

Alkali ocular burns in Martinique (French West Indies) Evaluation of the use of an amphoteric solution as the rinsing product

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Abstract

Precis: During the 4 years of this study, we noted 66 cases of alkali ocular burns, or approximately 16 cases per year, nearly half (45.5%) of which are due to an assault. For grade 1 and 2 burns the time elapsed to reepithelialization appears to be shorter when rinsed with Diphoterine* versus physiological solution.

Purpose: Comparison of the effectiveness of two rinsing solutions for emergency use: a physiological solution and an amphoteric solution (Diphoterine*, Laboratoires Prevor, Valmondois, France). Description of the clinical and progressive characteristics of alkali burns treated at the University Hospital Center of Fort de France in Martinique (French West Indies).

Design: Prospective consecutive observational case series and nonrandomized comparative study.

Participants: Sixty-six patients were included. The total number of burned eyes is 104. Forty-eight eyes (46%) were rinsed with physiological solution and 56 eyes (54%) with Diphoterine*.

Methods: All patients benefited from an ocular rinse with 500 ml of physiological solution or Diphoterine*, followed by a complete ophthalmologic exam. The ocular injuries were classified according to the Roper-Hall modification of the Hughes classification system. The same standardized therapeutic protocol was applied and adapted to the seriousness of the burn.

Main outcome measures: Demographic data, time to corneal reepithelialization, final best corrected visual acuity and complications were analysed.

Results: Twenty-eight (42.4%) patients have a unilateral burn and 38 (57.6%) patients have bilateral burns. In decreasing order of frequency, the circumstances surrounding the injury are: assaults in 45.5% of cases ($n = 30$), work-related accidents in 32% of cases ($n = 31$), and domestic accidents in 23% of cases ($n = 15$). For grade 1 and 2 burns the time elapsed to reepithelialization appears to be shorter when rinsed with Diphoterine* versus physiological solution (respectively): 1.9 ± 1 days versus 11.1 ± 1.4 days ($p = 10^{-7}$) and 5.6 ± 4.9 days versus 10 ± 9.2 days ($p = 0.02$). For grade 3 and 4 burns, there are complications in 11 cases (11.6%): 8 corneal opacities and 3 perforations.

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Conclusions: This study is the first conducted in humans that takes into account the type of ocular rinse product used in the progressive follow-up study of injuries. The time elapsed to reepithelialization is shorter with Diphoterine* for grade 1 and 2 burns. There are not enough cases of grade 3 and 4 burns to make a conclusion. Diphoterine* seems very effective in terms of its mechanism of action and the experimental and clinical results.

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1. Introduction

Chemical burns represent 7.7–18% of ocular traumas [1,2]. Alkali burns are responsible for serious injuries to the stroma and to the corneal endothelium, iris, and ciliary body. Bases cause the death of epithelial cells through saponification of fatty acids in the cell membrane and also facilitate the penetration of the product into the eye. The most severe injuries are associated with the destruction of limbal stem cells and result in recurring epithelial ulcerations, chronic stromal ulcers, profound stromal neovascularization, conjunctival covering or even corneal perforation [3]. The prognosis of chemical burns depends on the extent of the ocular surface damaged, the degree of intraocular penetration, and the concentration and nature of the agent involved.

Situated in the middle of the arch of the Lesser Antilles at a latitude of 14°36 north and a longitude of 62°34 west, Martinique is an island in the French West Indies. Alkali ocular burns are common among the 381,500 inhabitants of Martinique and are distinct because of the large proportion of assaults and the use of ammonia. Their social and sometimes legal consequences are serious [4]. Medical or surgical treatment of ocular burns are well-documented, but few studies have focused on the comparison between different solutions of ocular rinse in humans. The principal objective of our study is the comparison of the effectiveness of the emergency use of two rinsing solutions: physiological solution and an amphoteric solution, Diphoterine* (Laboratories Prevor, Valmondois, France). The secondary objective is the description of the clinical and progressive characteristics of alkali burns treated at the University Hospital Center of Fort de France in Martinique.

2. Patients and methods

This study was conducted in a prospective manner from January 1, 1998 to December 31, 2001, at the University Hospital Center of Fort de France in Martinique. This public hospital is the largest on the island and receives all of the ophthalmologic emergencies in Martinique. This study obtained a favorable recommendation from the Consultative Committee for the Protection of Persons in Biomedical Research authorized by the French Health Ministry. Patient consent was obtained in writing for each observation. The population studied includes all of the patients who came to the hospital emergency room, either on their own or transported by the emergency services (firemen ...) for an alkali ocular burn. Other etiologies of burns (acids, thermal,

plants ...) were excluded. For each patient, we noted the exact nature of the product causing the burn, the circumstances, and the delay between the accident and the first ocular irrigation performed by the victim or by a third party. The delay between the accident and the first action taken at the hospital, which is immediate ocular irrigation, was noted. From January 1, 1998 to December 31, 1999, the immediate ocular irrigation was performed after the instillation of anesthetic eye drops with 500 ml of physiological solution, and from January 1, 2000 to December 31, 2001, with 500 ml of Diphoterine*. Then, a complete ophthalmologic exam was performed and the ocular injuries were classified according to the Roper-Hall modification of the Hughes classification system [5–7] (Table 1). This classification, which includes 4 stages, establishes a prognosis from the initial phase. It is based on the extent of the stromal opacity and possible limbal ischemia. We noted the existence of possible associated palpebral injuries. The time elapsed to corneal reepithelialization was specified, as well as the final best corrected visual acuity and the incidence of complications if applicable. Whichever rinse product used (physiological solution or Diphoterine*) the same therapeutic protocol was applied. For the grade 1 and 2 burns: immediate ocular irrigation, verification of anti-tetanus vaccination, rifamycin drops six times/day, 2% ascorbic acid drops six times/day and tropicamide drops six times/day. The follow-up care for burns of grades 1 and 2 was performed in an outpatient setting. For the grade 3 and 4 burns: immediate ocular irrigation, verification of anti-tetanus vaccination, rifamycin drops six times/day, 2% ascorbic acid drops six times/day, dexamethasone-neomycin drops six times/day for 7 days, 1% atropine drops three times/day, 1 g of oral ascorbic acid three times/day and placement of an antisymblepharon ring. The patients with grade 3 and 4 burns are hospitalized for the follow-up care. The treatment is continued until complete corneal reepithelialization is achieved. When

Table 1
Classification of chemical burns

Grade	Clinical findings
1	Corneal epithelial damage; no ischemia
2	Cornea hazy; iris details visible; ischemia less than one-third at limbus
3	Total loss of corneal epithelium; stromal haze obscures iris details; ischemia of one-third to one-half at limbus
4	Cornea opaque; iris and pupil obscured; ischemia affects more than one-half at limbus

necessary, an analgesic treatment (paracetamol) is prescribed. The progression of the injuries was not carried out blindly and the patient was informed of the nature of the ocular rinse product used. The exploitation of data is carried out in a strictly anonymous, computerized manner. The statistical tests used are: chi-square for the comparison of frequencies, Fisher's exact test (chi-square with Yates correction for small sample size), and Student *t*-test for the comparison of means.

3. Results

Between January 1, 1998 and December 31, 2001, 66 patients were treated in the Ophthalmology Department of the University Hospital Center of Fort de France for alkali ocular burns. Twenty-eight (42.4%) patients have a unilateral burn and 38 (57.6%) patients have bilateral burns. The total number of eyes burned is 104. Table 2 shows the demographic characteristics and the nature of the burn. There are two times as many men as women (45/21). The average age is 38.2 ± 14.8 years. In decreasing order of frequency, the circumstances surrounding the burn are: assaults in 45.5% of cases ($n = 30$), work-related accidents in 32% of cases ($n = 21$) and domestic accidents in 23% of cases ($n = 15$). We note that the number of assaults differs between the first 2 years of the study, with 22 assaults (73% of cases), and the two following years, with 8 assaults (22% of cases). Alkali* is the most commonly used product: 32 cases (48.5%). Alkali* contains 15.3% ammonia and has a pH of 12.8. Javel* is the product in 10 cases (15.1%). Javel* contains 6.8% sodium hypochlorite and has a pH of 11.5. Included in the category of "others" are: soda-based cleansers and detergents, lime, and cement. Table 3 displays the overall characteristics of the burns. Forty-eight eyes (46%) were rinsed with physiological solution and 56 eyes (54%) with Diphoterine*. The grade 1 and 2 burns, with 84 cases, represent more than 80% of the cases. Palpebral injuries generally accompany the most serious burns. The grade 3 and 4 burns, 15 eyes (31.3%) are primarily in the

group rinsed with physiological solution. The group rinsed with Diphoterine* includes 51 eyes (91%) with grade 1 and 2 burns. In every case, the first ocular irrigation was carried out by the victim with tap water or mineral water. The average delay of this first irrigation is 1 h. The second irrigation performed at the hospital occurs 5 h after the accident. The average time elapsed to corneal reepithelialization is 9 ± 14.2 days. The final visual acuity is on average $20/22 \pm 20/70$. The total number of complications is 12 cases (11.6%): 9 corneal opacities and 3 perforations. Three cases of ocular hypertonicity observed from grade 3 burns were treated by hypotonic eye drops and oral acetazolamide. We did not observe symblepharon, ectropion, or entropion. Table 4 displays the results of the comparison between victims of an assault and victims of a work-related or domestic accidents. In the case of an assault, the victims are most often men, the lesions are bilateral in 22 cases (73.3%), and the product used is Alkali* in 26 cases (86.7%). We find the majority of the most severe burns of grade 3 and 4 in this group of burns by assault: 17 cases (32.7%) compared to only 3 cases (5.8%) of grade 3 burns in the group of work-related or domestic accidents. The time elapsed to reepithelialization is greatest and the final visual acuity lower. The delays between the first rinse and the hospital treatment (second rinse) are longer. Among the 12 complications, 11 cases (21.1%) belong to this group. One case of corneal opacity was observed in the group of work-related or domestic accidents. Table 5 compares the progress of the burns according to product used for the second rinse. For the grade 1 burns: the delays of irrigation differ by 30 min for the first rinse and 1 h for the second. The time elapsed to reepithelialization appears shorter when the second rinse was carried out with Diphoterine*: 1.9 ± 1 days versus 11.1 ± 1.4 days ($p = 10^{-7}$). No complications were observed in the grade 1 burns. For the grade 2 burns, the time elapsed to reepithelialization is also shorter with Diphoterine*: 5.6 ± 4.9 days versus 10 ± 9.2 days ($p = 0.02$). The delay of the first irrigation is practically identical in the two groups but in the Diphoterine* group, the burns were rinsed later ($p = 0.57$ NS). One case of corneal

Table 2
Demographic characteristics and the nature of the burn

	Total ($n = 66$)	Physiological solution ($n = 30$)	Diphoterine* ($n = 36$)	<i>p</i> -value
Male:female ratio	45/21	24/6	21/15	0.06 NS
Mean age (years)	38.2 ± 14.8	37.9 ± 14.7	38.5 ± 15.1	0.87 NS
Bilateral burn	38 (57.6%)	18 (60%)	20 (55.5%)	0.7 NS
Circumstances of the accident				
Assault	30 (45.5%)	22 (73.4%)	8 (22.2%)	0.0001
Work accident	21 (31.8%)	5 (16.6%)	16 (44.4%)	
Domestic accident	15 (22.7%)	3 (10%)	12 (33.4%)	
Nature of the product				
Alkali*	32 (48.5%)	23 (76.7%)	9 (25%)	0.0001
Javel*	10 (15.1%)	3 (10%)	7 (19.4%)	
Autres	24 (36.4%)	4 (13.3%)	20 (55.6%)	

n: number of patients, NS: no significant.

Table 3
Overall characteristics of ocular burns

	Total (n = 104)	Physiological solution (n = 48)	Diphoterine* (n = 56)	p-value
Grade 1	52 (50%)	17 (35.4%)	35 (62.5%)	0.002
Grade 2	32 (30.8%)	16 (33.3%)	16 (28.6%)	
Grade 3	12 (11.5%)	7 (14.6%)	5 (8.9%)	
Grade 4	8 (7.7%)	8 (16.7%)	0	
Eyelid burns	44 (42.3%)	29 (60.4%)	15 (26.8%)	0.0005
Delay of first irrigation (min)	53 ± 142	76.3 ± 177	33 ± 100	0.009
Delay of second irrigation (h)	4.7 ± 7.3	3.5 ± 4.7	5.8 ± 8.9	0.57 NS
Time elapsed to reepithelialization (days)	9 ± 14.2	16.3 ± 18.8	3.7 ± 5	10 ⁻⁷
Final visual acuity	20/22 ± 20/70	20/25 ± 20/70	20/20 ± 20/200	0.01
Complications				
Corneal opacity	9 (8.7%)	7 (14.5%)	2 (3.5%)	0.03
Perforation	3 (2.9%)	2 (4.1%)	1 (1.8%)	

n: number of eyes, NS: no significant.

opacity was observed among the burns rinsed with the physiological solution. For the grade 3 burns, the time elapsed to reepithelialization is also shorter: 20 ± 14.1 days versus 45.2 ± 23 days ($p = 0.21$ NS). Three of the 4 complications appear in the Diphoterine* group. They correspond to three grade 3 burns for which the second rinse was delayed: the 2 opacities of the cornea were rinsed 9 h after the accident and the perforation 12 h after the accident. All the injured eyes of grade 4 burns were rinsed with the physiological solution. The delay of the first irrigation is 263 ± 287 min, the delay of the second irrigation is 5.1 ± 4.3 h, the time elapsed to corneal reepithelialization is 27 days for the uncomplicated case, and the final visual acuity is 2.2 ± 3.1. The number of complications is 7 (87.5%): 5 opacities and 2 perforations of the cornea. In general, the delay of the first rinse carried out by the victim increases according to the seriousness of the burn. It is 18 min for the grade 1 burns and exceeds 4.5 h for the grade 4 burns.

4. Discussion

During the 4 years of this study, we noted 66 cases of alkali ocular burns, or approximately 16 cases per year, nearly half (45.5%) of which are due to an assault. Chemical burns occur for the most part in the context of industrial or domestic accidents. In Germany, 73% of burns are related to occupational accidents and are divided equally between agriculture, chemical, and mechanical industry [8]. In Melbourne, Australia, 71% of accidents are work-related, 23% are domestic accidents, and 2.5% are assaults [9]. The low level of industrialization in Martinique partly explains why only 30% of our observations are related to a workplace accident. Our proportion of assaults is significant and unusual. However, since 1976, Klein, then Beare in 1990, show the predominance of ocular burns by assault within certain socioeconomic settings. As in our study, the victim is most often a man, the assailant a woman, and the assault takes place in the home of the victim during a domestic

Table 4
Comparison of burns by assault and by occupational or domestic accidents

	Assault (30 patients)	Occupational and domestic accidents (36 patients)	p-value
Male:female ratio	4/26	19/17	0.003
Mean age (years)	37.6 ± 15	38.8 ± 14.7	0.7 NS
Bilateral burn	22 (73.3%)	16 (44.4%)	0.02
Alkali*	26 (86.7%)	6 (16.6%)	10 ⁻⁷
Javel*	1 (3.3%)	9 (25%)	
Others	3 (10%)	21 (58.4%)	
	Assault (52 eyes)	Occupational and domestic accidents (52 eyes)	p-value
Grade 1	17 (32.7%)	35 (67.3%)	0.00005
Grade 2	18 (34.6%)	14 (26.9%)	
Grade 3	9 (17.3%)	3 (5.8%)	
Grade 4	8 (15.4%)	0	
Delay of first irrigation (min)	97.8 ± 189	8.2 ± 25	10 ⁻⁶
Delay of second irrigation (h)	5.6 ± 7.4	3.9 ± 7.3	0.01
Time elapsed to reepithelialization (days)	11.7 ± 15.8	6.9 ± 12.5	0.0003
Final visual acuity	20/25 ± 20/70	20/22 ± 20/125	0.003
Corneal opacity	8 (15.4%)	1 (1.9%)	0.009
Perforation	3 (5.7%)	0	

NS: no significant.

Table 5
Characteristics of grade 1, 2 and 3 burns

	Total (n = 52)	Physiological solution (n = 17)	Diphoterine* (n = 35)	p-value
Grade 1				
Delay of first irrigation (min)	18.5 ± 51	25.6 ± 58	15 ± 48	0.49 NS
Delay of second irrigation (h)	3.2 ± 6	2.6 ± 3.6	3.4 ± 6.9	0.85 NS
Time elapsed to reepithelialization (days)	4.9 ± 9	11.1 ± 1.4	1.9 ± 1	10 ⁻⁷
Final visual acuity	20/20 ± 20/200	20/20 ± 20/100	20/20 ± 20/250	0.74 NS
Corneal opacity	0	0	0	–
Perforation	0	0	0	–
	Total (n = 32)	Physiological solution (n = 16)	Diphoterine* (n = 16)	
Grade 2				
Delay of first irrigation (min)	19.8 ± 52	17.3 ± 45	22.2 ± 60	0.79 NS
Delay of second irrigation (h)	6.9 ± 9.9	3.6 ± 6.1	10.2 ± 11.9	0.57 NS
Time elapsed to reepithelialization (days)	7.7 ± 7.5	10 ± 9.2	5.6 ± 4.9	0.02
Final visual acuity	20/22 ± 20/100	20/22 ± 20/80	20/20 ± 20/200	0.83 NS
Corneal opacity	1 (3.1%)	1 (6.2%)	0	0.5 NS
Perforation	0	0	0	–
	Total (n = 12)	Physiological solution (n = 7)	Diphoterine* (n = 5)	
Grade 3				
Delay of first irrigation (min)	150 ± 254	120 ± 264	193 ± 262	0.64 NS
Delay of second irrigation (h)	5.5 ± 4.9	3.1 ± 4.1	8.8 ± 4.1	0.04
Time elapsed to reepithelialization (days)	38.9 ± 23	45.2 ± 23	20 ± 14.1	0.21 NS
Final visual acuity	20/28 ± 20/70	20/28 ± 20/50	20/28 ± 20/70	0.8 NS
Corneal opacity	3 (25%)	1 (14.3%)	2 (40%)	0.21 NS
Perforation	1 (8.3%)	0	1 (20%)	

n: number of eyes, NS: no significant.

dispute [10,11]. In Jamaica, a neighboring island of Martinique, between 1981 and 1990, 562 chemical burns were treated in the hospitals: 13.3% were related to an assault. This proportion exceeds two-thirds in certain urban areas with a significant population density and a low social and economic status. The burns are mainly located at the level of the face; the eyes and the eyelids are injured in 19% of cases. In Jamaica, as in Hong Kong, the intention of the assailant is to disfigure his victim [12,13]. In Martinique, the product used by the assailant is Alkali* sold in a plastic bottle containing 15.3% ammonia and a pH of 12.8. The bottle is compressible, easy to open, and lacking a safety device. Alkali* is used as both a household cleaning product and as a purifier: when one takes possession of a house or when chasing bad spirits from the victim. Ammonia is also used in Africa. Ukponmwan reports 12 cases of ocular burns in Benin City, Nigeria, which has similar demographic characteristics to ours: all the victims are men, 10 cases result from an assault, and the number of complications appears more significant taking into account the delay of medical treatment [14]. One-fourth of the burns by work-related or domestic accidents are related to the handling of Javel*. This product is sold in a completely deformable soft plastic carton, without a security system for opening. This type of packaging is not absolutely adapted to the danger of the contents as Poulquien had already shown in 1972 [15].

Three cases of corneal perforations were noted. The incidence of this complication is probably related to the quantity of the product exposed to the eye but also with the

duration of contact between the product and the ocular surface; actually the first rinse was carried out at 5 min, 3 h, and 12 h, and the second rinse, respectively at: 12 h with physiological solution, 3 h with physiological solution, and 12 h with Diphoterine*. Local corticoids could also be incriminated because their use in the treatment of chemical burns is controversial. In decreasing the keratocyte migration, they inhibit collagen synthesis and delay scarring. However, they decrease stromal invasion by polynuclear neutrophils, possess an anti-collagenase action and limit the accumulation of stromal edema [16–18]. Donshik showed in the rabbit that the intensive use of local corticoids in the first week after the burn does not lead to a greater risk of corneal perforation [19]. In association with local and oral ascorbic acid, Davis suggests that local corticoids can be prescribed beyond the 8 days with a beneficial effect [20]. Corticoids favor infections, but we did not observe any infection during the use of treatment.

Diphoterine* is an external rinse solution of the skin and eye. It is a medical device under the European directive 93/42CEE, with the marking CE obtained on September 30, 1996. It has been used for several years in industry and by the Paris fire department. In the event of an accident, it has proven to be very effective in reducing the number of work days missed [21,22]. This is the first human study that takes into account the type of ocular rinse product in the progressive follow-up study of injuries. Forty-eight eyes were rinsed with physiological solution and 56 eyes with Diphoterine*. The time elapsed to reepithelialization is

shorter with Diphoterine* than with physiological solution: for grade 1 burns: 1.9 ± 1 day versus 11.1 ± 1.4 days, for grade 2 burns: 5.6 ± 4.9 days versus 10 ± 9.2 days and for grade 3 burns: 20 ± 14.1 days versus 45.2 ± 23 days. These results obtained with Diphoterine* are similar to those noted by Brodovsky in a retrospective study that included 177 burned eyes: from 2.5 to 4 days for grade 1 burns, from 5.4 to 7.7 for grade 2 burns, and from 10 to 19 days for grade 3 burns. In this study, a proportion of the patients benefited from a standardized therapeutic protocol including local corticoids, antibiotics, ascorbate and citrate, but the nature of the rinse liquid used for the medical treatment was not specified [9]. Diphoterine* is a solution containing a molecule that is multisite, amphoteric, and chelatic. Amphoteres, like ethylene-diamine-tetraacetate (EDTA), act by the capture of ions and neutralization by an amphophilic reaction. They can bind with acids or bases without altering the pH of the environment and without undergoing exothermic reaction. Diphoterine* possesses sites of chelation for acids with a pK_1 of 5.1 and for bases with a pK_2 of 9.3, its pH is 7.4, and its osmolarity 820 mosm/l. Diphoterine* is hypertonic and creates a movement of water from the hypotonic anterior chamber towards the surface of the hypertonic cornea. The OH^- ions migrate to the exterior of the ocular globe by this movement [21]. Several studies carried out in animals have compared Diphoterine* to the physiological solution as a rinse product in alkali burns. A rinse with Diphoterine* leads to a quicker return to normal extra-ocular pH, a lesser ascension as well as a slight drop, and faster and steeper descent of the intraocular pH curve. Epithelial necrosis was observed for all the burns; on the other hand, the stromal edema is much less significant with Diphoterine*. This edema is related to an impairment of endothelial cells. They are destroyed or greatly altered by the physiological solution, but only present a few morphologic variations with Diphoterine* [21,23–27]. Initial stromal edema is a pejorative factor: Kubota showed that its extent would actually correlate to the size of the consequently scarred corneal opacity [28]. In the observation of a grade 4 alkali burn reported by Gerard, irrigation with Diphoterine* would immediately manifest as a reduction of the corneal edema, objectified by an increase in the visual acuity [16]. In the course of all these studies, no harmful effects of Diphoterine* have been shown. A serious chemical burn often leads to a functional or even anatomical loss of the eye. The emergency treatment proposed long ago is to rinse by water or better yet by isotonic solutions of physiological solution with the goal of eliminating a maximum amount of the toxic agent but without any demonstration of intrinsic pharmacologic effectiveness. Diphoterine* seems very effective in terms of its mechanism of action and the experimental results obtained. Compared to the physiological solution, the healing time of corneal scarring from grade 1 and 2 burns is shorter with Diphoterine*. For grade 3 and 4 burns, there are not enough cases to judge the effectiveness of rinse with Diphoterine*.

Our study shows that the longer the delay between the accident and the rinse, the more serious the burn. The establishment of a standardized protocol in advising the susceptible workforce to seek treatment in emergencies of chemical ocular burns will contribute to reduce this delay.

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