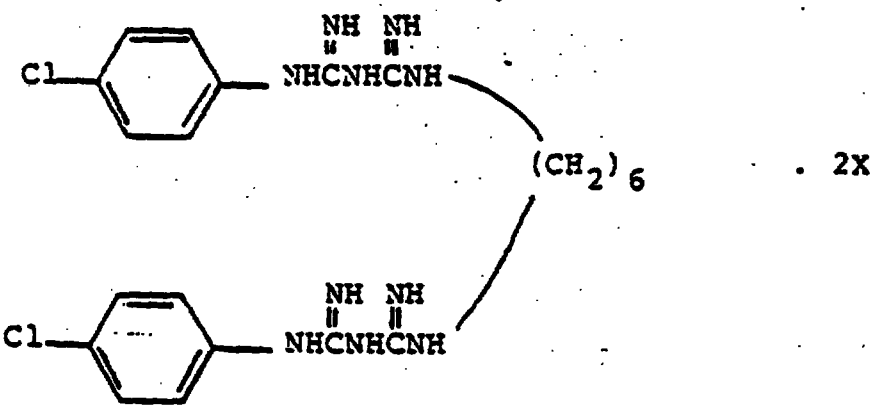
COMPOSITIONS CONTAINING CHLORHEXIDINE OR SALTS THEREOF

The present invention relates to antibacterial compositions comprising a synergistic mixture of 35-65 weight percent of chlorhexidine, or a salt thereof, and 65-35 weight percent of nalidixic or phosphanilic acid, or a salt thereof, the salts mentioned being pharmaceutically acceptable.

The invention described and claimed in Application No.80.13786 (2054195), from which the present application has been divided out, provides antibacterial compounds of the formula



wherein X is selected from the group consisting of sorbic acid, nalidixic acid and phosphanilic acid, and compositions containing same. Thus that invention relates to certain novel chlorhexidine salts and antibacterial dermatological compositions containing such salts.

The said salts comprise chlorhexidine disorbate, chlorhexidine dinalidixate and chlorhexidine diphosphanilate. Preferably, the chlorhexidine disorbate is employed as the monohydrate while the chlorhexidine diphosphanilate is employed as the dihydrate.

Chlorhexidine, nalidixic acid, phosphanilic acid and sorbic acid are known in the art. Moreover, as is shown in U.S. Patents 3,960,745, issued June 1, 1976, and 3,855,140, issued December 17, 1974, certain chlorhexidine salts are likewise known. Such salts include the hydrochloride, gluconate, isethionate, formate, acetate, glutamate, succinamate, monodiglycolate, dimethanesulphonate, lactate, di-isobutyrate and the glucoheptonate.

Polyhydroxycarboxylic acid salts of biguanides, such as, for example, chlorhexidine di-D-gluconate, are disclosed in U.S. Patent 2,990,425, issued June 27, 1961, as being highly soluble in water.

The oral antibacterial use of water soluble salts of chlorhexidine, such as the gluconate, acetate, fluoride, dihydrogen fluoride and the dihydrogen chloride, is disclosed in U.S. Patent 3,976,765, issued August 24, 1976.

An oral antibacterial composition comprising a combination of dodecyl-di-(aminoethyl)glycine and chlorhexidine or its digluconate, diacetate, dichloride or monofluorophosphate salts is disclosed in U.S. Patent 3,932,607, issued January 13, 1976.

Salts of chlorhexidine with certain sequestering amino carboxylic acids are disclosed in U.S. Patent 3,888,947, issued June 10, 1975. Preferred salts include, mono-chlorhexidine nitrilotriacetate, tri-chlorhexidine di-[diethylene triaminepentaacetate], mono-chlorhexidine-di-[N,N-dihydroxyethylamino-acetate], mono-chlorhexidine N-hydroxyethylenedi-aminetriacetate and mono-chlorhexidine di-[N-hydroxyethylethylenediaminetriacetate]. Such sequestrates are disclosed to have greater antibacterial activity than the corresponding bisguanido salt (confer column 3, lines 22 through 42 of the patent).

Bis-guanide hydroxyalkane sulphonic acid salts are disclosed in British Patent Specification 815,800. Such salts (including the isethionic acid salt, the 2:3-dihydroxypropane-1-sulphonic acid salt, the 3-chloro-2-hydroxypropane-1-sulphonic acid salt and the 2-hydroxypropane-1-sulphonic acid salt) are asserted to advantageously possess high solubility in water.

U.S. Patent 3,152,181, issued October 6, 1964, discloses monobiguanides having at least one alkoxy-propyl group having from about 11 to 19 carbon atoms attached to the N^1 or N^5 terminal nitrogen atoms. Such compounds are said to display exceptional antimicrobial activity and may be employed as the free base or, where water solubility is a factor in their use, as their salts with the inorganic and organic acids (such as mono and polycarboxylic and sulfur-containing mono and poly acids and acidic nitrogen compounds). Exemplary of acid salts are

the hydrochloride, hydrobromide, sulfate, phosphate, borate, phosphite, sulfite, sulfonate, nitrite, carbonate, nitrate, acetate, tartrate, propionate, oxalate, maleate, malate, picrate and β-ethoxypropionate salts. Examples of suitable acidic nitrogen compounds are theophylline, substituted theophyllines and similar purines, saccharin, phthalimide, benzoxazine-2, 4-diones, oxazolidine-2,4-dione and substituted oxazolidone-2,4-diones, N-p-methylbenzene sulfonyl-N'-n-butylurea, barbituric acids, mercaptobenzothiazole, 8-chlorotheophylline and succinimide. Patentees teach (at column 11, lines 36 through 70) that their monobiguanides can be employed with other medicaments.

As stated heretofore, nalidixic acid, phosphanilic acid and chlorhexidine are known in the art. The antibacterial agent, nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8 naphthyridine-3-carboxylic acid) is the subject of U.S. Patent 3,590,036, issued June 29, 1971. Nalidixic acid has not to the instant inventors' knowledge been heretofore utilized topically.

Phosphanilic acid ($p\text{-}NH_2C_6H_4PO_3H_2$, 4-aminobenzene phosphonic acid) has been synthesized (inter alia Doak et al. JACS 74 (1952)) and found to be active against various organisms (see for example Kuhn et al., Ber. 75,711 (1942); Klotz et al., JACS 69,473 (1947); and Thayer et al., Antibiotics and Chemotherapy, 3,256 (1953)).

U.S. Patent 3,159,537, issued December 1, 1964, teaches that certain phosphonic acid compounds, including phosphanilic acid, increase the oral absorption (viz. increase blood level) of tetracycline antibiotics.

Complexes of phosphanilic acid and an amino-acridine compound (preferably, 9-amino, 3-amino or 6-amino acridine) are disclosed in U.S. Patents 3,694,447, issued September 26, 1972 and 3,794,723, issued February 26, 1974, as having antibacterial and antifungal activity.

Phosphanilic acid has also been reported to show synergistic action with trimethoprim against a variety of bacteria (see U.S. Patent 4,125,610, issued November 14, 1978). It has also been reported to show synergistic action with neomycin and with streptomycin against Enterobacteriaceae (see Ciencia (Mexico) 17, 71-73 (1957)).

Finally, it should be noted that the topical anti-infective, chlorhexidine, (1,6-di(N-p-chloro-henyldianido)hexane) is long known to the prior art having been disclosed in U.S. Patent 2,684,924, issued July 27, 1954.

The present invention is based upon the following findings.

Mixtures of chlorhexidine or pharmaceutically acceptable salts of chlorhexidine (e.g. chlorhexidine digluconate) with nalidixic acid or pharmaceutically acceptable salts of nalidixic acid display synergism when used to prevent growth of microorganisms such as Klebsiella pneumoniae, Enterobacter cloacae, and Pseudomonas aeruginosa. The calculated synergism indices show that said mixtures should contain from 35 to 65 weight percent of chlorhexidine or a pharmaceutically acceptable chlorhexidine salt and from 65 to 35 weight percent of nalidixic acid or a pharmaceutically acceptable salt of nalidixic acid. Preferably said mixtures should contain an approximately equal weight percent of each of the above acceptable compounds selected.

Mixtures of chlorhexidine or pharmaceutically acceptable salts of chlorhexidine (e.g. chlorhexidine digluconate) with phosphanilic acid or pharmaceutically acceptable salts of phosphanilic acid display synergism when used to prevent growth of microorganisms such as Staphylococcus aureus, Streptococcus pyogenes, Streptococcus faecalis, and Pseudomonas aeruginosa. Said mixtures should contain from 35 to 65 weight percent of chlorhexidine or a pharmaceutically acceptable chlorhexidine salt and from 65 to 35 weight percent of phosphanilic acid or a pharmaceutically acceptable salt of phosphanilic acid. Preferably said mixtures should contain an approximately equal weight percent of each of the above acceptable compounds selected.

The present invention includes not only an antibacterial composition comprising a synergistic mixture of from 35 to 65 (e.g. approximately 50) weight percent of chlorhexidine, or a pharmaceutically acceptable

salt thereof, e.g. chlorhexidine digluconate, and from 65 to 35 (e.g. approximately 50) weight percent of nalidixic or phosphanilic acid, or a pharmaceutically acceptable salt thereof, but also a method of inhibiting the growth of a microorganism on an inanimate surface wherein the microorganism is one sensitive to the said composition (e.g. one of those respectively named in connection with nalidixic and phosphanilic acids and salts thereof in the last two preceding paragraphs) and wherein the microorganism is contacted with an amount of the said composition sufficient to inhibit its growth.

CLAIMS

1. An antibacterial composition comprising a synergistic mixture of from 35 to 65 weight percent of (a) chlorhexidine or a pharmaceutically acceptable chlorhexidine salt, and from 65 to 35 weight percent of (b) nalidixic acid or a pharmaceutically acceptable salt of nalidixic acid.

2. A composition according to claim 1 comprising approximately equal weight percents of (a) and (b).

3. An antibacterial composition comprising a synergistic mixture of from 35 to 65 weight percent of (a) chlorhexidine or a pharmaceutically acceptable chlorhexidine salt, and 65 to 35 weight percent of (b) phosphanilic acid or a pharmaceutically acceptable salt of phosphanilic acid.

4. A composition according to claim 3 comprising approximately equal weight percents of (a) and (b).

5. A composition according to claim 1, 2, 3 or 4 wherein (a) is chlorhexidine digluconate.

6. A method of inhibiting the growth of a micro-organism on an inanimate surface, wherein the micro-organism is one sensitive to a composition according to any of claims 1 to 5, and wherein the micro-organism is contacted with an amount of the said composition sufficient to inhibit its growth.

7. A method according to claim 6, wherein the micro-organism is Staphylococcus aureus, Streptococcus pyogenes, Streptococcus faecalis or Pseudomonas aeruginosa, and wherein the said composition comprises chlorhexidine, or a pharmaceutically acceptable chlorhexidine salt, with phosphanilic acid, or a pharmaceutically acceptable phosphanilic acid salt.

8. A method according to claim 6, wherein the micro-organism is Klebsiella pneumoniae, Enterobacter cloacae or Pseudomonas aeruginosa, and wherein the said composition comprises chlorhexidine, or a pharmaceutically acceptable chlorhexidine salt, with nalidixic acid, or a pharmaceutically acceptable nalidixic acid salt.

The text of the specification has been reprodnced by photocopying the applicants original typescript. It may contain a few amendments which are difficult to read. The original typescript containing these amendments may be inspected on the premises of the Patent Office