A review about Diphotérine®: the solution for first aid emergency decontamination of eye/skin chemical splashes

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Introduction

Chemical eye/skin burns can be serious injuries.Traditional decontamination solutions such as water and normal saline can decrease the severity of such burns, but do not always prevent injury. Both water and normal saline decontamination are passive decontamination. Another approach can be the use of an active eye/skin decontamination solution, called Diphotérine®. Its chemical and physical properties allow a polyvalent rinsing of chemical splashes with a rapid return to a physiological state. With the emergency use of Diphotérine® after-effects can be avoided.

Methods

We present different significant results obtained with Diphotérine® over the years, concerning its toxicology, *in vivo* and *in vitro* experiments, case reports and statistical studies.

Results

1 Innocuousness and properties

Table 1: *Summary od Innocuousness tests*

Test	Results	References
Ocular irritation	Non irritant	Test n°133/4, on rabbits, Safepharm Laboratories Limited, UK, 1987
In vitro Evaluation of the eye irritation potential of a medical device	No cytotoxic or irritant potential to the eye after a short (10 minutes) or prolonged (24 hours) time of contact	Test n°REL/032/05/IRRO/ELB, on human fibroblast cultures, test Integra, Italy, 2005
Cutaneous irritation	Non irritant	Test n°2005-024, *in vitro*, Dermal Irritection® test method, Integra, Italy, 2005
Ocular irritation of a residue of a washing of an acid with Diphotérine®	Non irritant	Test n°6463 TAL, on rabbits, hydrochloric acid, International Centre of Toxicology,France, 1990
Ocular irritation of a residue of a washing of a base with Diphotérine®	Non irritant	Test n°6462 TAL, on rabbits, sodium hydroxide, International Centre of Toxicology, France,1990
Oral toxicity	Oral LD_{50} > 2000 mg/kg ; non toxic, no death, normal evolution of weight, no abnormality at necropsy	Test n°6564 TAR, on rats, International Centre of Toxicology, France, 1990
Acute dermal Toxicity	Acute dermal LD_{50} > 2000 mg/kg; non toxic, no death, no sign of systemic toxicity or dermal irritation, normal evolution of weight, no abnormality at necropsy	Test n°133/9, on rats, Safepharm Laboratories Limited, UK, 1988
Sensitisation	Non sensitising	Test n°20030418ST, Magnusson and Kligman method, on Guinea pigs, OECD 406, CERB, France, 2003 (15)
Mutagenesis	Non mutagenic ; negative Ames test	Test n°29023 MMT, Bacterial reverse mutation Test on *Salmonella typhimirium* TA 1535, TA 1537, TA98, TA 100 et TA 102, *Escherichia Coli* WP2 uvrA, International Centre of Toxicology, France, 2005
Cytotoxicity	Non cytotoxic	Test n°REL/003/06/IRRC/ELB, ISO 10993-5 standard, Integra, Italy,2006
Anti-inflammatory potential	Non anti-inflammatory ; no cytotoxic or irritant effect observed on a 3D human epidermidis model	Test n°REL/011/06/FUNZ/ELB, MTT in vitro tests + pro-irritation potential IL-1α, Integra, Italy, 2006
Local skin tolerance	No irritant or toxic effect	Test n°20060537TL, on rabbit, CERB, France, 2007

No side effects have been reported in workplace use since Diphotérine® has been put on the market and due to the materiovigilance program put in place by Prevor Laboratory. *(1)*

2 *In vivo* experiments

Skin studies using rats *(2,3)*, comparing the effectiveness of rinsing with Diphotérine® *versus* a saline solution was carried out on an HCl concentrated burn. The significant statistical results show in Diphotérine's favour :

- The inflammation decreased based on an IL-6 parameters decrease,
- The pain sensation decreased based on a substance *P* decrease and a ,β-endorphin increase
- The size of the lesions decreased (*Fig 1*):
- An improvement of the healing.

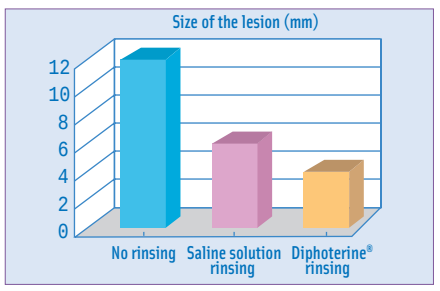

Figure 1 : *Impact of a rinsing with Diphotérine® on HCl concentrated burn on rats.*

Also in in vivo experiments, Diphotérine® as opposed to normal saline decreased the elevated pH in the anterior chamber of rabbit eyes exposed to concentrated ammonia *(4,5)* (*Fig 2*). No stromal oedema was observed after Diphotérine® rinsing whereas it appeared with saline solution rinsing *(Figures 3)*.

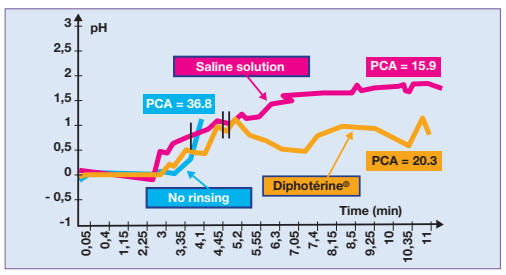

Figure 2: *Rinsing 3 min after contact with 0.01 ml of 15.3% ammonia*

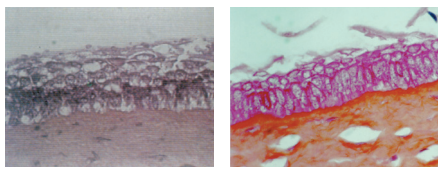

Figure 3a ***Figure 3b***

Figures 3: Histology of cornea rinsing 3 min after contact with ammonia.

3a : *After rinsing with saline solution, coagulated epithelium and oedematous stroma;*

3b: *After rinsing with Diphotérine®, vacuolisated and coagulated epithelium, normal stroma.*

3 *In vitro* results of the efficiency

The efficiency of the Diphotérine®, on almost all chemicals (acids, bases, oxidising agents, reducing agents, chelating agents and solvents), is due to its own physico-chemical properties: it is a polyvalent amphoteric, hypertonic, chelating molecule with active binding sites. These properties allows Diphotérine® to be as effective on acids as well as on bases, as seen in *fig. 4*, due to a fast return to the physiological pH zone. *(1)*

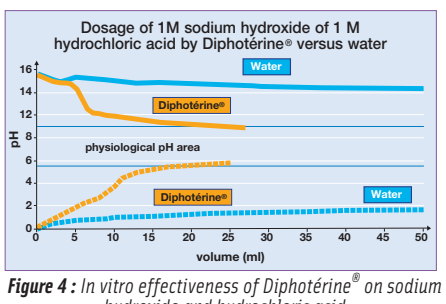

Figure 4 : *In vitro effectiveness of Diphotérine® on sodium hydroxide and hydrochloric acid*

4 Case report

First report :

In a study carried out by the Martinswerk company in Germany *(6)*, the superiority of Diphotérine® rinsing on bases, both in terms of effectiveness and rinsing safety, appeared to be confirmed in spite of the small size of the case series *(Table 2)*. The number of lost days following water rinsing and the high standard deviation illustrate this.

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

Rinsing Solution	Diphotérine®	Acetic Acid	Water
No secondary care*	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 los	0.18 % +/- 0.4	2.91 % +/- 4.3	8 % +/- 8.12

- Secondary care: Care required other than initial decontamination
- No secondary care was necessary with Diphotérine® rinsing. There was a significant difference ($p < 0.05$) between Diphotérine® and water concerning the need for secondary care.

Second report:

Another study (6) involved 375 splashes of concentrated acrylic acid (AA), the acrylate family (ethyl, methyl or butyl), concentrated sulfuric acid (H_2SO4 98% or Oleum), sodium hydroxide (NaOH) with a maximum concentration of 22% (5.5 M), and dimethylaminoethylethylacrylate (ADAME). ADAME was differentiated from other acrylates due to the seriousness of the burns it causes, especially in the eyes. The results are summarised in *Table 3* and are significantly in favour of Diphotérine®.

Table 3: *Evaluation of Water vs. Diphoterine® Rinsing at Atofina (Total Petrochemicals), France*

Rinsing	Water	Diphotérine®	*P*
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	

Third report:

The record of 24 cases of chemical splashes occurring in a German metallurgy facility (Mannesmann , Remscheid, Germany), during the years 1994-98 was collected by the occupational doctor *(7)* *(table 4)*. Initial Diphotérine® decontamination was done by the workers themselves or co-workers, immediately on the incident site. Then, all workers had been evaluated in the company infirmary where a second rinsing with Diphoterine® was done.

Table 4: *Body area by sort of chemical splash in 24 cases at Manessmann facility, Germany*

Splashes	Eye	Skin
Acids*	11	8
Bases**	4	1

** Acids involved : sulfuric, nitric, phosphoric, sulfamic (5-10%)*

*** Bases : calcium oxide, lye 30-45%, basic solution 30%*

For all of these 24 reported cases, no further treatment was required, there were no sequelae and only 3 workers (with ocular splashes) lost one workday due to hospital observation rather than injury.

5 Clinical study

A clinical study of ocular alkali burns found a significantly decreased time to re-epithelialization in Grades 1 and 2 burns when Diphotérine® was used as compared to normal saline *(8)* *(Table 5)*.

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

Re-epithelialization time in days	Diphotérine®	Saline Solution	*P* 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 Diphotérine®)

A case report of a Grade 4 ocular chemical burn found that initial Diphotérine® followed by appropriate topical treatment allowed progressive healing over 21 days and complete healing over 180 days without surgical intervention *(9)*.

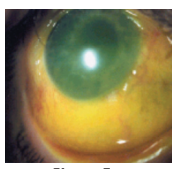

Figure 5a: *Initial burn, grade 4*

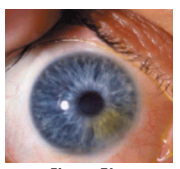

Figure 5b: *complete healing after 180 days*

Conclusion

The emergency use of Diphotérine® is a good method for the decontamination of ocular or cutaneous chemical splashes. It permits the decrease of loss of work and secondary care in all cases and no sequelae for the workers.

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