United States Patent Office 2,751,324
Patented June 19, 1956

2,751,324

ANTIBIOTIC COMPOSITIONS COMPRISING OXYTETRACYCLINE AND CARBOMYCIN

Arthur R. English, Mineola, N. Y., assignor to Chas. Pfizer & Co., Inc., Brooklyn, N. Y., a corporation of Delaware

No Drawing. Application July 18, 1952, Serial No. 299,758

4 Claims. (Cl. 167—65)

This application is concerned with certain antibiotic compositions. In particular, it is concerned with compositions of oxytetracycline (also known by the registered trademark "Terramycin") and carbomycin.

Oxytetracycline is a highly effective compound, especially useful in the treatment of infectious diseases. Carbomycin has been shown to be effective against a variety of different microorganisms. This compound is described in detail and claimed by the name of antibiotic P. A. 97 in the copending patent application of Fred W. Tanner, Jr., et al., filed on February 7, 1952, under Serial No. 270,298. It has now been found that compositions containing a oxytetracycline antibiotic and a carbomycin antibiotic act in a synergistic manner against certain microorganisms which cause serious infections in vivo. In particular, these compositions are quite effective against Micrococci and Streptococci, especially *Micrococcus pyogenes* and *Streptomyces faecalis*.

In this application, where reference is made to an oxytetracycline antibiotic, the term is meant to include not only amphoteric oxytetracycline, but salts of oxytetracycline with acids, such as hydrochloric or sulfuric acids, and with metals such as sodium, as well as other known, biologically active forms of the antibiotic. Not only may pure amphoteric oxytetracycline and salts thereof be used, but also crude products recovered from fermentation broths, concentrates thereof, and the like. Carbomycin is a basic compound which forms salts such as the sulfate or the hydrochloride; and the phrase "a carbomycin antibiotic" as used herein denotes not only the base per se, but its various salts and other biologically active derivatives.

Compositions containing from approximately 5 to approximately 95 parts by weight of an oxytetracycline antibiotic, together with from about 95 to about 5 parts by weight of a carbomycin antibiotic, exert the synergistic activity described above. It may be found that a particular organism is more susceptible to a certain formulation of these compositions than to others. For instance, one organism may be quite susceptible to a composition containing 10 parts of carbomycin with 90 parts of oxytetracycline, whereas another may be considerably more susceptible to a composition containing equal amounts of each of the component antibiotics. A minimum of bacteriological testing is required to determine the most useful of these compositions for combating any particular organism.

The compositions of this invention may be used in a variety of forms and manners, depending upon the particular microorganisms involved. Thus, the materials may be employed as disinfectants in vitro, or applied in vivo locally in forms of solutions, suspensions, powders, ointments and so forth. The compositions may also be injected intramuscularly for veterinary use in suitable media for such injections. For instance, a solution in saline or water may be employed. The oral administration of suitable preparations of the compositions of this invention may also be used for the treatment of certain

diseases. The oral preparations may take the form of capsules, tablets, elixirs, or other dry or liquid preparations. Care must be taken that, when solutions of these compositions are prepared, they are treated carefully to prevent decomposition. Storage should preferably be under conditions of refrigeration and solutions should be freshly prepared every few days.

The following examples are given by way of illustration and are not to be considered as the only manner in which this invention may be embodied. It is to be understood that protection hereof is only to be limited by the specific wording of the appended claims.

Example I

A composition was prepared containing 10% by weight of pure, crystalline carbomycin and 90% by weight of crystalline oxytetracycline hydrochloride. A sample of 2 milliliters of double strength standard bacteriological nutrient broth was placed in each of a number of test tubes. A portion of the antibiotic composition was added to each tube. This was followed by a 0.5-milliliter portion of a standard inoculum of *Micrococcus pyogenes* var. aureus. Finally, the volume of the mixture was diluted to 4 milliliters with sterile water. The tubes were incubated at 37° C. overnight and then were observed for evidence of growth of the microorganism as indicated by turbidity. From a series of such tests, all conducted under sterile conditions and to which varying amounts of the antibiotic composition were added, there was determined the minimum concentration of the composition required to inhibit growth of the microorganism in question. It was found that with the particular composition tested a total of 0.30 microgram of the composition per milliliter of the mixture was effective. However, when either carbomycin or oxytetracycline hydrochloride was used alone, 0.50 microgram of the antibiotic per milliliter of medium was necessary to achieve the same inhibition. When a mixture containing 25% of carbomycin and 75% of oxytetracycline was used, it was found that a total of 0.30 microgram of this composition was effective in inhibiting the growth of the organism. Compositions containing equal parts by weight of carbomycin and oxytetracycline, and a 10% carbomycin: 90% oxytetracycline formulation also proved effective at the same level. The utility of the new products for disinfecting purposes and other in vitro applications is thus demonstrated.

Example II

The effectiveness of compositions containing various proportions of amphoteric oxytetracycline and carbomycin base was tested in the same manner as in Example I against *Streptococcus faecalis* A121. Neither carbomycin nor oxytetracycline proved effective in inhibiting this organism at a level of 0.50 mcg./ml., whereas compositions of carbomycin with oxytetracycline ranging from 9 parts of oxytetracycline with 1 part of carbomycin to 1 oxytetracycline for 9 parts carbomycin, proved effective at levels of 0.30 microgram of the individual compositions per milliliter.

Example III

The effectiveness of compositions of carbomycin with oxytetracycline was tested in vitro against a strain of *Micrococcus pyogenes* var. aureus (Y-1) which had been found to be quite resistant to a variety of antibiotics. When oxytetracycline was tested alone against this microorganism, it was found that 50 micrograms were required per milliliter of medium to inhibit the organism. 2.5 micrograms of carbomycin hydrochloride per milliliter were required to inhibit this organism. However, a total of only 1.5 micrograms of a composition containing 75% by weight of carbomycin hydrochloride and 25% by weight of oxytetracycline hydrochloride per milliliter of

medium was necessary to inhibit this resistant organism. When a composition containing 90% of the carbomycin salt and 10% of oxytetracycline hydrochloride was tested, it was found that a total concentration of the composition containing 1.50 micrograms/milliliter was also effective in inhibiting the growth of the resistant organism. It is apparent that low levels of oxytetracycline very definitely increase the activity of carbomycin against this organism, despite the fact that oxytetracycline of itself has a relatively low level of activity on this particular organism. The novel compositions thus exhibit definite and unexpected synergism.

What is claimed is:

1. A bacteriologically active composition which comprises an oxytetracycline antibiotic and a carbomycin antibiotic.

2. A bacteriologically active composition which comprises a major proportion of an oxytetracycline antibiotic, together with a minor proportion of a carbomycin antibiotic.

3. A composition according to claim 2, wherein each of the two antibiotic constituents is in the form of a salt.

4. A bacteriologcially active composition which comprises between 5 and 95 parts by weight of oxytetracycline hydrochloride, together with between 95 and 5 parts by weight of carbomycin hydrochloride.

References Cited in the file of this patent

Neter et al.: "Synergistic effects of polymyxin B and terramycin on bacteria encountered in urinary tract infections." J. Urol., 67(5):773–775. 1952. Through Biol. Abstr., November 1952, p. 2807.

Tanner et al.: "Some Properties of Magnamycin." Antibiotics and Chemotherapy, September 1952, p. 441.

Welch et al.: "Bacterial Spectrum of Erythromycin, Carbomycin, Chloramphenicol, Aureomycin and Terramycin." Antibiotics and Chemotherapy, December 1952, pp. 693 to 696.

Hobby et al.: "The tuberculostatic activity of terramycin." Am. Rev. Tuberc., vol. 63, pp. 434 to 440, April 1951. Through Squibb Abstract Bulletin, vol. 24, No. 17, April 25, 1951, p. A–362.

Armstrong: "Effect of Combinations of Antibiotics." J. Lab. and Clin. Med., vol. 37, April 1951, pp. 584 to 592.