Diphoterine® eye/skin chemical splash decontamination solution: An updated review of safety and efficacy data

Hall AH[1], Mathieu L[2], Blomet J[2]
[1]Toxicology Consulting and Medical Translating Services, Azle and Springtown, Texas and Colorado School of Public Health, University of Colorado-Denver, Denver, Colorado, USA; [2]Laboratoire PREVOR, Valmondois, France

Accepted for poster presentation at the APAMT 2016 Congress, Singapore, 2016.

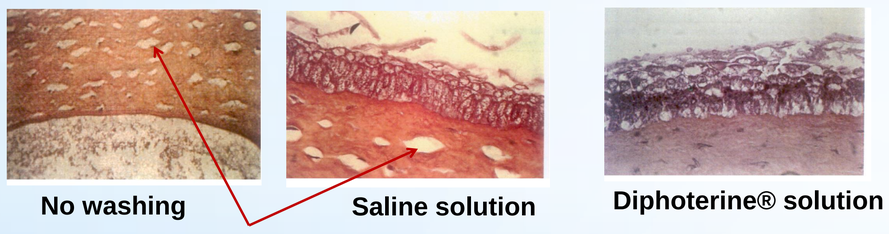
Innocuity of Diphoterine® solution

Test	Results
Ocular irritation	Non irritant
In vitro Evaluation of the eye	No cytotoxic or irritant potential
Cutaneous irritation	Non irritant
Ocular irritation of a residue	Non irritant
Ocular irritation of a residue	Non irritant
Oral toxicity	Non toxic, LD_{50} > 2000 mg/kg
Acute dermal Toxicity	Non toxic, LD_{50} > 2000 mg/kg
Sensitisation	Non sensitising
Mutagenesis	Non mutagenic
Cytotoxicity	Non cytotoxic
Anti-inflammatory potential	Non anti-inflammatory
Local tolerance on damaged skin/healthy skin	No irritant or toxic effects
Local skin tolerance	Non irritant

Formulation, classification of Diphoterine® solution

Aqueous saline solution containing Diphoterine®, amphoteric agent	
Medical device, Class IIa, CE 0459	can be used on healthy and damaged tissues
Does not contain phosphates	pH ranging between 7.2 and 7.7
Limpid and colourless liquid	Density : 1.034
Osmotic pressure : 820 mosmoles/kg	Sterile solution (by autoclave)

In vivo study in the rabbit eye: Burn due to concentrated ammonia



No stromal edema and significant decrease of pH with an inflection of the curve when washing with Diphoterine® solution

An In Vivo cutaneous prospective, randomized, blind study: Burn due to concentrated hydrochloric acid

Biomarkers	Results
IL_6	**Significantly decreased** by the washing with Diphoterine® solution compared to other washing solutions at 48 hours and 7 days, $0.001 < p < 0.05$
Substance P	**Decreased and significantly different** with Diphoterine® solution versus other groups at 6 and 48 hours, $p < 0.05$
B-Endorphin	**Significantly increased** when washing performed with Diphoterine® solution compared to no washing or other washing solutions after 7 days, $p < 0.05$

The differences in serum levels of biological markers and wound healing were likely due to the superior washing properties of Diphoterine® solution such that less HCl was left on the skin to produce injury (Cavallini, 2004).

Case Reports: Summary of observations when washing with Diphoterine® solution during an industrial chemical exposure (2014)

53 firms gave a testimony
64 victims of specified accidents
8 testimonies of « Everyday » use without special accident stories
16 accidents involving Acids
25 accidents involving Alkalis
37 eye exposures
35 skin exposures
8 combined eye and skin splashes

Firms have described the following effects:
- Decrease in secondary care
- Improvement of the symptoms during washing
- Less pain
- Decrease in severity of the burn injuries
- Decrease in sequelae
- Decrease in lost Time of Work

A retrospective comparative study at the hospital (Verbelen 2016): Rinsing with Diphoterine® or Hexafluorine® versus water

Title / Author	Comparison	Dipho/Hexa	Water	Results
Chemical injury: 4 years of experience with an advanced approach Verbelen 112 patients	Need for surgery (number)	5	43	p < 0.0001
	Average hospital stay per patient (Days)	3.48	7.76	P = 0.031

Less need for surgery, shorter hospital stay, patient go back earlier to work

Clinical data

CUTANEOUS BURN STUDIES

Title / Author	Study Type	Chemical	Time to rinse (minutes)		Area burned (%)	Burn outcome		Intervention Outcome				Observations / Conclusions
The clinical efficacy of Diphoterine® in the management of cutaneous chemical burns: A 2-year evaluation study Zack-Williams 131 patients	Comparative Study	"Alkali burns" n = 72 cases (55.0%)	Diphoterine (Dipho)	Water (H_2O)	TBSA(%)	Dipho	H_2O	Mean Pre-irrigation pH	Dipho	H_2O	Measured (Days)	Dipho	H_2O	P-value	The Diphoterine-treated patients were significantly younger (37.7 vs 43.2 years, p = 0.044) than those treated without. Patients who received Diphoterine presented to hospital significantly earlier than those who did not receive it (0.5 vs 2.55 days p = 0.006) There was a significant change in the wound pH pre- and post-application of Diphoterine® solution, compared to patients who were treated with water irrigation only, with a pH change of 1.076 vs 0.4 (p <0.05).
		"Acids" n = 24 cases (18.3%)	0.57	2.15		1.76	1.25		8.07	7.77	Injury to surgery	3.50	5.00	0.067**	
			n = 47	n = 84							Injury to heal time	9.00	7.00	0.258	
		"Other chemicals" n = 35 cases (26.7%)	p = 0.004*			p = 0.203			p = 0.369		Injury to discharge	2.0	2.0	0.469	
											Mean ΔpH	1.076	0.4	<0.05*	
Diphoterine® for alkali chemical splashes to the skin at alumina refineries Donoghue 180 patients	Comparative Study	"…strong alkali solutions (primarily sodium hydroxide)"	Dipho first	Water first, then Dipho	Body Surface Area (%)	Dipho	H_2O	Severity was recorded by medical personnel in the initial assessment. These results were not published with the article.			Severity	Dipho	H_2O		There were no sign of chemical burn in 52.9% of the group who applied Diphoterine first compared with 21.4% of the group who applied water first. Only 7.9% of the group who applied Diphoterine first had blisters or more severe signs compared with 23.8% of the group who applied water first. The differences were statistically significant (P < 0.001). After implementation of Diphoterine the "first aid" injury rate for chemical burns fell 24.7%.
			2.9	11		1.6	2.9				1 (no sign)	73 cases	9 cases		
			n = 135	n = 42							2 (erythema)	54 cases	23 cases		
			p = 0.001*			p = 0.233					3 (blisters)	10 cases	8 cases		
											4 (more severe)	1 case	2 cases		
												n = 138	n = 42		
Diphoterine® for Emergent Decontamination of Skin/Eye Chemical Splashes: 24 Cases Nehles	Case Series	**ACIDS**													No sequelae, no need for secondary care, no loss of work
		HNO_3 (53%)	"…nearly immediate (within the first 30-120 seconds after exposure)"			Head		Lost work days	0		No sequelae in any case.				
		H_2SO_4(20%)				Right cheek			0						
		H_2SO_4(20%)				Throax			0						
		H_3PO_4(16%)				Left forearm			0						
		H_2SO_4(20%)				Face			0						
		H_3PO_4(15%)				Right hand			0						
		H_3PO_4(75%)				Thorax, genitals			0						
		H_2SO_4(20%)				Right hand			0						
		BASES													
		NaOH (45%)	(same as acids)			Knee			0						

* statistically significant
** approaching statistical significance
TBSA – Total Body Surface Area

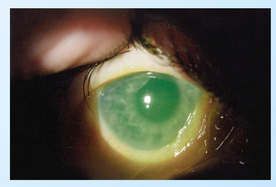
OCULAR BURN STUDIES

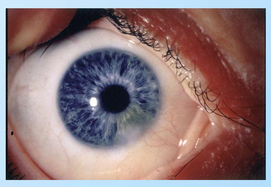
Title / Author	Study Type	Chemical	Time to rinse (minutes unless otherwise listed)	Area burned	Burn outcome		Intervention Outcome	Notes
Diphoterine for emergent decontamination of skin/eye chemical splashes: 24 cases. Nehles	Case Study	**ACIDS**					No sequelae in any case.	No sequelae, no need for secondary care, no loss of work
		H_3PO_4/HNO_3 (5/30-35%)	"…nearly immediate (within the first 30-120 seconds after exposure)"	Left eye (L)	Lost work days	0		
		H_2SO_4 (20%)		Right eye (R)		0		
		NH_2SO_3H (Powder)		R		0		
		H_2SO_4 (20%)		Not reported		0		
		NH_2SO_3H (Powder)		Not reported		0		
		H_2SO_4 (20%)		R		1		
		H_3PO_4/HNO_3 (5/35%)		L		1		
		H_2SO_4 (20%)		L		0		
		H_2SO_4/HNO_3 (5/35%)		L		1		
		H_2SO_4 (20%)		R		0		
		H_2SO_4 (20%)		L		0		
		BASES						
		NaOH (30%)		R		0		
		"Basic Solution" (30%)		R		0		
		Quicklime (CaO)		R		0		
		Quicklime (CaO)		L		0		

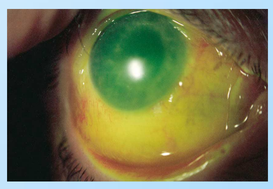
Title / Author	Chemical			Time to rinse (minutes)		Eyes		Severity	Time to reepithelialization (days)		Observations / Conclusions
Martinique (French West Indies) Evaluation of the use of an amphoteric solution as the rinsing product. Merle H Comparative study during 4 years 66 cases	Alkali n= 32 (48.5%)		Roper-Hall Modification of the Hughes Classification	Dipho	Phys	Dipho	Phys	**Grade I**	DAP	Phys.	Injuries were first irrigated with their respective solution at an average of the times listed (units in minutes). A second irrigation occurred 5 hours after the accident (5.1 ± 4.3 h). Significant difference for grade I and II. Not enough grade III to compare. All Grade IV injuries were rinsed with the physiologic solution and were therefore not included in this table.
	Dipho	Phys.	Grade I	15 ± 48	25.6 ± 58	n = 35	n = 17	• Corneal epithelial damage	1.9 ± 1	11.1 ± 1.4	
	9 (25%)	23 (76.7%)		p = 0.49, NS		Specific eye not recorded		• No limbal ischaemia • Good prognosis	p = 10^{-7}*, significant		
	p <0.0001*		Grade II	Dipho	Phys	Dipho	Phys	**Grade II**	DAP	Phys.	
	Javel[1] n = 10 (15.1%)			22.2 ± 60	17.3 ± 45	n = 16	n = 16	• Corneal haze, iris details visible	5.6 ± 4.9	10 ± 9.2	
	Dipho	Phys.		p = 0.79, NS		Specific eye not recorded		• <1/3 limbal ischaemia • Good prognosis	p = 0.02*, significant		
	7 (19.4%)	3 (10%)	Grade III	Dipho	Phys.	Dipho	Phys	**Grade III**	DAP	Phys.	
	No p-value reported			193 ± 262	120 ± 264	n = 5	n = 7	• Total epithelial loss, stromal haze, iris details obscured	20 ± 14.1	45.2 ± 23	
	"Other"[2] n = 24 (36.4%)			p = 0.64, NS		Specific eye not recorded		• 1/3-½ limbal ischaemia • Poor prognosis	p = 0.21, NS		
	Dipho	Phys.									
	20 (55.6%)	4 (13.3%)									

Title Author	Study Type		Chemical	Experimental groups	Pain level (inside CS cloud)	Time Interval between CS exposure and arrival… …at the 'ready-for-action' checkpoint	Residual Pain…	Observations / Conclusions
Prevention of CS "Tear Gas" eye and skin effects and active decontamination with diphoterine Bvrar 22 participants	Comparative Study	Chlorobenzylidene malononitrile (CS) tear gas	CS group n = 6	Exposed to only CS.	9.7±0.5	2:28±0:25	2.3±0.5	Pain was scored according to a 10-point scale. A control group with 200ml low-pressure spray containers filled with water were prepared; however, the but officers refused to use water sprays due to their previous bad experiences with water decontamination after CS exposure. An aqueous, hypertonic, amphoteric, and chelating solution used prior to entering a riot reduces pain and recovery time after CS exposure. Moreover, in cases of CS exposures, decontamination with the aqueous, hypertonic, amphoteric, and chelating solution reduces facial pain.
			Pre-exposure group n = 8	Faces sprayed with Diphoterine (200mL) just before CS exposure.	5.6±1.1*	1:26±0:44*	1.1±0.4*	
			Post-exposure group n = 8	Faces sprayed with Diphoterine (200mL) immediately after CS exposure.	9.1±0.4	2:30±0:48	1.4±0.7*	

Title Author	Study Type	Chemical	Time to rinse (minutes unless otherwise listed)	Area burned	Burn outcome	Intervention Outcome		Observations / Conclusions
An amphoteric rinse used in the emergency treatment of a serious ocular burn Gerard 1 Grade IV case report	Case Study	Ammonia (Alcali®): 15.3%, pH: 12.8	"…1 h after the accident."	Right eye	Grade IV Roper-Hall Classification	Time to Re-epithelialization (days)		Rinsing was enhanced by instillation of local anaesthesia with oxybuprocaine eye drops. No need for surgery. Among the different rinsing solutions available, Diphoterine® seems to be valuable even after a longer delay of more than 10 min.
					• Cornea opaque, iris and pupil obscured • >½ limbal ischaemia • Poor prognosis	"Progression to healing [began at]"	"Total re-epithelializtion"	
						21	180	
					Visual acuity 2/20	4/20	14/20	







References:

1. Hardwicke J, Hunter T, Staruch R, Moiemen N. Burns. 2012;38(3):383-7.
2. Hall AH, Blomet J, Mathieu L. Vet Hum Toxicol. 2002;44(4):228-31.
3. Mathieu L., Burgher F, Blomet J. J Chem Health & Safety, July/August 2007, 32-39
4. http://www.prevor.com/fr/liste-des-produits-testes-et-lavages-recommandes-pour-les-solutions-diphoterine-et-hexafluorine
5. Hall AH, Cavallini M, Mathieu L, Maibach HI. Cutan Ocul Toxicol. 2009;28(4):149-56.
6. Donoghue AM. Int J Dermatol. 2010;49(8):894-900.
7. Nehles J, Hall AH, Blomet J, Mathieu L. Cutan Ocul Toxicol. 2006;25(4):249-58.
8. Rihawi S, Frentz M, Schrage NF. Graefes Arch Clin Exp Ophthalmol. 2006;244(7):845-54.
9. Brvar M Human and Experimental Toxicology 2015, 1-6
10. Viala B, Blomet J, Mathieu L, Hall AH. J Emerg Med. 2005;29(1):5-8.
11. Merle H, Donnio A, Ayeboua L, Michel F, Thomas F, Ketterle J, et al. Burns. 2005;31(2):205-11.
12. Gérard M, Merle H, Chiambaretta F, Rigal D, Schrage NF. Burns 2002; 28: 670-673
13. Zack-Williams SDL, Ahmad Z, Moiemen NS. Ann Burns Fire Disasters. 2015 Mar 31; 28(1): 9-12
14. Cavallini M, Puggioni V, Gazzola R. J of Plastic Dermatol. 2010;6(2):145- 147
15. Schrage NF, Rihawi R, Frentz M, Reim M. Klin MonatsblAugenheilkd 2004, 221: 1-9B
16. Cavallini M, Casati A. European Journal of Anaesthesiology 2004, 21, 389-392
17. Cavallini M, de Broccard F, Corsi MM, Fassati LR, Baruffaldi Preis FW. Annals of burns and fire disasters 2004, XVII, 2, 1-5
18. Maibach HI, Hall AH, Chemical Skin Injury, Ed. Springer, 2014, ISBN 978-3-642-39778-3
19. Schrage NF, Burgher F,Blomet J, Bodson L, Gerard M, Hall AH, Josset P, Mathieu L, Merle H. Chemical Ocular Burns, Ed. Springer, 2011, ISBN 978-3-642-14549-0
20. Atiyeh B, Barret JP, Dahai H, Duteille F, Fowler Ann, Enoch S, Greenfield E, Magnette A, Rode H, Zhao-fan X. Wound International 2014
21. Merle H, Gérard M, Schrage N. J Fr Ophtalmol. 2008 ;31(5) :1-12
22. Deustsche Ophtahlmologische Gesellschaft. Leitlinie Nr. 8. Verletzungen des Auges und seiner Anhangsgebilde. 2011 :1-8
23. Lynn DD, Zukin LM, Dellavalle R. Cutan Ocul Toxicol. 2016 Aug 3:1-17
24. Verbelen J, Hoeksema H, Monstrey S. Nordic Burn Meeting, Uppsala, Sweden June 2016, oral presentation, to be published

PREVOR
ANTICIPATE AND SAVE
Toxicology Laboratory & Chemical Risk Management