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ANTIBIOTIC COMPOSITIONS COMPRISING
ERYTHROMYCIN AND NEOMYCIN

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This invention relates to antibiotic compositions, and more particularly relates to antibiotic compositions containing the two essential active ingredients, erythromycin and neomycin.

Due to the successful treatment of infectious diseases with antibiotic materials a considerable portion of the research effort in the medical art has been devoted to the search for new and better antibiotics. Due to the development of strains of organisms resistant to existing antibiotics, the development of patient sensitivity to existing antibiotics, and the desire for ever improved antibiotics, continuous research is and will be carried out in the never ending struggle against infectious diseases. In recent years an increasing amount of attention has been given to the development of antibiotic combinations which possess advantages not possessed by the individual members of the combination.

It is therefore an object of the present invention to provide a novel combination of antibiotics useful in combating infectious diseases. Another object of the pres-

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same sense as in those references and includes the therapeutically active, non-toxic salts and esters of both forms.

Prior to the present invention these antibiotics have never been combined. However considerable clinical and animal tests conducted with the combination have demonstrated the efficacy and unexpected properties thereof. Since neomycin is primarily regarded as a topical medication, the combination is also most useful in that form. For topical use in humans erythromycin-neomycin combinations are generally prepared in an ointment or lotion base such as those commonly known to the art. A powder base is also feasible for topical use. For animal use, such as bovine mastitis an ointment base is used with due regard to the special problems of administering such materials in the special conditions there involved. Such a base is more fully described in copending application Serial No. 444,641, filed July 20, 1954. The combination also is useful when prepared in a form suitable for oral administration, such as a tablet or in a conventional liquid oral vehicle.

The following examples are merely illustrative of the compositions of the present invention and are not to be construed as limiting.

EXAMPLE 1.—IN VITRO USE

In vitro, tests substantiate the synergistic effectiveness of the combination over the individual materials. The following table indicates the effect of erythromycin and neomycin alone and in combination against two of the most common organisms involved in bovine mastitis. The results given indicate the minimum inhibitory concentration (MIC) in micrograms per milliliter (mcg./ml.) of the antibiotics alone and in combination after 24 and 48 hours' incubation.

The effect of erythromycin and neomycin alone and in combination against certain organisms involved in bovine mastitis, in vitro

Organism	Single Antibiotics MIC, mcg./ml.		Combination Studies, MIC, mcg./ml. Ratio of Antibiotics in Combinations							
	Eryth.		Neo.		E1/N1		E9/N1		E1/N9	
	24	48	24	48	24	48	24	48	24	48
M. pyogenes var. aureus		.19		12		.09		.17		.075
Streptococcus dysgalactiae	.005	.02	6.0	25	.002	.005	.0045	.0045	.002	.004
					.002	.005	.0002	.0005	.018	.036

ent invention is to provide a combination of erythromycin and neomycin which possesses advantages unattainable from either alone. Still another object is to provide a combination of antibiotics which is highly effective in the treatment of a variety of cutaneous bacterial infections. Still another object of the present invention is to provide a novel combination of antibiotics which is especially effective in the treatment of bovine mastitis. Other objects will be apparent to one skilled in the art to which this invention pertains.

Neomycin is one of the newer antibiotics which has been fully described in Waksman in his recent work "Neomycin," Rutgers University Press, 1953. The word "neomycin" is used here in the same sense as it is used in that work and includes the various forms of neomycin (such as the B and C forms) and its active derivatives (such as the sulfate salt).

Erythromycin is an even newer antibiotic more fully described in one form in U. S. Patent No. 2,653,899, and in another form in Pettinga et al., J. A. C. S., 76: 569-571 (1954). The word "erythromycin" is used here in the

Moreover the overall effectiveness of the combination against all of the organisms commonly found in bovine mastitis establishes the efficacy of the combination in those situations in which a veterinarian or doctor has no time to determine the major causative organism in a particular case of bovine mastitis. It is possible to use less of the materials in combination to inhibit all of the organisms than either antibiotic alone. Among the more common organisms found in bovine mastitis are the following: *Pseudomonas aeruginosa*, *Aerobacter aerogenes*, *M. pyogenes* var. *aureus*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus uberis*, and *Corynebacterium pyogenes*. Using the method outlined in the table, the minimum inhibitory concentration of erythromycin alone for the whole group of organisms is 100 micrograms per milliliter after 24 hours' incubation; the minimum for neomycin alone is 25 micrograms per milliliter after 24 hours' incubation. Using the combination of erythromycin and neomycin in a one to one ratio, only twelve micrograms per milliliter of each of the two antibiotics is required. When the ratio of

erythromycin to neomycin is one to nine, only 1.2 micrograms per milliliter of erythromycin and eleven micrograms per milliliter of neomycin are required. From a practical standpoint the synergism of the combination as expressed in this way is more important than the synergism of the combination against particular organisms associated with the disease.

EXAMPLE 2.—CLINICAL USE

Using conventional pharmaceutical techniques one-half ounce tubes of the following kinds and amounts of materials were prepared:

Erythromycin	milligrams	5.0
Neomycin sulfate	do	5.0
Liquid petrolatum, U. S. P. XIV	grams	0.25
Methylparaben, U. S. P. XIV	milligrams	0.2
n-Butyl-p-hydroxybenzoate	do	1.8
Cholesterol, U. S. P. XIV	do	5.0
Microcrystalline wax	do	40.0
White petrolatum, U. S. P. XIV, q. s. ¹		

¹ Sufficient to make up one-half ounce.

The formulation containing the essential active ingredients as given above was tested in a large group of patients by several investigators and the results of these investigations were all favorable. They were used in a variety of cutaneous bacterial infections and produced prompt responses in impetigo, impetiginous dermatitis, folliculitis, paronychia, external otitis, cellulitis and secondarily infected eczema, burns and ulcers. In some cases of bacterial eczematous dermatitis that failed to improve significantly with other antibiotic preparations, this combination produced prompt clearing of the infection. Although neither of the individual antibiotics has been shown to have antifungal activity, the combination is capable of clearing lesions caused by secondary bacterial invaders even in situations where the primary causative organism is fungal in nature. One investigator used the combination in the treatment of pyodermas in nearly 200 patients. A partial report of his results can be found in Livingood et al., J. A. M. A. 153, 1266 (December 5, 1953). Another investigator treated about 150 cases of pyodermas with excellent results and no evidence of irritation and/or sensitization. Still another investigator used the combination on a considerable number of patients and reported that he had not observed a single case where there was an untoward reaction to treatment and indicated that it was his belief that the overall response was much faster than with any other antibiotic used since the days of penicillin.

EXAMPLE 3.—POWDER PREPARATION

A powder preparation of the composition of the present invention is prepared by conventional techniques. Each gram of such a preparation contains the following:

		Mg.
Neomycin sulfate powder	-----	6
Erythromycin	-----	6
n-Butyl-p-hydroxybenzoate	-----	1.8
5 Methylparaben, U. S. P.	-----	0.2
Lactose	-----	986

EXAMPLE 4.—ORAL TABLETS

Using conventional pharmaceutical techniques an oral dosage form containing the following ingredients can also be prepared.

Each tablet contains:

		mg	250
Neomycin	-----	mg	50
Erythromycin	-----	mg	50
15 Starch	-----	grains	.155
Sucrose	-----	do	.055
Light mineral oil	-----	do	.037
Calcium stearate	-----	do	.04
Guar gum	-----	do	.05

20 Starch, sucrose, and guar gum are used for granulation; the guar gum primarily for disintegration. The calcium stearate and mineral oil are used for lubricants.

The tablet can be enteric coated to protect the erythromycin by the use of a conventional enteric coating material, such as cellulose acetate phthalate.

It is to be understood that the invention is not to be limited to the exact details of operation or exact compositions shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the scope of the appended claims.

I claim:

1. A therapeutic composition comprising erythromycin and neomycin.

2. A therapeutic composition comprising as one essential active ingredient erythromycin, as a second essential active ingredient neomycin, and an ointment base.

3. A therapeutic composition comprising erythromycin as one essential active ingredient, neomycin as a second essential active ingredient, and a water and milk miscible vehicle.

4. A therapeutic composition comprising erythromycin, neomycin sulfate, and an ointment base.

References Cited in the file of this patent

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