

Comparative Studies on Toxicity of a New Streptomycin and Streptomycin Sulfate.* (18525)

ANTHONY M. AMBROSE

From the Pharmacology Laboratory, Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture, Albany, Calif.

Investigators at the Northern Regional Research Laboratory of the U. S. Department of Agriculture have recently reported the isolation in pure state of a new antibiotic, hydroxystreptomycin. It is produced by an organism, isolated from Japanese soil, which they believe to be different from other streptomycin-producing strains. The new species has been designated as *Streptomyces griseo-carneus* n. sp. On the basis of degradation experiments, Benedict *et al.* (1) have assumed that the new antibiotic differs from streptomycin only in having a hydroxy group in place of one of the hydrogens of the streptose methyl group. Accordingly, they have assigned the name "hydroxystreptomycin" to the new member of the streptomycin series.

One mg analytically pure hydroxystreptomycin trihydrochloride, when assayed against *Bacillus subtilis*, NRRL B-765 (ATCC 6633), was found to be equivalent to 784 μ g of streptomycin base. The hydroxystreptomycin trihydrochloride used in these studies was prepared in the Northern Regional Research Laboratory and assayed 596 μ g/mg (76% pure). The streptomycin sulfate assayed equivalent to 621 μ g of pure free base per mg and was 78% pure.[†]

In the present studies we have compared the acute toxicity of hydroxystreptomycin trihydrochloride against the toxicity of streptomycin sulfate in white mice by subcutaneous administration. Both samples of streptomycin were dissolved in glass distilled water just before use, and the pH of each solution

was measured with a glass electrode. The pH of a 10% solution of hydroxystreptomycin trihydrochloride was 7.1; that of a 10% solution of streptomycin sulfate was 4.8, which was adjusted to 6.2 with solid sodium bicarbonate. At least 10 mice (sexes equally divided) were used at each dosage level in determining the toxicity of the 2 streptomycins. For hydroxystreptomycin trihydrochloride, 46 mice were used and for streptomycin sulfate, 60 mice were used. The approximate LD₅₀, as determined by Trevan's method, was found to be as follows: for hydroxystreptomycin trihydrochloride, 865 mg/kg; and for streptomycin sulfate, 970 mg/kg.

The reactions observed in mice receiving either of the two streptomycins were essentially the same as those reported in the literature for streptomycin. With doses above the LD₅₀, death of mice usually occurred within 30 minutes after injection. Death was invariably due to respiratory paralysis; the heart continued to beat for some time after the respiration had ceased. At these elevated dosage levels some mice developed convulsions, particularly with doses of 1000 to 1200 mg/kg. With the lower range of dosage (400 to 800 mg/kg) most of the mice failed to show serious symptoms. For 30 days following administration, all surviving mice were observed daily for any local tissue reaction at site of injection and for delayed neurotoxic effects. In none of the mice was there any evidence of tissue reaction (irritation, necrosis), or neurotoxic symptoms (changes in gait and posture, ataxia, vestibular dysfunction).

From the above observations, it is concluded that hydroxystreptomycin trihydrochloride has about the same order of toxicity for mice by subcutaneous administration as streptomycin sulfate.

* Report of a study made under the Research and Marketing Act of 1946.

1. Benedict, R. G., Stodola, F. H., Shotwell, O. L., Borud, A. M., and Lindenfelser, L. A., *Science*, 1950, v112, 77.

† Data supplied by Fermentation Division, Northern Regional Research Laboratory, Peoria, Illinois.