SCIENTIFIC REVIEWS

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

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ABSTRACT. Eye/skin chemical splashes are a significant problem 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 1/3 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 1998, there were a total of 2,201,158 human poison exposure cases, including 873 poisoning fatalities. There were a total of 186,509 dermal exposure cases (8.0%) and 134,689 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-year 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 (13/192), 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.

Diphotherine 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 Diphotherine 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

Diphotherine has been shown in vitro to neutralize approximately 600 chemical compounds, including acids, bases, ox-
dizing agents, reducing agents, solvents, irritants, alkylating agents (e.g., sulfur mustard), and radionuclides (239/240Uranium, 210/Ce-
Pium, 90/Srtrontium/90Yttrium) (5-7). The most recent list of spe-
cific chemical compounds tested can be obtained on the internet at www.proriv.com. In vitro, approximately 20 ml of amphot-
eric Diphosphine was more efficacious than a similar volume of
water for returning IN hydrochloric acid or IN sodium hydrox-
ide solutions to physiological pH, an equivalent volume of wa-
ter resulted in a pH of 2 for acids or 12 for bases (8).

Experimental Animal Studies

Safety. The LD50 in male and female Sprague-Dawley rats
administered a single oral dose of Diphosphine 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 LD50 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 LD50 indicate that Diphosphine is essentially
nontoxic.

Tests for eye and skin irritation in New Zealand white rab-
bits were also performed. In the eye irritation study, 0.1 ml of
Diphosphine was instilled into the conjunctival sac of 1 eye of
each rabbit. No water irrigation was done. During 7 d of obser-
vation, no irritation was observed (11). In the same species, 0.5 ml
of Diphosphine 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. Follow-
ing a 72-h observation period, some mild erythema and edema
was observed in some, but not all, rabbits. In these exper-
imental conditions, Diphosphine was classified as mildly irrit-
ting to rabbit skin (12).

In addition to testing for the ocular and skin irritation of
Diphosphine, 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 ac-
id neutralization residues was 5.84 and the pH of the so-
dium 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 de-
tails.) In this double-blind study, rabbits had severe corneal
burns induced in one eye by instillation of 1N sodium hydrox-
ide. After 30 seconds, irrigation was done with 500 ml of either
normal saline or Diphosphine (15). There was no indication that
Diphosphine produced any adverse ocular effects as compared to
normal saline.

Efficacy. The efficacy of Diphosphine as compared to nor-
mal 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
Diphosphine. Therefore, irrigation of the exposed eye was done
3 times daily with normal saline following the protocol for treat-
ment of severe alkaline ocular burns in this study facility. There
were no differences between treatment groups in corneal opaci-
fication, epithelial healing, disruption of the epithelial healing
process, or corneal ulcerations. There were less severe lentic
and irido alterations, less irido stromal atrophy, and less lens
opacifications in the Diphosphine-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 applica-
tion of filter paper soaked in concentrated sodium hydroxide
to the cornea, ocular lavage was done for 3 min with running wa-
ter, an isotonic tears solution, or Diphosphine. Following 3 min
of lavage with either water or the isotonic tears solution, the
external ocular pH was approximately 9.7. In contrast, follow-
ing Diphosphine lavage, the external ocular pH almost immedi-
ately returned to physiological values. When the eye was irri-
gated with water, the intra-ocular pH became increasingly alk-
aline over about 1 min, while lavage with Diphosphine inhibited
this pH increase. With water lavage, intra-ocular pH only re-
turned to physiological levels after 4 h, while this occurred by 1
h when Diphosphine was utilized.

Regardless of the lavage solution utilized, the corneal epi-
thelial surface was destroyed and ulcerations developed over the
first few minutes. Stromal edema, however, was much less
when Diphosphine was utilized rather than water. The end-
thelial cells (responsible for corneal re-growth) were com-
pletely 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 Diphosphine was utilized. These results sug-
gest that Diphosphine is more efficacious for decontamination
of caustic eye exposures than either plain water or isotonic
artificial tears solution (1,16).

Normal saline and Diphosphine irrigation following experi-
mental ammonium hydroxide eye burns have also been com-
pared in a rabbit model (17). Ammonium hydroxide 15.3% (pH
12.8) was instilled into rabbit eyes followed by either no irri-
gation, irrigation with 250 ml normal saline, or Diphosphine iriga-
tion at various times from 1 to 30 min after exposure. End-
points were anterior chamber pH, anterior chamber ammonium
hydroxide concentration, and histological evaluation of the
exposed corneas. Both lavage fluids produced lower ammox-
ium hydroxide concentrations in the anterior chamber. The
anterior chamber pH was lower 7 min after Diphosphine iriga-
tion as compared to normal saline. On histopathological ex-
amination, corneal stromal edema was found following lavage
with normal saline, but not after Diphosphine irrigation. Overall,
Diphosphine 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 vi-
sual acuity testing, slit lamp examination, and confocal cor-
neal microscopy and then underwent eye irrigation with 600 ml
of Diphosphine for 5 min (18). The same ocular evolutions
were performed immediately after irrigation and 3 d later. Al-
though 6/10 subjects had decreased visual acuity immediately
after rinsing and there were some mild epithelial changes,
these effects completely resolved over 3 d and were not differ-
ent from the mechanical effects of eye rinsing with other
fluids, including water. These results indicate no significant

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eye injury occurs in healthy subjects following 5 min of Diphotrine irritation.

Case Reports
German and French patients with occupational chemical exposure decontaminated with Diphotrine were reported to the Diphotrine manufacturer between 1991 and 1999. These patients had exposures as follows: 98% sulfuric acid on the eye (1 worker) and the face, neck, and shoulder (1 worker); 100% nitric acid on the hand; 98% 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 Diphotrine 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 (5).

Other cases of efficacious chemical skin splash decontamination reported to the manufacturer have involved 100% acetic acid, 60% 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, sputtering, cleaning, placing process materials in a chemical bath, and eye/skin contact with inadvertently spilled material. Splash had exposed the eye in 15 cases - 11 with acids and 4 with bases. The skin was involved in 5 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 Diphotrine at the worksite and a second lavage with Diphotrine when the worker reached the infirmary (dictated by company policy), the outcome was as follows: no additional treatment required other than initial Diphotrine decontamination; lost work time = 1 day 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 Diphotrine 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 Diphotrine 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 Diphotrine, no additional treatment was required, there was no lost work time, and no sequelae occurred.

Workplace Observational Studies

Observational studies of Diphotrine decontamination of eye/skin occupational chemical splashes have been performed. The first was conducted by the French Institut National de Recherche 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 Diphotrine), whether there was lost work time, and whether any additional treatment was needed beyond initial decontamination. There were 146 total cases of eye/skin splashes with a variety of chemical substances including acids, alkanes, 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 it difficult to draw clear conclusions, the following conclusions were reached: Diphotrine was efficacious for decontamination of eye/skin splashes with acids and alkalies, and the addition of water decontamination either before or after Diphotrine did not improve efficacy. Requirements for additional chemical irritation/burn treatment were decreased by the use of Diphotrine as the initial decontamination method. When used for ocular chemical splashes, Diphotrine 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 Martinwerk 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 Diphotrine 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 Diphotrine 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 Diphotrine 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. Diphotrine 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, Diphotrine 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 Diphotrine. Diphotrine 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 Diphonteine.

In the ATP:FINA facility, Saint-Avold, France, 375 workers with eye/skin exposure to 5 priority chemicals (acrylates, 98% butylate, oleum, 22% sodium hydride, 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 ophthalmological consultations when Diphonteine® was used for initial decontamination as compared to water (24).

**CONCLUSIONS**

Diphonteine is more efficacious than water lavage for the decontamination of eye/skin chemical injury. Its active chemical-physical properties make Diphonteine® 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.

**REFERENCES**


"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

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