SCIENTIFIC REVIEWS

Diphoterine for Emergent Eye/Skin Chemical Splash Decontamination: A Review*

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ABSTRACT. Eye/skin chemical splashes are a significant problem. 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 actively decontaminates approximately 600 chemicals, including acids, alkalis, oxidizing and reducing agents, irritants, lacrimators, solvents, alkylating agents, and radionuclides. 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 not already bound to tissue receptors. Diphoterine chemical reactions are not exothermic. Diphoterine and its acid/alkali decontamination residues are not irritating to the eyes or skin; it is essentially nontoxic. Diphoterine can prevent eye/skin burns following chemical splashes and results in nearly immediate pain relief.

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 there were approximately 7,000 serious occupational injuries from chemical burns in France in 1984, with about ½ of these involving the eyes (1). These chemical burns were responsible for approximately 120,000 lost work days and 250 cases of permanent disability.

In the US, national data on exposures reported to Poison Centers are maintained by the American Association of Poison Control Centers in its Toxic Exposure Surveillance System (2). This database records toxicant exposures reported to participating Poison Centers, includes all exposure routes, and covers a wide variety of potentially toxic exposures including those to chemicals.

In the TESS database for 1999, there were a total of 2,201,156 human poison exposure cases, including 873 poisoning fatalities. There were a total of 185,509 dermal exposure cases (8.0%) and 134,669 ocular exposure cases (5.8%). Of the 873 fatalities, 12 (1.3%) were from dermal exposure and 1 (0.1%) was from ocular exposure.

Reviewing Workers' Compensation records from West Virginia during a 1-y period, Islam et al found that eye burns (thermal as well as chemical) had an incidence rate of 28.0/100,000 employees (3). There were 183 ocular burn injuries that resulted in medical care reimbursement, payment for lost wages, or permanent partial disability benefits. Ocular chemical exposures in this group 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 the acute conjunctivitis cases (12/41), overall the most frequent cause of these conditions.

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" (4). However, such solutions provide only passive decontamination by rinsing the chemical off the cornea and conjunctiva or skin. A better approach is to combine this rinsing activity with *active* chemical decontamination.

Diphoterine is an eye/skin chemical splash decontamination solution. It is a polyvalent, slightly hypertonic, amphoteric, water-soluble molecule that binds acids, bases, oxidizing agents, reducing agents, solvents, irritants, alkylating agents, and radionuclides. Its chemical reactions are not exothermic (do not release heat which could damage exposed tissues).

METHODS

Previously published and currently unpublished studies on the safety and efficacy of Diphoterine as a decontamination solution for eye/skin chemical splashes were reviewed. Experimental animal and human studies cited 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).

RESULTS

In Vitro Studies

Diphoterine has been shown *in vitro* to neutralize approximately 600 chemical compounds, including acids, bases, oxi-

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dizing agents, reducing agents, solvents, irritants, alkylating agents (ie sulfur mustard), and radionuclides (^{238}Uranium, ^{137}Cesium, ^{90}Strontium/^{90}Yttrium) (5-7). The most recent list of specific chemical compounds tested can be obtained on the internet at: www.prevor.com. *In vitro*, approximately 20 ml of amphoteric Diphoterine was more efficacious than a similar volume of water for returning 1N hydrochloric acid or 1N sodium hydroxide solutions to physiological pH; an equivalent volume of water resulted in a pH of 2 for acids or 12 for bases (8).

Experimental Animal Studies

Safety. The LD_{50} in male and female Sprague-Dawley rats administered a single oral dose of Diphoterine and observed for 14 d was >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 (9). In the same species, the acute dermal LD_{50} was >2,000 mg/kg (10). Exposure was by 24-h 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. These LD_{50}'s indicate that Diphoterine is essentially nontoxic.

Tests for eye and skin irritation in New Zealand white rabbits were also performed. In the eye irritation study, 0.1 ml of Diphoterine was instilled into the conjunctival sac of 1 eye of each rabbit. No water irrigation was done. During 7 d of observation, no irritation was observed (11). In the same species, 0.5 ml of Diphoterine was applied to either intact or abraded skin under occlusion for 24 h, at which time the occlusive patch was removed and distilled water irrigation was done. Following a 72-h observation period, some mild erythema and edema was observed in some, but not all, rabbits. In these experimental conditions, Diphoterine was classified as mildly irritating to rabbit skin (12).

In addition to testing for the ocular and skin irritation of Diphoterine, eye irritation tests were also performed 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 the pH of the sodium hydroxide neutralization residues was 8.82. In New Zealand white rabbits administered a single eye instillation of 0.1 ml of these neutralization residues and observed for 8 d, there was no eye irritation (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 500 ml of either normal saline or Diphoterine (15). There was no indication that Diphoterine produced any adverse ocular effects as compared to normal saline.

Efficacy. The efficacy of Diphoterine as compared to normal saline for initial irrigation of 1N sodium hydroxide exposure was studied in rabbit eyes (15). After 30 sec of exposure, irrigation was done with 500 ml of either 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 (1,16). Endpoints were extra- and intra-ocular pH and histology. Following a 1-min application of filter paper soaked in concentrated sodium hydroxide to the cornea, ocular lavage was done for 3 min with running water, an isotonic tears solution, or Diphoterine. Following 3 min of lavage with either water or the isotonic tears solution, the external ocular pH was approximately 9.7. In contrast, following Diphoterine lavage, the external ocular pH almost immediately returned to physiological values. When the eye was irrigated with water, the intra-ocular pH became increasingly alkaline over about 1 min, while lavage with Diphoterine inhibited this pH increase. With water lavage, intra-ocular pH only returned to physiological levels after 4 h, while this occurred by 1 h when Diphoterine 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 Diphoterine was utilized rather than water. The endothelial cells (responsible for corneal re-growth) 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 Diphoterine was utilized. These results suggest that Diphoterine is more efficacious for decontamination of caustic eye exposures than either plain water or isotonic artificial tears solution (1,16).

Normal saline and Diphoterine irrigation following experimental ammonium hydroxide eye burns have also been compared in a rabbit model (17). Ammonium hydroxide 15.3% (pH 12.8) was instilled into rabbit eyes followed by either no irrigation, irrigation with 250 ml normal saline, or Diphoterine irrigation at various times from 1 to 30 min after exposure. 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 7 min 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.

Human Volunteer Study

Ten healthy adult subjects were initially evaluated with visual acuity testing, slit lamp examination, and confocal corneal microscopy and then underwent eye irrigation with 500 ml of Diphoterine for 5 min (18). The same ocular evaluations were performed immediately after irrigation and 3 d later. Although 5/10 subjects had decreased visual acuity immediately after rinsing and there were some mild epithelia l changes, these effects completely resolved over 3 d and were not different from the mechanical effects of eye rinsing with other fluids, including water. These results indicate no significant eye injury occurs in healthy subjects following 5 min of Diphoterine irrigation.

Case Reports

German and French patients with occupational chemical exposure decontaminated with Diphoterine were reported to the Diphoterine manufacturer between 1991 and 1999. These patients had exposures as follows: 98% sulfuric acid on the eyelid (1 worker) and the face, neck, and shoulder (1 worker); 100% nitric acid on the hand; 96% sulfuric acid on the face and neck; 50% sodium hydroxide on the forearm; and 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 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 the manufacturer have involved 100% acrylic acid, 50% acrylamide, dimethylethylamine, and p-chloro-m-cresol (8).

Case Series (Brief Review)

From 1994 to 1998, 24 workers had inadvertent acid or base chemical eye/skin exposures in a German metallurgy facility (19). 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 and 4 with bases. The skin was involved in 9 cases - 8 with acids and 1 with a base.

Acid eye splashes (n=11) involved such chemicals as phosphoric acid/nitric acid mixtures and sulfuric acid in concentrations from 5% to 35%. Such exposures would not be considered benign. Following initial decontamination with Diphoterine at the worksite and a second lavage with Diphoterine when the worker reached the infirmary (dictated by company policy), the outcome was as follows: no additional treatment required other than initial Diphoterine decontamination; lost work time = 1 d each for 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 (n=8), compounds involved were nitric acid, sulfuric acid, and phosphoric acid in concentrations from 15 to 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.

One worker sustained a splash of 45% sodium hydroxide on 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 occurred.

Workplace Observational Studies

Observational studies of Diphoterine decontamination of eye/skin occupational chemical splashes have been performed. The first was conducted by the French Institut National de Research et de Sécurité (INRS; National Institute for Research and Safety) (20,21). This study involved workers with chemical eye/skin splashes voluntarily reported to the INRS using a standardized data collection form. 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 initial decontamination. There were 145 total cases of eye/skin splashes with a variety of chemical substances including acids, alkalis, oxidizers, 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 the addition of water decontamination either before or after Diphoterine did not improve efficacy. Requirements for additional chemical irritation/burn treatment were decreased by the use of Diphoterine as the initial decontamination method. When used for ocular chemical splashes, Diphoterine was associated with nearly immediate pain relief.

A second comparative workplace study of decontamination methods in 45 occupational accidents involving sodium hydroxide or other strong bases (pH 14 or greater) was done at 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, dilute acetic acid solution, and Diphoterine for 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.

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 dilute acetic acid solution or water. No simple or more significant chemical irritation/burn treatment was required when Diphoterine was the initial decontamination method, but there were required when dilute acetic acid solution or water was utilized.

A similar workplace study in the Rhone Poulenc facility at La Rochelle, France, was performed between 1987 and 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 to 1988, water decontamination was done. In 1989, Diphoterine decontamination was added. Data for 1990 were not reported. During 1991 and 1992, some water decontamination was still done, but the majority of exposed workers were decontaminated with Diphoterine. Diphoterine decontamination was directly associated with decreased severity of irritation/burns following acid/alkali chemical eye/skin splashes, and no lost work time occurred in the last 2 y of the study when the majority of exposed workers were decontaminated with Diphoterine.

In the ATOFINA facility, Saint-Avold, France, 375 workers with eye/skin exposure to 5 priority chemicals (acrylates, 98% sulfuric acid, oleum, 22% sodium hydroxide, or dimethylaminoethyl acrylate) had a significantly decreased incidence of lost work time, a significantly decreased incidence of long-term sequelae, and a non-significant trend for lesser burn center or ophthalomogical consultations when Diphoterine® was used for initial decontamination as compared to water (24).

CONCLUSIONS

Diphoterine is more efficacious than water lavage for the decontamination of eye/skin chemical splashes. Its active chemical-physical properties make Diphoterine® the best currently available eye/skin decontamination solution. As a water-soluble compound, it also has a passive rinsing effect. Its use in industrial workplaces has resulted in decreased lost work time, and the prevention of long-term sequelae. Its use also has precluded the need for eye/skin burn treatments.

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"If a dog will not come to you after having looked you in the face, you should go home and examine your conscience."
-- Woodrow Wilson

"Money will buy you a pretty good dog, but it won't buy the wag of his tail."
-- Unknown