BLOOD AND URINE CONCENTRATION OF PROMIN, DIASONE, AND PROMIZOLE IN THE TREATMENT OF LEPROSY*

By

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Clinical reports on the chemotherapy of leprosy with promin, diasone, and promizole have been reported in the literature (1, 2, 3, 4, 5, 6). Promin is the sodium salt of p,p'-diamino-diphenyl-sulfone-N, N'-di-(dextrose sodium sulfonate). Diasone is disodium formaldehyde sulfoxylate diaminodiphenyl sulfone. Promizole is 4,2'-diamino-phenyl-5-thiazole sulfone. Diamino-diphenyl sulfone, the basic chemical from which these drugs are derived, seems to be the active principle of each. These drugs have proved more valuable in the treatment of leprosy than any previous treatment tried at the National Leprosarium.

Promin treatment was initiated at this institution in March 1941. This drug is given intravenously, beginning with a dose of 1 Gm. daily, which dose is increased to 5 Gm. daily. Because of possible toxic reactions, treatments are discontinued for one week following each two weeks of daily intravenous injections.

Diasone therapy was started in July 1943. Treatment is usually begun with a dose of 0.33 Gm. by mouth daily for a period of two weeks, when the dose is increased to 0.66 Gm. a day. After a few weeks, the dose of 1.0 Gm. a day is tolerated by the majority of the patients, with a rest period of two weeks for every two months of treatment.

Promizole was started at Carville in March, 1945. It is administered by mouth in tablet form. At first 0.5 to 1.0 Gm. is given three times a day. After one to two weeks this dose is gradually increased, varying with individual tolerance, up to 6 to 7 Gm. a day.

In our early studies on treatment with sulfones, it was found that only traces of promin remained in the blood six to eight hours following the intravenous administration of 5 Gm. Occasionally, in patients with severe renal impairment, 20 to 30 mgm. per cent were observed. Diasone blood levels were found to average 1 mgm.

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per cent twelve hours after the evening dose in patients taking 1 Gm. daily. With daily doses of 6 to 7 Gm. of promizole, it was found that blood levels decline rapidly and reach 1 to 2 mgm. per cent twelve hours after the last dose, large amounts being eliminated in the urine.

Since leprosy is a chronic disease, affecting many of the tissues of the body, and dramatic cures are not obtainable with sulfone treatment, it has been found necessary to continue the use of large doses over long periods of time. It is advantageous in controlling treatment to know the sulfone concentrations in the blood, and to know the rate of elimination, even though no dogmatic schedule of dosage will give predictable blood levels, because of individual variations in absorption, retention, and excretion.

The present report is based upon 575 determinations of the amounts of sulfones in the blood and urine made over a period of six months. They are as follows:

Promin—106 patients taking the drug from one to six years

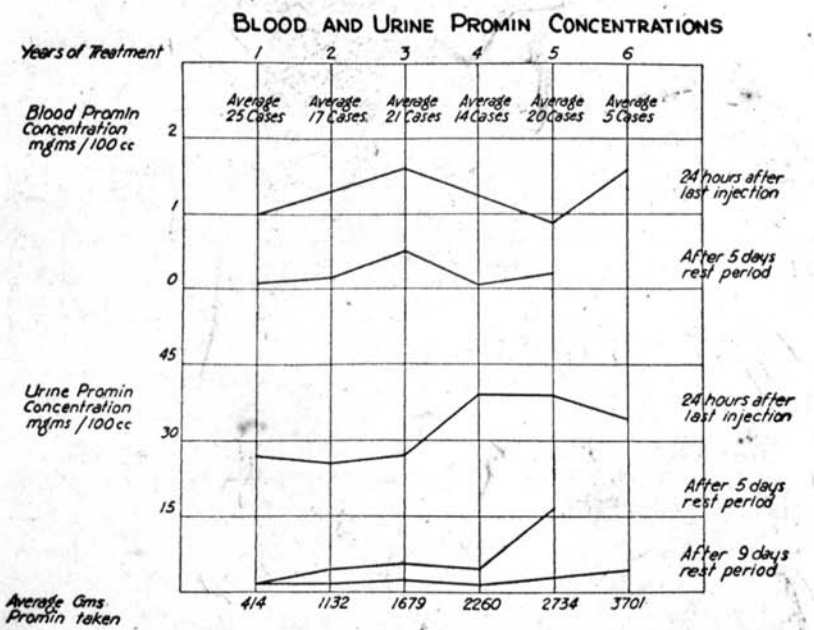
Diasone—68 patients taking the drug from one to four years

Promizole—13 patients taking the drug from one-half to one and one-half years.

The blood for the determinations was always drawn at the same hour of the day, between 8 and 9 a.m., and therefore in constant relation to the time of administration of the compounds. The urine sulfone concentrations were based upon twenty-four hour specimens collected from 7 a.m. to 7 a.m. the next morning. The method used for the determinations was that of Bratton and Marshall (7) utilizing the Klett-Summerson photoelectric colorimeter for the readings. In determining the promin, diasone, and promizole concentrations, the possibility of the presence of other sulfones, such as sulfathiazole and sulfamylon, was eliminated. All analyses were completed the same day. It has been recommended (8) that the blood be filtered immediately as the precipitate has a tendency to absorb the drug. The non protein nitrogen of the blood was determined simultaneously with the sulfones in 176 of the cases.

CONCENTRATION OF PROMIN IN THE BLOOD AND URINE

The results shown in figure 1 are averages from patients receiving single daily intravenous doses of 5 Gm. Determinations were made at intervals of twenty-four hours, five days, and nine days. Excretion of the drug was determined quantitatively in the urine of the same patients. The patients were selected for the number of years on this form of therapy. Only 5 of the original 10 patients



who have been on promin for six years were available for study. There was considerable variation in the blood concentration on the same dose. The minimum and maximum blood and urine concentrations made twenty-four hours after the last injection are shown in table 1.

TABLE 1. *Minimum and maximum concentration of promin in blood and urine twenty-four hours after last injection.*

Years of treatment	Total amount of promin taken	Blood concentration		Urine concentration	
		Minimum	Maximum	Minimum	Maximum
	Gm.	Values expressed in mgm. per 100 cc			
6	5,148	trace	3.6	18.0	86.0
5	5,383	trace	2.3	1.0	18.0
4	5,839	trace	2.0	4.2	85.0
3	3,072	trace	3.0	2.5	95.0
2	2,236	0	2.6	2.3	285.0
1	905	trace	2.1	4.0	80.0

Appreciable amounts of promin were still present in the blood of patients who had taken the drug for from three to six years, after a nine day rest period and prior to the resuming of treatment. The values ranged between 0.5 mgm. to 1.0 mgm. per cent. Figure 1 indicates the urinary output for these cases.

During the course of treatment we have encountered an unusual variability in the metabolism of promin in 12 other patients who were treated from one to six years. Blood values from 10.2 to 50.0 mgm. per cent were noted in the absence of renal impairment. The blood non protein nitrogen for this group ranged between 25 - 50 mgm. per 100 cc. These patients were all ambulatory and in good clinical and physical condition. There had been no previous medication with other sulfones, which would affect the readings. No toxic manifestations and no effect on the red or white blood cells were noted. The dosage was reduced to 2 Gm. per day for one week in each case, after which another blood and urine estimation was made and in each case the usual normal values obtained. The results in this group are shown in table 2 and have not been included in the results shown in figure 1 because of the high values.

TABLE 2. *Unusual concentrations of promin in the blood and urine*

Case No.	Year treatment started	Blood promin	Urine promin	Non protein nitrogen	24-hr. Urine output
		mgm. per 100 cc			cc
1050	1942	10.2	3.0	38	900
		* 1.1	12.0		1200
1150	1943	25.0	20.0	42	980
		* 1.3	24.0	38	1800
1548	1943	46.0	26.0	48	900
		* 1.2	40.0		1280
868	1943	22.0	34.0	45	980
		* 1.5	12.0		1600
1512	1944	48.0	21.0		940
		* 1.2	22.0	45	1100
1580	1944	12.0	30.0		910
		* 0.9	37.0	38	1400
1441	1944	10.0	6.0	42	1200
		* 0.9	14.0		1980
1608	1946	50.0	10.0	50	840
		* 18.0	22.0		1200
1778	1946	15.0	10.0	50	1200
		* 6.0	6.0		1420
1621	1946	38.0	25.0	45	910
		* 1.3	32.0		1800
1776	1946	12.0	25.0	46	1200
		* 1.2	29.0		1840
1820	1946	20.0	6.0	50	960
		* 1.3	148.0		1100

* Results one week later

The blood promin concentration on 13 patients having a blood non protein nitrogen from 50 to 70 mgm. per 100 cc. showed a minimum of 0.5 and a maximum of 18.0 mgm. per cent promin with an average of 2.6 mgm. per cent. Only one patient had a high blood promin concentration. The urinary promin concentration for this group was 1 to 37 mgm. per 100 cc.

Eleven patients, bacteriologically negative and paroled, had blood and urine promin concentrations from a trace to 3.2 mgm. per cent blood, and 16 to 42 mgm. per cent in the urine.

High values may be encountered at any time during promin therapy. These seem to be of a transitory character. Unless there is definite renal impairment or other toxic manifestations, reducing the drug to 2 Gm. per day for a week and then re-checking the concentration has been a safe procedure in our patients.

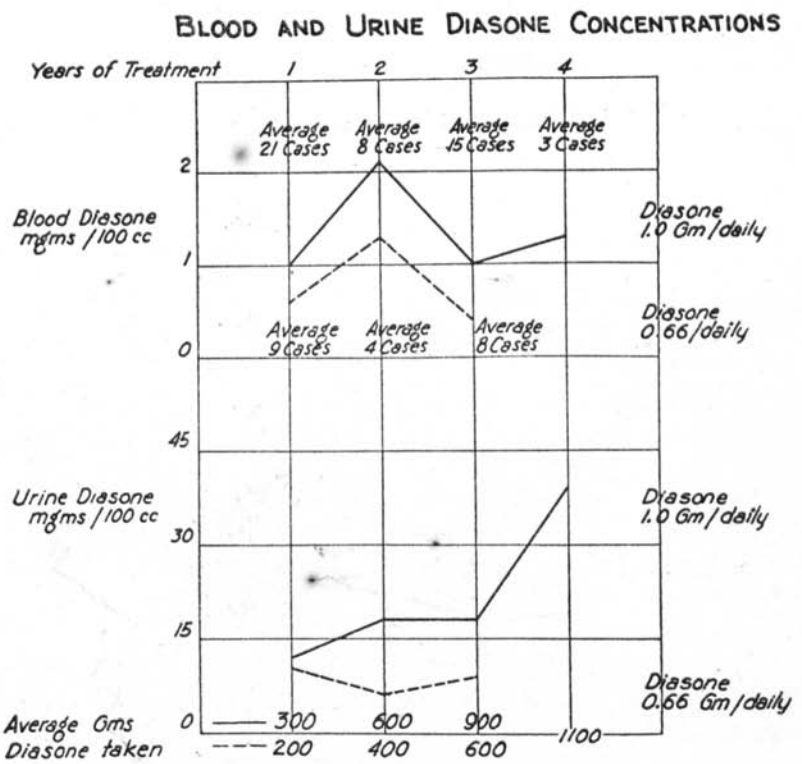
Promin has been administered for six years without any ill effects. Though the cumulative action is slow, it can be assumed that promin is stored in the tissues and liver since a number of the patients continued to excrete small amounts of the drug nine days after the last dose. One patient who had taken the drug for six years had a urine concentration of 0.7 mgm. per cent after a rest period of four weeks during which time no sulfone was taken.

There was no correlation between the blood promin levels and the clinical progress of the patient, including those patients which are bacteriologically negative and paroled.

Marked variations have been observed in the ability of different individuals to absorb the drug. Comparable doses give dissimilar blood levels in different patients. The drug is administered upon an empirical system of dosage and not according to the concentration in the blood.

CONCENTRATION OF DIASONE IN THE BLOOD AND URINE

The results of figure 2 are averages from 21 patients receiving daily oral doses of 0.66 Gm. of diasone and from 47 patients receiving 1.0 Gm. daily. All cases had the usual rest period with an occasional break in administration due to nausea or other slight toxic manifestations. With the administration of 0.66 Gm. a day, blood levels were maintained at a range of 0.0 to 1.0 mgm. per cent with an average of 0.4 mgm. per cent on a group of 8 patients taking the drug for a period of three years. Four cases taking the drug



for two years had an average blood concentration of 1.3 mgm. per cent with a range of a trace to 2.5 mgm. per cent. The 9 patients on treatment for one year had blood levels from 0.0 to 4.0 mgm. per cent with an average of 0.6 mgm. The minimum and maximum urinary diasone concentrations for this group are as follows:

Years of treatment	*Range of diasone concentration mgm. per 100 cc urine*	
	Minimum	*Maximum*
3	3.8	12.0
2	4.0	8.0
1	2.4	32.0

With the administration of 1.0 Gm. diasone daily, blood levels were maintained at a level varying from a trace to 2.0 mgm. per cent in 3 patients taking the drug for four years. Fifteen patients taking the drug for three years had levels from 0.0 to 3.6 mgm. per cent. Eight patients taking the drug for two years had levels of 1.5 to 3.2 mgm. per cent. Levels varying from a trace to 2.5 mgm. were

noted in 21 patients taking diasone for one year. The minimum and maximum urinary concentrations on this group are as follows:

Years of treatment	*Range of diasone concentration mgms. per 100 cc urine*	
	Minimum	*Maximum*
4	8.0	100.0
3	1.2	38.0
2	6.0	34.0
1	2.8	34.0

The blood non protein nitrogen was determined in 52 patients on diasone therapy. The range was from 30 to 65 mgm. per 100 cc with an average of 42 mgm. The patient having a non protein nitrogen of 65 mgm. had a blood diasone level of 2.9 mgm. per cent, with a urinary diasone level of 8.0 mgm. per cent. In our observations, patients who had a blood non protein nitrogen of 40 to 50 mgm. per 100 cc did not exhibit higher blood diasone levels than patients with a non protein nitrogen of 30 to 40 mgm. per 100 cc, which would indicate that slight renal impairment did not prevent the elimination of this drug through the kidney.

Although the optimal dose of diasone for leprosy has not been established, Faget and Pogge (3) are of the opinion that 1.0 Gm. a day is the maximum dose which should be administered over an extended period of time. Urinary diasone levels observed in our cases suggest a rather definite renal threshold for this compound since treatment extended over a period of four years indicates an increased urinary diasone concentration rather than a higher blood level, the dose being constant. This finding seems to be in agreement with those of Petter and Prenzlau (9) who found that diasone concentrations did not increase in proportion to an increase in dosage from 1.0 Gm. to 2.0 Gm. daily, but the urinary concentration did increase.

TABLE 3. *Concentration of promizole in the blood and urine*

No. of years treatment	No. of cases	Dose of promizole	Blood concentration	Urine concentration
		Gm.	values expressed in mgms. per 100 cc	
1/2 to 1½ years	13	6-7 daily	Minimum trace Average 0.98 Maximum 1.9	Minimum 125 Average 344 Maximum 800

Table 3 presents the blood and urine concentrations in 13 cases who have been on promizole therapy for six months to one and a half years with a daily dose of 6 to 7 Gm. of the compound. The

average blood promizole concentration is approximately the same as that of diasone in the group taking 1.0 Gm. daily. The urine promizole concentration greatly exceeds the concentrations in the urine of diasone or promin. A brochure on promizole (8) in the treatment of tuberculosis states in substance that promizole in the body undergoes conjugation into a more soluble product. This brochure states "Acetylation of promizole on the amino group of the benzene ring probably does not occur. However, it is evident that the amino group of the thiazole ring is at least partially bound resulting in a more soluble conjugate, giving a urinary concentration of over 300 mgm. per cent, while promizole itself is soluble only to 40 per cent. This latter type of conjugation does not affect the results by the present methods of testing for free or total values of promizole." This probably accounts for the high urinary concentrations noted in our cases. Urinary concentrations as high as 800 mgm. per cent were found without formation of calculi in the urinary tract. The urine of the promizole group is of a deep cherry-red color. This color has also been observed at the Mayo Clinic, in their experimental work with promizole in man. They attribute this color to a red dye-like substance of low toxicity.

The blood non protein nitrogen was determined in 6 of the cases in this group and ranged between 32 to 40 mgm. per 100 cc.

SUMMARY

A total of 575 determinations of the concentration of promin, diasone, and promizole in the blood of 187 patients were made over a period of six months. The non protein nitrogen of the blood was determined simultaneously on 176 of the patients.

Promin administered by the intravenous route in 5 Gm. daily doses, over a period of from one to six years, establishes average twenty-four hour residual blood concentrations of 1.0 to 1.6 mgm. per cent, except in unusual cases.

Marked variations were observed in the ability of different individuals to absorb promin, the dose being comparable.

High concentrations of promin in the blood may be encountered at any time during promin therapy. These seem to be of a transitory character and will return to normal by reducing the drug to 2.0 Gm. daily for a period of one week.

Appreciable amounts of promin were still present in the blood of patients after a nine-day rest period, who had taken the drug for from three to six years.

It can be assumed that promin is stored in the tissues and liver since a number of the cases continued to excrete small amounts of the drug nine days after the last dose.

There is no correlation between the blood promin levels and the clinical progress of the patient.

With the administration of 1.0 Gm. of diasone daily for a period of from one to four years, blood levels were maintained at a level varying from 0.0 to 3.6 mgm. per cent. The maximum concentration in the urine was 100.0 mgm. per cent. With a dose of 0.66 Gm. daily the concentration in the urine was 32.0 mgm. per cent.

In our observations, slight renal impairment as evidenced by the non protein nitrogen of the blood, did not prevent the elimination of diasone through the kidney. Urinary diasone levels suggested a rather definite threshold for this compound since treatment extended over a period of four years indicated an increased urinary diasone concentration rather than a higher blood level.

The daily administration of 6 to 7 Gm. of promizole for a period of one-half to one and one-half years, maintained a blood concentration of a trace to 1.9 mgm. per cent.

The urine promizole concentration greatly exceeds the concentration in the urine of diasone or promin. Urinary concentrations as high as 800 mgm. per cent were found without formation of calculi in the urinary tract.

ACKNOWLEDGMENT

Acknowledgments are due to Dr. George L. Fite for reviewing the manuscript and to Odon A. Amedee, Medical Technician, for technical assistance.

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