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INJECTABLE PENICILLIN REPOSITORY PREPARATION CONTAINING OIL AND GELLED OIL

William M. Ziegler, Clementon, N. J., assignor, by mesne assignments, to American Cyanamid Company, New York, N. Y., a corporation of Maine

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This invention relates to pharmaceutical preparations. More particularly, this invention relates to injectable therapeutic compositions containing penicillin which will prolong the therapeutic blood levels of penicillin, and to a process for the preparation of these compositions.

In the past, a common method for the administration of penicillin involved the introduction of penicillin in physiologic saline or water through the intramuscular route. This method was highly unsatisfactory in that the penicillin had a tendency to decompose or was rapidly absorbed in the body fluids and then eliminated in the urine. As a result, high levels of pencillin endured in the blood for only brief periods of time. To effect a high blood level of penicillin, it was necessary to give frequent injections of the antibiotic. In view of the fact that satisfactory results in the therapeutic use of penicillin are secured only when effective blood levels are maintained over a prolonged period of time, i. e. several days, the inconvenience and obvious disadvantages of this method precluded its widespread acceptance and use. Further disadvantages included the poor stability of penicillin in physiologic saline and also the loss in potency of the antiobiotic material in this medium, particularly at elevated temperatures.

Numerous attempts have been made to overcome the disadvantages of the foregoing method, but none of them has been highly satisfactory. For example, the advantages of prolonged therapeutic blood levels of penicillin following a single injection has been established by the use of a composition containing penicillin in suspension in a mixture of oil and beeswax (Romansky U. S. 2,443,778). However, the inclusion of wax in this vehicle was found to be disagreeable to the patient and was proved to be the apparent cause of a number of unfavorable local reactions such as sensitization of the patient together with the resulting allergic reactions. Numerous cases of fibrosis were likewise reported. Further, the residual beeswax was dissolved with great difficulty, requiring some 25 to 30 days for complete assimilation, and in extreme cases, necessitating removal by surgery.

Another injectable preparation, disclosed in U. S. 2,518,510, comprising a suspension of finely divided penicillin particles containing peanut oil having a hydrophilic substance such as pectin dispersed therein, is considered to obviate some of the disadvantages of the Romansky formulation discussed supra but has likewise failed to provide the desired repository effect.

It has now been discovered that effective therapeutic blood levels of penicillin can be obtained for prolonged periods of time by the administration of an injectable substantially anhydrous repository penicillin composition comprising a therapeutically effective salt of penicillin distributed in a vehicle composed of an innocuous, non-toxic oil and an aluminum salt of a phosphoric ester of an alcohol, said alcohol being selected from the group consisting of alkyl or arylalkyl alcohols possessing 6 to 18 carbon atoms, alkoxyalkyl alcohols possessing from 6 to 18 carbons and aryloxyalkyl alcohols.

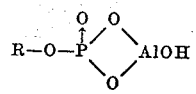
This depot or repository composition, when parenterally injected, is capable of holding any desired dose of the therapeutically active substance, releasing it in the blood stream only gradually over an extended period of time so that large doses may be easily and conveniently administered by this method.

The preparation is characterized by a low viscosity at room temperature being highly fluid in nature and thus can be very easily injected parenterally by means of a hypodermic needle. By limiting the particle size of the penicillin to a pre-determined range, the antibiotic remains in suspension and does not settle out. Injections of the aforedescribed composition containing 75,000 units of penicillin in animals have provided blood levels in excess of 0.03 unit per cc. of blood for periods of time in excess of 96 hours.

This preparation is further characterized by its excellent stability as it has been held at a temperature of 56° C. for a period of 2 months without any appreciable loss in potency or any physical change in appearance.

The formulation is prepared by heating a mixture containing an aluminum salt of a phosphoric ester together with an innocuous, non-toxic oil such as for example sesame oil, at a temperature of about 125° C. until the white color disappears and the mixture becomes somewhat translucent. The product is cooled and to it is added, a therapeutically active salt of penicillin. This is followed by ball milling the mixture for about sixteen hours and the desired product in its final form is poured into a suitable container or receptacle.

The aluminum salts utilizable in the present invention can be represented by the following formula:



wherein R is a member selected from the group consisting of an alkyl radical containing from 6 to 18 carbon atoms, an arylalkyl radical, an alkyloxyalkyl radical containing from 6 to 18 carbon atoms and an aryloxyalkyl radical. Specific compounds which are included within the purview of this invention include aluminum octadecylphosphate, aluminum cetylphosphate, aluminum hexylphosphate, aluminum 2-ethylhexylphosphate, aluminum laurylphosphate, aluminum decyl-phosphate, aluminum β - phenoxyethylphosphate, aluminum γ - phenylpropylphosphate, aluminum butyloxyethyl phosphate, aluminum ethoxybutyl phosphate, aluminum phenethyl phosphate, etc.

In addition to the sesame oil which is used in the preparation of the formulation, it has been found in practice that other injectable oils such as cottonseed, maize, peanut, olive, etc., may be similarly employed with highly satisfactory results. The oil that is used in the formulation must be highly refined and contain a minimum amount of readily oxidizable material and moisture, the latter in amounts not exceeding 0.05%. Before compounding, the oil must be sterilized, sterilization being effected using any one of the well known conventional methods.

The injectable formulation contains the penicillin salt in a finely divided state in which the particle size of the salt is of mixed sizes but wherein substantially all of the particles of penicillin are between 1 to 200 microns in size and preferably, less than 50 microns in size.

The penicillin embodied in the preparation may be a mixture of one or more of these specific penicillins such as are commonly obtained in the production of penicillin G, K, or any of the other known penicillins, or it

may be a penicillin which consists mainly or wholly of one of these specific penicillins. It is preferable, however, to use a penicillin which is rich in penicillin G, primarily because of the excellent therapeutic qualities of this specific salt. The penicillin used may be either in the form of amorphous penicillin or preferably in the form of a crystalline penicillin.

This preparation differs markedly from that disclosed in U. S. 2,507,193 wherein penicillin is suspended in an oil that has been gelled with aluminum stearate, in that the aluminum phosphate salt used in this invention does not "dissolve" in the oil to produce a gel but instead, the oil dissolves in the aluminum salt forming an insoluble gel-like material that apparently coats the penicillin particles. Likewise, this new and highly improved preparation is distinguishable from that disclosed in U. S. 2,518,510 in that the protective gel is not hydrophilic in nature. Since the gel is insoluble in the oil, it coats the particles in the oil so that when the preparation is brought into contact with the aqueous body fluids, a slow penetration of the penicillin salt is effected through this insoluble coating.

Additional advantages and features of this new and highly improved preparation are set forth in the following example which discloses the principle of the invention and the preferred embodiment of applying that principle. It is understood, however, that the example is merely illustrative and not limitative in nature, being capable of various other modifications:

EXAMPLE

The preparation of a typical gelling agent such as for example aluminum cetylphosphate is illustrated as follows:

To a solution of 24 grams of cetyl alcohol in 20 cc. of benzene chilled in an ice bath was added 10 cc. of phosphorus oxychloride. The resulting solution was allowed to stand until the evolution of fumes of hydrogen chloride almost ceased and then the solution was heated to 70° C. for a few minutes. After cooling, the solution was poured onto 200 grams of ice, and a 5% solution of sodium hydroxide was added from time to time to keep the pH between 3.0 and 8.0 while hydrolysis occurred. The final solution was adjusted to a pH of 6.8 and then heated to expel the benzene. This hot solution was added with stirring to a hot solution of 45 grams of potassium aluminum sulfate (or 32 grams of aluminum sulfate hydrate), and boiled for ten minutes while the pH was adjusted to 5.0 to 6.0. The mixture was then filtered, washed with water and then dried in air.

One-tenth mol quantities of alcohols such as octadecyl, lauryl, decyl, octyl, etc. can likewise be treated in the same fashion to secure corresponding aluminum salts.

The products are white, infusable powders that burn on ignition to a voluminous white ash.

The alkylphosphoryl chloride can be prepared within temperatures ranging from 0°–60° C., but preferably between 25°–30° C. The hydrolysis is preferably effected at a temperature ranging between 20°–30° C., but temperatures between 0°–90° C. likewise provide satisfactory results. The formation of the aluminum salt is preferably accomplished at a temperature ranging between 80°–90° C. but can proceed satisfactorily at room temperatures or even at temperatures slightly below. Any soluble aluminum salt or double salts such as alums, may likewise be used. The volume of solvents used is not critical.

FORMULATION

One-gram quantities of an aluminum salt, such as for example, aluminum cetyl phosphate prepared in the manner indicated above were heated in 50 cc. of sesame oil at a temperature of 125° C. for about 15 minutes until the white color disappeared and the material became somewhat translucent. The mixture was allowed to cool. To 22.5 grams of this mixture was added 10 grams of procaine penicillin. The mixture was then ball milled for sixteen hours and then filled in vials.

It should be mentioned that the heating temperatures of the mixture containing the oil and aluminum phosphate salt are limited only by the cracking point of the various oils used.

The quantity of aluminum salt is preferably about 8% by weight of volume of the oil used, satisfactory results having likewise been obtained when quantities ranging from 1 to 15% were used. An intramuscular injection of 0.25 cc. of the formulation prepared above containing 75,000 units of penicillin, produced a maximum blood level of 0.09 unit per cc. of blood 96 hours after injection.

The following table shows an average of the animals indicating penicillin blood levels of 0.03 unit per cc. or above at the indicated hour after an intramuscular injection of 0.25 cc. of a formulation containing varying amounts of aluminum salt and 75,000 units of penicillin. Consequent blood samples were taken at the intervals indicated. Blood levels were determined by a microbiological plate assay method using *S. lutea*. A control was also drawn before injection.

Rabbit penicillin blood levels

Formulation Injection Containing 75,000 units of Procaine Penicillin G	Significant Blood Levels at—			
	24 Hours	48 Hours	72 Hours	96 Hours
2% Al Octadecylphosphate in Sesame Oil	*3/3(1.11)	2/3(0.50)	2/3(0.12)	0/3
2% Al Cetylphosphate in Sesame Oil	5/5(0.68)	3/5(0.06)	3/5(0.05)	0/5
4% Al Cetylphosphate in Sesame Oil	5/5(0.67)	5/5(0.23)	2/5(0.07)	0/5
8% Al Cetylphosphate in Sesame Oil	5/5(0.58)	5/5(0.14)	4/5(0.11)	3/5(0.05)
2% Al Laurylphosphate in Sesame Oil	3/3(1.07)	3/3(0.26)	1/3(0.35)	1/3(0.03)
2% Al Decylphosphate in Sesame Oil	3/3(0.29)	3/3(0.30)	2/3(0.10)	1/3(0.09)
2% Al Octylphosphate in Sesame Oil	3/3(1.42)	3/3(0.26)	3/3(0.14)	1/3(0.06)
2% Al Hexylphosphate in Sesame Oil	3/3(0.80)	3/3(0.27)	1/3(0.07)	0/3
2% Al 2-Ethylhexylphosphate in Sesame Oil	3/3(0.50)	3/3(0.41)	3/3(0.15)	2/3(0.04)
2% Al β-Phenoxyethylphosphate in Sesame Oil	3/3(0.55)	3/3(0.44)	3/3(0.37)	3/3(0.08)
2% Al γ-Phenylpropylphosphate in Sesame Oil	3/3(1.23)	3/3(0.39)	3/3(0.21)	1/3(0.04)
Sesame Oil alone (Control)	2/4(0.33)	0/4	0/4	0/4

* Numerator indicates the number of animals showing levels; denominator indicates number of animals injected.

The foregoing results indicate that the action of penicillin may be greatly prolonged by the intramuscular injection of a mixture containing a therapeutic penicillin salt, an aluminum salt and an innocuous non-toxic oil.

The preparations herein described are effective against many gram positive organisms, both aerobic and anaerobic, as well as against gonococci and meningococci. Likewise, pneumococcic infections are similarly susceptible. The injection of these preparations is characterized by only slight pain and discomfort together with the absence of soreness at the point of injection.

While the present invention has been described with particular reference to the use of crystals of procaine penicillin, it is understood that other commercially available salts of penicillin such as sodium, potassium, calcium and amine salts, i. e. triethylamine, in crystalline and amorphous form can likewise be used. By the reduction of crystalline particles to less than about 200 microns and preferably less than about 50 microns, pro-

longed blood levels are obtained when the salts are dispersed in a vehicle composed of an aluminum salt and oil.

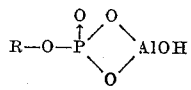
It should likewise be mentioned that therapeutic salts of penicillin of any desired potency may be employed. However, to produce satisfactory penicillin blood levels for extended periods of time, it is preferred to use highly potent products. Compositions of penicillin salts in the vehicle composed of an aluminum salt and oil can be prepared containing less than or more than 300,000 units of penicillin.

It is understood that the data and example herein given are intended to be exemplary only in character, the invention being directed essentially to the incorporation of an available penicillin salt in a vehicle comprising the non-toxic innocuous oil and aluminum salt disclosed herein.

It will be apparent, therefore, that the invention is capable of being employed with varying constituents such as for example, different salts of penicillin, different aluminum phosphate salts and different oil vehicles. It is obvious from the foregoing that the invention is capable of various modifications and that, therefore, it is intended and desired to embrace within the scope of this invention such modifications and changes that are necessary to adapt it to varying conditions and uses, as defined by the scope of the appended claims.

I claim:

1. An injectable antibiotic preparation capable of maintaining effective therapeutic blood levels over an extended period of time which comprises a therapeutic salt of penicillin, an innocuous non-toxic oil, and a gel of an innocuous non-toxic oil and a quantity of an aluminum salt ranging from 1 to 15% by weight of the total volume of said oil, said aluminum salt being represented by the following formula:



wherein R is a member selected from the class consisting of an alkyl group containing from 6 to 18 carbon atoms, an arylalkyl group containing from 6 to 18 carbon atoms, an alkyloxyalkyl group containing from 6 to 18 carbon atoms and an aryloxyalkyl radical containing from 6 to 18 carbon atoms, the gel being insoluble in the first mentioned innocuous non-toxic oil.

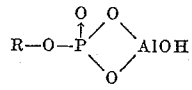
2. An injectable antibiotic preparation capable of maintaining effective therapeutic blood levels over an extended period of time which comprises procaine penicillin, an innocuous non-toxic oil, and a gel of an innocuous non-toxic oil and aluminum octadecylphosphate.

3. An injectable antibiotic preparation capable of maintaining effective therapeutic blood levels over an extended period of time which comprises procaine penicillin, an innocuous non-toxic oil, and a gel of an innocuous non-toxic oil and aluminum laurylphosphate.

4. An injectable antibiotic preparation capable of maintaining effective therapeutic blood levels over an extended period of time which comprises procaine penicillin, an innocuous non-toxic oil, and a gel of an innocuous non-toxic oil and aluminum decylphosphate.

5. An injectable antibiotic preparation capable of maintaining effective therapeutic blood levels over an extended period of time which comprises procaine penicillin, an innocuous non-toxic oil, and a gel of an innocuous non-toxic oil and aluminum octylphosphate.

6. An injectable antibiotic preparation capable of maintaining effective therapeutic blood levels over an extended period of time which comprises procaine penicillin, an innocuous non-toxic oil, and a gel of an innocuous non-toxic oil and an aluminum salt represented by the following formula:



wherein R is a member selected from the class consisting of an alkyl group containing from 6 to 18 carbon atoms, an arylalkyl group containing from 6 to 18 carbon atoms, an alkyloxyalkyl group containing from 6 to 18 carbon atoms and an aryloxyalkyl radical containing from 6 to 18 carbon atoms, the gel being insoluble in the first mentioned innocuous non-toxic oil.

7. An injectable antibiotic preparation capable of maintaining effective therapeutic blood levels over an extended period of time which comprises an innocuous non-toxic oil having dispersed therein particles of a therapeutic salt of penicillin G coated with a gel of innocuous non-toxic oil and aluminum cetylphosphate, the amount of aluminum cetylphosphate present in the gel ranging from 1% to 15% by weight of the total amount of non-toxic oil present in the preparation.

References Cited in the file of this patent

UNITED STATES PATENTS

2,340,331	Knutson et al.	Feb. 1, 1944
2,416,985	Farrington et al.	Mar. 4, 1947
2,507,193	Buckwalter	May 9, 1950