JCI The Journal of Clinical Investigation

A THERAPEUTIC AND PHARMACOLOGICAL STUDY OF SULFADIAZINE, MONOMETHYLSULFADIAZINE, AND DIMETHYLSULFADIAZINE IN LOBAR PNEUMONIA

Jesse G. M. Bullowa, Herman D. Ratish

J Clin Invest. 1944;23(5):676-681. https://doi.org/10.1172/JCI101538.

Research Article

A THERAPEUTIC AND PHARMACOLOGICAL STUDY OF SULFADIAZINE, MONOMETHYLSULFADIAZINE, AND DIMETHYLSULFADIAZINE IN LOBAR PNEUMONIA [1]

By JESSE G. M. BULLOWA [2] AND HERMAN D. RATISH [3]

(From the Medical Service, Harlem Hospital, Oswald LaRotonda, M.D., Director, Department of Hospitals, and the Littauer Pneumonia Research Fund of New York University College of Medicine, New York City)

(Received for publication October 28, 1943)

The methyl salt of sulfathiazole was discarded because it produced peripheral neuritis (1). It was subsequently discovered that hens were sensitive indicators of this toxicity (2). However, only by trial in patients could the applicability of the avian observations to man be validated, though a shorter trial with less damage would have been possible had this avian test been known sooner.

Roblin and his coworkers (3) who prepared sulfadiazine also described its monomethyl and dimethyl homologues. When tested on hens, the toxicity for peripheral nerves found with the methyl salt of sulfathiazole was not encountered in the methyl compounds of sulfadiazine. Because of the absence of injury to the peripheral nerves, these new drugs have been offered for clinical investigation (4 to 6). New sulfonamides must be equally potent, mole per mole, to compete with or supplant their predecessors. Effective concentrations must be maintained by the same or less frequent administration. They must be less toxic and must be detoxicated to substances less likely to form crystal aggregates which may irritate or block the renal tubules. After animal trial, the effect on patients must be determined because the pharmacological properties may be different in the human or may be modified both by disease and by the temperature of the patients. Accordingly we have studied the effects of monomethylsulfadiazine [4] and dimethylsulfadiazine (7) in acute respiratory disease.

In vitro observations of the effect of equivalent concentrations of sulfadiazine, monomethylsulfadiazine, and dimethylsulfadiazine run in parallel

TABLE I

*Comparative blood concentrations with sulfadiazine, monomethylsulfadiazine, and dimethylsulfadiazine**

Drugs	Cases	Mgm. of "free" drug per 100 cc. of blood		
		Hours		
		24	48	72
Sulfadiazine	1	5.8	8.1	6.5
	2	5.2	10.4	7.7
	3	6.7	4.9	8.0
	4	6.7	5.3	3.0
	5	7.0	10.9	10.1
	6	9.4	5.9	10.0
Monomethyl-sulfadiazine	1	6.0	11.0	**
	2	15.0	18.0	
	3	3.2	10.0	
	4	7.0	16.0	
	5	7.6	9.0	
	6	8.4	12.8	11.7
	7	7.8	6.8	6.6
	8	17.8	17.8	15.3
	9	8.8	11.2	
	10	17.2	18.8	13.8
	11	19.8	11.0	
	12	5.6	17.6	18.0
	13	10.0	7.0	
	14	9.2	16.0	10.2
	15	12.2	19.2	17.0
	16	14.4	19.8	16.4
	17	8.6	18.6	14.2
	18	15.8	12.0	14.2
Dimethyl-sulfadiazine	1	5.4	3.3	8.0
	2	8.4	10.8	6.3
	3	3.8	1.9	1.7
	4	5.5	3.8	1.6
	5	9.8	6.8	9.5
	6	8.9	9.6	4.2
	7	9.6	4.6	3.8
	8	5.5	9.2	1.0

* These drugs were given 4 grams *statim* and 1 gram every 4 hours day and night.

** Blood levels not taken where blank spaces appear.

[1] This study received additional support from the Metropolitan Life Insurance Co., and from Mr. Bernard M. Baruch, Mr. Bernard M. Baruch, Jr., Miss Belle N. Baruch, and Mrs. H. Robert Samstag.

[2] Deceased November 9, 1943.

[3] Brewer and Co., Inc., Research Laboratories, Worcester, Mass.

[4] We are indebted to Lederle Laboratories, Incorporated, Pearl River, New York, for generous supplies of these drugs.

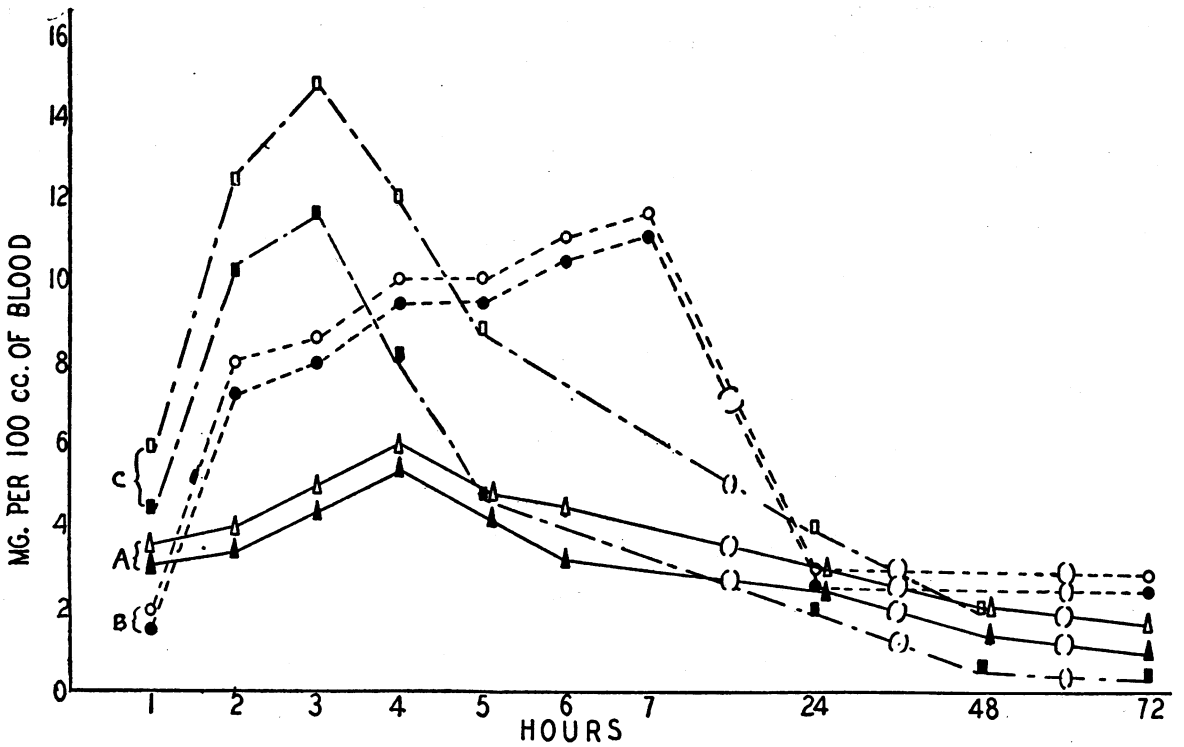

FIG. 1. AVERAGE CONCENTRATIONS OBTAINED IN THE BLOOD AFTER SINGLE ORAL 4 GRAM DOSES

A. Sulfadiazine (Average of 7 subjects)
B. Monomethylsulfadiazine (Average of 5 subjects)
C. Dimethylsulfadiazine (Average of 4 subjects)

Legend: □○△=Total drug ■●▲=Free drug

on a B. Friedlander B organism, a pneumococcus III, and a pneumococcus VI did not show significantly superior bactericidal action of the methyl salts.

PHARMACOLOGY

Sulfadiazine, monomethylsulfadiazine, and dimethylsulfadiazine are readily absorbed from the gastrointestinal tract. When they are administered orally, high concentrations may be obtained. High initial levels may be attained rapidly with all 3 drugs but they are maintained only with sulfadiazine and monomethylsulfadiazine (Table I).

When equal quantities are administered, monomethylsulfadiazine gives higher blood levels than sulfadiazine. The average concentrations of sulfadiazine, monomethylsulfadiazine, and dimethylsulfadiazine, obtained in the blood after single oral doses, are shown in Figure 1. In 7 subjects, at the end of 4 hours, a 4 gram dose of sulfadiazine resulted in blood levels ranging from 3.4 to 6.0 mgm. with an average of 5.2 mgm. of the free drug per 100 cc. In 5 subjects, at the end of 4 hours, a 4 gram dose of monomethylsulfadiazine resulted in blood levels ranging from 4.8 to 14.0 mgm. with an average of 9.4 mgm. of the free drug per 100 cc. Corresponding conjugated values were 0.5 to 2.2 mgm. with an average of 0.9 mgm. per 100 cc. of blood. Under similar conditions, free dimethylsulfadiazine in the blood reached concentration peaks varying from 6.0 to 11.7 mgm. with an average of 8.4 mgm. per 100 cc. The corresponding conjugated dimethylsulfadiazine values ranged from 1.0 to 4.3 mgm. with an average of 4.3 mgm. per 100 cc. of blood. With all the drugs, measurable amounts were found in the blood for approximately 72 hours.

When a *statim* dose of 4 grams was followed by 1 gram every 4 hours day and night, it was found that levels of sulfadiazine and monomethylsulfadiazine were well maintained. Blood concentrations for sulfadiazine ranged from 1.7 to 14.8

TABLE II

Comparative urinary recoveries of sulfadiazine and its mono and dimethyl analogues

Dose drug ingested	Conjugated drug in total recovery	Recovery		
		Free	Conjugated	Total
grams	*per cent*	*per cent*		
SULFADIAZINE				
2¦	7.7	60.0	5.0	65.0
2	31.6	65.0	30.0	95.0
3	73.3	13.3	36.6	49.9
3	41.6	23.3	16.6	39.9
3	22.0	23.3	6.6	29.9
3	40.9	43.3	30.0	73.3
5	40.9	26.0	18.0	44.0
5	28.0	36.0	14.0	50.0
5	66.6	20.0	40.0	60.0
5	33.3	40.0	20.0	60.0
5	33.3	28.0	14.0	42.0
11	28.8	33.6	13.6	47.2
14	44.7	41.4	33.5	74.5
22	69.6	11.3	25.9	37.2
MONOMETHYLSULFADIAZINE				
4	43.7	45.0	35.0	80.0
4	51.5	40.0	42.5	82.5
4	50.0	42.5	42.5	85.0
4	41.3	42.5	30.0	72.5
18	75.0	20.0	60.0	80.0
18	19.6	70.0	17.2	87.2
19	58.6	32.6	46.3	78.9
DIMETHYLSULFADIAZINE				
4	20.0	70.0	17.5	87.5
4	48.4	42.5	40.0	82.5
4	40.0	45.0	30.0	75.0
4	31.1	57.5	26.0	83.5
20	47.9	44.0	40.5	84.5
26	55.3	18.9	23.4	42.3
28	58.8	38.5	55.0	93.5
31	74.5	22.9	67.1	90.0
38	47.8	41.1	39.7	80.8
41	78.8	16.6	61.9	78.5
45	83.8	15.1	78.6	93.7

mgm. per 100 cc.; of this amount, 10 to 13 per cent was in the conjugated form. Blood levels for monomethylsulfadiazine ranged from 3.2 to 23.0 mgm. per 100 cc. and approximately 18 per cent was in the conjugated state.

The administration of dimethylsulfadiazine by the same regimen resulted in high initial levels which were not satisfactorily maintained. Following a peak, the concentrations diminished in many instances to as low as 1.0 or 2.0 mgm. per 100 cc. of blood. Continuing the dose of 1 gram every 4 hours did not again elevate the level of dimethylsulfadiazine. In some cases, the levels were fairly well maintained.

In each of the 3 drugs, following a single dose, approximately 50 per cent of the total amount recovered in the urine was excreted in the first 24 hours. In 72 hours, the amount of sulfadiazine (free and conjugated) recovered from the urine varied from 30 per cent to 95 per cent. For monomethylsulfadiazine (free and conjugated), the variation was 72 to 87 per cent. Dimethylsulfadiazine (free and conjugated) varied from 73 to 85 per cent.

About 35 per cent of the amount of sulfadiazine recovered from the urine was conjugated, of monomethylsulfadiazine 50 per cent, and of dimethylsulfadiazine 45 per cent. The total amount of sulfadiazine recovered from the urine ranged from 11.3 to 65 per cent of the free and 6.6 to 40.0 per cent of the conjugated drug. For monomethylsulfadiazine, the variations were 20.0 to 70.0 per cent of the free and 17.2 to 60.0 per cent of the conjugated. For dimethylsulfadiazine, it was 15.1 to 70.0 per cent of the free and 17.5 to 78.6 per cent of the conjugated (Table II).

TOXICITY

In the 14 sulfadiazine, 7 monomethylsulfadiazine, and 11 dimethylsulfadiazine cases studied pharmacologically, fluid intake was not forced. The patients however, took water freely. The daily urinary volume in all cases varied from 770 to 1800 cc. In a number of patients treated with dimethylsulfadiazine, there was a marked polyuria up to 4000 cc. Nausea and vomiting occurred in about 10 per cent of all patients taking sulfadiazine (8) and 2.6 per cent of those taking monomethylsulfadiazine. Leukopenia and anemia were not encountered. Delirium was unusually frequent with the methyl homologues whereas in 588 sulfadiazine-treated patients, only 8 instances or 1.3 per cent were observed, and of the 38 dimethylsulfadiazine-treated patients, 12 were in delirium. Three of these became delirious before therapy started and continued so afterwards. Nine patients became delirious during the therapy, a 23.6 per cent incidence. In this series, 3 patients vomited following the ingestion of the drug, and hematuria occurred in 1 patient. In the dimethylsulfadiazine group, 13 of the 64 cases, or 20.3 per cent, became delirious

after the drug was administered. One of the monomethylsulfadiazine-treated patients developed hematuria and anuria and was cystoscoped. Cystoscopy revealed a blocked ureter and large crystal aggregates floating in the urine of the bladder, and embedded in the mucosa of the bladder. The drug was discontinued. The patient was relieved of his anuria by ureteral irrigation and recovered.

Of the 38 patients treated with monomethylsulfadiazine, 4 died. Two of these deaths occurred 10 to 12 hours after commencing the administration of the drug.

The first instance of death 10 hours after commencement of therapy occured in a patient who had a B. Friedlander A infection with a left lower lobe involvement. The drug was started on the second day of his illness and he had received a total of 6 grams prior to the onset of delirium. Following the administration of the drug, he vomited, became delirious, and died in a convulsion. He had received a total of 8 grams.

The second instance of death which occurred 12 hours following the beginning of drug therapy was that of a

TABLE III

Delirious cases and deaths in patients treated with monomethylsulfadiazine

Patient	Day of disease admitted to hospital	Sex	Age	Pneumococcus type	Lobes involved	Day of disease therapy began	Total no. of days drug given	Blood levels: Day of disease	Blood levels: Mgm. per 100 cc.	Initial temp. drop in hours after therapy began	No. of grams of drug given before initial drop in temp.	Delirium: Day of disease of onset	Delirium: Temp. at onset	Delirium: No. of grams of drug given prior to onset	Delirium: Total no. of grams drug given	Delirium: No. of days in delirium	Delirium: Day of disease delirium terminated	Delirium: Day of disease drug stopped	Outcome
			years																
W. H.	4	M	38	IX	RUL RML X-ray	4	6	5 7	10.0 7.0	30	11	5	103°	9	29	4	9	10	Recovered
H. B.	4	M	43	III	RLL	4	7	5 7 8	14.4 19.8 16.4	40	7	6	101.4°	15	37	4	10	10	Recovered
R. F.	6	M	24	I	LLL X-ray	6	4	7 10	11.2 2.0	32	15	8	99°	15	19	2	10	9	Recovered
J. T.	4?	M	38	XII	LLL	4?	2		.			On admission	103°	0	7	?	?	?	Patient was in shock on admission and died 12 hours after therapy began
W. E.	8	M	35	VII	RUL–RML RLL X-ray	8	8	9 11 13 16	8.6 18.6 14.2 6.8	28	9	9	104.8°	6	39	3	12	12	Recovered
J. N.	?	M	42	XVII	RLL–RML	?	3	? 5/13	6.0			On admission			18				Died in delirium 52 hours after the drug was given. Received 340,000 units of anti-pneumococcic serum.
E. B.	2	M	38	BFA	LLL	2	1	?						6	8				Died in convulsions 10 hours after therapy was started. This patient vomited.
N. T.	?	M	72	VIII	LLL–RLL	?	2	? 6/5	2.8			On admission			8				Died 28 hours following drug therapy.
J. W.	4	M	28		RLL–X-ray	4	4	6 7 9	19.8 11.0 7.8	44	11	8	99°	23	23	2	10	7	Recovered
W. S.	?	M	32	VI	RLL–LLL	?	4	? 5/22 5/24 5/25	5.6 17.6 18.0	76	19	? 1	101°	14	23	2	3?	5?	Recovered
V. C.	2	F	46		RML–RLL X-ray	2	3	4	18.0			6	102°	18	18	2	8	6	On the 6th day of the disease, monomethylsulfadiazine was discontinued. The patient was in delirium. On the 7th day of illness sulfathiazole was administered. Patient recovered.
G. T.	2	M	32	XI	LLL	2	4	3 5	9.4 19.8	48	5	4	101°	10	16	2	6	5	Recovered

All patients received monomethylsulfadiazine, 4 grams *statim* and 1 gram every 4 hours day and night.

TABLE IV

Comparative mortalities with sulfadiazine, monomethylsulfadiazine, and dimethylsulfadiazine

	Sulfadiazine			Monomethyl-sulfadiazine			Dimethyl-sulfadiazine		
	Cases	Deaths	Per cent	Cases	Deaths	Per cent	Cases	Deaths	Per cent
Total	232	31	13.4	38	4	10.3	64	10	15.8
Total minus deaths within 24 hours after therapy began	219	18	8.2	36	2	5.5	61	7	11.4

patient suffering from a pneumococcus Type XII pneumonia involving the left lower lobe. The drug was started on the fourth day of his disease and he had received a total of 7 grams. He was delirious on admission and continued in delirium after the drug was administered and without modification of his condition otherwise.

A third death occurred 52 hours after the drug was started. The patient was suffering from a Type XVII pneumococcus pneumonia with right lower lobe and right middle lobe involvement. The drug was administered on admission and he received a total of 18 grams in 3 days. He was admitted in delirium from which he did not recover. Additional therapy included 340,000 units of the pneumococcus XVII antiserum.

The fourth death occurred 28 hours after therapy was instituted. X-ray revealed left lower lobe and right lower lobe involvement. He received 8 grams in 2 days. He was delirious on admission and continued so after the administration of the drug.

In addition to the 4 fatal cases, there were 8 instances of delirium. The time of onset of delirium following the administration of the drug varied from 1 to 4 days. Some deliria were mild. The patients were out of contact as shown by hallucinations and irrelevancy. Other delirious patients were active and required restraints.

In 1 patient, aged 43, delirium started on the 6th day of his illness, 46 hours after the drug was given. He had received 15 grams at the time of onset of the delirium. This patient recovered from a pneumococcus III with right lower lobe involvement. He received a total of 37 grams in 7 days. The initial temperature drop occurred 40 hours after the drug was started.

In another patient, aged 35, delirium started on the 9th day of his disease. He had received 6 grams of monomethylsulfadiazine at the time of onset of delirium. This patient recovered from a pneumococcus VII pneumonia. X-ray revealed right upper lobe, right middle lobe, and right lower lobe involvement. He received a total of 39 grams in 8 days. The initial temperature drop occurred following the ingestion of 9 grams of the drug (28 hours). Hiccoughs occurred soon after the drug was given and were not relieved by oxygen-carbon dioxide inhalation.

In a 3rd patient, aged 24, delirium occurred on the 8th day of his illness after 15 grams of monomethylsulfadiazine were administered. The drug was started on the 6th day of his disease. This patient recovered. He had a pneumococcus Type I pneumonia. X-ray showed left lower lobe involvement. He received a total of 19 grams in 4 days. The initial temperature drop started after he had received 15 grams of the drug.

A 4th patient, aged 38, became delirious on the 5th day of his illness, 26 hours after the drug was started. He received 9 grams prior to the onset of delirium. This patient recovered from a pneumococcus Type IX pneumonia. X-ray showed right upper lobe and right middle lobe involvement. He had received a total of 29 grams in 6 days. The initial fall in temperature occurred after he received 11 grams of the drug.

Other instances of delirium are indicated in Table III.

Table IV offers the mortality comparison of the drugs studied. In 232 cases treated with sulfadiazine, there were 31 deaths or a mortality of 13.4 per cent. In this series, 13 deaths occurred within 24 hours after therapy began, making the mortality after 24 hours of therapy 8.2 per cent. Four out of the 38 cases treated with monomethylsulfadiazine, or 10.5 per cent, died. In this series, 2 deaths occurred within 24 hours after therapy started, with a mortality of 5.5 per cent after 24 hours of therapy. Of the 64 patients treated with dimethylsulfadiazine, 10 patients, or 15.6 per cent, died. In this group, 3 cases died within 24 hours following therapy, a mortality of 11.4 per cent.

Sulfadiazine, when effective, will generally cause a drop in temperature in about 24 hours following its administration. With monomethylsulfadiazine, we observed 28 cases that followed this trend while 10 patients required more than 24 hours before the temperature fell.

SUMMARY

Monomethylsulfadiazine and dimethylsulfadiazine, like sulfadiazine, are readily absorbed from the gastrointestinal tract. Blood concentrations, when equal doses are given, are generally higher for monomethylsulfadiazine than for sulfadiazine. Rapid attainment and maintenance of high blood levels may be accomplished with monomethylsulfadiazine. In the urine, about 35 per cent of the amount of sulfadiazine recovered was conjugated; of monomethylsulfadiazine, 50 per cent; and of dimethylsulfadiazine,

45 per cent. The incidence of mental disturbances with monomethylsulfadiazine was 23.6 per cent; with dimethylsulfadiazine, 20.3 per cent; and with sulfadiazine, 1.3 per cent. Gross hematuria was observed with sulfadiazine and monomethylsulfadiazine. Polyuria was noted with dimethylsulfadiazine. The mortality in cases of pneumonia treated with the 3 drugs was,—sulfadiazine 8.2 per cent in 232 cases; monomethylsulfadiazine, 5.5 per cent in 38 cases; for dimethylsulfadiazine, 11.4 per cent in 64 cases.

BIBLIOGRAPHY

1. Little, S. C., Nervous and mental effects of the sulfonamides. J.A.M.A., 1942, **119**, 467.
2. Bieter, R. N., Baker, A. B., Beaton, J. G., Shaffer, J. M., Seery, T. M., and Orr, B. A., Nervous injury produced by sulfonamides and some of its derivatives in the chicken. J.A.M.A., 1941, **116**, 2231.
3. Roblin, R. O., Jr., Williams, J. H., Winnek, P. S., and English, J. P., Chemotherapy: Some sulfanilamide heterocycles. J. Am. Chem. Soc., 1940, **62**, 2002.
4. Goodwin, R. A., Jr., Peterson, O. L., and Finland, M., Absorption and excretion of sulfamethyldiazine in human subjects. Proc. Soc. Exper. Biol. and Med., 1942, **51**, 262.
5. Welch, A. D., Mattis, P. A., Latven, A. R., Benson, W. M., and Shields, E. H., Sulfamerizine: A comparison of sulfamerizine with sulfadiazine on the basis of absorption, excretion and toxicity. J. Pharmacol. and Exper. Therap., 1943, **77**, 357.
6. Murphy, F. D., Clark, J. K., and Flippin, H. F., Studies on 2-sulfanilamido-4-methyl-pyrimidine (sulfamerazine, sulfamethyldiazine) in man. Am. J. M. Sc., 1943, **205**, 717.
7. Rose, F. L., Martin, A. R., and Bevan, H. G. L., Sulphamethazine (2-4′ aminobenzenesulphonylamino-4; 6 dimethyl pyrimidine); new heterocyclic derivative of sulphanilamide. J. Pharmacol. and Exper. Therap., 1943, **77**, 127.
8. Ratish, H. D., Shackman, N. H., and Bullowa, J. G. M., The pharmacodynamics of sulfadiazine in man. New England J. Med., 1942, **226**, 596.