JCI The Journal of Clinical Investigation

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W. T. Longcope, … , M. M. Wintrobe, Val Jäger

J Clin Invest. 1946;25(4):528-533. https://doi.org/10.1172/JCI101734.

Research Article

CLINICAL USES OF 2,3-DIMERCAPTOPROPANOL (BAL). VII. THE TREATMENT OF ARSENICAL DERMATITIS WITH PREPARATIONS OF BAL

By W. T. LONGCOPE, JOHN A. LUETSCHER, JR., M. M. WINTROBE, AND VAL JÄGER

(From the Medical Clinic, the School of Medicine, Johns Hopkins University and Hospital, Baltimore)

(Received for publication February 5, 1946)

The development of 2,3-dimercaptopropanol (British Anti-Lewisite, BAL) by Peters, Stocken, and Thompson (1) has made available a potent antidote for arsenical poisoning. Study of the chemical combination of arsenic with sensitive enzymes and cells indicated that the arsenic could, under certain circumstances, be removed from the cells, and that enzymes could be reactivated by the action of BAL (1, 2). BAL administered to animals exerted both protective and therapeutic effects against local and systemic injury by toxic arsenicals (1, 2). These observations strongly suggested that BAL might be useful in arsenical poisoning in man, and cautious trials were initiated in this hospital at the end of 1942.

METHODS

Patients were admitted to a special ward which was in part arranged for the care of civilians employed at Edgewood Arsenal, under contract between the Johns Hopkins Hospital and the U. S. Employees Compensation Commission, and in cooperation with the Chemical Warfare Service. A detailed clinical study was made of these patients both before and after the administration of BAL. BAL was given by inunction in 1 to 10 per cent ointment (3) and later by intramuscular injection in 5 to 10 per cent solution in peanut oil containing benzyl benzoate (4). Dosage was at first varied and rather small because of the lack of information on the therapeutic and toxic effects of BAL.

Arsenic in the urine was determined by the method of Magnuson and Watson (5) in the laboratory of Dr. H. Eagle. Chemical analyses of the blood were made under the direction of Dr. Mary Buell.

RESULTS

1. *Dermatitis due to diphenylamine chlorarsine*

A number of workers exposed to the dust of this chemical (also known as Adamsite or DM) developed intractable dermatitis involving the exposed areas of the face, neck and arms. Most of these patients gave a positive patch test to DM. The itching, burning, erythematous and papular eruption proved resistant to ordinary forms of treatment. They were therefore transferred from Edgewood Arsenal to our special ward for investigation. In 6 of the 7 patients, the dermatitis had persisted for 18 to 50 days before they were admitted to the hospital.

The application of BAL in ointment caused intense burning of the affected areas, but this lasted for less than an hour, after which the patients received great relief from the previous itching and discomfort. Daily applications were made, beginning with as low as 100 mgm., and increasing to 500 mgm. per day in each case. The dermatitis cleared completely in from 2 to 8 days, with an average of a little over 5 days. The patients served as their own controls in these studies, since the eruption had been present for very different lengths of time before treatment, and had failed to respond to other forms of therapy (removal of irritant and application of boric ointment and BAL ointment base) prior to the use of BAL.

In attempting to conduct controls during the course of these observations, BAL in ointment was applied to the lesion on one arm, and the ointment without BAL to the lesion on the opposite arm. Both lesions healed with about equal rapidity. It was known that BAL is absorbed readily through the skin and it therefore occurred to us that the improvement might be due to the systemic action of BAL as well as to its local effect. BAL was therefore applied to unaffected portions of the skin. These inunctions caused no discomfort and therefore comparatively large amounts of ointment could be employed. The results were highly satisfactory, and the dermatitis

[1] This investigation was carried out under contract with the Office of Scientific Research and Development, Committee on Medical Research, OEMcmr-253.

cleared under this method of application as rapidly as when the inunction had been made to the eruption itself.

The arsenic excretion in the urine increased during treatment (6), suggesting that arsenic had been released from combination with the cells.

2. Arsenical dermatitis occurring during anti-syphilitic therapy

Fifteen patients referred to the hospital from several clinics because of exfoliative dermatitis produced by anti-syphilitic arsenical drugs have been treated with BAL. Four of these patients received daily inunctions of BAL in ointment (5 to 10 per cent) for periods of 3 to 11 days. The average daily dose of BAL was 500 mgm. The application of this ointment was extremely painful and in one instance so agonizing that morphine was required. The exquisite pain lasted from ½ to 2 hours, but the relief from itching and burning was so marked within 12 to 24 hours that the patients often asked for further treatments. Applications had to be made over different areas each day, otherwise there developed a local pustular dermatitis due, we thought, to BAL itself. In many instances there was a dramatic improvement within 48 hours in the arsenical dermatitis (Figures 1 and 2). This was often most noticeable over the area anointed.

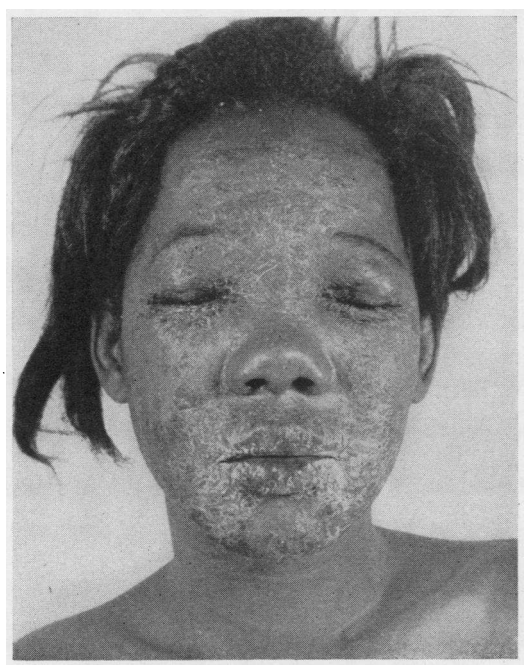

FIG. 1. CASE 4, TABLE I
Showing exfoliating dermatitis of face on May 13, 1943.

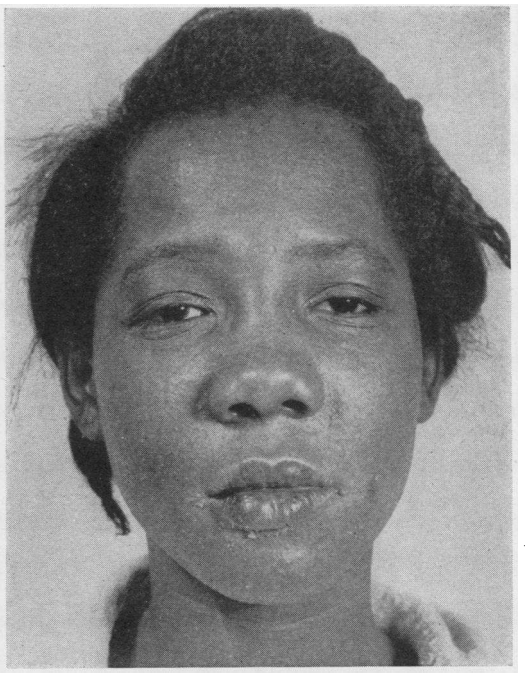

FIG. 2. CASE 4, TABLE I
On May 17, 1943, 4 days later than Figure 1, after 1 gram BAL in ointment.

Eleven patients were treated with intramuscular injections of BAL in 5 to 10 per cent solution in peanut oil and benzyl benzoate. The daily dose of BAL varied from 100 to 450 mgm. a day, the average being 300 mgm. Individual injections ranged from 100 to 200 mgm., averaging 150 mgm. One or more courses of treatment lasting 4 to 10 days were given.

Three patients had disagreeable symptoms from 20 minutes to 1 hour after injection of BAL. One patient complained of aching pains in the muscles of the legs, and one patient had burning of the mouth, with nausea and vomiting. These 2 patients were receiving 3.5 and 3.7 mgm. of BAL per kgm. of body weight at 6-hour intervals.[2]

[2] While our studies were in progress, the effects of injection of large doses of BAL in peanut oil were tested in human volunteers (4, 10, 11). The results demonstrated that a single dose of more than 3 mgm. of BAL per kgm. of body weight is likely to cause distressing symptoms, but that injections could be repeated at inter-

TABLE I—*Treatment with 5 per cent and 10 per cent BAL in ointment*

Date of adm.	No.	Sex	Age	Color	Arsenical	Amt.	Doses	Onset of dermatitis after last dose	Duration of dermatitis before adm.	Extent of dermatitis	Duration of treatment	Total BAL	Relapses	No. of courses of BAL	Duration of dermatitis after 1st dose BAL	Complications
						grams		*days*	*days*		*days*	*grams*				
2/25/43	1	F	19	C	Neoarsphenamine	3.0	5	3	11	+++ Generalized patchy, exfoliative. No fever	1st C. 11 2nd C. 3 Total 14	4.0 } 5.5 1.5 }	1	2	19 days	None
3/31/43	2	F	22	C	Neoarsphenamine	2.7	5	7	12	+++ Exfoliative, generalized, mod. T. 101 to 102	4	3.0	0	1	12 days	Cutaneous abscess
5/ 4/43	3	F	40	W	Neoarsphenamine 2nd course	0.45	1	1	10	++++ Generalized, exfoliative T. 101	1st C. 5 2nd C. 3 Total 8	2.5 } 4.0 1.5 }	1	2	16 to 22 days	Cystitis
5/12/43	4	F	20	C	Diarsenol 2nd course	0.3	1	1 to 8	5	Exfoliative face	4	2.0	0	1	6 days	None

Symptoms disappeared when injections were stopped in one case and the dosage reduced in the other. A third patient had nausea ½ hour after each injection of a small dose of BAL (1.8 mgm. per kgm.). This patient had jaundice as well as dermatitis, and was probably more sensitive to gastrointestinal disturbance (1). One patient developed an abscess of the buttock at the site of an injection, an unexpectedly rare occurrence considering the distressing condition of the skin through which the injection must be made and the frequency of spontaneous abscesses.

The results are presented in Tables I and II. It is impossible in such a small series of cases to evaluate the effects of route of administration or dosage. The results appeared to be beneficial in all cases as judged by the patients' subjective reactions. Itching and burning often diminished within 24 hours, and were greatly improved in 48 hours. At about this time objective improvement in the skin usually became apparent and sometimes progressed to rapid and complete healing of the dermatitis within as few as 6 days. More often some evidences of the dermatitis persisted and complete healing occurred only after several weeks. During this time the patients' complaints were much relieved, and the skin showed only residual changes rather than continuation of inflammation. The dermatitis in 5 patients was prolonged because of mild relapses following cessation of treatment. These relapses usually responded to a second and even third course of BAL. We received a strong impression that treatment should be continued for at least 6 days and preferably longer, since ½ of the patients treated for less than 6 days developed a relapse of the dermatitis, while only 2 of the 9 patients treated 6 days or more showed a recurrence of the dermatitis.

The clinical improvement of these patients was accompanied by a considerable increase in the excretion of arsenic in the urine (6). A similar increase followed a second or third course of BAL during treatment of the relapses.

The observation that relapses of the dermatitis might occur when treatment by BAL was dis-

vals of 3 to 4 hours with a minimal cumulative toxicity, an important point since large amounts of BAL may be given in this way.

TABLE II

Treatment with 5 per cent to 10 per cent BAL intramuscularly

Date of adm.	No.	Sex	Age	Col.	Arsenical	Amt.	Doses	Onset of dermatitis after last dose	Duration of dermatitis before adm.	Extent of dermatitis	Duration of treatment	Total BAL	Relapses	No. of courses of BAL	Duration of dermatitis after 1st dose BAL	Complications
						grams		*days*	*days*		*days*	*grams*				
8/4/43	1	F	38	C	Neoarsphenamine 2nd course. History of dermatitis	0.3	1	1	8	++++ Generalized exfoliative T. 102 to 105	1st C. 3 2nd C. 3	0.3 0.45 } 0.75	1	2	14 days	Infection B. hem. streptococcus and staphylococcus. Sulfadiazine
8/12/43	2	F	25	W	Mapharsen 2nd course. History of dermatitis	0.015	2	Day of last dose	2	++++ Generalized edema, erythema papular T. 102	4	0.85	0	1	9 days	
11/25/43	3	F	19	W	Neoarsphenamine 2nd course	3.6	6	Day of last dose	10	++++ Generalized exfoliative, red T. 99 to 101	1st C. 4 2nd C. 3 3rd C. 3	0.9 0.45 1.5 } 2.85	2	3	39+ days	
3/10/44	4	F	38	C	Mapharsen 2nd course	0.30	5	2	8	++ Vesicular, arms and face	6	1.35	0	1	12 days	Jaundice
6/19/44	5	F	25	C	Neoarsphenamine	3	7	3	8	++++ Generalized erythema, papular T. 102 to 105	1st C. 6 2nd C. 6	1.86	1	2	51 days	Jaundice Fever, relapsing
7/14/44	6	M	43	C	Mapharsen	1.50	25	3 before last dose	10	++++ Generalized acute, red, exfoliative T. 101	8	1.8	0	1	53 days	Multiple abscesses of skin and lymph nodes
10/16/44	7	F	37	W	Neoarsphenamine	0.9	3	11 ?	11	+++ Generalized maculo-papular erythema weeping T. 101 to 103	6	1.8	0	1	17 days	
11/11/44	8	F	19	C	Neoarsphenamine	1.9	4	8	15	++++ Generalized exfoliating edema T. 102 to 105	6	2.35	0	1	80 days	Perineal abscess. Abscesses of skin, multiple; fever 2 months. Penicillin
4/26/45	9	M	36	C	? 2nd course. History of dermatitis	?	3	After 2nd dose	3	++++ Generalized edema, erythema papulo-vesicular T. 99.6 to 101	10	4.3	0	1	13 days marked improvement	Abscess of buttocks
5/15/45	10	F	16	C	Neoarsphenamine	?	6	After 1st dose	21	++++ Generalized vesicular crusting, weeping T. 100.8	7	2.85	0	1	8 days	
4/2/45	11	F	25	C	Neoarsphenamine	2.4	4	2	35	++++ Generalized T. 100.2	8	1.8	0	1	16 days	

continued, but could be controlled by reinstituting treatment, and that the excretion of arsenic in the urine increased during each course of treatment by BAL, but decreased rapidly each time that the administration of BAL was omitted. suggested very strongly that there was a relationship between the 2 sets of conditions. Such a correlation might be interpreted as an indication that the intramuscular injections of BAL resulted in a liberation of arsenic from the tissues of the body, and that this release of arsenic was followed by clinical improvement.

DISCUSSION

We have been very favorably impressed with the response to the administration of BAL in exfoliative dermatitis. The patients described a considerable relief of symptoms. The objective improvement was often equally impressive, but complete healing was frequently delayed for several weeks. It may be possible to eliminate the mild relapses which prolonged the course of ⅓ of our patients, by continuing the treatment for as long as a week or more after the initial rapid improvement occurs.

In addition to the relief of the patient's symptoms and the objective improvement in the skin after the use of BAL, we had the impression that the patient's illness was shortened. Because of the variability of the disease, it is difficult to obtain any accurate information on the duration of arsenical exfoliative dermatitis. It is said to last "seldom less than 8 weeks and often as long as 12 or more" (7).

During the past 20 years, 49 patients have been admitted to the Johns Hopkins Hospital for arsenical exfoliative dermatitis, and have been followed throughout the course of the disease in the hospital and its out-patient department. The precipitating agents were neoarsphenamine (23 cases), arsphenamine (10 cases), mapharsen (3 cases), and in several cases the less commonly used

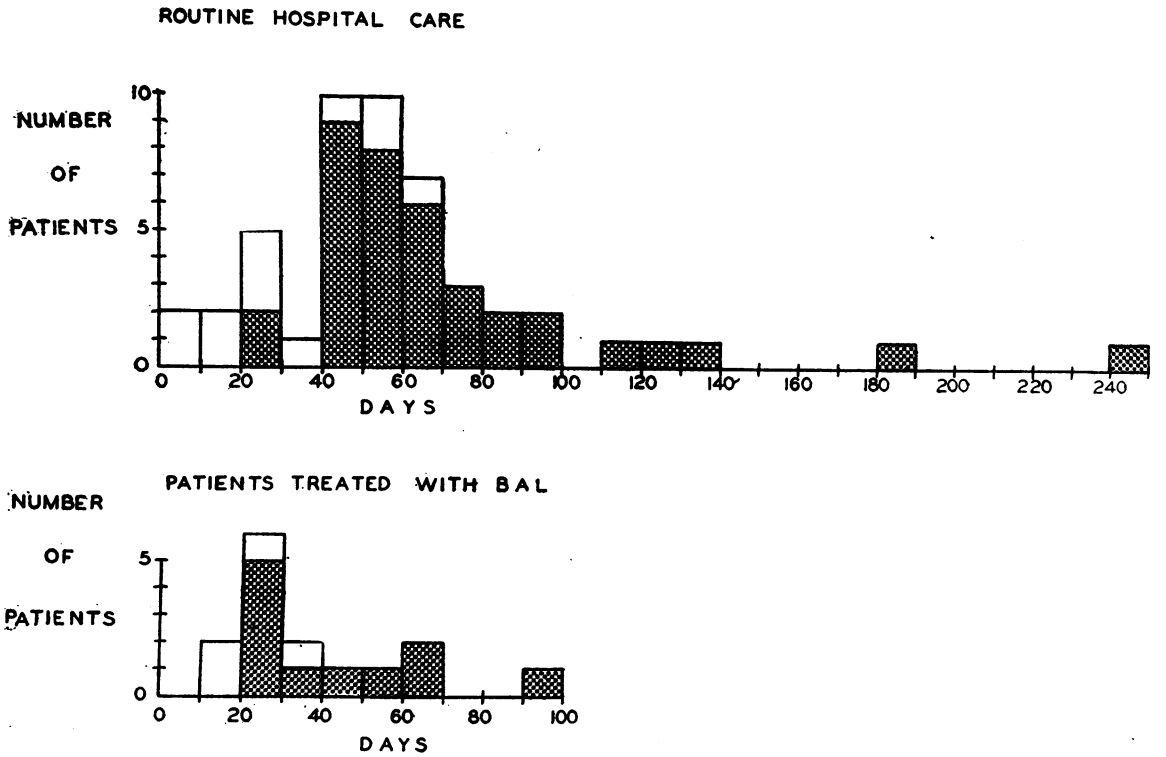

FIG. 3. COMPARISON OF THE TOTAL DURATION OF EXFOLIATIVE DERMATITIS IN 49 ATTACKS IN 46 PATIENTS NOT TREATED WITH BAL, WITH THE TOTAL DURATION IN 15 COMPARABLE PATIENTS TREATED WITH BAL

Open squares: Patients receiving 1 or 2 injections, often small test doses, of arsenical drug. Shaded squares: Patients receiving 3 or more therapeutic doses of arsenical drug.

arsenical drugs. There was no evidence that the dermatitis produced by one of these arsenicals differed in severity or duration from the group as a whole. It is clear, however, that dosage and repeated injections may affect the duration of the reaction. Figure 3 shows that exfoliative dermatitis following only 1 or 2 injections of arsenic (often small doses because of suspected hypersensitivity) was frequently quite brief, in contrast to the generally more prolonged course in patients who received 3 or more therapeutic doses of an arsenical drug. Three deaths occurred in this latter group of 36 patients.

The dermatitis in the patients treated with BAL was probably of somewhat greater average severity than in the control group. The patients were admitted to the hospital at about the same time (average of both series was the 10th day).

In the group treated with BAL, there were a number of patients who recovered with unexpected rapidity (Figure 3). This difference from the control series is most evident in the patients who received 3 or more therapeutic doses of arsenic. On the other hand, the cases who received smaller and fewer doses might have recovered spontaneously at this time, and little can be said about the effect of BAL on the duration of the disease. No deaths occurred in the 15 patients who received BAL, although 3 deaths occurred in the control series of 49 patients and far higher mortality rates have been reported in patients with severe exfoliative dermatitis (8, 9).

SUMMARY AND CONCLUSIONS

Twenty-two cases of arsenical dermatitis have been treated with 2,3-dimercaptopropanol (BAL).

Seven of these patients with an intractable, localized dermatitis caused by diphenylamine chlorarsine improved within a few days after the inunction of BAL in ointment.

Fifteen cases of generalized, exfoliative dermatitis following the use of antisyphilitic arsenicals have been treated with inunction or injection of BAL. Symptomatic and objective improvement regularly followed the administration of BAL. The duration of the dermatitis in over ½ of the patients treated with BAL was shorter than in a comparable group of patients who were not treated with BAL.

A mild recurrence of the dermatitis was frequent when treatment was not continued for at least 1 week. Six such relapses cleared quickly after reinstitution of therapy.

BAL in ointment was quite painful when applied to inflamed skin, while intramuscular injections were much less disturbing. No serious constitutional reaction to BAL was observed with the small doses employed.

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