STUDIES OF THE ABSORPTION, EXCRETION, AND DISTRIBUTION IN THE BODY OF THE SULFONES USED IN THE TREATMENT OF LEPROSY

SISTER HILARY ROSS, B. S.
From the Laboratories of the National Leprosarium
Carville, Louisiana

During the past eight years intensive treatment with the sulfones has been carried out continuously in a large group of patients at this institution. During this period all forms of active leprosy have been beneficially influenced by the use of promin, diasone, promizole, promacetin and sulphetrone. It is now generally accepted that this group of drugs constitutes the therapy of choice in leprosy.

From toxicity studies and determinations of blood and urine sulfone levels, correlated with therapeutic effects obtained, it has been found that a daily dose of 5 grams intravenously in the case of promin, 1 gram orally in the case of diasone, 3 grams orally in the case of promacetin, and 3 to 4 grams orally in the case of sulphetrone consistently give good results (5).

Rest periods are observed every third week in the case of promin, and for a period of two weeks every two months with the other drugs. Although it might be expected that drug sensitivity would be produced by such a routine, this has not been our experience. Blood and urine determinations have proved that rest periods are not only desirable but necessary to avoid toxic manifestations. They presumably allow the release of the drugs from storage depots before critical levels are reached.

Unusually high concentrations of promin in the blood and urine have been found in patients as long as 9 days following the last dose of the drug. One patient, who had taken the drug for 6 years, had a urine concentration of 0.7 milligrams per 100 cubic centimeters after an enforced rest period of 4 weeks during which time no sulfone or sulfonamide drug had been administered (7). It has been shown that in the case of sulphetrone greater concentrations of the drug may sometimes be encountered in the skin than in the blood stream (4). It is thought that all sulfones are stored in the skin, and that possibly the liver acts as a storage reservoir. Further studies on the fate of these drugs seemed indicated, and such studies are the basis of this report.

METHODS AND MATERIAL

The patients selected had been on sulfone treatment for from 4 months to 7 years. Two skin biopsy specimens were obtained from each patient, one from a presumably normal area and the other from a lepromatous area. Each piece of skin weighed from 10 to 200 mgm. Subcutaneous fat was avoided. Venous blood was withdrawn at the same time the skin specimens were taken and before the morning dose of sulfone was administered, usually at 9 a. m. Morning specimens of urine were obtained from all patients, and from a certain number of them morning specimens of feces. The study also included tissue obtained from orthopedic cases at operation, at which time blood was also withdrawn and a morning specimen of urine was obtained. While this work was in progress we had opportunity to determine the sulfone content of the internal organs of 6 treated patients who had come to autopsy. The cases studied are summarized in Table 1.

The method used for the determinations was that of Bratton and Marshall (2), with modifications for sulphetrone as recommended by Brownlee (3) and for promacetin as recommended by Bratton (1). All analyses were for free sulfone, and not for the acetylated or conjugated form. The Klett-Summerson photoelectric colorimeter was used for the readings. For the feces determinations, a blank of undiazotized filtrate was run in parallel with each specimen because of the presence of a slight

TABLE 1.—*The numbers of cases in which tissue determinations were made, and the numbers of examinations involved in the present study.*

Drug administered	Number of cases	Number of exaninations made			
		Blood	Urine	Tissue	Feces
Biopsied cases					
Promin	8	8	8	8	8
Diasone	11	11	11	22	5
Promacetin	6	6	6	12	6
Sulphetrone	7	7	7	14	3
Operation cases					
Promin	1	1	1	1	0
Diasone	5	5	5	14	0
Promacetin	1	1	1	1	0
Autopsied cases					
Promin	2	0	0	15	0
Diasone	4	0	0	21	0

color, the intensity of which varied with each of the specimens. It was found that 1 gm. of feces, selected from approximately 100 gm., was sufficient for the analysis. All stool specimens were soft, which eliminated the possibility of accumulation of the drug in the intestine due to constipation.

At the beginning the findings with tissue specimens indicated extremely high concentrations, but that was due to the use of procaine as the local anesthetic, which is diazotized in the Bratton and Marshall procedure. This has been the experience of other workers in leprosy, notably certain of those in India. A suitable anesthetic was found in the drug called metycaine.

Metycaine hydrochloride, chemically is racemic-3-benzoxyl-1-(2-methylpiperidino)-propane hydrochloride. It is a local anesthetic which produces prompt anesthesia by either subcutaneous injection or topical application to mucous membranes and similar surfaces. Pharmacologic studies on animals indicate that its toxicity following subcutaneous injection is lower than that of cocaine and comparable to that of procaine; given intravenously, it was found to be approximately three times as toxic as procaine. It is considered an approximate equivalent of procaine for spinal anesthesia (6).

RESULTS

1. BIOPSIED CASES

The concentrations of the various sulfones in the blood, urine, feces and tissue specimens of 32 patients are presented in Table 2, which is subdivided according to the particular drugs which the patients were receiving at the time.

(*a*) *Promin.*—The results obtained in 8 patients who had been on intravenous promin therapy for from 4 months to 7 years, with daily doses of 2.5 to 5.0 gm., are shown in the first section of Table 2. Two of them had had other sulfone therapy previously. Case 1028 had been on diasone therapy for 4 years prior to promin therapy, and Case 1959 had been on promacetin for 5 months. Case 1050 had had no sulfone for 3 days prior to the test. Tissue analyses were made on 4 of these 8 patients; for cosmetic reasons we were unable to get tissue specimens from all of them.

The blood and urine concentrations were similar to those previously reported from this laboratory (7). All of the feces specimens were negative. In 2 of the cases the tissue concentration approximated that of the blood, while in the other 2 it was slightly higher than the blood concentration. No differences were found in comparative determinations of leproma tissue and presumably normal skin tissue of the same patient.

TABLE 2.—*Concentrations of sulfones in blood, urine, feces and skin tissue of biopsied cases, including specimens from (A) normal and (B) lepromatous areas.*

Reg. No.	Time treated	Dosage (gm.)	Blood (mgm.%)a	Urine (mgm.%)a	Feces (mgm.%)b	Tissue (mgm.%)b	Remarks
(a) Promin							
1050	7 yrs.	2.5	trace	5.0	Neg.	A 0.5 B 0.5	Off drug 3 days
1063	6 yrs.	5.0	0.6	80.0	Neg.	A 0.8 B 0.8	
1892	6 mos.	2.5	trace	13.0	Neg.	A 0.4 B 0.5	
1995	5 mos.	5.0	0.5	22.0	Neg.	A 0.4 B 0.4	
1028	5 mos.	5.0	1.0	55.0	Neg.	------	Had taken diasone 4-years
1806	5 mos.	5.0	1.6	225.0	Neg.	------	
1930	4 mos.	2.5	0.6	35.0	Neg.	------	
1959	4 mos.	5.0	0.9	70.0	Neg.	------	Had taken promaces tin 5 months
(b) Diasone							
1958	16 mos.	1.0	1.2	20.0	17.9	A 1.4 B 1.0	
1838	15 mos.	1.3	0.9	21.0	16.5	A 1.6 B 1.4	
1851	14 mos.	1.3	0.8	24.0	7.8	A 0.8 B 0.9	
862	5 yrs.	1.0	0.6	28.0	120.0	A 1.3 B 1.1	
1579	17 mos.	0.66	1.8	13.0	50.0	A 1.6 B 1.3	On promin for 7 ye ar
1852	1 yr.	1.0	1.1	10.0	------	A 1.3 B 1.2	
1766	2½ yrs.	1.0	0.9	15.0	------	A 1.0 B 1.0	
1352	4 yrs.	1.0	1.0	16.0	------	A 1.2 B 1.3	
1981	4 mos.	0.33	0.5	20.0	------	A 0.9 B 1.0	
1843	4 yrs.	1.3	1.9	44.0	------	A 2.1 B 1.1	
1954	1 yr.	1.0	0.6	10.0	------	A 0.6 B 0.8	On promin for 3 years. No drug for 48 hrs.

TABLE 2.—(continued)

Reg. No.	Time treated	Dosage (gm.)	Blood (mgm.%)a	Urine (mgm.%)a	Feces (mgm.%)b	Tissue (mgm.%)b	Remarks
(c) Promacetin							
1992	7 mos.	3.0	1.6	47.0	290.0	A 1.2 B 1.2	Had 1.0 gm. for 4 months
2009	5 mos.	1.5	1.0	40.0	600.0	A 0.6 B 0.7	
1974	11 mos.	4.0	1.8	58.0	125.0	A 1.6 B 0.9	Had 0.5 gm. for 4 months
1964	11 mos.	3.0	1.3	72.0	------	A 1.0 B 0.9	Had 1.0 gm. for 8 months
1831	6 mos.	1.0	1.3	46.0	250.0	A 1.0 B 1.0	
1966	12 mos.	4.0	1.2	145.0	250.0	A 1.0 B 0.9	Had 1.5 gm. for 1 month
(d) Sulphetrone							
1810	1 yr.	3.0	5.8	90.0	920.0	A 3.4 B 3.2	
1988	7 mos.	3.0	1.0	30.0	560.0	A 0.6 B 0.7	
1996	9 mos.	3.0	4.6	116.0	680.0	A 3.5 B 3.4	Had 1.5 gm. for 4 months
1997	9 mos.	2.0	4.5	250.0	------	A 2.1 B 2.1	Had 1.0 gm. for 4 months
1943	16 mos.	2.0	4.0	90.0	------	A 2.2 B 2.3	Had 1.0 gm. for 1 year
1108	7 mos.	2.0	2.1	96.0	------	A 1.2 B 1.3	Had small doses of promin irregularly
1940	16 mos.	2.5	5.0	92.0	------	A 4.2 B 4.0	

a Milligrams per 100 cubic centimeters.
b Milligrams per 100 grams.

(*b*) *Diasone.*—The concentrations of diasone in 11 patients who had been on that drug for from 4 months to 5 years, with daily doses of 0.33 to 1.3 gm., are shown in the second section of Table 2. Two of the patients had had previous sulfone therapy. Case 1579 had been on promin for 7 years, and Case 1954 for 3 years, before taking diasone. Case 1954 had had no

sulfone for 2 days before the test. Tissue analyses were made on all of this group, and feces determinations were made in 5 of them.

The blood and urine concentrations were similar to those previously reported (7). There was a wide variation in the amount of diasone excreted in the feces, the largest amount being noted in the case which had been on diasone therapy for 5 years. The tissue concentrations were found to be slightly higher than the blood levels in 8 cases. In 6 instances the concentration was slightly higher in the tissue obtained from a normal area than in the lepromatous tissue.

After the completion of this work, there appeared a report by Michael Smith (8) in which he states that diasone is recovered from the feces in amounts varying from 20 to 67 per cent of the daily oral intake, and he believes that this represents unabsorbed diasone. Although we have made few stool examinations, our blood and urine studies made over a period of six years do not indicate that such large percentages of diasone are unabsorbed except in rare instances, as in one of our cases which showed 120 mgm. per 100 gm. of the feces. That patient was on diasone for five years, and could have established a tissue saturation (if there is such in sulfone therapy). It is appreciated, however, that daily variations in the output of sulfones can take place. We have noted such variations in blood and urine concentrations of the same patients, the dosages being constant.

(*c*) *Promacetin.*—The concentrations of promacetin found in 6 patients who had been on that drug for from 5 months to 1 year, with daily doses of from 1 to 4 gm., are shown in the third section of Table 2. Tissue analyses were made on the entire group, and feces examinations were made on 5 of the cases.

The blood concentrations varied from 1.2 to 1.8 mgm. per cent, those of the urine from 40 to 145 mgm., and those of the feces from 125 to 600 mgm. The tissue concentration was less than that of the blood in each of the cases. In Case 1974 it was higher in the normal tissue than in the tissue obtained from a lesion.

We have made a study of the blood and urine concentrations of promacetin over a period of 12 months, and have found blood levels to be low in comparison with dosages, the urinary output being quite high. Of the 17 cases studied, 16 showed that the drug was still being excreted in the urine 12 days after the last

dose was taken, and at the time of their drug-rest period. Even though there is evidence of storage depots, the large amount found in the feces would indicate that this drug is not entirely absorbed from the intestine. Excretion of sulfone through the bile duct does not seem to take place in promin therapy, since sulfones could not be detected in the feces of the 12 cases studied, but whether or not this is true of the sulfones which are administered orally we cannot say.

(*d*) *Sulphetrone.*—The concentrations of sulphetrone in 7 patients who had been on that drug for from 7 to 16 months, with daily doses of 2.0 to 3.0 gm., are shown in the fourth section of Table 2. Tissue analyses were made on the entire group, and the feces concentrations were determined in 3 cases.

The blood concentrations ranged from 1.0 to 5.8 mgm. per cent, the urine concentrations from 30 to 250 mgm., and the feces concentrations from 560 to 920 mgm. The tissue concentration was less than that of the blood in each of the cases studied. Very little difference existed between the values obtained in the normal and the lepromatous tissues in this group of patients.

We are completing a study of sulphetrone concentration in the blood and urine of patients who have been on that drug for a period of 12 months. Our values are comparable with those recorded by Smith (8). As with other sulfones, our patients continue to eliminate sulphetrone after a 14-day rest period, which indicates release of the drug from storage depots.

Smith found that 70 to 100 per cent of sulphetrone may be recovered from the feces. In our experience we have not found 100 per cent sulphetrone so eliminated. In the sulphetrone leaflet (4) it is stated that:

> Administered orally, "Sulphetrone" is absorbed chiefly from the small intestine. Initially only about 50 per cent of the ingested drug is absorbed, but on continued administration this proportion gradually increases until up to 75 per cent of the amount given may be absorbed.

From our blood and urine concentrations, it would seem that approximately 50 per cent of sulphetrone is absorbed, even after one year's therapy.

2. SURGERY CASES

The concentrations of sulfones in the tissues removed by surgery are given in Table 3. Blood and urine determinations were made at the same time. Five of the patients were taking diasone in doses of from 0.3 to 1.0 gm. daily; 1 of the 5 had received no drug for 17 days prior to the operation. One patient

taking promacetin had not received any of the drug for 3 weeks; and 1 patient taking promin, 5 gm. daily, had been off the drug for a week.

TABLE 3.—*Concentration of sulfones in tissues removed during orthopedic operations.*

Reg. No.	Drug	Dosage (gm.)	Operation and tissues (mgm.%)		Blood (mgm. %)	Urine (mgm. %)	Remarks
1366	Diasone	1.0	*Large toe:*		0.4	8.0	No sulfone 1 week prior to operation
			Skin	trace			
			Muscle	trace			
			Tissue scraped from bone	trace			
949	Diasone	1.0	*Removal of leg:*		0.8	20.0	
			Skin	neg.			
			Muscle	30.0			
1989	Diasone	0.33	*Removal of leg:*		0.6	60.0	
			Skin	neg.			
			Muscle	1.0			
660	Diasone	0.33	*Removal of leg:*		trace	-----	
			Skin	trace			
			Muscle	trace			
			Nerve	trace			
1965	Diasone	0.66	*Surgery of hand:*		neg.	neg.	No sulfone for 17 days prior to operation
			Skin	neg.			
			Tendon	1.7			
1957	Promacetin	1.0	*Lesion on leg removed.*		neg.	0.5	No sulfone for 3 weeks prior to surgery
1050	Promin	5.0	*Keloid from:*		trace	0.9	No sulfone forl week
			Elbow	neg.			

Traces of diasone were found in the skin, muscle, and tissue scraped from the bone in one patient who had taken no sulfone for a week. Another patient who had been off sulfones for 17 days had a diasone concentration of 1.7 mgm. per cent in the tendon removed, with a negative skin sulfone concentration. In 2 cases, skin taken from the leg after amputation was found to be negative while the muscle contained 1 and 30 mgm. per cent,

respectively. These results indicate storage of the sulfones in the tissues.

3. AUTOPSIED CASES

The results of the analyses of the postmortem tissues obtained from 6 cases which had been on sulfone therapy during life are shown in Table 4. Four of these patients had severe nephritic involvement prior to death, one had far-advanced tuberculosis, and one, hospitalized for an injury of the hip, died of peritonitis. Five of the cases had had no sulfone therapy for from 1 to 3 weeks prior to death.

Case 1723.—The sulfone concentration in the tissues of this case was higher than those observed in the blood and skin of the cases on whom biopsies were made. This patient received 0.66 gm. of diasone daily from July 1945 to March 1946, and 1.0 gm. daily from March 1946 to July 1, 1949; his death occurred on July 8, 1949. Nasal sprays of promin solution were administered daily over a period of several years. In July 1948 microscopic hematuria was noted, but the patient remained ambulatory. In April 1949 he was admitted to the infirmary with edema of both legs. His blood nonprotein nitrogen at this time was 108 mgm. per cent; it had been 35 mgm. in 1945. It is thought that the sulfones present in the various tissues of this case were due to an accumulation of the drug as a result of poor kidney function.

Case 1133.—The sulfone concentrations of the skin, liver, ulnar nerve and kidneys in this case, treated with promin, were so high that they seem fallacious. This patient died of far-advanced tuberculosis and had very little kidney damage. His blood nonprotein nitrogen was 55 mgm. per cent several weeks before death. In earlier studies ([7]) we have encountered an unusual variability in the metabolism of this drug. Blood values as high as 10.2 to 50.0 mgm. per cent were noted in patients who were in good clinical and physical condition. These findings were transitory, since the levels returned to normal after cessation of treatment for a week. Since this patient had promin therapy up to the time of his death, the high values found in the tissues may have been, in part, transitory.

Case 2036.—In this case the skin, liver, kidneys, spleen, heart, lung, and ulnar nerve were all found negative for sulfone. This patient was treated with promin intravenously in doses varying from 2.5 to 5.0 gm. daily from August 1946 to June 1948, the total received being 1,517 gm. There were no toxic manifestations during this time. He left the hospital against medical advice on June 11, 1948, and returned on October 5, 1949. Three weeks prior to readmission, the patient had experienced dizziness and convulsions. Physical examination on admittance showed pitting edema of the legs and ankles. His blood nonprotein nitrogen was 140 mgm. per cent, and his albumin-globulin ratio was 0.8. Albuminuria, granular casts and a severe secondary anemia were also noted at this time. The patient stated that he took two tablets of diasone daily for 14 months without medical supervision and without benefit of blood and urine examinations, but the severe kidney complications found are attributed to arteriosclerosis. He was hospitalized 26 days before death, at which time no sulfones were taken. The pathologist reported marked renal amyloidosis and arterial and arteriolar nephrosclerosis.

TABLE 4.—*Sulfone concentration* in the tissues of 6 autopsied patients.*

Reg. No.	Skin	Liver	Kidneys	Spleen	Heart	Lung	Nerve	Drug	Duration of treatment	Illness prior to death	Remarks
1286	Neg.	Neg.	Neg.	Neg.	----	----	----	Diasone	3 yrs.	Uremia	No sulfones for 3 weeks prior to death
1926	Neg.	1.0	1.1	Neg.	----	----	----	Promin Promacetin	2 mos. 7 mos.	Nephritis	No sulfone for 2 weeks prior to death
1723	3.5	4.0	6.2	2.6	----	----	----	Diasone	3 yrs.	Nephritis	No sulfone for 1 week prior to death
1133	53.4	50.0	25.0	Neg.	Neg.	Neg.	30.0	Promin	21 mos.	Tuberculosis, far advanced	Ileum and testes negative for sulfones
2036	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Promin Diasone	2 yrs. 14 mos.	Arteriosclerosis	No sulfone for 26 days prior to death
1756	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Diasone	3 yrs.	Peritonitis	No sulfone for 3 weeks prior to death

* Milligrams per 100 grams.

Case 1756.—The skin, liver, kidneys, spleen, heart, and lungs were all found negative for sulfone. This patient, who was on diasone therapy from 1946 to 1949 in doses of 1 gm. daily, received no sulfone therapy for 3 weeks prior to death.

Case 1286.—The skin, liver, kidneys, and spleen were all found negative for sulfone. This patient had received diasone in doses of 0.33 to 1 gm. daily for 5 years, but none for 3 weeks prior to death. Death was due to uremia, and the blood nonprotein nitrogen level was 148 mgm. per cent a few weeks before death.

Case 1926.—The skin and spleen in this case were negative for sulfone, while the liver and kidneys had concentrations of 1.0 and 1.1 mgm. per cent, respectively. He had received promin intravenously for 2 months, and promacetin orally for 7 months, but no sulfone therapy for 2 weeks prior to death. On admission in 1948 his blood nonprotein nitrogen was 35 mgm. per cent; and one year later, and again shortly before death, the concentration was found to be 65 mgm. per cent, with an albumin-globulin ratio of 1.0. Albuminuria was not noted until shortly before death.

SUMMARY AND DISCUSSION

The absorption, excretion and distribution of the sulfones —promin, diasone, promacetin, and sulphetrone— have been studied in a small group of patients who had had sulfone therapy for from 4 months to 7 years.

The establishment and maintenance of effective blood levels depend upon dosage, frequency of administration, rate of absorption, rate of drug inactivation—if any—within the body, extent of binding by plasma and other tissue proteins, and rate of excretion. In this study, and in previous work in our laboratory, it has been found that promin, diasone, promacetin, and sulphetrone are retained in the body up to 14 days after cessation or treatment, and in occasional cases as long as 4 weeks. The similarity of findings in the blood, urine and tissues indicates that there are little differences in distribution regardless of whether the sulfone is given orally as in the case of diasone, promacetin and sulphetrone, or intravenously in the case of promin.

Ideally, a sulfone should be completely absorbed when given by the oral route. Our findings, which are similar to those of Smith (8), indicate that diasone, promacetin and sulphetrone are not completely absorbed since these drugs are found in the feces, the largest amounts being found in those cases taking promacetin and sulphetrone. Whether or not some of this concentration is due to excretion of the drug in the bile is not certain, but we were not able to detect any sulfone in the feces of patients who were receiving promin intravenously.

The kidneys serve as the major channel of excretion for the

drugs that are absorbed. Although the rate of excretion varies with the different compounds, it is relatively rapid. Abnormal intestinal activity and impaired renal function may disturb the normal pattern of absorption and excretion. It has been our experience that different individuals exhibit marked variations in their ability to absorb the drug, comparable doses giving dissimilar blood levels in different patients. It has also been observed that the absorption of identical doses of a sulfone may vary markedly in the same patient at different times.

It is evident that all of the sulfones studied penetrate the tissues. The skin concentrations, in most of the cases, were about the same whether the drug was given intravenously or orally. Tissues removed during surgical operations reveal a tendency to storage of sulfone, since one case showed traces of diasone in skin, muscle and tissue 7 days after the last dose was administered, and another case showed some in the tendon 17 days after the last dose of diasone was taken. Little differences were noted, in comparative determinations of biopsy specimens from the same patient, in the concentrations in leproma skin tissue and presumably normal skin.

From our observations on postmortem tissues, the liver, spleen, kidneys, skin, and nerves serve as organs of concentration or storage of the sulfones studied.

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