Experimental animal studies:**

### Safety:

The LD₅₀ in male and female Sprague-Dawley rats administered a single oral dose of Diphoterine® and observed for 14 days was greater than 2,000 mg/kg. At the 2,000 mg/kg dose, there was no mortality, body weight gain was normal, and there were no abnormal necropsy findings.) In the same species, the acute dermal LD₅₀ was greater than 2,000 mg/kg. Exposure was by 24-hour semi-occluded application to approximately 10% of the total body skin area following hair removal. At the 2,000 mg/kg dose there were no deaths, body weight gain was normal, there were no abnormal findings at necropsy, and there was no skin irritation.¹⁰ These LD₅₀’s indicate that Diphoterine® is essentially nontoxic.

Tests for eye and skin irritation in New Zealand white rabbits were also carried out. In the eye irritation study, 0.1 mL of Diphoterine® was instilled into the conjunctival sac of one eye of each rabbit. No water irrigation was done. During 7 days of observation, no irritation was observed.” In the same species, 0.5 mL of Diphoterine® was applied to either intact or abraded skin under occlusion for 24 hours, when the occlusive patch was removed and distilled water irrigation was done. Following a 72-hour observation period, some mild erythema and edema was observed. In these experimental conditions, Diphoterine® was classified as mildly irritating to rabbit skin.¹²
In addition to testing for ocular and skin irritation of Diphoterine® itself, eye irritation tests were also carried out with the residues from in vitro neutralization of concentrated hydrochloric acid and concentrated sodium hydroxide. The pH of the acid neutralization residues was 5.84 and that of the sodium hydroxide neutralization residues was 8.82. In New Zealand white rabbits given a single eye instillation of 0.1 mL of these neutralization residues and observed for 8 days, there was no eye irritation.\textsuperscript{13-14}

One currently unpublished German study involves both safety and efficacy issues. (See under Efficacy below for more details.) In this double-blind study, rabbits had severe corneal burns induced in one eye by instillation of 1N sodium hydroxide. After 30 seconds, irrigation was done with either 500 mL of normal saline or Diphoterine®. There was no indication in this study that Diphoterine® produced any adverse ocular effects as compared to normal saline.\textsuperscript{15}

**Efficacy:**

The efficacy of Diphoterine® as compared to normal saline for initial irrigation of 1N sodium hydroxide exposure was studied in rabbit eyes. After 30 seconds, irrigation was done with either 500 mL of normal saline or Diphoterine®. Thereafter, irrigation of the exposed eye was done 3 times daily with normal saline following the protocol for treatment of severe alkali ocular burns in the study facility. There were no differences between treatment groups in corneal opacification, epithelial healing, disruption of the epithelial healing process, or corneal ulcerations. There were less severe lens and iris alterations, less iris stromal atrophy, and less lens opacifications in the Diphoterine® treated group.

A second rabbit model of sodium hydroxide ocular burns was conducted by Josset et Al.\textsuperscript{1,16} Endpoints were extra- and intra-ocular pH and histology. Following a one-minute
application of filter paper soaked in concentrated sodium hydroxide to the cornea, ocular lavage was done for 3 minutes with running water, an isotonic tears solution, or Diphtherine®. Following 3 minutes of lavage with either water or the isotonic tears solution, the external ocular pH was approximately 9.7. In contrast, following Diphtherine® lavage, the external ocular pH almost immediately returned to physiological values. When the eye is irrigated with water, the intra-ocular pH became increasingly alkaline over about 1 minute, while lavage with Diphtherine® inhibited this pH elevation. With water lavage, intra-ocular pH only returned to physiologic levels after 4 hours, while this occurred by 1 hour when Diphtherine® was utilized.

Regardless of the lavage solution utilized, the corneal epithelial surface was destroyed and ulcerations developed over the first few minutes. Stromal edema, however, was much less when Diphtherine® was utilized as compared to water. The endothelial cells (responsible for corneal regrowth) were completely destroyed when water was used, were only partially destroyed when the isotonic artificial tears solution was used, and only developed morphologic variations with very few cells destroyed when Diphtherine® was utilized. These results suggest that Diphtherine® is more efficacious for decontamination of caustic eye exposures than either plain water or an isotonic artificial tears solution.

Normal saline and Diphtherine® irrigation following experimental ammonium hydroxide eye burns have also been compared in a rabbit model. Ammonium hydroxide 15.3% (pH 12.8) was instilled into rabbit eyes followed by either nothing, irrigation with 250 mL of normal saline, or Diphtherine® irrigation at various times from 1 to 30 minutes. Measured endpoints were anterior chamber pH, anterior chamber ammonium hydroxide concentration, and histological evaluation of the exposed corneas. Both lavage fluids produced lower ammonium hydroxide...
concentrations in the anterior chamber. The anterior chamber pH was lower at 7 minutes after Diphoterine® irrigation as compared to normal saline. On histopathological examination, corneal stromal edema was found following lavage with normal saline, but not after Diphoterine® irrigation. Overall, Diphoterine® was superior to normal saline for decontamination of ocular ammonium hydroxide exposure in this model.7

Human volunteer studies:

Ten healthy subjects aged 31 ± 4.5 years were initially evaluated with visual acuity testing, slit lamp examination, and confocal corneal microscopy and then underwent eye irrigation with 500 mL of Diphoterine® over 5 minutes. The same ocular evaluations were performed immediately after irrigation and 3 days later. Although 5/10 subjects had decreased visual acuity directly after rinsing and there were some mild epithelial changes, all these effects had cleared completely by three days and are not different from the effects of mechanical eye rinsing with other fluids. These results indicate that no significant eye injury occurs in healthy subjects following 5 minutes of Diphoterine® irrigation.18

Case reports:

Four German and 2 French patients with occupational chemical exposure decontaminated with Diphoterine® were reported to Laboratoire Prévor from 1991-1999. These 6 patients had exposures as follows: 96% sulfuric acid on the cheek; 100% nitric acid on the hand; 96% sulfuric acid on the face and neck; 50% sodium hydroxide on the forearm; 98% sulfuric acid on the face, neck, and shoulders; a solid flake of sodium hydroxide in the left eye. All were immediately decontaminated with Diphoterine® at the worksite and then evaluated in the facility infirmary. In these 6 workers, there were no sequelae, there was no need for further treatment beyond initial decontamination, and there was no lost work time.8
Other cases of efficacious chemical skin splash decontamination reported to Laboratoire Prévor have involved 100% acrylic acid, 50% acrylamide, and dimethylethylamine (an alkylating agent). 19

Case Series (brief review):

During 1994-1998, 24 workers had inadvertent acid or base chemical eye/skin exposure in a Gem-ian metallurgy facility.9. Industrial processes involved in these exposures included: degreasing, neutralization, material transfer, stripping, suctioning, cleaning, placing process materials in a chemical bath, and eye/skin contact with inadvertently spilled material. Splashes involved the eye in 15 cases: 11 with acids; 4 with bases. The skin was involved in 9 cases: 8 with acids; 1 with a base.

Acid eye splashes involved such chemicals as an phosphoric acid/nitric acid mixtures and sulfuric acid in either solid forms or concentrations from 5% to 35%. Such exposures would not historically be considered to be benign. however, following initial decontamination with Diphoterine® at the worksite and a second lavage with Diphoterine® when the worker reached the infirmary (not necessary needed but dictated by company policy), the outcome was as follows: no additional treatment required other than initial Diphoterine® decontamination; lost work time: 1 day each in 3 workers; no sequelae.

For ocular base splashes in the above facility (n= 5), patients were exposed to 30% sodium hydroxide, a “basic solution” at 30%, or calcium oxide at unknown concentrations. Outcomes following the above decontamination protocol were: no need for additional treatment beyond initial Diphoterine® decontamination, no lost work time, and no sequelae.
For acid skin splashes, compounds involved were nitric acid, sulfuric acid, and phosphoric acid in concentrations from 15-75%. Following initial worksite decontamination with Diphoterine® and secondary lavage with the same compound in the company infirmary, no additional treatment was necessary, there was no lost work time, and there were no sequelae.

In this case series, there was only 1 worker who sustained a splash of 45% sodium hydroxide to the knee. Following initial worksite and secondary infirmary skin decontamination with Diphoterine®, no additional treatment was required, there was no lost work time, and no sequelae.

**Occupational epidemiological studies:**

Two types of workplace epidemiological studies of Diphoterine® decontamination of eye/skin chemical splashes have been done. The first was conducted by the French Institut National de Research et de Sécurité (INRS; National Institute for Research and Safety). This was published as 2 separate papers in French.20,21 This study was of workers with chemical eye/skin splash exposures voluntarily reported to the INRS using a standardized data collection form supplied by the organization.

Endpoints evaluated were what type of initial and secondary lavage was done (water and/or Diphoterine®), whether there was lost work time, and whether any additional treatment was needed beyond decontamination. These 2 studies describe 145 total cases of eye/skin splashes with a variety of chemical substances including acids, alkalis, oxidants, solvents, and glues. While the wide variety of substances involved and the variations in time of decontamination and combinations of decontamination measures used make comparisons difficult, the following conclusions were reached:
Diphoterine® was efficacious for decontamination of eye/skin splashes with acids and alkalis, and combination with water decontamination did not improve its efficacy; outcome endpoints such as severity of chemical irritation/burns, lost work time, and requirements for additional chemical irritation/burn treatment were in general all improved by the use of Diphoterine® as the initial decontamination method.

Two further occupational eye/skin splash studies have been done (but currently are not published). The first was a comparative study of decontamination methods in 45 occupational accidents involving sodium hydroxide or other strong bases (pH 14 or greater) from Martinswerk Gmbh, Bergheim, Germany.22 This facility produces aluminum oxide and aluminum hydroxide and uses caustic soda (sodium hydroxide) in both solid and liquid forms. The study compared the use of water, acetic acid solution, and Diphoterine® in eye/skin splashes with the above chemicals using outcome endpoints of: lost work time; no additional chemical irritation/burn treatment required; simple chemical irritation/burn treatment required; or more significant chemical irritation/burn treatment required.

This study concluded that there was a significant reduction in lost work time following sodium hydroxide and other strong base eye/skin splashes when Diphoterine® was the initial decontamination method as compared to acetic acid solution or water. No simple or more significant chemical irritation/burn treatment was required when Diphoterine® was the initial decontamination method as were required when acetic acid solution or water were utilized.

A comparative study of the use of Diphoterine® in the Rhone Poulenc facility at La Rochelle, France, was performed from 1987–1992.23

Chemicals involved in eye/skin splashes were acids and sodium hydroxide. Diphoterine® and water decontamination were compared
using outcome endpoints of lost work time and requirements for additional chemical irritation/burn treatment. During 1987-88, water decontamination was done; in 1989, Diphoterine® decontamination was added; data for 1990 were not reported; during 1991-92, some water decontamination was still done, but the majority of exposed workers were decontaminated with Diphoterine®. Use of Diphoterine® decontamination was directly related to decreased severity of irritation/burns following acid/alkali chemical eye/skin splashes and no lost work time occurred in the last 2 years of the study when the majority of exposed workers were decontaminated with Diphoterine®.

**CONCLUSION**

Based on the data reviewed here, Diphoterine® represents a significant improvement over plain water or other available solutions for decontaminating eye/skin chemical splashes.
REFERENCES


23. Girard D: Historique de l’utilisation de la Diphoterine® sur the site Rhone-Poulenc La Rochelle [French] [History of the utilization of Diphoterine® at the La Rochelle RhonePoulenc plant]. Study performed at the Rhone-Poulenc Chimie plant, La Rochelle, France, 1987-1992 (unpublished).