

## UNITED STATES PATENT OFFICE

2,530,480

## THERAPEUTIC PREPARATIONS FOR INTRAMUSCULAR AND SUBCUTANEOUS INJECTION AND METHODS OF MAKING THE SAME

George Philo Pitkin, deceased, late of Bergenfield, N. J., by Winifred M. Pitkin, administratrix, Bergenfield, N. J., assignor, by mesne assignments, of one-half to The Jacques Loewe Research Foundation, Inc., New York, N. Y., a corporation of New York

No Drawing. Application January 21, 1944,  
Serial No. 519,206

8 Claims. (Cl. 167—82)

1

The present invention relates to therapeutic preparations for intramuscular and subcutaneous injection and methods of making the same, and is more particularly directed toward preparations containing various drugs (singly or combined) such as stimulants, narcotics, sedatives and anticoagulants and carried in a menstruum or vehicle such that the dosage which can be administered and the duration of its effectiveness is greatly increased as compared to the best practices heretofore available.

The present application is a continuation in part of application of George Philo Pitkin, Serial No. 332,483, filed April 30, 1940, now abandoned.

An object of the invention is to provide an agent for causing a stimulant, narcotic, sedative or anticoagulant to function according to a greater prolonged relatively uniform efficiency under conditions that are inherently fully controlled.

Another object of the invention is to provide such an agent which shall not directly or otherwise cause the production of harmful or undesirable physiological effects.

Another object of the invention is to devise a novel vehicle or controlling agent for various drugs such as stimulants, narcotics, sedatives and anticoagulants whereby an interaction occurs between the agent and certain component elements of the body, especially the blood, and whereby the drug is separated as by a semi-permeable membrane, permitting the drug to act in its normal manner but at a controlled, non-toxic rate; and a supplemental object is to provide an improved composition of treatment or of chemically creating a reservoir of a drug by joint action of an agent with a component of the body.

A particularly important object of the invention is to furnish a vehicle for such a drug whereby the drug is subjected to a plurality of stages of permeable encapsulation, the first being applicable to very small particles or molecules of the drug, and the second being applicable for permeable encapsulation of the injected drug in mass by reduction of active near-by red blood cells, whereby the drug is initially controlled preparatory to its final essential encapsulation without which the retardation of drug absorption would be often erratic.

Another object of the invention is to provide an improved composition for the control of such a drug against undue absorption and change from its required condition from the moment of injection until such a later stage when the systemic attack on the drug may increase and hence require a change in the environment of the drug.

2

A further object of the invention is to provide methods whereby the vehicle or menstruum may be made preliminarily to the addition of the therapeutic preparation to be employed, as well as to the methods of incorporating the therapeutic preparation in the menstruum and rendering of the material suitable for use by the medical profession.

Among the drugs referred to are stimulants such as suprarenin, digitalis, and ephedrine, and narcotics such as morphine, "Pantopon," "Dilaudid," codeine, the amnesia producing agent hyoscine hydrobromide, also known as scopolamine, and the sedative sodium phenobarbital; further the drugs herein contemplated are such as produce a toxic action so that only relatively small doses thereof may be used. For example, a small dose is given before the operation and at certain time intervals thereafter. The curve of narcotic action is almost equally positive and negative, the latter representing undesirable depressor effects and being indicative of intervals of substantial pain. If, to the contrary, the dosage is increased, a substantial toxic effect is induced, which may be a source of considerable danger to the patient. In an operative case, only one injection of a substantial dose of the narcotic may suffice, the narcotic action being nevertheless substantially free of the toxic effect and being at relatively uniform strength over a period of time that is in fact substantially greater than what was heretofore obtainable with several injections at the usually prescribed intervals of time. Experiment and clinical application of the narcotics have shown that the toxicity is reduced from four to eight times depending upon the drug. In the case of a drug such as "Suprarenin," also known as adrenalin, a greatly increased dose of the same may be injected to form an intramuscular reservoir from which the protected drug is fed at a predetermined rate to conform to the normal secretion of the suprarenal gland to thus create or regulate a hyper-elimination or a hypo-elimination. Thus the local vasoconstrictor properties of suprarenin may be prolonged for twenty-four to thirty hours as against the seven or eight minutes heretofore available by intramuscular injection. Furthermore, a prolonged therapeutic action is obtainable with such stimulants as are synergistic and hence substantially cumulative in effect to suprarenin, such as digitalis, strychnine, strophanthin, belladonna, and caffeine.

While solutions can be prepared with a cohesive tenacious adhesive substance such as gelatin to

cause substantially molecular encapsulation of a drug upon injection, it was observed that when preparations were prepared with gelatin per se and injected into the body that they would not retain their viscous cohesive properties on contact with the alkaline body fluids. The jelly-like substance formed was somewhat granular, would break up with slight pressure and was almost insoluble. It resembled commercial gelatin in appearance and had similar strength. The deterioration of the gelatin as it occurs in the living tissues can be demonstrated by immersing pure gelatin in citrated blood, blood serum or aqueous solution and keeping it at body temperature for three or four hours. The loss of the cohesive properties permitted a premature release of the therapeutic drugs. It was found that if the solution was acidified with 99% acetic acid, the viscosity of the solution could be maintained for a longer time and the action of the therapeutic agents could be extended in the same ratio. It was further found that when 7½% dextrose was added to the solution the deterioration could be prevented and its adhesive quality prolonged for and in excess of twenty-four hours. By increasing all three ingredients to various strengths primary absorption could be delayed for three or four hours and total elimination prevented far in excess of forty-two hours.

Moreover it was found that the acetic acid by breaking down red blood corpuscles, creates a relatively neutral zone that thus improves or reinforces the semi-permeable viscous partition or membrane and in any case causes the bulk encapsulation of the drug, this being the second state of retardation and control of the rate of absorption of the drug.

It was discovered that stable, dependable, intramuscular or subcutaneous solutions could be produced by including therein a cohesive adhesive substance preferably in the nature of gelatin, acidified with acetic acid and fortified with dextrose so as to increase and stabilize its viscosity sufficiently not to materially inhibit the absorption of the therapeutic medicinal agents; to prolong and retard the release of the therapeutic agents such as heparin, "Suprarenin," morphine and/or scopolamine for a definite duration without delaying their elimination after their therapeutic functions have been performed.

For the surgical shock preventing, pain-relieving solution the use of suprarenin, morphine sulphate and hyoscine hydrobromide (scopolamine) is preferred. However, other salts may be substituted for use such as ephedrine hydrochloride or sulphate "Pantopon," "Dilaudid" and phenobarbital sodium. In producing the intramuscular solution, the proportions may be greatly varied, depending upon the various conditions to be met, but the preferred solutions contain by weight 12% to 30% gelatin, 5% to 12% dextrose, .3% to 1.5% acetic acid, .002% of "Suprarenin," .05% of morphine and .005% of hyoscine hydrobromide, the balance being distilled water. Such amounts of gelatin, dextrose and acetic acid have been found to be sufficient to fortify the solution and regulate the elimination of the therapeutic agents from twenty-four to thirty hours. Two mgs. of "Suprarenin" are sufficient to compensate for the impaired function of the suprarenal gland, maintain blood pressure, stimulate respiration, prevent perspiration and increase oxygen consumption until the impaired suprarenals can function for themselves. Fifty mgs. of morphine sulphate will relieve pain .9 mg. of scopolamine

will overcome apprehension far in excess of twenty-four hours.

In general there is considerable latitude in the proportions employed. The proportions may be considerably varied depending upon different factors, certain of which mutually affect each other. Among these factors are the particular patient who is being treated, his general condition, the degree of anesthesia to be induced, the blood pressure that is to be maintained, the duration of time of the treatment, the nature of the drugs used, the technique and ideas of the attending physician, and numerous other factors.

Where narcotics are involved, good results have been obtained with solutions prepared as follows: (1) C. P. gelatin 15. grams, dextrose powder 7.5 grams, acetic acid .35 gram, suprarenin 200 mgs., morphine sulphate 5 grams, and hyoscine hydrobromide 90 mgs., distilled water in sufficient quantities to make 100 c. c., the dose to be applied pre-operatively to surgical cases in averages of 1 c. c. of this solution; (2) "Suprarenin" 2 mgs., hyoscine hydrobromide .9 mg., morphine sulphate 50 mgs., gelatin 150 mgs., dextrose 75 mgs., acetic acid 3.5 mgs., distilled water to make 1 c. c. This ratio is particularly adopted for surgical procedures wherein spinal anesthesia is employed, to allay apprehension, a drop in blood pressure, shock and post-operative pain. With inhalation anesthesia, the amount of suprarenin per cubic centimeter may be dropped to .3 mg. without affecting the duration of the morphine or scopolamine. If the heart rate is slow ephedrine (50 mgs.) may be substituted for the suprarenin. The ingredients of the solution may be combined in the following manner: 15 grams of gelatin is dissolved in 60 c. c. of sterile distilled water over a water bath in which the temperature is maintained between 185° and 194° F., the temperature is permitted to fall to between 122° and 131° F. when the dextrose, acetic acid and one percent. of iso-amyl-hydrocuprein (eucupin) dihydrochloride is added to prevent oxidization of the acetic acid when heated, and a sufficient amount of distilled sterile water to make 95 c. c., is placed in sterile containers and allowed to age, tested for bacterial contamination and tested for duration of viscosity. As mentioned previously, the solution is adaptable to any therapeutic agents that are commonly given or administered by intramuscular or subcutaneous injection. If the solution is satisfactory, it is warmed to 105° F., the "Suprarenin," hyoscine hydrobromide and morphine are added, dissolved by agitation and a sufficient quantity of distilled water is finally added to make 100 c. c.

A preferred procedure is, however, to prepare a menstruum or vehicle of double strength, and a solution of the therapeutic agent also of double strength and mix the two. For example, 1000 cc. of menstruum with 32% gelatin, 15% dextrose and 1% acetic acid may be prepared as follows: Adding to 320 grams of medicinal grade of gelatin 450 cc. of cold sterile distilled water, stirring constantly to moisten all the particles of gelatin. Melt the gelatin on a water bath, rubbing out any lumps that may occur. If desired, the gelatin solution may be subjected to vacuum to draw off air bubbles, cooled, congealed, reliquified and re-evacuated and then warmed. 150 grams of powdered dextrose is added to the gelatin solution which is stirred until the dextrose goes into solution, or add 150 cc. glucose water-white. If desired, the solution may be boiled in a vacuum.

Strain and add 10 cc. of glacial acetic acid. To this it is preferable to add 2 grams of eucupin and agitate until dissolved and then, to preserve from contamination, add 10 cc. to 50 cc. of 10% chlorbutanol in alcohol. The solution is made up to 1000 cc. It will become a solid at room temperature. Where the therapeutic agent is a narcotic, a stimulant or sedative (such as those above named and others of similar nature and characteristics) the desired amount of the agent, or agents, employed is dissolved in 900 cc. of distilled water and thereafter its temperature should never be raised above 110° F., preferably not over 100° F. The gelatin mixture is warmed to approximately 100° F. and the second solution is made up to 1000 cc. The two solutions are thoroughly mixed so that the percentage of the components has been cut in half; the mixture is allowed to cool, reliquified and placed in ampules. The ampules are closed under vacuum, or the oxygen may be replaced by nitrogen.

If the gelatin is not subjected to greater heat or boiled, the light amber color will be preserved. The chlorbutanol may be incorporated in the second solution, if desired. The alcohol to dissolve the chlorbutanol acts as a preservative and a hardening agent for the gelatin. It prevents liquification with age. The use of equal quantities of the two solutions is convenient, but not necessary, and the percentage ranges may vary as above set forth.

The widespread use of heparin which is an important agent for the prevention and treatment of thrombosis and thrombotic conditions, has been retarded by the necessity for its administration by a continuous venous drip or by repeated intravenous injections. This cumbersome and costly technique which requires constant, trained supervision best carried out in an institution cannot be employed for the protracted periods which are required for some thrombotic states. Moreover, the huge amounts of heparin required by this technique to reach therapeutic levels entails an expense which often prevents the use of this valuable drug. By depositing the heparin incorporated in the new menstruum subcutaneously or intramuscularly a slow and equable absorption of the drug is accomplished, the administration is simplified, and the amount of heparin necessary to achieve the desired results is materially reduced. Heparin can also, in this manner, be safely, practically and economically administered over long periods of time.

The preparation of ampules containing heparin is as follows:

The double strength menstruum may be prepared as before. The heparin solution is prepared by dissolving epinephrine in a few drops of 19% HCl then add distilled water sufficient for dissolving ephedrine-sulphate, eucupin dihydrochloride, chlorbutanol, and heparin, add sufficient distilled water to make up to double strength volume and then add the menstruum to make up the final volume. The preferred formula is:

|                                         |                        |       |
|-----------------------------------------|------------------------|-------|
| Cryst. sodium salt of heparin.....      | milligrams.....        | 100.0 |
| Epinephrine hydrochloride.....          | do.....                | 1.0   |
| Ephedrine sulphate.....                 | do.....                | 25.0  |
| Chlorbutanol.....                       | do.....                | 0.5   |
| Eucupin dihydrochloride.....            | do.....                | 1.0   |
| Double strength menstruum q. s. ad..... | cubic centimeters..... | 2.0   |

Double the amount of heparin may be used; the vasoconstrictors epinephrine hydrochloride and ephedrine sulphate may be omitted, where not

desired, or the amount of menstruum reduced to about one-half, but then the heparin tends to remain in crystal form.

After mixing thoroughly, the product is filled in the presence of nitrogen into amber ampules and submitted to steaming-steam sterilization on three successive days for 15 minutes on each day. Each batch undergoes a sterility test and a pH control.

The solute for the menstruum or vehicle contains gelatin, dextrose and acetic acid in predetermined proportions and these are 12 to 30 parts gelatin, 5 to 12 parts dextrose and .3 to 1.5 parts acetic acid so that when dissolved in water the percentage composition may be brought by dilution to within the ranges stated.

Since the vehicle is aqueous, the drugs used should be sufficiently water soluble to maintain equality of tension or tonicity with the solution to prevent any drug from precipitating out when the composition has been standing for a long time. Encapsulation of the drug or therapeutic agent proceeds in two stages, first molecular encapsulation, or encapsulation in finely divided condition, by means of a viscous vehicle, the viscosity of which must not be so low as to permit unduly rapid release of the drug, nor so high as to slow up the feed of the drug to a point of reduced efficiency. It is noted that the gelatin, dextrose and acetic acid cooperate to produce a desired viscosity. The first stage of encapsulation is no sufficient for the results herein required, because it is not sufficiently stable for any substantial length of time and may cause premature release of the drug to produce some of the highly undesirable results herein pointed out. The second stage of encapsulation, which is the bulk encapsulation, due to the action of acetic acid in the environment of the tissues, assures full control over a long period of time without any erratic action. The molecular encapsulation is, however, important for bridging the time, during which the acetic acid may act, and causes release of the acetic acid after the injected mass has established its pocket in the tissues so that the required stable conditions have been prepared for the bulk encapsulation. The hemolytic membrane for the encapsulation usually disappears in two to four days.

It will thus be seen that the new hypodermic solution that has a coefficient with most drugs used for hypodermic subcutaneous or intramuscular medication, will prolong the therapeutic effects of narcotics as morphine, "Pantopon," codeine, "Dilaudid" and sedatives for from the proverbial three to four hours to twenty-four or thirty-six hours, and obviates the possibility or dangers of toxic reactions. Relatively large doses of morphine may be used and the administration of heparin may be greatly improved.

Doses such as 3/4 grain of morphine and "Pantopon" 1 grain have been administered to a great many surgical cases (over 160 prior to the filing of application Serial No. 332,483) without experiencing any toxic reactions. When this large amount of the narcotic was administered, the reactions observed in the patients for the twenty-four hours following were comparable to 1/8 or 1/4 grain of morphine, dissolved in sterile water and injected into the patient. In the 160 cases this preparation has been used as a pre-operative narcotic and sedative, none of the patients has had post-operative pains or required post-operative hypodermic of morphine or other narcotic. The relative percentage of

post-operative distension and ileus has been nil during the first forty-eight hours after operation. Nausea and vomiting have been materially reduced, sweating and perspiration have not been observed in any of the cases nor have respiratory complications occurred.

The respirations have been maintained between 20 and 30, an increase rather than a decrease. The heart rate is accelerated and the pulse volume increased. The systolic blood pressure in normal cases rises 20 to 30 points, diastolic pressure remains about the same, in hypertension cases with a pressure 85/50 due to shock or bleeding, the pressure immediately rises to within normal limits, that is 130/70. A low pulse pressure is increased to within normal limits. The blood pressure has been maintained from 20 to 42 hours which has been impossible with suprarenin heretofore. In none of the cases have the patients experienced or complained of generalized body itching, erythema at the site of injection or urticaria. The pupils are not contracted as with morphine, they become dilated due to the "Adrenalin" reaction, hours before the effects of the opiate disappear. There have been no complaints of pain at the site of injection.

This preparation was devised for a pre-operative sedative and post-operative narcotic. In many surgical cases, it was given one or two hours before the operation and in none of these cases have the patients required a post-operative injection of morphine within the first twenty-four hours after operation. The majority have remained pain-free for longer than thirty hours. In the 160 cases in which it was given there have only been three that have required morphine during the stay in the hospital. It is not affected by high temperatures or by dehydration of the patient. It does not inhibit the intestinal secretions as does morphine, thereby eliminating constipation. Post-operative distension and ileus have been reduced between 60% and 75%. It increases carbohydrate metabolism and liver glycogen. It increases oxygen consumption and raises the respiratory quotient, oxygen metabolism is increased from 40% to 60%, respirations are increased, varying from 20 to 30 per minute, tidal volume is increased, not decreased as with morphine.

Its use does not endanger the new-born child, resuscitation is not delayed or impaired. Morphine or Pantopon given in this way do not cause "blue babies" due to the increased oxygen metabolism.

When more than one drug is added for therapeutic purposes the liberation of these drugs from the solution and the absorption thereof into the body tissues or fluids are interdependent upon each other; that is, one drug cannot be liberated more freely nor absorbed more readily than can its companion drugs. The prolongation of the retention and the delayed action of the absorption permits larger amounts to be used at one time, prolongs the action and reduces the toxicity. The preparation can be sterilized and sealed in ampules, sealing and testing the latter for leakage and further sterilizing the same and becomes a ready-to-use preparation which retains its potency in the ampules for a very long time — possibly indefinitely — and only needs warming to body temperature to render it ready for use.

The various ingredients and formulas herein given are intended for illustration and it will be

appreciated that others may be found equivalent thereto within the scope of the appended claims or in accordance with the principles herein set forth. It may be added that the new composition of matter resembles blood serum, particularly human blood serum, in appearance and consistency, but possesses a greater viscosity than the same, while being desirably free of oils, fats and proteins except that it contains a colloidal substance, namely gelatin. Differently stated, the new composition of matter resembles a concentrated blood serum and possesses fibrinogen-like blood clotting properties, with retardation of oxidation (normally occurring within twenty minutes) of such unstable stimulants as "Adrenalin," ephedrine, "Pituitrin," "Antuitrin," "Pitressin," "Pitocin" and others. The vehicle must naturally be ultimately absorbable by the patient so as not to leave any foreign body.

As the gelatin, dextrose and acetic acid are inactive except in the manner that they function to control release of the drug or therapeutic agent, and it seems possible to advantageously use this mixture with the many drugs mentioned herein, it is believed that it may also be used for similar purposes with substantially all water soluble drugs suitable for subcutaneous or intramuscular injection.

What is claimed is:

1. A new composition of matter for intramuscular or subcutaneous injection comprising a composition resembling a concentrated blood serum in appearance and consistency and having fibrinogen-like properties, including a water soluble drug for such injection, and an aqueous slowly absorbable vehicle therefor comprising gelatin, dextrose and acetic acid and serving to encapsulate the drug for a prolonged regulated release of the drug from the intramuscular or subcutaneous situs while protecting the encapsulated drug from oxidation, the gelatin and dextrose producing sufficient viscosity of the vehicle approximately equal to that of the human blood and serving to molecularly encapsulate the drug to protect the same substantially subsequent to the injection, and the acetic acid being sufficient to break down at least part of the red blood corpuscles in the tissues directly adjacent to the injection field so that the field thus produced, in cooperation with the viscous ingredients produces bulk encapsulation for the said prolonged regulated release of the drug.

2. A new composition including a water soluble drug for intramuscular or subcutaneous injection, and an absorbable aqueous vehicle therefor comprising in approximate proportions by weight

|                  | Per cent |
|------------------|----------|
| Gelatin .....    | 12 -30   |
| Dextrose .....   | 5 -12    |
| Acetic acid..... | 0.3- 1.5 |

and substantially the entire balance being water.

3. A new composition of matter comprising a water soluble drug for intramuscular or subcutaneous injection, and an aqueous, slowly absorbable gelatin containing vehicle therefor having sufficient viscosity to cause a preliminary molecular encapsulation of the drug upon injection thereof, and the second component including acetic acid sufficient to break down the adjacent red blood cells, to thus cause a prolonged regulated release of the drug.

4. In the preparation of an aqueous menstruum for a therapeutic agent to be injected intramuscularly or subcutaneously, and having

a solute containing gelatin, dextrose and acetic acid in predetermined proportions which are within 12 to 30 parts gelatin, 5 to 12 parts dextrose and .3 to 1.5 parts acetic acid, and wherein measured quantities of said ingredients are preselected in said predetermined proportions, and a quantity of water is preselected insufficient to dilute the menstruum to less than 12% to 30% gelatin, 5% to 12% dextrose and .3% to 1.5% acetic acid, the steps which comprise dissolving the gelatin in distilled water, subjecting the solution to vacuum to draw off air bubbles, allowing it to cool and congeal, reliquifying and re-evacuating, then dissolving the dextrose and the acetic acid in the gelatin solution and boiling the mixture in a vacuum.

5. The method which includes the preparation of the menstruum of claim 4, cooling the menstruum under negative pressure, reliquifying, then when the menstruum is liquified and under negative pressure adding an injectible therapeutic agent and water to bring the percentage range to 12% to 30% gelatin, 5% to 12% dextrose and .3% to 1.5% acetic acid, and sealing the preparation in ampules.

6. A concentrate for the menstruum or vehicle for water soluble therapeutic agents adapted for intramuscular or subcutaneous injection, said concentrate comprising water and a solute consisting of 12-30 parts gelatin, 5-12 parts dextrose and .3-1.5 parts acetic acid such that on further dilution a menstruum or vehicle having 12% to 30% gelatin, 5% to 12% dextrose and .3% to 1.5% acetic acid may be obtained.

7. In the bulk manufacture of therapeutic preparations for intramuscular or subcutaneous injection, the method which comprises dissolving

gelatin in sterile warmed distilled water, then adding to the gelatin solution dextrose and acetic acid, then diluting, aging and testing the solution, there being 12 to 30 parts gelatin, 5 to 12 parts dextrose, .3 to 1.5 parts acetic acid in said solution, then dissolving in the solution when at a temperature approximately 100° F. a water soluble injectible therapeutic agent and diluting the solution to have a composition containing 12% to 30% gelatin, 5% to 12% dextrose and .3% to 1.5% acetic acid.

8. The method of making a therapeutic preparation for intramuscular or subcutaneous injection in the treatment of a patient, which comprises dissolving gelatin in sterile warmed distilled water, then adding to the gelatin solution dextrose and acetic acid, then diluting, aging and testing the solution, there being 12 to 30 parts gelatin, 5 to 12 parts dextrose, .3 to 1.5 parts acetic acid in said solution, then dissolving in the solution when at a temperature approximately 100° F. a water soluble injectible therapeutic agent and diluting the solution to have a pH compatible with body tissue and containing 12% to 30% gelatin, 5% to 12% dextrose and .3% to 1.5% acetic acid plus the therapeutic agent, and placing the preparation in sealed ampules.

WINIFRED M. PITKIN,

*Administratrix of the Estate of George Philo Pitkin, Deceased.*

#### REFERENCES CITED

The following references are of record in the file of this patent:

Spain: *Journal of Allergy*, vol. 10, pages 209 to 214 (1939).