PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Antibiotic Compositions for Oral Use

We, AMERICAN CYANAMID COMPANY, a corporation organised under the Laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to improved antibiotic compositions of the tetracycline type

In the past years antibiotic therapy has been very widespread. Normally a single antibiotic, chosen for its known effectiveness against a diagnosed or suspected microorganism, has been used; and for most antibiotics recommended daily dosage has been determined. Proposals have been made to use different types of antibiotic in a combined dose. With a few microorganisms, such as those causing enterococcal endocarditis and some resistant strains of staphylococcus, combinations of antibiotics of different types have proven effective. Also in some cases combinations of an antibacterial and an antifungal have been used. Many if not most of the proposed compositions have either been no more effective than a single antibiotic or in some cases there has been serious antagonism.

There is a vital distinction between medical rather than chemical types of antibiotics, namely those which *in vitro* are bactericidal rather than bacteriostatic. Only in the case of bactericidal antibiotics have there been useful combination compositions. The bacteriostatic antibiotics, of which the tetracyclines with which the present invention deals are members, have either shown antagonism, for example in combinations of the tetracyclines and penicillin, or lack of useful improved results. It should be noted that the distinction between bactericidal and bacteriostatic antibiotics is one which is only of significance in tests made *in vitro*. When tests are made in living animals or men, all that can be determined is whether or not a drug shows good antibacterial activity. It cannot be determined whether the test animal or man recovered because the antibiotic actually killed bacteria on contact with them, that is to say was bactericidal, or whether it was merely bacteriostatic and inhibited or very greatly reduced the rate at which the bacteria reproduced themselves. In the case of such bacteriostatic activity the ordinary defenses of the body may be the ones which showed an antibiotic as being satisfactory antibacterial efficacy. Even in tests made *in vitro* there is not always an absolutely hard and fast qualitative difference between a bacteriostatic antibiotic and a bactericidal one. In many cases an antibiotic in one concentration shows bacteriostatic activity but if the concentration is enormously increased may actually kill the bacteria with which it comes in contact. Nevertheless, the differences are sufficiently great so that the distinction between the types of antibiotics is one which is made in practice, and it is this practical interpretation which is to be put on the terms used in the present application.

Even in the case of combinations of bactericidal antibiotics there is only one instance where the antibiotics were chemically of similar nature. This is a combination of streptomycin and dihydrostreptomycin. This combination was proposed and has been used in the hope that it would reduce the serious side effect of nerve deafness of streptomycin alone. There is strong controversy as to whether this improved result has been obtained and, in any event, it should be emphasized that

[*Price 4s. 6d.*]

here, as in the case of the few medically accepted combined antibiotics, we are dealing with two bactericidal products.

The present invention is directed to a combination of tetracyclines, all of them of course being bacteriostatic antibiotics which have been considered unsuitable for combination antibiotic therapy. Results are obtained with the compositions of this invention which show as high antibacterial activity in the blood of patients to whom the antibiotic composition has been given, but the side effects which are often very undesirable, such as nausea, and gastro-intestinal disturbances are eliminated or drastically reduced over those of comparable doses of a single antibiotic. As a result, the problems of side effects with most patients are not significant with the preferred doses which will be set out below. It should be noted that in certain very severe infections, it is not unusual to give a greatly increased antibiotic dose even at the risk of some side effects. After all, a patient with a dangerous infection presenting a serious risk of death will accept a considerable amount of discomfort which may be involved with extremely large doses. Even here, as will be shown below, the maximum dose for extremely severe cases is still markedly reduced and so, while side effects are not completely eliminated in such cases, they are quite substantially reduced. The compositions of the present invention are a mixture of tetracycline itself, hereinafter abbreviated TC, chlortetracycline, abbreviated CTC, and demethylchlortetracycline, abbreviated DMCTC. The combination may also include oxytetracycline, abbreviated OTC in place of all or part of the TC; methacycline, 6-deoxy-6 demethyl-6-methylene - 5 - oxytetracycline in place of all or part of the DMCTC; minocycline, 7-methylamino - 6 - deoxy - 6 - demethyltetracycline, in place of all or part of the DMCTC and doxycycline, 6α - methyl - 6 - deoxy - 5 - hydroxytetracycline, in place of all or part of the DMCTC. Such combined antibiotic compositions are therefore included in the broader aspects of the present invention. Further each tetracycline may be either in the form of its free base or a non-toxic acid addition salt thereof.

An absolutely exact numerical dosage is of no meaning because we are dealing with a mixture of antibiotics and not materials which react in fixed proportions to form a single new chemical compound. Also the reactions of patients vary, and there is no such thing as an absolutely precise quantitative dose figure which has particular meaning in antibiotic therapy. Nevertheless, it has been found that a particularly effective minimum daily dose is one of 600 mg. given in the form e.g. of 2 capsules or tablets daily each containing 300 mg. of active ingredients consisting of 115 mg. of TC and/or OTC, 115 mg of CTC and 70 mg. of DMCTC and/or methacycline and/or doxycycline. The corresponding maximum doses recommended for extreme cases are double the figures given above so that an effective daily dosage ranges from 500 mg. to 1200 mg. of the active ingredients of the antibiotic composition. The antibiotics are preferably combined in the ratio of from 30% to 50% by weight TC (and/or OTC), from 30% to 50% by weight CTC and from 15% to 50% by weight DMCTC (and/or methacycline and/or doxycycline). A most preferred ratio of TC (and/or OTC), CTC and DMCTC (and/or methacycline and/or doxycycline) is in the proportion of one part by weight each of TC (and/or OTC) and CTC and 0.6 parts by weight of DMCTC (and/or methacycline and/or doxycycline) in the form of their free bases or acid addition salts.

It should be noted that side effects are not determined solely by the total intake during a day but are greatly affected by the amount of antibiotics in any single dose. For this reason it is customary to give the antibiotics in two or more doses during twenty-four hours.

In the composition of the present invention we are dealing with very closely related antibiotics of the bacteriostatic type which have not been considered acceptable or practically useful in combination antibiotic therapy. The compositions of the present invention produce antibacterial activities in blood serum at all times during twenty-four hours after administration in excess of a dose of TC equal to the total weight of the composition. The composition is, therefore, more effective than the same amount of TC and gives considerably better antibacterial activities in blood serum over the total period. At the same time, as stated above, undesirable side effects, such as nausea and gastro-intestinal disturbances, are either eliminated entirely or so drastically reduced that they do not involve any significant problems with most patients with the preferred daily doses.

The improved antibacterial activities in the blood of patients as determined by antimicrobial microbiological assay are obtained not only without offsetting side effects but with a great reduction and, in the case of most patients, complete elimination of the side effects which were encountered before. It is not desired to limit the present invention to any theory of the mechanism by which this desirable result is obtained. It is possible that the tetracyclines have synergistic properties without any comparable effect on side effects, but the invention is in no sense limited to this particular theory, which is advanced as only one of a number of possible explanations. What is known is that improved antibacterial activities with greatly reduced or eliminated undesirable side effects are ob-

tained as compared with the same total dose of each antibiotic when taken alone.

It is an advantage of the invention that the improved results are obtained when the composition is used in any of the customary forms for therapy i.e. includes a pharmaceutically acceptable carrier; thus for example a powdered mixture of the tetracyclines with a suitable excipient may be filled into a gelatin capsule for oral use. Tablets may be made with a suitable binder such as acacia gum, cornstarch, or gelatin, with suitable disintegrating agents such as cornstarch (which may thus perform a dual function), potato starch or alginic acid and lubricants such as stearic acid, magnesium stearate, or talc,; or syrups or drops may be prepared with suitable sweetening agents, or flavouring agents. In each form the improved results of the present invention are obtained. It should be noted that the tetracyclines need not be in the form of the free bases and, in fact, it is generally desirable to use the antibiotics in the form of non-toxic acid addition salts, e.g. the hydrochloride salts or Mannich derivatives thereof.

The invention will be described in greater detail in conjunction with the following specific examples in which the parts are by weight unless otherwise specified.

EXAMPLE 1

TC HCl	41.3
CTC HCl	41.7
DMCT HCl	25.0
Lactose, U.S.P.	43.0

The active ingredients and lactose are blended together thoroughly to form a homogeneous mixture. The powder is used to fill hard gelatin capsules of a suitable size at a gross filled weight of 360 milligrams. Each capsule then contains a total of 250 milligrams of antibiotics in the proportion of one part each of TC HCl and CTC HCl and 0.6 parts of DMCT HCl.

The composition described above was tested clinically on twelve subjects, six of whom first received TC HCl in the quantity above, namely 250 mg., and six of whom received a capsule of the three antibiotics. Blood samples were taken at regular intervals during twenty-four hours and antibacterial activities were determined. One week later the subjects who were given the TC HCl were given a capsule of the three antibiotics and the subjects who were given a capsule of the three antibiotics the first week were given a capsule of TC HCl. Antibacterial activity was determined by microbiological assay procedures using a standard test for tetracycline antibiotics. The results appear in the following table, which also gives the percentage increase of antibacterial activities in the serum as compared to TC HCl. The study indicates that higher and more sustained antibacterial activity in blood serum is produced by the capsules containing the combination of antibiotics as compared to the tetracycline capsules. It is well known that certain patients are exceptions in that the absorption of a particular antibiotic is not satisfactory. In the case of the patients tested as described above all of the patients showed adequate antibacterial activity by the above test. It is a further advantage of the present invention that it is much less likely that any one patient would fail to acquire adequate antibacterial activity for all of the drugs than would be the case where only a single antibiotic was used. In the test above described, none of the patients showed any undesirable side effects.

TABLE 1

Antibiotic Activity as TC HCl in Blood Serum (mcg./ml.)

ANTIBIOTIC	Hours after Dose 1	3	6	12	24
TC HCl	1.22	1.98	1.36	0.83	0.35
Mixture	1.71	4.47	3.30	1.83	0.77
Percent increase of Mixture compared to TC HCl	40%	126%	143%	120%	120%

The data in the table are expressed as geometric averages in accordance with standard investigating procedure.

EXAMPLE 2
TABLET

TC . HCl	960
CTC . HCl	960
DMCTC . HCl	580
Lactose, U.S.P.	410
Corn Starch (for mix)	50
Corn Starch (for paste)	40
	3000
Magnesium Stearate, U.S.P. (1%)	30
	3030

EXAMPLE 3
TABLET

CTC . HCl	960
OTC . HCl	960
DMCTC . HCl	580
Lactose, U.S.P.	410
Corn Starch (for mix)	50
Corn Starch (for paste)	40
	3000
Magnesium Stearate, U.S.P. (1%)	30
	3030

EXAMPLE 4
TABLET

TC . HCl	960
CTC . HCl	960
Methacycline . HCl	580
Lactose, U.S.P.	410
Corn Starch (for mix)	50
Corn Starch (for paste)	40
	3000
Magnesium Stearate, U.S.P. (1%)	30
	3030

The three antibiotics, lactose and corn starch (for mix) are blended together. The corn starch (for paste) is suspended in 35 parts of water and heated with stirring, to form a paste. This paste is then used to granulate the mixed powders. Additional water is used, if needed. The wet granules are passed through a U.S. standard No. 8 hand screen and dried at 120°F. The dry granules are passed through a U.S. standard No. 16 screen. The mixture is lubricated with 1% magnesium stearate and compressed into tablets (tablet weight 303 mg.), giving a total of 250 mg. of antibiotic per tablet.

EXAMPLE 5
ORAL SYRUP OR DROP PREPARATION

	percent w/v
CTC free base TC free base DMCTC free base	2.0 — 12.0
Complex colloidal magnesium-aluminum silicate	0.3 — 1.0
Sodium phosphate monobasic	0.07 — 0.7
Sodium phosphate dibasic	0.02 — 0.2
Methyl paraben	0.08
Propyl paraben	0.02
Sucrose	0.0 — 30.0
Red dye F.D. and C. No. 2	0.003— 0.15
Cherry flavor	0.06
Distilled water	25.0 — 60.0
Sorbitol aqueous solution to make	60.0 — 100.0

The above syrup or pediatric drop preparation has a pH of about 4.0—6.0. In formulating the syrup or pediatric drop preparation other ingredients can be used in place of those shown in the above formulation. For example, suspending agents such as Veegum magma (Complex colloidal magnesium-aluminum silicate) can be replaced by bentonite magma, gum tragacanth, carboxymethyl cellulose, methyl cellulose, "Carbopol" (registered Trade Mark) 934 (carboxy vinyl polymer of high molecular weight). The phosphates used as buffers in the above formulation can be replaced by citrates or tartrates. Instead of methyl and propyl parabens other preservatives such as alkali metal benzoates, or sorbic acid can be used. Also in the above formulation, the sugar and sorbitol can be replaced as a whole or in part by corn syrup, glycerol or invert sugars. Also the adjuvants, such as dyes and flavors can be replaced in whole or in part by "Sequestrene" (registered Trade Mark) or bisulfites.

EXAMPLE 6
ORAL SYRUP OR DROP PREPARATION

An oral syrup or pediatric drop preparation may be formulated substantially as in Example 5 above, but substituting the calcium salts of the tetracyclines for tetracycline free bases. The pH of the preparations should be adjusted to 8.0 — 9.0 by suitable buffer adjustments.

WHAT WE CLAIM IS:—

1. A tetracycline antibiotic composition comprising (A) tetracycline and/or oxytetracycline, (B) chlortetracycline, and (C) demethylchlortetracycline and/or methacycline and/or doxycycline, each tetracycline being

The data in the table are expressed as geometric averages in accordance with standard investigating procedure.

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TC.HCl	960
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EXAMPLE 4
TABLET

TC.HCl	960
CTC.HCl	960
Methacycline.HCl	580
Lactose, U.S.P.	410
Corn Starch (for mix)	50
Corn Starch (for paste)	40
	3000
Magnesium Stearate, U.S.P. (1%)	30
	3030

The three antibiotics, lactose and corn starch (for mix) are blended together. The corn starch (for paste) is suspended in 35 parts of water and heated with stirring, to form a paste. This paste is then used to granulate the mixed powders. Additional water is used, if needed. The wet granules are passed through a U.S. standard No. 8 hand screen and dried at 120°F. The dry granules are passed through a U.S. standard No. 16 screen. The mixture is lubricated with 1% magnesium stearate and compressed into tablets (tablet weight 303 mg.), giving a total of 250 mg. of antibiotic per tablet.

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	percent w/v
CTC free base TC free base DMCTC free base	2.0 — 12.0
Complex colloidal magnesium-aluminum silicate	0.3 — 1.0
Sodium phosphate monobasic	0.07 — 0.7
Sodium phosphate dibasic	0.02 — 0.2
Methyl paraben	0.08
Propyl paraben	0.02
Sucrose	0.0 — 30.0
Red dye F.D. and C. No. 2	0.003— 0.15
Cherry flavor	0.06
Distilled water	25.0 — 60.0
Sorbitol aqueous solution to make	60.0 — 100.0

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either in the form of the free base or a non-toxic acid addition salt thereof.

2. A composition according to Claim 1 which comprises from 30% to 50% of component (A), from 30% to 50% of component (B), and from 15% to 50% of component (C); said percentages being based upon the total weight of the active ingredients.

3. A composition according to Claim 2 which comprises the components (A), (B) and (C) in the weight ratio of 1:1:0.6 respectively.

4. A composition according to any preceding Claim in which component (A) is tetracycline and component (C) is demethylchlortetracycline.

5. A composition according to any preceding Claim including a pharmaceutically acceptable carrier.

6. A composition according to any preceding Claim in unit dosage form and comprising 115 mg of component (A), 115 mg of component (B), and 70 mg of component (C).

7. A tetracycline antibiotic composition substantially as described in any of the Examples herein.

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