THE DETERMINATION OF THE DOSAGE–MORTALITY RATIO OF PENTOTHAL SODIUM WITH TOXIC DOSES OF SULFANILAMIDE FOLLOWING * †

PAUL H. LORHAN, M.D., GRETCHEN GUERNSEY, M.D., AND ALBERT E. PUGH, M.A.
Kansas City, Kansas

IN an earlier report (1) the toxicity of pentothal sodium was found to be approximately the same whether or not the experimental animals were previously treated with therapeutic doses (that is, 0.15 Gm. per Kg. of body weight) of sulfanilamide. The above dose agrees fairly well with that established by Long and Bliss (2) who used 0.11 Gm. of sulfanilamide per kilogram for human therapy. Specifically, the $L.D._{50}$ for pentothal sodium was 84.85 ± 4.00 mg. per Kg., while animals which had received therapeutic doses of sulfanilamide showed an $L.D._{50}$ for pentothal sodium of 85.21 ± 6.56 mg. per Kg.

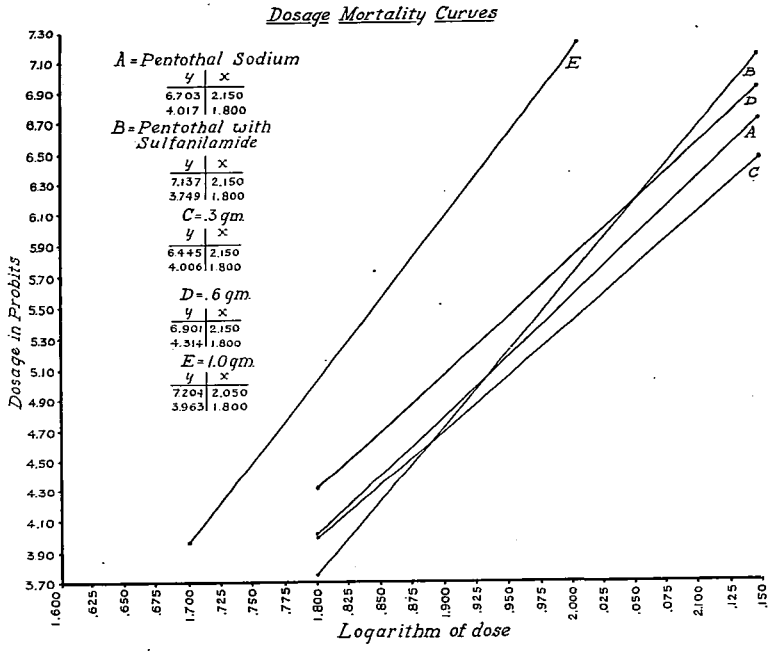
Adriani (3), in his experiments on rats which had been given 0.5 to 1.0 Gm. of sulfanilamide per Kg. over a period of three days, noted that the mortality under anesthesia, particularly with the thiobarbiturates, was increased by such treatment. Nelson (4) describes this dose of sulfanilamide (0.5 to 1.0 mg. per Kg.) as fatal to rabbits. Marshall, Cutting and Emerson (5) gave a group of young rats 0.16 to 0.35 Gm. of sulfanilamide per Kg. daily for sixty-five days without apparent toxic effect. They repeated the experiment, using 0.46 to 1.02 Gm. of sulfanilamide per Kg. per day without toxic manifestations. These authors conclude that the toxicity of the drug for rats appears to be small, although it is not devoid of harmful effects.

The present study is a continuation of work on pentothal sodium and sulfanilamide, with the dosage of sulfanilamide increased so that it is comparable to that used by Adriani (3), Marshall et al (5) and Nelson (4). The animals used were white Wistar rats, aged 6 weeks to 3 months, and weighing approximately 150 Gm. Sulfanilamide was prepared by dissolving the crystals in distilled water to make a 2 per cent solution. The first group of 96 rats received 0.3 Gm. of sulfanilamide per Kg. intraperitoneally for seven days. On the eighth day pentothal sodium in 2½ per cent solution was given intraperitoneally in doses ranging from 60 to 120 mg. per Kg., each dose being given to a group of nine or ten rats. Eighty rats received intraperitoneal injections of 0.6 Gm. of sulfanilamide per Kg. daily for seven days and on the eighth day were divided into groups of ten and given pentothal

* From the University of Kansas School of Medicine, Kansas City, Kansas.
† From the Hixon Laboratory for Medical Research and the Department of Anesthesia.

sodium in doses from 60 to 110 mg. per Kg. Sixty-five rats received daily intraperitoneal injections of 1.0 Gm. of sulfanilamide per Kg. for four days and on the fifth day were given pentothal sodium 50 to 100 mg. per Kg. in five groups of ten rats and one group of fifteen.

By the method of Bliss (6) the L.D.$_{50}$ for pentothal was determined for each group of rats from the data obtained. The L.D.$_{50}$ as previously



GRAPH 1. Dosage mortality curves. *A*. Corrected curve for pentothal sodium alone. *B*. Corrected curve for pentothal sodium subsequent to sulfanilamide therapy 0.15 Gm. per Kg. *C*. Corrected curve for pentothal sodium following sulfanilamide therapy with 0.3 Gm. per Kg. *D*. Corrected curve for pentothal sodium after 0.6 Gm. of sulfanilamide per Kg. *E*. Corrected curve for pentothal sodium after a toxic dose of 1.0 Gm. per Kg. of sulfanilamide.

calculated (1) for pentothal sodium alone was 84.85 $\pm$ 4.00 mg. per Kg., and with preliminary therapeutic doses (0.15 Gm. per Kg.) of sulfanilamide the L.D.$_{50}$ for pentothal was 85.21 $\pm$ 6.56 mg. per Kg. These figures agree very closely. With 0.3 Gm. of sulfanilamide per Kg. the L.D.$_{50}$ of pentothal is 87.63 $\pm$ 3.48 mg. per Kg. This result is comparable to the previous data. The increase of 2.46 mg., although not significant, is of interest in that it agrees with the finding of Kohn-

Richards (7) that, within limits, sulfanilamide is stimulating, but that it becomes depressing if these limits are exceeded.

For the group that received 0.6 Gm. of sulfanilamide per Kg. the $L.D._{50}$ of pentothal sodium is calculated as 78.13 ± 3.90 mg. per Kg. A definite decrease in the pentothal dosage-mortality ratio is noted with this dose of sulfanilamide. This indicates that if therapeutic doses of sulfanilamide are exceeded the susceptibility to pentothal sodium given subsequently is increased. For the rats which received 1.0 Gm. of

TOXICITY OF PENTOTHAL SODIUM AND OF PENTOTHAL SODIUM SUBSEQUENT TO SULFANILAMIDE THERAPY

No.	Pentothal Sodium Dosage Mg.	Pentothal Sodium No. of Rats Dead / No. of Rats Used	Pentothal Sodium with Sulfanilamide in Gm.			
			No. of Rats Dead		No. of Rats Used	
			0.15	0.3	0.6	1.0
1.	40	0/10				
2.	50	1/10	0/10			1/10
3.	55	1/10				
4.	60	1/10	1/10	2/10	1/10	6/10
5.	65	2/10				
6.	70	3/10	2/10	4/19	11/20	0/15
7.	75		3/10			
8.	80	3/10	4/10	10/20	8/20	6/10
9.	90	5/10	6/10	6/18	6/10	10/10
10.	100	6/10	7/10	5/9	7/10	10/10
11.	110	9/10	9/10	9/10	10/10	
12.	120			9/10		
13.	140	10/10				
	$L.D._{50}$	84.85 ± 4.00	85.21 ± 6.56	87.63 ± 3.48	78.13 ± 3.90	64.58 ± 3.43

sulfanilamide per Kg. the $L.D._{50}$ of pentothal sodium was found to be 64.58 ± 3.43 mg. per Kg. Pentothal sodium following this dose of sulfanilamide is definitely more toxic, with a decrease in the median lethal dose of 20.59 mg. per Kg.

The above data are of interest clinically from an experimental viewpoint, when sulfanilamide therapy is in progress and pentothal sodium is to be used as an intravenous anesthetic. From our findings it would appear that if the therapeutic dosage of sulfanilamide has not been exceeded, administration of pentothal sodium is not contraindicated in rats. As a therapeutic dose Long and Bliss (2) used 0.11 Gm. of

sulfanilamide per Kg. for human therapy. However, if a much larger dose of sulfanilamide is used definite toxicological effects are noted and susceptibility to pentothal is increased. With a dosage of 0.6 to 1.0 Gm. of sulfanilamide per Kg. our findings approximate those of Adriani (3), who found that more of the animals receiving sulfanilamide in this dosage died under barbiturate anesthesia than of those not previously treated with sulfanilamide. With a dose of 1.0 Gm. of sulfanilamide per Kg. our rats exhibited marked toxic symptoms of a neurological nature: ataxia, vestibular disturbances, weakness or paralysis of the hind legs, roughness of the coat with loss of sheen, hyperpnea and gray cyanosis especially marked around the mouth and feet. Marshall, Cutting and Emerson (5) also record these neurological findings.

CONCLUSIONS

1. Sulfanilamide in dosage of 0.3 Gm. per Kg. in rats does not decrease the $L.D._{50}$ of pentothal sodium given subsequently to rats.
2. Sulfanilamide in doses of 0.6 to 1.0 Gm. per Kg. produces toxic effects which render white rats more susceptible to pentothal sodium.
3. With a dosage of 1.0 Gm. per Kg. marked neurological symptoms are observed in white rats.

REFERENCES

1. Lorhan, Paul H.; Guernsey, Gretchen, and Pugh, Albert E.: To be published, Jour. Lab. & Clin. Med.
2. Long, P. H., and Bliss, Eleanor A.: Para-Aminosulfonamide and its Derivatives, Arch. Surg. 34: 351 (Feb.) 1937.
3. Adriani, John: Effects of Anesthetic Drugs upon Rats Treated with Sulfanilamide, Jour. Lab. & Clin. Med. 24: 1066 (July) 1939.
4. Nelson, A. A.: Histopathological Changes in Hens and Rabbits Following Administration of Sulfanilamide and Sulfunilyl Sulfanilamide, Pub. Health Rep. 54: 106 (Jan. 27) 1939.
5. Marshall, E. K.; Cutting, W. C., and Emerson, Kendall: The Toxicity of Sulfanilamide, J. A. M. A. 110: 252 (Jan. 22) 1938.
6. Bliss, C. I.: The Determination of the Dosage-Mortality Curve from Small Numbers, Quart. J. of Pharm. & Pharmacol. 11: 192 (Jan., March) 1938.
7. Kohn-Richards, Richard: Personal communication.
