AQUOUS POST-SURGICAL INJECTION BY INFILTRATION WITH A LOCAL ANESTHETIC, A SUBSTANTIALLY WATER-INSOLUBLE LOCAL ANTI-INFLAMMATORY GLUCOCORTICOID, AND AN ANTIBIOTIC

Joel P. Smith, 567 C Doctors Blvd., 490 Peachtree St. NE., Atlanta, Ga., 30308

No Drawing. Filed Oct. 8, 1965, Ser. No. 494,236

5 Claims. (Cl. 167—52)

This application is a continuation-in-part of application Ser. No. 215,284, filed Aug. 7, 1962, now abandoned.

This invention relates to therapeutic compositions and processes of administration thereof and, more particularly, to therapeutic compositions consisting essentially of a substantially water-insoluble anti-inflammatory glucocorticoid, a water-soluble, injectable local anesthetic and a penicillin compound and to processes of administering said compositions to human subjects.

The post-operative period incidental to local surgical intervention in human subjects is frequently accompanied by bodily reactions of both a local and systemic nature. An ideal composition for the treatment of these bodily reactions would be one that combats most, if not all, of the said bodily reactions and, additionally, renders unnecessary repeated treatment of the subject; that is, the ideal composition would be one that provides relief and, moreover, has prolonged therapeutic effect for a period of several days, thereby obviating repeated treatment. Such a composition has not been provided prior to that of the instant invention.

Illustrative surgical interventions which give rise to the said bodily reactions are the excision of cysts, boils, carbuncles, hereditary moles, and the like; the removal of foreign bodies in the subcutaneous area of the tissue; the excision of polyps and growths; the surgical removal of warts; and the intervention techniques known as tonsillectomy and adenotonsillectomy.

Other areas of local treatment wherein the compositions are advantageously beneficial are, for example, blocking injection of peripheral nerves and intrasynovial injection.

The compositions and processes of the invention have provided beneficial, unexpected prolonged action, especially in the treatment of the reactions accompanying tonsillectomy and adenotonsillectomy.

The invention provides sterile therapeutic preparations suited for use by the infiltration technique, consisting essentially of a sterile, substantially water-insoluble, local anti-inflammatory glucocorticoid; a sterile, water-soluble, injectable local anesthetic; and a sterile, repository-type penicillin compound. The compositions must be sterile; and the process of administration must be carried out under sterile conditions, for the compositions are injected by infiltration into the local area subjected to the surgical intervention.

In accordance with the particular physical form of the embodiment of the invention, the compositions are compounded under sterile conditions as sterile, substantially dry combinations adapted for aqueous suspension and subsequent injection by infiltration, and as sterile therapeutic suspensions adapted for the said injection by infiltration. The latter physical forms of the inventive composition include a sterile aqueous carrée adapted for injection by infiltration.

The compositions provide beneficial and unexpectedly prolonged relief of the bodily reactions associated with the local treatment; for example, by combatting pain and edema in the area, by reducing the possibility of secondary infection and by controlling such infection if it does occur, and, especially in the case of tonsillectomy and adenotonsillectomy, by providing a speedier return to a nonrestricted intake of solid and fluid food. The latter of the operative techniques are often accompanied by secondary bleeding and malodorous breath, and these bodily reactions are also effectively controlled by the compositions and processes of the invention.

As above mentioned, regardless of the physical form of the therapeutic preparation, it must be sterile. The term "substantially water-insoluble, local anti-inflammatory glucocorticoid" means those that do not readily diffuse away from the area of local infiltration; for example, the acetates of cortisone, hydrocortisone, methylprednisolone, prednisolone, the butyl acetate of prednisolone, the diacetate of triamcinolone, and the acetone of triamcinolone. The operative amount of the said glucocorticoids in the aqueous suspensions ranges from about 1 to about 8 milligrams per millilitre, preferably from about 4 to about 5 milligrams. The term "water-soluble, injectable local anesthetic" means those which are susceptible of injection into a local area without causing undue systemic effects and are sufficiently water-soluble to provide anesthetic action practically immediately after the infiltration; for example, chloroprocaine hydrochloride, benzylamine hydrochloride, lidocaine hydrochloride, mepivacaine hydrochloride, and procaine hydrochloride. The operative proportion of the local anesthetic in the inventive suspensions ranges from about 0.5 to about 3 percent by weight, preferably 1 to 2 percent. The term "repository-type penicillin compound" means those substantially water-insoluble penicillin compounds which provide prolonged activity, for example, benzathine penicillin G, chloroprocaine penicillin-O, and procaine penicillin-G.

The operative amount of the penicillin compound in the suspensions is from about 150,000 to about 300,000 units per millilitre, preferably 200,000 units. The term "sterile aqueous carrier adapted for injection by infiltration" means a liquid aqueous carrier, for example, water for injection, which, as above stated, must be sterile and preferably contains a non-toxic suspending agent, for example, polyethylene glycol 4000, polyvinylpyrrolidone and polysorbate 80; a non-toxic isotonic agent, for example, sodium chloride, dextrose, and the like; and a preservative, for example, methylparaben and propylparaben, and the like.

It has been found that a small particle size of no more than about 20 microns is preferred for the water-insoluble components of the preparations, whether the preparation is in the form of the dry, sterile therapeutic preparation adapted for aqueous suspension or in the form of the sterile aqueous suspension. Such a particle size is obtained by micromization techniques.

As above stated, the therapeutic suspensions are administered by infiltration into the area of the local surgical intervention; for example, into each tonsillar fossa in tonsillectomy and adenotonsillectomy. Depending upon the size of the fossa, 3 to 4 millilitres are injected into this highly vascular area of mucous membrane. Upon administration in this manner, unexpectedly prolonged beneficial effects lasting from about 6 to 10 days are provided, and the period of restricted intake of food and fluid is reduced.

For blocking of peripheral nerves and intrasynovial injection, the dose is from 1 to 3 millilitres.

Water-soluble penicillin compounds can be included in the inventive compositions, for example, sodium penicillin G and sodium penicillin O.

The following examples describe the manner and process of making and using the invention and set forth the best mode contemplated by the inventor of carrying out his invention but are not to be construed as limiting.
Example 1.—Substantially dry, sterile therapeutic preparation adapted for aqueous suspension

400 vials of a sterile therapeutic preparation for suspension by the addition of a sterile aqueous carrier are prepared as follows:

Gms.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine hydrochloride</td>
<td>64</td>
</tr>
<tr>
<td>2-chloroprocaine penicillin O, micronized</td>
<td>650</td>
</tr>
<tr>
<td>Methylprednisolone acetate, micronized</td>
<td>16</td>
</tr>
</tbody>
</table>

The above ingredients are mixed, placed in each of 400 sterile 10 ml. vials. The vials are plugged and heat-sealed aseptically.

For suspension and subsequent injection by infiltration, a sterile aqueous carrier, q.s. to 10 ml., is added aseptically to the contents of a vial and the whole is well mixed. Injection by infiltration of 3 ml. into the post-operative area of tonsillectomy provides prolonged relief of local pain and tissue edema.

Example 2.—Sterile, therapeutic aqueous suspension

4000 mls. of a sterile, aqueous therapeutic suspension are prepared from the following types and amounts of ingredients:

- Polyethylene glycol 4000, USP gms. 120
- Sodium chloride gms. 24
- Preservative mgs. 332
- Lidocaine hydrochloride gms. 64
- Water for injection, USP g.q.s. ad mls. 3000

The above ingredients are dissolved in a portion of the water for the injection; the solution is made up to volume with q.s. water for injection and mixed well. The whole is sterilized by passage through a bacteria-retaining filter into a sterile container.

Gms.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-chloroprocaine penicillin O, micronized</td>
<td>650</td>
</tr>
<tr>
<td>Methylprednisolone acetate, micronized</td>
<td>16</td>
</tr>
</tbody>
</table>

These two ingredients are combined and well mixed; the combination is sterilized with ethylene oxide, and the ethylene oxide is removed under vacuum. The sterilized combination is added under aseptic conditions to the sterile lidocaine hydrochloride solution, the mixture is made up to 4000 mls. with water for injection, well mixed, and filled into sterile multiple-dose containers for injectable suspensions. Each milliliter of the final suspension contains 16 mgs. of lidocaine hydrochloride, 150,000 units of the penicillin compound, and 4 mgs. of methylprednisolone acetate in a sterile aqueous carrier adapted for injection by infiltration.

The injection by infiltration of four mls. of sterile suspension into the locale of adenotonsillectomy provides prolonged relief of the post-operative bodily reactions.

Example 3.—Compartmentalized vials

Vials are prepared by dry-filling sterile lidocaine hydrochloride and sterile 2-chloroprocaine penicillin O in the required amounts into the lower compartment of a sterile two-compartment vial. A sterile center seal is provided in each vial, and the upper compartment is filled with a sterile aqueous suspension of methylprednisolone acetate in the required proportion.

Thereafter each vial is aseptically plugged and ring sealed.

At the time of use the separated components are well mixed, and three mls. of the final suspension are used for the injection by infiltration into the locale of surgical intervention.

Example 4.—Substantially dry, sterile therapeutic preparation

A preparation equivalent to that of Example 1 is prepared by substituting 64 gms. of procaine hydrochloride for the lidocaine hydrochloride, 600,000 units of procaine penicillin G for the 2-chloroprocaine penicillin O, and 16 gms. of the acetone of triamcinolone for the methylprednisolone acetate.

Example 5.—Sterile, aqueous therapeutic suspension

Suspensions equivalent to that of Example 2 are prepared by substituting the other anti-inflammatory glucocorticoids in the disclosed amounts and proportions for the methylprednisolone acetate; the other local anesthetics in the disclosed amounts and proportions for the lidocaine hydrochloride; and the other repository penicillin compounds in the required amounts and proportions for the 2-chloroprocaine penicillin O.

Example 6.—Compartmentalized vials

400 vials containing separated active components are prepared for extemporaneous mixing at the time of use of an aqueous suspension prepared therefrom.

Lower compartment:

Gm.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xylocaine hydrochloride</td>
<td>64</td>
</tr>
<tr>
<td>2-chloroprocaine penicillin-O (888 units/mg.)</td>
<td>676</td>
</tr>
</tbody>
</table>

Screen these ingredients, blend thoroughly and fill 1.85 gm. into each of 400 vials of 10 ml. capacity. Sterilize with ethylene oxide gas. Insert center seal in each vial.

Upper compartment:

Gm.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile vehicle, q.s. ad</td>
<td>25 microns</td>
</tr>
<tr>
<td>Polyethylene glycol 4000 gms.</td>
<td>4200</td>
</tr>
<tr>
<td>Sodium chloride gms.</td>
<td>120</td>
</tr>
<tr>
<td>Metyrapone pentamethinium chloride gms.</td>
<td>57.5</td>
</tr>
<tr>
<td>Water for Injection, USP g.q.s. ad mls.</td>
<td>4200</td>
</tr>
</tbody>
</table>

Fill 10.5 ml. of the methylprednisolone acetate suspension into the upper compartment of each vial. Plug and add ring seal. As required for infiltration injection, the separated contents are thoroughly mixed in the vial and withdrawn aseptically.

What is claimed is:

1. A process of combatting local and systemic bodily reactions incidental to local surgical intervention in human subjects which comprises the injection by infiltration after surgery into the surgical locale of a sterile liquid combination of an antibiotic, a substantially water-insoluble, local anti-inflammatory glucocorticoid, an injectable local anesthetic, and an aqueous carrier adapted for injection by infiltration.

2. A process of combatting local and systemic bodily reactions incidental to local surgical intervention in tonsillectomy and adenotonsillectomy in human subjects which comprises injection by infiltration into the surgical fossae of a sterile liquid combination of an antibiotic, a substantially water-insoluble, local anti-inflammatory glucocorticoid, an injectable local anesthetic, and an aqueous carrier adapted for injection by infiltration.

3. A solid therapeutic preparation adapted for aqueous suspension and subsequent injection by infiltration consisting essentially of a substantially dry, sterile long-acting combination of from about 1 mg. to about 8 mg. of a micronized, substantially water-insoluble, local anti-inflammatory glucocorticoid; from about 5 mg. to about 30 mg. of a water-soluble, injectable local anesthetic; and from about 150,000 units to about 300,000 units of a micronized, repository-type penicillin compound.

4. A sterile, aqueous therapeutic suspension for injection by infiltration consisting essentially of a long-acting combination of from about 0.4% to about 0.5% by weight of a sterile, micronized, substantially water-insoluble, local anti-inflammatory glucocorticoid; from about 1.0% to
about 2% of a water-soluble, injectable local anesthetic; from about 150,000 units to about 300,000 units per ml. of a sterile, micronized repository-type penicillin compound; and a sterile aqueous carrier adapted for injection by infiltration.

5. A sterile, aqueous therapeutic suspension for injection by infiltration consisting essentially of a long-acting combination of a sterile aqueous carrier adapted for injection by infiltration, about 4 mgs. per milliliter of sterile micronized methylprednisolone acetate, about 150,000 units per milliliter of sterile micronized chloroprocaine penicillin O, and about 1.6% w./v., of lidocaine hydrochloride.

References Cited


LEWIS GOTT, Primary Examiner.
S. K. ROSE, Assistant Examiner.