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INJECTABLE PENICILLIN COMPOSITIONS

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This invention relates to repository products and to methods for obtaining the same. More particularly, the invention relates to compositions containing the antibiotic known as penicillin.

At the present time it is the practice to administer salts of penicillin by intramuscular injection using saline solution as a vehicle. When pencillin is administered in this manner it is quickly absorbed and large quantities appear in the blood stream soon after injection. These high blood levels of penicillin rapidly disappear due to the rapid excretion and destruction of the antibiotic. It is therefore necessary to reinject penicillin at two- or three-hour intervals if detectable amounts are to be maintained in the blood stream. In an effort to overcome this rapid elimination of penicillin, diodrast (the chemical combination of 3,5-diiodo-4-pyridone-N-acetic acid and diethanolamine which contains about 50% iodine) or p-aminohippuric acid have been administered with penicillin to interfere with renal function and thus depress the excretion of penicillin [Proc. Soc. Exp. Biol. and Med., 53, 30 (1943) and Science, 100, 107 (1944)]. This unnatural physiological method has many obvious disadvantages in addition to the fact that it is not particularly effective in accomplishing its purpose of maintaining high blood levels of penicillin over long periods of time.

Another method of maintaining blood levels of penicillin after intramuscular injection which has been proposed in the retarding of the absorption of penicillin by placing an ice pack over the area of injection to limit the local circulation [(Science, 100, 432 (1944)]. This method does not appreciably delay the absorption of penicillin and is very cumbersome and extremely uncomfortable.

More recently the use of vegetable oils and beeswax-peanut oil mixtures have been suggested as vehicles for penicillin because of their slow rate of absorption [Science, 100, 412 (1944) and Science, 100, 196 (1944)]. Even when using these slowly absorbed vehicles for penicillin it is necessary to reinject penicillin every three or four hours to maintain adequate therapeutic blood levels of the antibiotic.

One of the objects of this invention is to continuously maintain therapeutic blood levels of penicillin in humans and in animals for considerable periods of time.

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Another object of the invention is to prevent the customary rapid elimination and destruction in vivo of penicillin. One of the objects of the invention is to obtain the maximum therapeutic effect per unit of penicillin administered.

It is also an object of this invention to obtain more constant blood levels of penicillin.

A further object of the invention is to provide repository compositions containing penicillin which are stable and which are easy to administer.

Still another object of this invention is to provide repository compositions containing penicillin which do not cause undesirable physiological reactions on administration to humans or animals.

I have found that by intramuscular injection of a suspension of a penicillin salt in a vehicle comprising a natural oil containing a small amount of an organic compound possessing vasoconstrictor properties that it is possible to continuously maintain therapeutic blood levels of penicillin over a long period of time. I have also found that this period of time when using my new preparations is several times greater than obtained when one injects a saline solution of a vasoconstrictor and a penicillin salt or an oil or oil-wax suspension of a penicillin salt not containing any vasoconstrictor. By the practice of my invention I have found that more constant blood levels of penicillin are obtainable. This insures the presence of adequate amounts of penicillin for the exercise of a continuous therapeutic effect between injections. The penicillin compositions of the present invention are stable and do not cause undesirable physiological reactions on administration to humans or animals. These products do not cause pain in the region of injection and are easily injected in the conventional manner.

Examples of the vasoconstrictors which I may use in the preparation of my new penicillin compositions are epinephrine, 1-a-hydroxy-b-methylamino - 3 - hydroxyethylbenzene, 2 - naphthylmethylimidazoline, ephedrine, propadrine, 1-a-hydroxy-b - methylamino - 4 - hydroxyethylbenzene and the like. I have found that only very small amounts of the vasoconstrictor need be

used in my new preparations to accomplish the desired repository effect. For example, in my oil suspension preparations, as little as 0.00005 g. of epinephrine per ml. of the preparation is sufficient to enhance the repository action to a very marked degree. However, as high as 0.002 g. of epinephrine per ml. may be used without causing significant rise in blood pressure, although for a margin of safety and to prevent a nervous or restless feeling, it is preferable to use less than about 0.001 g. per ml.

By "small amounts" of vasoconstrictors as used herein and in the appended claims, I intend to include those proportions of vasoconstrictors which can be used with a therapeutic dosage of penicillin to produce effective prolonged vasoconstriction without the undesirable nervous reactions which result when too much of the vasoconstrictor is used. The limits of these proportions will vary somewhat but are readily determined by simple experiment.

In the preparation of my new products I may use any bland, non-irritating natural oil such as peanut oil, sesame oil, cottonseed oil, castor oil, corn oil, olive oil, rape seed oil, coconut oil and the like. I have found that particularly valuable products are obtained when such natural oils also contain a small amount of dissolved wax such as beeswax, spermaceti and similar waxes. These latter mixtures when incorporated with a vasoconstrictor and used as vehicles for penicillin salts prolong the action of penicillin considerably more than similar compositions not containing wax.

The therapeutic blood level of penicillin concentration in humans is between 0.02 and 0.03 Oxford units per ml. of blood serum. The maintenance of this therapeutic blood level of penicillin in humans is indicated by urinary excretion of over about 1000 Oxford units of penicillin per hour.

In accordance with the present invention one to one and a half times the therapeutic blood levels of penicillin may be maintained for at least twelve hours by a single intramuscular injection of as little as 100,000 Oxford units of penicillin. The invention therefore makes it possible to treat infections and diseases which yield to penicillin therapy by not more than two intramuscular injections of penicillin per twenty-four hours in contrast to the customary eight to twelve intramuscular injections required when using penicillin salts in aqueous or in saline solutions.

The invention is illustrated by the following examples.

Example 1

3 ml. of refined peanut oil and 2.5 mg. of epinephrine are added to 500,000 Oxford units of calcium penicillin contained in a small glass bottle. Two or three sterile glass beads are added, the mixture warmed to about 40° C., the bottle stoppered and shaken for ten minutes to insure dispersion of the particles of penicillin. The mixture is then diluted to 5 ml. with refined peanut oil and shaken to insure homogeneity.

This therapeutic preparation is uniform suspension of calcium penicillin which is stable and suitable for intramuscular injection into humans or animals. Injection of 1 ml. of this product furnishes 100,000 Oxford units of calcium penicillin the action of which is continuously maintained above the therapeutic level for about 12 hours.

Example 2

4.0 ml. of warm (about 40° C.) refined peanut oil and 1 mg. of epinephrine are added to 1,000,000 Oxford units of dry calcium penicillin contained in a small glass bottle. The bottle is stoppered and shaken to disperse the penicillin salt. The mixture is then diluted to 5 ml. with refined peanut oil.

This therapeutic preparation is stable and contains 200,000 Oxford units of calcium penicillin per ml. On intramuscular injection of this preparation into humans or animals the therapeutic blood level of penicillin is maintained for at least twelve hours.

Table I shows representative blood levels obtained following the intramuscular injection of the penicillin preparation prepared as described in this Example.

Table I

Data obtained by intramuscular injection of 1 ml. of the above preparation (100,000 Oxford units of calcium penicillin and 0.2 mg. of epinephrine per ml. in peanut oil) into human patients.

Patient No.	Penicillin blood concentration at the end of — hours in Oxford Units per ml. serum [1]			
	6 hours	8.5 hours	10 hours	12 hours
50	0.14	0.05	0.05	0.04
51	0.09	0.05	0.04	0.04

[1] Determined by the modified method of Rosenblatt as described in J. Bact., 48, 599 (1944).

Example 3

3 ml. of warm (about 35° C.) refined peanut oil and 0.5 mg. of epinephrine are added to 500,000 Oxford units of calcium penicillin contained in a small glass bottle. The bottle is stoppered, shaken well to disperse the penicillin salt and then the mixture diluted to 5 ml. with refined peanut oil.

This therapeutic preparation is stable and contains 100,000 Oxford units of calcium penicillin per ml. When 1 ml. of this preparation is injected intramuscularly into humans the effect of the penicillin maintained several times as long as in similar preparations not containing epinephrine.

Example 4

3 ml. of refined peanut oil and 2.5 mg. of neosynephrine are added to 500,000 Oxford units of calcium penicillin contained in a small glass bottle. Two or three sterile glass beads are added, the mixture warmed to about 40° C., the bottle stoppered and shaken for ten minutes to insure dispersion of the particles of penicillin. The mixture is then diluted to 5 ml. with refined peanut oil and shaken to insure homogeneity.

This therapeutic preparation is a uniform suspension of calcium penicillin which is stable and suitable for intramuscular injection into humans or animals. Injection of 1 ml. of this product furnishes 100,000 Oxford units of calcium penicillin the action of which is continuously maintained above the therapeutic level for about 12 hours.

Example 5

3 ml. of warm (about 40° C.) refined peanut oil and 1.25 mg. of neosynephrine are added to 500,000 Oxford units of calcium penicillin contained in a small glass bottle. The bottle is stoppered, the mixture agitated to disperse the penicillin salt and the mixture diluted to a volume of

5 ml. with refined peanut oil and the mixture shaken to insure homogeneity.

This stable preparation contains 100,000 Oxford units of calcium penicillin per ml. and when injected into human subjects maintains therapeutic blood levels of penicillin over much longer periods of time than similar preparations not containing a vasoconstrictor drug.

EXAMPLE 6

3 ml. of warm (about 40° C.) peanut oil and 1.2 mg. of 2-naphthylmethylimidazoline are added to 300,000 Oxford units of calcium penicillin contained in a small glass bottle. The bottle is stoppered, shaken well to disperse the penicillin salt and diluted to a volume of 4 ml. with refined peanut oil.

This stable preparation contains 75,000 Oxford units of calcium penicillin and when administered by the intramuscular route to human subjects maintains a therapeutic blood level of penicillin for a much longer period of time than a similar preparation not containing the vasoconstrictor drug.

EXAMPLE 7

3 ml. of refined peanut oil and 2.5 mg. of epinephrine are added to 500,000 Oxford units of sodium penicillin contained in a small glass bottle. Two or three sterile glass beads are added, the mixture warmed to about 40° C., the bottle stoppered and shaken for ten minutes to insure dispersion of the particles of penicillin. The mixture is then diluted to 5 ml. with refined peanut oil and shaken to insure homogeneity.

This therapeutic preparation is uniform suspension of sodium penicillin which is stable and suitable for intramuscular injection into humans or animals. Injection of 1 ml. of this product furnishes 100,000 Oxford units of sodium penicillin the action of which is continuously maintained above the therapeutic level for about 12 hours.

EXAMPLE 8

3 ml. of refined peanut oil and 2.5 mg. of neosynephrine are added to 500,000 Oxford units of sodium penicillin contained in a small glass bottle. Two or three sterile glass beads are added, the mixture warmed to about 40° C., the bottle stoppered and shaken for ten minutes to insure dispersion of the particles of penicillin. The mixture is then diluted to 5 ml. with refined peanut oil and shaken to insure homogeneity.

This therapeutic preparation is a uniform suspension of sodium penicillin which is stable and suitable for intramuscular injection into humans or animals. Injection of 1 ml. of this product furnishes 100,000 Oxford units of sodium penicillin the action of which is continuously maintained above the therapeutic level for about 12 hours.

EXAMPLE 9

2.5 mg. of epinephrine and 3 ml. of warm (about 40° C.) refined peanut oil containing 3% by weight of dissolved beeswax are added to 500,000 Oxford units of calcium penicillin contained in a small glass bottle. The bottle is stoppered and shaken well to disperse the penicillin salt. The mixture is diluted to a volume of 5 ml. with warm refined peanut oil containing 3% by weight of dissolved beeswax and shaken again to insure homogeneity.

This stable therapeutic preparation contains 100,000 Oxford units of calcium penicillin per ml. Therapeutic blood levels of penicillin are maintained for at least twelve hours following the intramuscular injection of 1 ml. of this preparation.

EXAMPLE 10

2.5 mg. of 2-naphthylmethylimidazoline and 3 ml. of warm (about 45° C.) refined peanut oil containing 3% dissolved beeswax are added to 500,000 Oxford units of calcium penicillin contained in a small glass bottle. Two or three sterile glass beads are added and the mixture shaken for five minutes. The mixture is made up to a volume of 5 ml. with warm refined peanut oil containing 3% beeswax.

When 1 ml. of this stable composition which contains 100,000 Oxford units of calcium penicillin per ml. is injected intramuscularly into human subjects therapeutic blood levels of penicillin are maintained for at least twelve hours.

EXAMPLE 11

3 ml. of warm cottonseed oil and 2.5 g. of 1-a-hydroxy-b-methylamino-4-hydroxyethylbenzene are added to 500,000 Oxford units of calcium penicillin contained in a small glass bottle. The bottle is stoppered and the mixture shaken to disperse the penicillin salt. The mixture is diluted to a volume of 5 ml. with cottonseed oil and mixed well.

This stable therapeutic product contains 100,000 Oxford units of calcium penicillin per ml. and when administered to humans in dosages of 100,000 Oxford units gives therapeutic blood levels of penicillin for a period of about twelve hours.

EXAMPLE 12

2 ml. of warm coconut oil and 0.9 mg. of epinephrine are added to 300,000 Oxford units of calcium penicillin in a small glass bottle. The bottle is stoppered and the mixture shaken to disperse the penicillin salt in the oil. The mixture is diluted to a volume of 3 ml. with warm coconut oil and shaken to insure homogeneity.

This stable preparation contains 100,000 Oxford units of calcium penicillin per ml. and when administered to humans by the intramuscular route maintains therapeutic blood levels over a much larger period of time than similar preparation not containing epinephrine.

EXAMPLE 13

A mixture consisting of 1 mg. of epinephrine and 8 ml. of warm refined corn oil is added to 500,000 Oxford units of calcium penicillin contained in a small glass bottle. The bottle is stoppered, the mixture shaken to disperse the penicillin salt and the preparation diluted to a volume of 10 ml. with refined corn oil.

This preparation is stable and contains 50,000 Oxford units of calcium penicillin per ml.. When this product is administered intramuscularly to humans therapeutic blood levels of penicillin are maintained over a much longer period of time than by administration of the same quantity of similar preparation not containing epinephrine.

EXAMPLE 14

2.5 mg. of epinephrine and 4 ml. of warm sesame oil are added to 500,000 Oxford units of calcium penicillin contained in a small glass bottle. The bottle is stoppered, shaken to disperse the penicillin salt and the mixture diluted to a volume of 5 ml. with sesame oil.

This preparation which contains 100,000 Oxford units of calcium penicillin is stable and when injected intramuscularly into humans results in therapeutic blood levels over much longer periods of time than corresponding preparation not containing epinephrine.

The great superiority of the penicillin preparations of the present invention over the known penicillin preparations is readily apparent from examination of Table II which shows the rapid urinary excretion of penicillin in human patients following intramuscular injections of 1 ml. of various control preparations of penicillin known from the prior art, as compared to the more prolonged urinary excretion of my new preparations.

prising a suspension of a penicillin salt in a non-aqueous vehicle comprising an injectable natural oil containing a small amount of an organic compound possessing vasoconstrictor properties, said composition, upon injection, providing prolonged therapeutic blood levels of penicillin as compared with the blood levels attainable upon injection of similar compositions containing no vasoconstrictor and with the blood levels attain-

Table II

	Patient No.	Formula per ml.	Oxford Units of Penicillin Excreted at the end of — hours and — hours [1]					Total percent Penicillin Excreted
			3 hours	5 hours	7 hours	9 hours	24 hours	
Control Prepn. #1	4	50,000 Units of sodium penicillin in water [2]	57,600	5,000	0	0	0	62
Control Prepn. #2	2	50,000 Units of sodium penicillin+0.5 mg. epinephrine in water [2]	36,400	5,000	700	0	0	42
Control Prepn. #3	18	100,000 Units of calcium penicillin in peanut oil	32,500	1,150	0	0	0	33.7
	19		45,600	3,000	200	0	0	48.8
Prepn. described in Example 1.	6	100,000 Units of calcium penicillin+0.5 mg. epinephrine in peanut oil.	24,100	14,800	12,600	5,400	5,000	62
	7		28,500	18,000	13,000	5,300	2,600	67
	12		37,240	24,000	6,300	7,600	1,700	77
	13		22,750	29,300	[3]	6,000	315	58
Prepn. described in Example 3.	30	100,000 Units of calcium penicillin+0.1 mg. epinephrine in peanut oil.	21,000	5,500	1,000	500	0	27.5
	31		4,300	5,300	12,000	2,000	1,200	14
Control Prepn. #4	14	100,000 Units of calcium penicillin+3% beeswax in peanut oil.	3,500	5,200	1,250	250	250	10
	15		14,350	5,280	3,300	1,560	1,000	24.5
Prepn. described in Example 9.	1	100,000 Units of calcium penicillin+0.5 mg. epinephrine+3% beeswax in peanut oil.	1,800	9,500	6,400	[3]	18,400	36
	16		11,730	12,570	10,395	4,836	2,680	42
	17		1,500	3,200	8,540	11,500	6,500	31

[1] Oxford Units of penicillin determined by the Oxford Plate Test as described by Fleming.
[2] 2 cc. of this preparation administered, a total of 100,000 Oxford Units.
[3] Samples not collected.

The penicillin products of the present invention when administered to humans or animals by the intramuscular route give blood levels which in duration, continuity and intensity are similar to those shown in Table I above for the specific preparation described in Example 2.

The penicillin suspensions of the invention are more easily prepared by warming the vehicle to enhance its fluidity. However, I have found that in many cases it is not necessary to first warm the vehicle to obtain a homogeneous suspension of the penicillin salt.

While in the above examples I have used the free bases of the vasoconstrictors it should be understood that I may also use any non-toxic acid addition salt of these compounds in the preparation of my new therapeutic products. I have found that little or no reaction takes place between these acid addition salts of the vasoconstrictor and the penicillin salts when they are suspended in the oil media of the present invention. Some specific examples of the nontoxic acid addition salts of the vasoconstrictors which I may use are the hydrochloride, sulfate, phosphate, nitrate, acetate, citrate and tartrate salts.

Any non-toxic salt of penicillin may be used in the preparation of the penicillin products herein described. For example, some of the penicillin salts which I may use instead of the calcium and sodium salts shown in the above examples are the ammonium, potassium, lithium and magnesium salts of penicillin.

While suspensions of the present invention slowly settle out, I have found that they do not pack and that they may be immediately and uniformly resuspended with ease.

What I claim is:

1. An injectable therapeutic composition comparable upon injection of similar compositions containing no oil.

2. An injectable therapeutic composition comprising a suspension of a penicillin salt in a non-aqueous vehicle comprising an injectable natural oil containing a small amount of epinephrine, said composition, upon injection, providing prolonged therapeutic blood levels of penicillin as compared with the blood levels attainable upon injection of similar compositions containing no vasoconstrictor and with the blood levels attainable upon injection of similar compositions containing no oil.

3. An injectable therapeutic composition consisting of a suspension of calcium penicillin in a non-aqueous vehicle comprising peanut oil containing a small amount of epinephrine, said composition, upon injection, providing prolonged therapeutic blood levels of penicillin as compared with the blood levels attainable upon injection of similar compositions containing no vasoconstrictor and with the blood levels attainable upon injection of similar compositions containing no oil.

4. An injectable therapeutic composition comprising a suspension of calcium penicillin in a non-aqueous vehicle comprising an injectable natural oil containing a small amount of an organic compound possessing vasoconstrictor properties, said composition, upon injection, providing prolonged therapeutic blood levels of penicillin as compared with the blood levels attainable upon injection of similar compositions containing no vasoconstrictor and with the blood levels attainable upon injection of similar compositions containing no oil.

5. An injectable therapeutic composition comprising a suspension of sodium penicillin in a

non-aqueous vehicle comprising an injectable natural oil containing a small amount of an organic compound possessing vasoconstrictor properties, said composition, upon injection, providing prolonged therapeutic blood levels of penicillin as compared with the blood levels attainable upon injection of similar compositions containing no vasoconstrictor and with the blood levels attainable upon injection of similar compositions containing no oil.

6. An injectable therapeutic composition comprising a suspension of sodium penicillin in a non-aqueous vehicle comprising peanut oil containing a small amount of epinephrine, said composition, upon injection, providing prolonged therapeutic blood levels of penicillin as compared with the blood levels attainable upon injection of similar compositions containing no vasoconstrictor and with the blood levels attainable upon injection of similar compositions containing no oil.

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