THE CLINICAL EFFICACY OF DIPHOTERINE® IN THE MANAGEMENT OF CUTANEOUS CHEMICAL BURNS: A 2-YEAR EVALUATION STUDY

L'EFFICACITÉ CLINIQUE DE LA DIPHOTÉRINE® DANS LA PRISE EN CHARGE DES BRÛLURES CHIMIQUES : UNE ÉTUDE DE 2 ANS

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SUMMARY. Diphoterine® is an amphoteric irrigating agent for the treatment of chemical burns and rapidly neutralises both acids and alkalis faster than water alone. Diphoterine® is widely used as a first aid agent in a wide range of industries globally. This is a retrospective review of the clinical use of Diphoterine® on chemical burns in an adult tertiary referral burn centre, often with a delay of several hours after the injury. Patients admitted with chemical burns within 24 hours of the incident with an abnormal wound pH or in pain, were treated with Diphoterine® spray. Over a 32-month period, 1,875 burn referrals were admitted of which 131 (7%) were chemical burns. Diphoterine® was used in 47 patients (36%). The male to female ratio for the 131 patients was 4:1. Alkaline burns were the commonest (55%). Patients who received Diphoterine® were significantly younger (38 vs 43 years; p=0.05) and presented earlier (0.5 vs 2.55 days; p=0.004). There was a significant change in the wound pH pre- and post-application of Diphoterine®, compared to patients who were treated with water irrigation only, with a pH change of 1.076 vs 0.4 (p <0.05). There was no significant difference in the time to healing, the length of hospital stay, or need for surgery. In conclusion, based on our retrospective cohort, Diphoterine® could be a valuable tool for use in hospital settings to neutralise both alkaline and acid burns.

Keywords: Diphoterine®, amphoteric, chemical, hypertonic

RÉSUMÉ. *La solution Diphotérine® est un agent d'irrigation amphotère pour le traitement des brûlures chimiques qui neutralise les acides et alcalis plus rapidement que l'eau seule. La Diphotérine® est largement utilisé comme un premier agent de l'aide dans un large éventail d'industries au monde. Nous présentons une revue rétrospective de l'utilisation clinique de la Diphotérine® sur les brûlures chimiques. Cette revue se base sur les données d'un centre de référence tertiaire pour les brûlés adultes où souvent les patients se sont présentés avec un retard de plusieurs heures après la blessure. Tous les patients atteints de brûlures chimiques, admis entre les 24 heures suivant l'incident dans la douleur ou avec le pH anormale de la plaie, ont été traités avec la Diphotérine® appliquée par pulvérisation. Sur une période de 32 mois, 1 875 références de brûlures ont été admis dont 131 (7%) étaient des brûlures chimiques. La Diphotérine® a été utilisée chez 47 patients (36%). Le rapport hommes-femmes pour les 131 patients était de 4: 1. Les brûlures alcalines étaient les plus fréquentes (55%). Les patients qui ont reçu la Diphotérine® étaient significativement plus jeunes (38 v 43; p = 0,05) et si sont présentés plus tôt par rapport aux patients plus âgés (0,5 v 2,55 jours; p = 0,004). Il y avait un changement significatif dans le pH avant et aprés l'application de la Diphotérine®, par rapport aux patients qui ont été traités avec l'irrigation de l'eau seulement, avec un changement de pH de 1,076 v 0,4 (p <0,05). Il n'y avait pas de différence significative dans le temps de la guérison, la durée de séjour à l'hôpital, ou le besoin de chirurgie. En conclusion, sur la base de notre cohorte rétrospective, la Diphotérine® pourrait être un outil précieux en milieu hospitalier pour neutraliser des brûlures alcalines et à l'acide.*

Mots-clés*: Diphotérine®, amphotère, chimique, hypertonique*

Introduction

Around 25,000 products used at home and in industry are known to be responsible for causing chemical burns. A range of chemicals, such as acids, alkalis and chemical agents, each with their own individual biochemical prop-

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erties, can cause such burns. The mechanisms by which these injuries occur are also wide-ranging, from household accidents, occupational exposures to acts of war. Overall, such burns account for an increasing proportion of admissions to our centre, equating to 7% of all burn referrals. Diphoterine® has been used in our centre since 2010. Produced in France by Prevor laboratory, Diphoterine® is a polyvalent, amphoteric, chelating washing agent, which is slightly hypertonic and rapidly neutralises chemical burns to the eyes and skin. When compared with using distilled water or normal saline, it is known to remove the offending chemical up to 4 times faster than saline alone, which results in significantly less severe blistering. For pH normalisation, up to 17 times less volume of Diphoterine® is required compared to water alone. The safety of Diphoterine® is proven and thus it can be used in large doses corresponding to LD50 value of > 2000mg/Kg by oral and dermal routes of exposure in rats. Diphoterine® cutaneous safety was also demonstrated by Mathieu et al. in 2007.[1] Using non-burnt guinea pigs, they demonstrated Diphoterine® is well tolerated as no animal developed an allergenic response to the reagent between 24-48 hours post exposure. In the acute setting, Diphoterine® has analgesic properties and its use in the rat model has shown significant reductions of substance P release whilst increasing the release of β-endorphins. Its use has also led to reductions in inflammatory markers after its application in rats. In severe, large chemical burns Diphoterine® may reduce severity of associated injuries. Despite the number of encouraging animal studies, there are few published human studies and these are often restricted to chemically induced eye injuries, case-based studies or those based in an industrial setting. To our knowledge, this is the first independent evaluation study of the delayed use of Diphoterine® in cutaneous chemical burns.

Materials and methods

We retrospectively reviewed all burns referrals to the University Hospital Birmingham between January 2010 and September 2012 (32 months). The hospital's local governance committee approved the study. The protocol in our burns centre is to treat the patients suffering from chemical burns with Diphoterine® within 24 hours of injury. Patients who present after this watershed period are managed with water irrigation only. Forty-seven patients with chemical burns and Diphoterine® irrigation were compared to 84 patients irrigated with water only.

Patients' data were collated from paper files, electronic patient records and our local British Isles Burn Injury Database (BIBID). The data was securely entered into a Microsoft Excel® spreadsheet (Microsoft® Corporation, Redmond, WA, USA). Each patient was coded confidentially using their unique patient identifier followed by the fields of BIBID descriptors. The data included standard measures such as demographics, causative agents, burn injury details, referring regions, anatomical areas affected and admission pH check figures. Patients were divided into groups based on whether or not they had received Diphoterine®. After the data was appropriated from categorical variant to numerical this was then transferred to Statistical Analysis in Social Science (SPSS) (IBM® Corporation, version 21, Armonk, New York, USA) for definitive statistical analysis.

Given the multiple aims of the study, a variety of statistical methods were used to analyse the data. The primary outcomes included the timings from injury to healing/surgery, time to discharge, operative intervention and changes of pH in both patient groups who were and were not treated with Diphoterine®. Other standard determinants such as patient demographics and total burn surface area (TBSA) were also collected.

To compare the means for a normally distributed data set, for example age, an independent t-test was performed as the two groups were independent, and assumption of equal data variance was produced from Levene's test. For non-normally distributed data, median value calculation was followed by a Mann Whitney U Test. A p value of <0.05 was considered to be significant for all of the statistical tests in this study.

Results

Table I below highlights the key results in the data collected. A total of 1,875 burn referrals were received in the 32-month study period of which 131 (7%) were chemical burns. The mean age for these 131 patients was 41.24 years. Predominantly men sustained chemical burns with a ratio

Table I - Comparison of Diphoterine® and non-Diphoterine® groups

Measured Outcome	*Diphoterine®*	*Non-Diphoterine®*	*P Value*
n (Patients)	47	84	-
Age (Years)	37.70	43.20	0.044*
Time to Presentation (Days)	0.57	2.15	0.004*
Injury to surgery†	3.50	5.00	0.067**
Injury to heal time†	9.00	7.00	0.258
Injury to discharge†	2.0	2.0	0.469
Length of stay (Days)	1.75	1.58	0.800
TBSA (%)†	1.76	1.25	0.203
Surgical Intervention	10	10	0.211
pH Change	1.076	0.4	0.000*

† Indicates non-normally distributed data

* statistically significant

** approaching statistical significance

of 104:26 (4:1). There was no significant difference between the age of males versus females, 41.38 vs. 40.70 years, $P = 0.836$. Alkali burns accounted for 72 (55.0%), acids 24 (18.3%) whilst other chemicals accounted for 35 (26.7%) of the cases. The most commonly injured areas of the body included the right hand (13%), face (10%) and the knees (9%). The perineum and scalp were the least commonly affected areas in our study (0.5% overall). Only 47/131 (36%) received Diphoterine® during our study period. These were the patients who presented early and had altered pH. The average pre-irrigation pH of patients receiving Diphoterine® was 8.07 compared to 7.77 in those not receiving it. This difference was not statistically different equating to a p value of 0.369. Those patients who received Diphoterine® had an average change in pH of 1.076 in comparison to 0.4 in those who were treated solely with water ($P<0.05$). The Diphoterine®-treated patients were significantly younger (37.7 vs 43.2 years, $P = 0.044$) than those treated without Diphoterine®. Understandably, patients who received Diphoterine® presented to hospital significantly earlier than those who did not receive it (0.5 vs 2.55 days $P = 0.006$). The TBSA between the Diphoterine® and water-only treatment groups did not vary significantly. The use of Diphoterine® was not associated with reduced median length of stay ($P = 0.200$), injury to healing times ($P = 0.74$) or the total number of grafting operations ($P = 0.211$). Using the chi-squared test, there was also no significant difference in the operative rate between those who received and did not receive Diphoterine® ($P = 0.323$).

Discussion

This is the first evaluation of the delayed use of Diphoterine® for treating cutaneous burns exclusively in the hospital setting. Diphoterine® is widely used as first aid by ambulance services and fire-fighters in Sweden and France. Delayed presentation of small chemical burns to a tertiary referral burns centre was sought to be a factor against its use. The largest review of Diphoterine® use in the literature to date was published by Donoghue 2010.[2] This study was performed in an industrial setting to examine the benefit of Diphoterine® as a first aid measure. Individuals who had alkaline splash, either received Diphoterine® or water. In this study, 52.9% of the patients treated with Diphoterine® initially showed no evidence of cutaneous injury compared with 21.4% in those treated with water alone. Subsequently, the "first aid" injury rate decreased significantly by 24.7% (95% CI 0.5 - 43.0%). Diphoterine® is not readily available as a first aid in many of the UK industry establishments where chemical burns are likely to occur. It is also not available for ambulance crews or emergency departments.

Other smaller studies have reported the use of Diphoterine® in small number case reports or in animal models. However, the methodology of the study by Viala et al., published in 2005,[3] was severely criticised. A summary of the previous literature on Diphoterine® use is shown in *Table II*. Although many studies included within *Table II* confirm the improved neutralisation of chemical burns using Diphoterine® over water alone, very few studies have consistent and clinically relevant outcomes to patients sustaining chemical burns.

In this study, 47/131 patients (36%) received Diphoterine® during their admission or assessment. The patients receiving Diphoterine® according to our outline protocol, on average were significantly younger, presented earlier and had reduced time for first surgery. However, this did not quite reach statistical significance. The patients re-

Table II - A summary of previous clinical and animal studies involving Diphoterine®

Author	*Year*	*Type of Study*	*Area of Body Studied*
Brent	2013	Review	Skin
Goldich et al.	2013	Experimental (animal)	Eyes
Chau et al.	2012	Systematic review	Eyes
Palao et al.	2010	Review	Skin
Fosse et al.	2010	Experimental	Skin
Donoghue	2010	Clinical Case Series	Skin
Hall et al.	2009	Review animal	Skin
Mathieu et al.	2007	Experimental animal	Skin
Nehles et al.	2006	Case Summary	Eyes & Skin
Viala et al.	2005	Preliminary Studies	Eyes & Skin
Merle et al.	2005	Prospective Objective Case Series	Eyes
Cavallini et al.	2004	Experimental (animal)	Skin
Cavallini & Casati	2004	Experimental (animal)	Skin
Hall et al.	2002	Review	Eyes & Skin
Schrage et al.	2002	Experimental (animal)	Eyes

ceiving Diphoterine® had significant changes in their pH tests pre- and post-measurements. On average these patients presented after 0.57 days, equating to roughly 12 hours. Our indications for Diphoterine® application were early presentation (within 24 hours), abnormal pH and/or a painful burn. The statistically significant finding of a pH change after 12 hours justifies the checking of a pH on delayed presentation and the continual use of Diphoterine® until all 3 of the indications are no longer relevant. The timely application of Diphoterine® leads to faster correction of abnormal pH and this therapeutic intervention could limit the zone of stasis described by Jackson in 1947, resulting in the reversal of damage in this sensitive area. The delay in presentation in the Diphoterine® and non-Diphoterine® groups may be explained by the patients with more severe injuries presenting to the emergency department sooner, while those who perhaps had more minor injuries managed them at home themselves initially. Later on, 24-72 post-burn, these patients may have realised that their burns were not healing and subsequently presented late. As per protocol, these patients were not treated with Diphoterine®, which may explain the differing results and outcomes between the groups.

Similar body topographical distributions were seen in the burns recorded in this study and a previous study in our unit. The distributions likely reflect the fact that most patients are right handed and gloves were not always worn when using these chemical products at home. Facial and eye burns were frequently documented in the literature. The same was noted in our study as almost half of the chemical burns involved hands and eyes. Merle et al.[4] reported that when Diphoterine® eye wash is used for grade I and grade II corneal injuries, following chemical injury, re-epithelialisation rates are greater than with saline wash alone.

Conclusion

The authors are aware of the limitations of this study. Firstly, the data collection in this study is entirely retrospective and thus the interpreted data was only as good as what was documented in the information tools that were assessed. Secondly, the authors also appreciate that the favourable change in the pH in the Diphoterine® group may be attributed to the earlier application compared to water irrigation alone. Future randomised study is required for better comparison and for standardised objective assessment of burn healing, which will need to be prospectively documented. Future larger, prospective randomized trials would also be required to determine the optimum timing of Diphoterine® use in cutaneous chemical burns®. Anecdotally, patients treated with Diphoterine® had lower analgesic demand. This will be explored in detail in a follow-up study in due course.

This study demonstrates the potential utility of Diphoterine® in a tertiary burn centre. This was demonstrated by the significant changes in pH between the patients treated with Diphoterine® and those who were not. However, a larger prospective randomized controlled trial is needed to prove this efficacy. Any future study would have to consider the differences in analgesic requirements between the two patient groups.

Although Diphoterine® is considered effective for the delayed treatment of chemical burns, there are still some significant barriers before first aider, ambulance paramedics and Emergency Department staff would be able to use it. Diphoterine® costs up to $83 per canisters; usually 1 canister is used per patient. The high cost of this product may prohibit its routine availability and usage amongst front-line healthcare providers.

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