Diphoterine®,
An Amphoteric, Polyvalent, Hypertonic Eye/Skin Chemical Splash Decontamination Solution:
14 Years Updated Data

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Introduction I

- Reviews of Diphoterine® Safety and Efficacy were published in the early 2000s
  - In French (Minaro et al, 2000)
  - In English (Hall et al, 2002)
Introduction II

Since these reviews were published, newer studies have shown:

- Diphoteren®’s **EFFICACY** for decontamination of eye/skin splashes with nearly all chemicals
- **SAFETY:** Its lack of irritancy, sensitizing properties, tissue absorption, or toxicity
- Its **CLINICAL INTEREST** for both emergent and delayed decontamination
Methods

Review of:

- Published Papers
- Textbook Chapters
- Presented Congress Abstracts
- Manufacturer’s Data
Results I

- Retrieved Data fall into 2 main categories:
  - Studies of *Safety*
  - Studies of *Efficacy*
Results II
Studies of Safety

- Normalization of pH
  - Prevor’s Laboratory: Beaker study with pH and temperature probes
  - Diphoterine® or water and 1M HCl or NaOH
    - HCl/NaOH + Diphoterine®: pH returned to physiologically tolerable levels (5.5-9.0)
    - HCl/NaOH + Water: pH remained 2 (HCl) or 12 (NaOH)
Results III
Studies of Safety
Tetramethylammonium Hydroxide

- **In vitro MTT cell viability study**
  - Required 17 times more water than Diphoterine® to achieve physiologically tolerable pH
  - Diphoterine® rinsing: 2/3 of cells viable
  - Water rinsing: only 1/3 of cells viable
Results IV
Studies of Safety
(Hall et al, 2009)

*In vitro* Dermal Irritation test:
Non-irritating; Maximum Human Irritancy Equivalent (HIE) score 0.8

Ames bacterial reverse mutation test:
No mutagenic activity in *S. typhimurium* or *E. coli*

Cytotoxicity in Murine fibroblasts:
No cytotoxic effects up to 24 hours of exposure

Skinthetic® *in vitro* tolerability and percutaneous absorption test:
Minimal percutaneous absorption ($3.2 \times 10^{-3} \%$ of initial dose absorbed after 6 hours)

Guinea pig skin sensitization study:
No irritation and no skin sensitization at 24 and 48 hours
Results V
Studies of Safety
(Hall et al, 2009)

- **Normal Human Volunteer Studies**
  - **Dermal Tolerance Study:**
    - In 55 normal human volunteers:
      - Average Irritation Index (IIM) 0.00 (non-irritating)
  
- **Dermal Sensitization Study:**
  - In 161 normal human volunteers:
    - 1st 5 applications: non-irritating
    - Subsequent applications: slightly irritating
    - Considered *hypoallergenic and had minimal risk of inducing contact sensitization*

- **Manufacturer’s post-marketing surveillance:**
  - No reports of adverse effects on the eyes or skin
Results VI
Studies of Efficacy

- **Rats with skin exposure to concentrated HCl** (Cavallini and Casati, 2004; Cavallini et al, 2004)
  - As compared to decontamination with normal saline, rats decontaminated with Diphoterine® had:
    - Decreased burn area
    - Improved wound healing at 7 days post-exposure
    - Decreased blood levels of Substance P (an indication of decreased pain)
    - Increased blood levels of β-endorphin (an indication of decreased pain)
    - Decreased blood levels of IL-6, TNF$_{\alpha}$ and NO (markers of decreased inflammation)
Results VII
Studies of Efficacy

- Rabbits with skin exposure to concentrated $\text{H}_2\text{SO}_4$ and $\text{NaOH}$

  - (Wang, 2009; Wang and Zhang, 2008)
    - As compared to rabbits decontaminated with Sodium Bicarbonate solution or Tap Water ($\text{H}_2\text{SO}_4$) or Boric Acid solution or Tap Water ($\text{NaOH}$), those decontaminated with Diphoterine® had:
      - No generation of excessive heat
      - $\text{pH}$ returned to physiologically tolerable range with much lesser volumes
      - More rapid wound healing
Studies of Efficacy
Clinical Studies

Australia (Donoghue, 2010)

- Independent study of 180 aluminum refinery workers in Western Australia exposed to alkaline chemical substances
- Workers chose initial decontamination with Water first ($n=42$) or Diphotherine® first ($n=138$)
- TBSA was a median of 1% with maximum of 38%
- No difference between groups in duration of alkaline substances skin contact
- Significantly better ($p<0.001$) outcomes in the Diphotherine® first group
## Results IX
**Studies of Efficacy**
**Clinical Studies**
Australia (Donoghue, 2010)

Chemical Burn Severity by First Decontamination Solution (Adapted from Mathieu et al, 2014)

<table>
<thead>
<tr>
<th>Clinical Severity</th>
<th>Water First</th>
<th>Diphoterine® First</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>9 (21.4%)</td>
<td>73 (52.9%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>23 (58.4%)</td>
<td>54 (31.9%)</td>
</tr>
<tr>
<td>Blisters</td>
<td>8 (19%)</td>
<td>10 (7.2%)</td>
</tr>
<tr>
<td>More Severe</td>
<td>2 (4.8%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Totals</td>
<td>42 (100%)</td>
<td>138 (100%)</td>
</tr>
</tbody>
</table>
Studies of Efficacy
Clinical Studies

- Comparison of Burn Severity Rates at Alcoa, Inc. sites where Diphoterine is or is not available (Data courtesy of Alcoa, Inc. and the United Steelworkers Union)

<table>
<thead>
<tr>
<th>Site</th>
<th>Burn Severity Rate</th>
<th>Water/Diphoterine® Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Australia</td>
<td>0.16</td>
<td>Diphoterine®</td>
</tr>
<tr>
<td>Jamaica</td>
<td>0.00</td>
<td>Diphoterine®</td>
</tr>
<tr>
<td>Latin America</td>
<td>0.00</td>
<td>Diphoterine®</td>
</tr>
<tr>
<td>Europe</td>
<td>0.00</td>
<td>Diphoterine®</td>
</tr>
<tr>
<td><strong>Port Comfort, TX, USA</strong></td>
<td><strong>0.72</strong></td>
<td><strong>Water</strong></td>
</tr>
</tbody>
</table>
Results XI
Studies of Efficacy
Clinical Studies

- **Belgium** (Verbelen et al, 2016)
  - Retrospective review of patients with chemical splash injuries presenting to the ED of the Universitair Ziekenhuis Gent, Gent, Belgium between 01/01/2008 and 12/31/2015
  - Decontaminated with water only (n=66) or Diphoterine® (sometimes preceded by water) (n=43)
  - Significantly less surgical procedures required in the Diphoterine® group (n=5) than in the water group (n=43) (p<0.001)
  - Significantly shorter average hospital stay: Diphoterine® (3.48 days); water (7.66 days) (p<0.31)
Germany (Nehles et al, 2006)

- 24 cases of industrial acid or alkaline chemical eye/skin splashes
- Initial Diphtherine® decontamination at the worksite; secondary Diphtherine® decontamination in the company infirmary
- No need for treatment other than decontamination
- No sequelae
- No Lost Worktime
Results XIII
Studies of Efficacy
Clinical Studies

- **India** (Kulkarni, 2006)
  - 110 patients with industrial chemical splash injuries presenting to the Boisar Clinic Tarapur, India during a 10-month period
  - Ocular splashes (n=62); skin splashes (n=48)
  - Water only decontamination at the worksite (n=71)
  - Diphtherine® only decontamination at the Clinic (approx. 20 minutes delay) (n=31)
  - 8 patients had both
**Results XIV**

*Studies of Efficacy*

*Clinical Studies*

- **India** (Kulkarni 2006)
  - In the group with Diphoterine® decontamination as compared to the water only group:
    - Significantly less lost worktime (p<0.01)
    - Significantly lesser hospitalization cost (p<0.01)
    - Better average increase in visual acuity scores (Diphoterine® 84%; water 19%)
    - Significantly less pain following decontamination: average pain score decrease (Diphoterine® (3.67); water (2.12) (p<0.01)
Results XV
Studies of Efficacy
Clinical Studies

- Glycolic Acid skin peeling in normal volunteers (Cavallini et al, 2014)
  - 25 normal volunteers with 70% Glycolic Acid applied to the volar surface of both forearms for 5 minutes
  - Left forearm sites washed with water; right with Diphotherine®
  - Average tissue pH after 5 minutes: 0.7
  - Average pH increase after washing: water 2.7; Diphotherine® 3.33
Independent Systematic Review

Lynn et al, Cutan Ocular Toxicol (in press)

Conclusion

“...our review found that Diphoterine is a safe product and appears to be highly effective in improving healing time, healing sequelae, and pain management of chemical burns on the skin and eyes of humans. ... we recommend that this product be readily available to emergency responders, hospitals and companies...”
Conclusion

These summarized reports from the early 2000s to the present show that Diphoterine® solution is basically innocuous and more efficacious than water for first aid decontamination of eye/skin chemical splashes.