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## Comparative Therapeutic Efficiency of Sulfapyridine and Sulfathiazole in Mice Infected with Pneumococcus Types II and III.

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Sulfathiazole, a thiazole derivative of sulfanilamide, was studied by Fosbinder and Walter,[1] as well as Lott and Bergeim.[2] The toxicity was subsequently investigated by VanDyke, *et al.*,[3] who found

[1] Fosbinder, R. J., and Walter, L. A., *J. Am. Chem. Soc.*, 1939, **61**, 2032.

[2] Lott, W. A., and Bergeim, F. H., *J. Am. Chem. Soc.*, 1939, **61**, 3593.

[3] Van Dyke, H. B., Greep, R. O., Rake, G., and McKee, C. M., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 410.

repeated administrations of sulfathiazole or sulfapyridine in 2% concentration in the food of mice an indication that sulfathiazole is more toxic than sulfapyridine. If, however, 1% concentrations of the drugs were fed to mice, there was no difference in the toxicity. They found sulfapyridine more toxic for monkeys; sulfathiazole fed for 14 to 21 days caused a negligible loss of weight, while sulfapyridine feeding resulted in greater weight loss. Long, *et al.*,[4] found that the acute toxicity of sulfathiazole (as measured by the parenteral injection of the sodium salt) for mice is one-third greater than that of sulfanilamide, and about half that of sulfapyridine. McKee, *et al.*,[5] found that the therapeutic effects of sulfathiazole and sulfapyridine are equal in mice infected with various types of pneumococci and treated by administering the drugs in 1% diet. Barlow and Homburger[6] reported that the chemotherapeutic effect of sulfathiazole in mice with pneumococcus infection is definitely superior to sulfanilamide, and compares very favorably with sulfapyridine.

Chemically, sulfathiazole is 2-(p-aminobenzene sulfonamido) thiazole; it is sparingly soluble in water at room temperature, more soluble in boiling water from which it can be recrystallized. In the present investigation the compound used was prepared in the authors' laboratories and melted at 198-199°. Analysis showed nitrogen, 16.38%, theory 16.47%. Additional sulfathiazole purchased from commercial houses, which had the same chemical properties, was also included in this study.

Sulfathiazole is tolerated by rabbits *per os* in a dose of 3 to 5 g per kg of body weight, while the maximum tolerated dose of sulfapyridine, as reported by us previously,[7] is 2 g per kilo. Mice receiving sulfathiazole in aqueous suspension *per os* tolerated 10 to 15 g per kilo, while sulfapyridine was tolerated in a dose of 20 g per kilo.

*Therapeutic Effect.* The mice used in this study were infected intraperitoneally with 20 to 200 minimum lethal doses of types II or III pneumococcus of which the average minimum lethal dose was 0.5 cc of 1:10,000,000 dilution of broth culture. The culture was

[4] Long, P. H., Haviland, J. W., and Edwards, L. B., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 238.

[5] McKee, C. M., Rake, G., Greep, R. O., and Van Dyke, H. B., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 417.

[6] Barlow, O. W., and Homburger, E., PROC. SOC. EXP. BIOL. AND MED., 1940, **43**, 317.

[7] Raiziss, G. W., Severac, M., Moetsch, J. C., and Clemence, L. W., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 434.

TABLE I.
Comparative Therapeutic Effects of Sulfapyridine and Sulfathiazole Administered by Mouth in Types II and III Pneumococcic Infection in Mice.

| Type of pneumococcus | Drug | No. mice used | % of survivals in days | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 14 | 21 | 28 |
| II | Sulfapyridine | 40 | 100 | 100 | 93 | 85 | 65 | 50 | 43 | 28 | 28 | 28* |
| | Sulfathiazole | 60 | 100 | 90 | 82 | 73 | 52 | 25 | 13 | 5 | 3 | 3 |
| | Controls | 58 | 5 | 0 | | | | | | | | |
| III | Sulfapyridine | 26 | 100 | 100 | 85 | 77 | 65 | 54 | 38 | 12 | 12 | 12 |
| | Sulfathiazole | 33 | 94 | 82 | 58 | 27 | 18 | 15 | 6 | 3 | 3 | 3 |
| | Controls | 25 | 48 | 48 | 8 | 0 | | | | | | |

*In our earlier work[7] we reported a smaller percentage of survivals following sulfapyridine treatment than we do in the present investigation. The difference in results is due to the fact that in our previous work the first dose of sulfapyridine was administered one and one-half hours after infection, and only two doses per day were given the first two days. In the present work we treated the mice immediately after infection, and have given three doses per day for five consecutive days. The maximal number of treatments in our earlier work was ten; in the present experiments eighteen doses were administered.

prepared as follows: Mice were infected intraperitoneally with 1 to 1.5 cc of the straight culture. When the mouse died (usually within 6 to 8 hours) it was autopsied and a loop full of heart blood was inoculated into the blood broth media. This culture was ready for use in 14 to 16 hours.

The drugs were given by mouth in a dose of 10 mg. The mice were dosed three times daily, at 9 a.m., 5 p.m., and 12 m. for 5 days, at 9 a.m. and 5 p.m. on the sixth day, and at 9 a.m. on the seventh day—a maximum of 18 treatments. Table I presents a summary of the results obtained in several experiments.

*Summary.* Studies of the toxicity disclose that sulfathiazole administered *per os* to rabbits is less toxic than sulfapyridine. On the other hand, administered the same way to mice sulfapyridine appeared to be less toxic than sulfathiazole. It is obvious that the absorption and elimination, and the resulting toxicity of the drug depend upon the species of animal used. In Types II and III pneumococcus infection, the therapeutic effect of sulfapyridine is superior to that of sulfathiazole, based on the oral dose only and with no blood level determinations.