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Reduction of Toxicity of 2-Sulfanilamidopyrimidine (Sulfadiazine) by Phenylazo-alpha-alpha-diaminopyridine Hydrochloride (Pyridium) in the Mouse.

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The possibility of antagonism in systemic toxicity between the sulfonamides and other compounds has begun to receive attention during the past year. McCarty[1] found that para-aminobenzoic acid has no effect on the acute fatal toxicity of sulfapyridine in mice. David, *et al.*,[2] reported that pentobarbital exerted a protective action against the toxicity of intravenously administered heparin-sodium sulfapyridine mixtures in dogs. Richards[3] found that small doses of urethane or pentobarbital decrease the fatal toxicity of intravenously administered sodium sulfapyridine in rabbits and dogs. In the present paper it is shown that the acute toxicity of 2-sulfanilamidopyrimidine (sulfadiazine) in the mouse is reduced by phenylazo-alpha-alpha-diaminopyridine hydrochloride (pyridium). The toxicity of sulfanilamide is not affected by this compound.

The percent mortality in a group of mice injected subcutaneously with a given dose of sulfonamide was compared, under the same experimental conditions, with the mortality in groups receiving this dose and, in addition, doses of 10, 30 or 100 mg of pyridium per kg. For each experiment, 3 groups consisting of 8 to 15 mice each were employed. A total of 269 mice was used in the experiments here reported. The sodium salts of sulfadiazine and sulfanilamide* were injected subcutaneously in concentrations of 5 to 10%. Pyridium was injected in a 0.2% solution or a 0.5% suspension. When both sulfonamide and pyridium were employed, they were injected within a few seconds of each other into widely separated sites. The mice were given water and food *ad lib.* and the number of deaths occurring in 4 days noted.

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[1] McCarty, M., PROC. SOC. EXP. BIOL. AND MED., 1941, **46**, 133.

[2] David, N. A., Phatak, N. M., Donnell, H., and Vers, H., *J. Am. Pharm. Assn.*, 1941, **30**, 38.

[3] Richards, R. K., *J. Lab. and Clin. Med.*, 1941, **26**, 1256.

* The sodium salts were prepared according to the directions of Marshall, Bratton and Litchfield.[4] Sodium sulfadiazine, furnished through the courtesy of the Nepera Chemical Co., was also employed.

[4] Marshall, E. K., Jr., Bratton, H. C., and Litchfield, J. T., Jr., *Science*, 1938, **88**, 597.

The results are shown in Table I. Experiment 1 is a control, showing that pyridium in doses of 30 and 100 mg per kg did not cause any deaths ascribable to the drug. Walton and Lawson[5] found a 20% mortality in rats receiving 200 mg of pyridium per kg intravenously, and a 100% mortality at a dose of 450 mg per kg.

Experiments 2, 3, and 4 show that 1.5 g of sulfadiazine led to a mortality of from 80 to 100%. This dose of sulfadiazine together with doses of 30 or 100 mg of pyridium per kg resulted in a much lower percent mortality, the higher dose appearing somewhat more effective in this respect. Thus, in experiment 4, a dose of 100 mg of pyridium per kg decreased the mortality from 93 to 25%. All 3 experiments showed this reduction in mortality.

Since the percent mortality in the preceding experiments was

TABLE I.
Effect of Pyridium on Toxicity of Sulfonamides.

Pyridium, mg/kg	No. of mice	No. dead in 4 days	Mortality, %
	Exp. 1. Control—No Sulfonamide.		
0	10	1	10
30	10	1†	10
100	15	1†	7
	Exp. 2. 1.5 g Sodium Sulfadiazine per kg.		
0	10	8	80
30	10	3	30
100	10	3	30
	Exp. 3. 1.5 g Sodium Sulfadiazine per kg.		
0	10	10	100
30	10	9	90
100	14	9	65
	Exp. 4. 1.5 g Sodium Sulfadiazine per kg.		
0	15	14	93
30	15	12	80
100	12	3	25
	Exp. 5. 1.2 g Sodium Sulfadiazine per kg.		
0	10	5	50
30	10	1	10
100	10	0	0
	Exp. 2a. 2.0 g Sodium Sulfanilamide per kg.		
0	10	7	70
10	9	4	44
30	8	3	38
100	11	8	73
	Exp. 3a. 2.0 g Sodium Sulfanilamide per kg.		
0	10	8	80
30	10	6	60
100	10	9	90
	Exp. 4a. 2.0 g Sodium Sulfanilamide per kg.		
0	10	5	50
10	10	5	50
30	10	6	60

†These mice were found to have been eaten by the others in the cage, and probably do not represent pyridium toxicity.

[5] Walton, R. P., and Lawson, E. H., *J. Pharm. and Exp. Therap.*, 1934, **51**, 200.

higher than that which Feinstone, *et al.*,[6] have reported for a dose of 1.5 g of sulfadiazine per kg (43.5%), it was decided to determine the effect of pyridium on the toxicity of a smaller dose of sulfadiazine. Experiment 5 shows that the mortality at a dose of 1.2 g of sulfadiazine per kg was 50%. The simultaneous administration of this dose and 30 mg of pyridium per kg reduced the mortality to 10%, and when the sulfadiazine and 100 mg of pyridium per kg were given, no deaths resulted.

In contrast to the effect of pyridium on the toxicity of sulfadiazine, this substance had no effect on the toxicity of sulfanilamide, as may be seen from examination of experiments 2a, 3a, and 4a.‡

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Increase in Weight of Gonads Following Injection of Single Male Rat Pituitary.*†

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When increases in ovarian weight of the sexually immature rat have been employed in determining the gonadotropic content of the rat pituitary it has been necessary to implant[1] or inject[2] more than

[6] Feinstone, W. H., Williams, R. D., Wolff, R. T., Huntington, E., and Crossley, M. L., *Bull. Johns Hopkins Hosp.*, 1940, **67**, 427.

‡ The writer is indebted to Dr. W. J. Youden of the Boyce Thompson Institute for Plant Research for a statistical analysis of these results. The alive : dead ratio of all the mice in experiments 2 to 5 should be 59:77 if the pyridium had no effect on the toxicity of the sulfadiazine. Calculation of chi square from the differences between the calculated expectations and the mortalities at the concentrations of 0, 30 and 100 mg of pyridium per kg yields a value of 22.82, "a value highly improbable if the ratio were really the same for all concentrations." An analysis of the variance showed that, if the pyridium were really without effect, the decrease in the toxicity of the sulfadiazine obtained would occur *by chance* only once in something like one hundred instances, and certainly not more often than once in fifty.

* Journal Series Paper of the New Jersey Agricultural Experiment Station, Rutgers University, Department of Dairy Husbandry.

† This study has been aided in part by a grant from the National Dairy Products Corporation.

[1] Evans, H. M., and Simpson, M. E., *Am. J. Physiol.*, 1929, **89**, 371.

[2] Hellbaum, A. A., and Greep, R. O., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 902.