

1

2,734,844

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

No Drawing. Application October 18, 1951,
Serial No. 251,992

7 Claims. (Cl. 167—65)

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 penicillin 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 antibiotic 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

2

distributed in a vehicle composed of an innocuous, non-toxic oil and a ferric salt of a higher fatty acid.

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 i. e. several days. Thus, by using this method and the repository composition set forth above, large doses of the antibiotic material providing therapeutically effective blood levels for as long as 4 days may be easily and conveniently administered.

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 predetermined range, the antibiotic remains in suspension and does not settle out. Injections of the aforescribed 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.

The formulation is prepared by heating a mixture containing the ferric salt of a higher fatty acid together with an innocuous, non-toxic oil such as for example sesame oil, at a temperature ranging between 100°–175° C. until the desired reaction, i. e. swelling of the salts or slight thickening of the oil, has occurred. The product is cooled and to it is then added a therapeutically active salt of penicillin. This is followed by ball milling the mixture for a period of about sixteen hours and the desired product in its final form is then poured into a suitable container or receptacle.

For the purpose of this invention, the term, higher fatty acid, is defined as a fatty acid containing 16 to 18 carbon atoms. Specific salts which are included within the purview of this invention include ferric suboleate, ferric substearate, ferric subpalmitate, ferric sublinoleate, etc.

The preferred salts used in the preparation of the above indicated vehicle are:

$\text{Fe}(\text{OH})_2\text{OCOC}_{17}\text{H}_{35}$ —Ferric substearate

$\text{Fe}(\text{OH})_2\text{OCOC}_{17}\text{H}_{33}$ —Ferric suboleate with some

$\text{Fe}(\text{OH})(\text{OCOC}_{17}\text{H}_{35})_2$ probably present (H_{33})

In referring to the aforementioned compounds as ferric substearate, ferric suboleate, etc., the prefix "sub" is meant to indicate the fact that these compounds contain substantially all of the stearate, oleate, etc. in the monoform with but minor or inconsequential amounts of the stearate, oleate, etc. in the di-form.

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, peanut, corn, 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 ferric salt used in this invention does not "dissolve" in the oil to produce a gel but instead, the oil dissolves in the ferric salt thus 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 examples which disclose the principle of the invention and the preferred embodiment of applying that principle. It is understood, however, that the examples are merely illustrative and not limitative in nature, being capable of various other modifications:

EXAMPLE I

One gram of ferric substearate was added to 50 cc. of sesame oil which had been warmed to 100° C. The mixture was heated to a temperature of 125° C. for fifteen minutes and then allowed to cool.

Ten grams of procaine penicillin was added to 22.5 grams of the mixture prepared above and the resulting mixture was ball milled for sixteen hours. After this period of time, the mixture was then poured into suitable vials or containers.

EXAMPLE II

One gram of ferric suboleate was added to 50 cc. of sesame oil which had been warmed to 100° C. The mixture was heated to a temperature of 125° C. for fifteen minutes and then allowed to cool.

Ten grams of procaine penicillin was added to 22.5 grams of the mixture prepared above and the resulting mixture was ball milled for sixteen hours. After this period of time, the mixture was then poured into suitable vials or containers.

EXAMPLE III

One gram of ferric subpalmitate was added to 50 cc. of sesame oil which had been warmed to 100° C. The mixture was heated to a temperature of 125° C. for fifteen minutes and then allowed to cool.

Ten grams of procaine penicillin was added to 22.5 grams of the mixture prepared above and the resulting mixture was ball milled for sixteen hours. After this period of time, the mixture was then poured into suitable vials or containers.

The quantity of ferric salt that is used is preferably about 2% by weight of volume of the oil used, satisfactory results having likewise been obtained when quantities ranging from 1 to 10% 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 0.14 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 a metallic 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% Ferric Suboleate in sesame oil.....	3/3(0.29)	3/3(0.19)	2/2(0.06)	0/2
2% Ferric Substearate in sesame oil.....	3/3(0.29)	3/3(0.23)	3/3(0.05)	1/3(0.14)
2% Al Monostearate in sesame oil (Prior Art Control).....	6/6(0.51)	6/6(0.21)	6/6(0.09)	3/6(0.05)
Sesame oil alone (Control).....	2/4(0.33)	0/4	0/4	0/4

¹ One animal died.

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, a ferric salt of a higher fatty acid, 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, pneumococcal 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, prolonged blood levels are obtained when the salts are dispersed in a vehicle composed of a ferric salt of a higher fatty acid and an 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 a vehicle composed of a ferric salt of a higher fatty acid and oil can be prepared containing less than or more than 300,000 units of penicillin.

It is understood that the data and examples 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 a non-toxic innocuous oil and a ferric salt of a higher fatty acid as 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 ferric salts of higher fatty acids, 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 particles of a therapeutic salt of penicillin coated with a gel comprising an innocuous non-toxic oil dissolved in a ferric salt of a higher fatty acid, the coated particles being dispersed in an innocuous non-toxic oil, the amount of ferric salt ranging from 1

5

to 10% by weight of the total amount of innocuous non-toxic oil.

2. An injectable antibiotic preparation capable of maintaining effective therapeutic blood levels over an extended period of time which comprises particles of procaine penicillin coated with a gel comprising an innocuous non-toxic oil and ferric suboleate, the coated particles being dispersed in an innocuous non-toxic oil.

3. An injectable antibiotic preparation capable of maintaining effective therapeutic blood levels over an extended period of time which comprises particles of procaine penicillin coated with a gel comprising an innocuous non-toxic oil and ferric subpalmitate, the coated particles being dispersed in an innocuous non-toxic oil.

4. An injectable antibiotic preparation capable of maintaining effective therapeutic blood levels over an extended period of time which comprises particles of procaine penicillin coated with a gel comprising an innocuous non-toxic oil dissolved in ferric substearate, the coated particles being dispersed in an innocuous non-toxic oil and the amount of ferric substearate ranging from 1 to 10% by weight of the total amount of innocuous non-toxic oil.

5. An injectable antibiotic preparation capable of maintaining effective therapeutic blood levels over an extended period of time which comprises particles of procaine penicillin coated with a gel comprising an innocuous non-toxic oil dissolved in ferric substearate, the coated particles being dispersed in an innocuous non-toxic oil and the amount of ferric substearate being about 2% by weight of the total amount of innocuous non-toxic oil.

6

6. An injectable antibiotic preparation capable of maintaining effective therapeutic blood levels over an extended period of time which comprises particles of procaine penicillin substantially all of which are less than about 200 microns in size, the particles being coated with a gel comprising an innocuous non-toxic oil dissolved in ferric substearate and the coated particles being dispersed in an innocuous non-toxic oil, the quantity of ferric substearate being about 2% by weight of the total amount of 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 procaine penicillin and a gel of an innocuous non-toxic oil and a ferric salt selected from the group consisting of ferric suboleate and ferric substearate, said gel being insoluble in said first mentioned non-toxic oil and containing an amount of ferric salt ranging from 1% to 10% by weight of the total amount of non-toxic oil.

References Cited in the file of this patent

UNITED STATES PATENTS

2,507,193 Buckwalter May 9, 1950

OTHER REFERENCES

Fischer: "The Lyophobic Colloids." Thomas, Springfield, Ill., 1933, pgs. 164 to 170.

Klemgard: "Lubricating Greases." Reinhold, New York, N. Y., 1937, pgs. 684 to 685.