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PATENT SPECIFICATION

812,138

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COMPLETE SPECIFICATION

Improvements relating to Antibiotic Composition

We, AMERICAN CYANAMID COMPANY, a corporation organised under the laws of the State of Maine, United States of America, of 30, Rockefeller Plaza, New York, State of New York, 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 an intramuscularly acceptable broad spectrum antibiotic composition.

In many instances in the treatment of humans or animals with antibiotics it is desirable that the material be administered by intramuscular injection such that it is certain that the desired therapeutic dose of the antibiotic is received and retained by the patient. Intravenous administration is difficult and sometimes causes harmful side effects. Unfortunately, however, some antibiotics are not suitable for intramuscular injection because satisfactory blood levels of suitable duration are not obtainable, pain on injection is experienced and necrosis often occurs. Tetracycline and oxytetracycline are among the antibiotics which are difficult to administer by the intramuscular route.

An object of the present invention is to provide a composition which gives better blood levels, less tissue damage, and causes less pain and irritation in intramuscular tetracycline and oxytetracycline preparations.

In accordance with the invention an intramuscularly acceptable antibiotic composition is provided, comprising an antibiotic selected from the group consisting of tetracycline and oxytetracycline and their acid and basic salts, a soluble source of magnesium ions, a soluble source of absorption enhancing non-toxic acid ions (as hereinafter defined), said source being solid in the dry state, and a non-toxic local anesthetic. Said components are present in such form and amounts that in water an aqueous solution or suspension is formed having a pH of less than 5 and preferably less than 4.5.

Tetracycline and oxytetracycline are sufficiently soluble at the lower pH ranges that they may be administered in therapeutic sized doses in solution in a volume which is conveniently administered intramuscularly. Near the upper limits of the pH range, some of the antibiotic may remain suspended as fine particles in the solution, and may be injected as such a suspension. The compositon is not objectionally painful and does not cause undue tissue damage nor local reaction in either human or animal subjects, as either a solution or a suspension. For uniformity of dispersion, and for trade acceptance, a solution is preferred. The formation of a clear solution is itself proof of the absence of insoluble contaminants.

The antibiotic may be present as tetracycline or oxytetracycline hydrochloride as a most readily available commercial form, but also may be used as the hydrobromide, the sulfate, the nitrate, the citrate, the ascorbate, the gluconate, or the neutral form or as a salt with a base such as the sodium, potassium, ammonium, calcium or magnesium salts. When the antibiotic component is utilized in the neutral form or as one of the basic salts, the other constituents must necessarily be such that the pH is within the desired limits. For many purposes the individual salts of a single antibiotic are preferred, for other purposes mixtures of salts or mixtures of antibiotics are considered therapeutically advantageous.

The absorption-enhancing non-toxic acid ions are selected from ions of water-soluble, non-toxic, hydroxycarboxylic and thiocarboxylic acids and lactones of such acids including citrate ions, ascorbate ions, gluconate ions, and thioglycollate ions and ions from soluble mineral acid salts of amino acids.

The magnesium is present as a soluble ionizable form of magnesium such as a magnesium halide, including hydrates, such as magnesium chloride hexahydrate, or magnesium sulfate or the magnesium may be present as a salt with one of the absorption enhancing acids such as magnesium citrate. The soluble magnesium ions appear to induce a reduction in tissue damage. Magnesium chloride hexa-

[*Price 3s. 6d.*]

hydrate is very convenient as the magnesium ion source but does cause some complications in the preparation of sterile compounds as the hydrate of magnesium chloride can release moisture which can cause complications in the sterilization of the final product. However, it is a completely satisfactory component and may be conveniently sterilized first and then aseptically added to a mixture if the mixture is not conveniently sterilizable as such. The magnesium ions may also be added as magnesium sulfate, magnesium nitrate, magnesium bromide or any other non-toxic inorganic salt or as a salt with a non-toxic organic acid including magnesium acetate, magnesium glycinate, magnesium citrate and magnesium ascorbate.

Of the local anesthetics, procaine hydrochloride is the best known at present. Other materials may be used as local anesthetics which are related in structure to procaine, or the local anesthetics which have different configurations. Such anesthetics include xylocaine which is diethylaminoacet-2,6 xylidide, hydroxy-procaine which is diethylaminoethyl-o-hydroxy-p-aminobenzoate, 2-chloroprocaine which is diethylaminoethyl - o - chloro - p - hydroxybenzoate, piperocaine which is 3-(2-methylpiperidino)-propylbenzoate, hexylcaine which is 1-cyclohexylamino-2-propylbenzoate, diethoxin which is diethylaminoethyl-4-ethoxybenzoate, tetracaine which is dimethylaminoethyl-p-n-butylaminobenzoate and larocaine which is diethylaminonepentyl-p-aminobenzoate. These local anesthetics may be used in the free form but are more conveniently used as an acid salt, preferably the hydrochloride.

The soluble hydroxycarboxylic or thiocarboxylic acid added either as the acid itself or in form which in solution gives anions equivalent to those from the free acid, has the unique advantage of increasing the rate of absorption and utilization of the antibiotic and is referred to as an absorption enhancer. Various explanations as to why this should be so range from the effect that such materials have or may have on a metabolic cycle such as the Krebs cycle to the complexing proclivities of this component with various heavy metals which might otherwise complex with the antibiotic. Both theories may be correct. By using such an absorption enhancer the rate of absorption of the antibiotic in the preparation becomes such that an intramuscular injection gives higher blood levels.

The hydroxycarboxylic or thiocarboxylic acid constituent is conveniently added in part as the free acid to assist in pH control. At least some or all of the absorption enhancer may be added as a salt. When citric or ascorbic acids are used they may be conveniently added in part as the sodium salt or other harmless salt. Some of the acid may be added as the magnesium salt or a salt with the antibiotic. By having part of the acid present as a salt the pH of the final solution is somewhat higher than would otherwise be the case.

In the past it has been considered desirable to formulate intramuscular preparations so that the pH would be near the normal pH of the body tissue. In the present instance the antibiotic would be insoluble at such a pH. Unexpectedly the present preparation may be injected at an acid pH within the range of preferably about 1.9 to 2.25 without undue tissue irritation or pain. Any pH below 5 is satisfactory for injection, but a pH below about 4.5 is preferred so that the antibiotic is in solution for intramuscular administration.

The solubility of the antibiotic is influenced by the other ions present. At a concentration of 50 milligrams of antibiotic per milliliter in the presence of ascorbate ions, the pH can be as high as 4.8 with the antibiotic remaining in the solution for several hours. With citrate ions the pH may be as high as 4.3 and the solution will remain clear for several hours. At a lower pH the solution will remain clear for a longer period or indefinitely. It is not necessary that the solutions be clear for administration but a clear solution is more acceptable to the medical profession and there is less danger of non-homogeneity.

Tissue irritation and pain, particularly with the use of tetracycline, is far less than would be anticipated from comparative studies on other antibiotics.

The non-toxic acid absorption enhancer may be any which is intramuscularly acceptable, but ascorbic acid is particularly useful as it also has a physiological function, and a preparation containing ascorbic acid for pH control and increased absorption of the antibiotic augments the body's reserve of vitamin C which increase is desirable during times of sickness and stress.

Citric acid gives slightly higher blood levels than ascorbic acid and is essentially free from pain on administration, but compositions containing this acid are harder to prepare from the formulating standpoint.

The constituents for the present mixture are conveniently prepared as a sterile, dry powder prior to administration and are kept in sterile vials in dry form. Before use, water may be added to form a clear solution of the desired strength. A suitable solution is one in which the antibiotic, the magnesium ions and the absorption-enhancing ions are each present at a concentration of between 10 and 100 milligrams per milliliter. This solution is stable for a period of at least 24 hours, which is long enough for administration in hospital use.

Alternatively one or more of the more storage stable constituents of the composition may be present in the aqueous diluent. The anesthetic particularly may be present in the aqueous diluent as may the solution of magnesium ions or the hydroxycarboxylic or thiocarboxylic acids or lactones of such acids or mix-

tures of them. It is more convenient, however, to have all of the constituents except the water present in the completed vial to reduce the possibility of error in compounding at the time of administration and also to obviate the necessity for a separately labelled diluent. Water for injection is normally available in hospitals and a doctor's kit, so that by using a common source of water for injection, the number of preparations which must be on hand is reduced.

The proportions may vary over a considerable range with advantageous results. Any appreciable fraction of the absorption enhancing non-toxic acid adjuvant contributes towards an increased rate of absorption and higher blood levels. It is preferred that approximately as much of the absorption enhancing non-toxic acid ions as of the antibiotic be present and up to about 3 times as much as the absorption enhancing non-toxic acid ions as of the antibiotic may be advantageously used. Larger proportions of the acid, particularly if ascorbic acid is used, are not deleterious. Less than equal weight proportions of the acid are advantageous, but not as effective as if the equal weight be used.

From about 1 to 15 milligrams per milliliter of magnesium ion in the injection preparation are useful. About 2 to 6 milligrams per milliliter is preferred. The antibiotic is preferably present in the range of 10 to 100 milligrams per milliliter of injected solution, calculated as the antibiotic hydrochloride. 50 milligrams per milliliter is a particularly convenient therapeutic concentration level. Higher or lower concentrations may be used but concentrations below 10 milligrams per milliliter require volumes of diluent which are larger than is normally desired.

The amount of the anesthetic should be enough for effective local anesthetic effect. With procaine hydrochloride from 0.5 to 40 milligrams per milliliter is a very effective range and from 2 to 20 milligrams per milliliter is a preferred range. With more or less potent anesthetics the concentration can be proportionately adjusted.

In the compounding of the material for injection it is desirable that the materials be stored dry to ensure storage stability.

To prepare the sterile material the components may be individually sterilized and then blended, or they may be mixed and then sterilized by appropriate means such as irradiation with high frequency radiation or neutrons.

The antibiotic may be discolored if heated in the presence of the magnesium ion. It is a preferred embodiment of this invention to mix the antibiotic, the anesthetic and the hydroxycarboxylic or thiocarboxylic acid or lactone thereof in a finely ground state and sterilize the mixture with ethylene oxide. The magnesium ion component which may be present as magnesium chloride hexahydrate can be sterilized by heating, for example, at 110° C. for about 12 hours with regrinding if caking is noticed. Part of the water content may be lost by this treatment. The sterile magnesium ion component is then asceptically blended with the remaining constituents and sterilely filled into containers.

With other magnesium compounds, the final composition may be sterilized after admixture with ethylene oxide or heat.

By way of illustration certain examples of the compositions of the invention and results which have been obtained in both man and animal are shown below. In the Examples all parts are by weight.

EXAMPLE 1

500 parts of tetracycline hydrochloride, 500 parts of anhydrous citric acid and 200 parts of procaine hydrochloride were ground together in a screen grinder (Fitzpatrick) and then sterilized by exposing the mixture to ethylene oxide, containing sufficient carbon dioxide so as to be non-explosive, at 40° C. for 7 hours. 500 parts of magnesium chloride hexahydrate were heated at 110° C. for 12 hours then ground and reheated for an additional 12 hours at 110° C. The moisture content was reduced to about the equivalent of 4 molecules of water of crystallization. The sterilized magnesium chloride was blended aseptically with the other constituents and filled into glass vials each vial containing 500 milligrams of antibiotic and designed to be made up to 10 milliliters of solution having 50 milligrams per milliliter of antibiotic activity.

The dry preparation when dissolved in water by the addition of sterile water in such quantities that the solution formed had a concentration of 50 milligrams of antibiotic activity per milliliter gave a pH of approximately 1.5. The solution was clear and remained clear on standing.

The above composition was injected intramuscularly in dogs at a dosage level of 2 milligrams per pound of body weight. No undue evidence of irritation or pain was observed. The blood levels in micrograms per milligram of tetracycline hydrochloride were found to be:

3.02	½ hour
2.58	1 hour
1.78	2 hours
1.49	4 hours
1.58	6 hours
1.18	8 hours
0.50	12 hours
0.18	24 hours

giving a 12 hour mean of 1.73.

Also six human patients were injected intramuscularly with a total of 100 milligrams of tetracycline hydrochloride dissolved in 2 cc. of water prepared from the above composition. The tetracycline hydrochloride levels—blood serum in micrograms per milliliter were as follows:—

Subject	2 hours	4.5 hours	7 hours
E	1.0	0.74	0.42
Ly	0.72	0.69	0.62
M	0.97	0.94	0.77
N	1.27	1.27	0.99
P	0.86	0.79	0.65
V	0.88	0.56	0.53
Average	0.95	0.83	0.66

These blood levels represent a therapeutically effective dosage level.

EXAMPLE 2

A composition was prepared following the procedure set forth in Example 1 containing:

500 parts	Tetracycline HCl
500 parts	$MgCl_2 . 6H_2O$
1250 parts	Ascorbic Acid
200 parts	Procaine HCl

When made up with water to a concentration of 50 milligrams per milliliter of tetracycline activity, the pH was 1.9. When injected intramuscularly at a dosage level of 2 milligrams per pound of body weight in dogs, the average blood levels in micrograms per milliliter for four dogs was found to be:

2.09	½ hour
2.46	1 hour
2.01	2 hours
1.30	4 hours
1.62	6 hours
0.97	8 hours
0.84	12 hours
0.22	24 hours

giving a 12 hour mean of 1.61.

2 milliliters of the solution were also injected intramuscularly into a series of persons so that each patient received a total of 100 milligrams of tetracycline hydrochloride. In 5 patients the tetracycline hydrochloride levels—blood serum in micrograms per milliliter were as follows:—

Subject	2 hours	4.5 hours	7 hours
L	1.12	1.25	0.95
K	0.64	0.69	0.51
T	1.05	0.79	0.67
Ch	0.75	0.71	0.71
Cz	0.54	0.49	0.43
Average	0.85	0.79	0.73

EXAMPLE 3

A composition was prepared consisting of:

500 parts	Tetracycline Hcl
750 parts	Magnesium Citrate ("Soluble")
200 parts	Procaine Hcl

These components were ground together and sterilized by exposure to a mixture of ethylene oxide containing sufficient carbon dioxide so as not to be explosive at 40° C. for 7 hours. The composition was stored in glass vials. When ready for use the solution was made up by adding sufficient water to give a concentration of 50 milligrams per milliliter of tetracycline as the hydrochloride. When made up with water to a concentration of 50 milligrams per milliliter of tetracycline activity, the pH was 3.2 When injected at a dosage level of 2 milligrams per pound of body weight in dogs, the average blood levels in micrograms per milliliter for four dogs was found to be:

1.92	½ hour
2.69	1 hour
2.15	2 hours
1.44	4 hours
1.23	6 hours
1.06	8 hours
0.88	12 hours
0.33	24 hours

giving a 12 hour mean of 1.62.

EXAMPLE 4

Vials were prepared by mixing in each vial

100 mg.	Teracycline HCl
100 mg.	$MgCl_2 . 6H_2O$
200 mg.	Gluconic acid
40 mg.	Procaine HCl

Water was added to the vials to give 100 milliliters of solution and the thus prepared solution injected intramuscularly in dogs at a dosage level of 2 milligrams of tetracycline hydrochloride per pound of body weight. The average blood levels were:

	micrograms per milliliter
1 hour	2.7
2 hours	2.78
4 hours	2.47
8 hours	1.02

EXAMPLES 5—10

A group of dogs were injected intramuscularly with solutions of the antibiotics at a dosage level of 2 milligrams of antibiotic per pound of body weight. The solutions were made up by mixing the antibiotic with a solution containing the other components. Identical results are obtainable by adding water to vials containing a mixture of the solid components. For solutions containing the components shown, the blood levels in micrograms per milliliter at the time shown, is an average for three dogs.

In addition to the components listed below, each solution also contained 50 milligrams per milliliter of magnesium chloride hexahydrate, and 20 milligrams per milliliter of procaine hydrochloride.

Ex. No.	Antibiotic Mg./ml.	Acid Mg./ml.	Blood levels at hours Micrograms per milliliter 1	2	4	6	8
5	50 Tetracycline (neutral)	225 gluconic	2.67	2.18	2.27	2.3	1.19
6	50 tetracycline hydrochloride	12.5 citric	2.73	1.88	1.83	1.13	1.33
7	50 Tetracycline hydrochloride	25 citric	2.63	1.85	2.16	1.50	0.95
8	50 tetracycline hydrochloride	50 citric	2.35	2.03	1.89	0.98	1.15
9	50 oxytetracycline hydrochloride	50 citric	3.55	3.36	2.18	1.85	1.19
10	50 oxytetracycline hydrochloride	225 gluconic	3.45	2.65	2.37	1.65	1.13

WHAT WE CLAIM IS:—

1. An intramuscularly acceptable broad-spectrum antibiotic composition, comprising an antibiotic selected from the group consisting of tetracycline and oxytetracycline and their acid and basic salts, a soluble source of magnesium ions, a soluble source of absorption enhancing non-toxic acid ions (as hereinbefore defined), said source being solid in the dry state, and a non-toxic local anesthetic.

2. A composition according to claim 1, in which said components are present in such form and amounts that in water an aqueous solution or suspension is formed having a pH of less than 5 and preferably less than 4.5.

3. A composition according to claim 1 or 2, in which said soluble source of magnesium ions is selected from non-toxic inorganic and organic magnesium salts.

4. A composition according to claim 1 or 2, in which said soluble source of absorption enhancing non-toxic acid ions is selected from ions of water-soluble non-toxic hydroxy carboxylic and thiocarboxylic acids and lactones of such acids, including citrate ions, ascorbate ions, gluconate ions, and thioglycollate ions and ions from soluble mineral acid salts of amino acids.

5. A composition according to claim 1 or 2, in which said local anesthetic is selected from the group consisting of procaine, hydroxy-procaine, xylocaine, 2-chloroprocaine, piperocaine, hexylcaine, diethoxin, tetracaine and larocaine, preferably as hydrochloride salts thereof, and is preferably present in an amount whose physiological effect is approximately equal to that obtained from 2 to 20 milligrams per milliliter of procaine hydrochloride.

6. An intramuscularly acceptable broad-spectrum antibiotic composition, substantially as hereinbefore described.

7. An aqueous solution obtained by adding water to the composition according to any of claims 1 to 6, preferably until the antibiotic, the magnesium ions and the absorption-enhancing ions are each present at a concentration of between 10 and 100 milligrams per milliliter.

8. A method of preparing a composition according to any of claims 1 to 6, which comprises: mixing the antibiotic, the source of absorption-enhancing ions and the anesthetic, exposing the mixture to ethylene oxide until sterile, separately heating the source of magnesium ions until sterile, and aseptically blending said components.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

Reference has been directed in pursuance of Section 9, sub-Section (1) of the Patents Act, 1949, to patent No. 739,736.

ERRATUM

SPECIFICATION NO. 812,138

Page 1, line 1, *for* "Cynamid" *read* "Cyanamid".

THE PATENT OFFICE,
17th August, 1959

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* C L M S *

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7	50 Tetracycline hydrochloride	25 citric	2.63	1.85	2.16	1.50	0.95
8	50 tetracycline hydrochloride	50 citric	2.35	2.03	1.89	0.98	1.15
9	50 oxytetracycline hydrochloride	50 citric	3.55	3.36	2.18	1.85	1.19
10	50 oxytetracycline hydrochloride	225 gluconic	3.45	2.65	2.37	1.65	1.13

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2. A composition according to claim 1, in which said components are present in such form and amounts that in water an aqueous solution or suspension is formed having a pH of less than 5 and preferably less than 4.5.

3. A composition according to claim 1 or 2, in which said soluble source of magnesium ions is selected from non-toxic inorganic and organic magnesium salts.

4. A composition according to claim 1 or 2, in which said soluble source of absorption enhancing non-toxic acid ions is selected from ions of water-soluble non-toxic hydroxy carboxylic and thiocarboxylic acids and lactones of such acids, including citrate ions, ascorbate ions, gluconate ions, and thioglycollate ions and ions from soluble mineral acid salts of amino acids.

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