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ANDROGENIC COMPOSITION

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This invention relates to an improved method for the parenteral administration of testosterone, testosterone derivatives and other androgenic materials for therapeutic purposes.

Testosterone, testosterone derivatives and other androgenic materials have been administered parenterally for therapeutic purposes in a variety of ways. One method consists in injecting a solution of the medicament in a suitable oil such as that of corn, peanut or sesame. This method has the following chief disadvantages: (*a*) it occasionally results in an undesirable, yet natural, walling-off of the injected oil globule thus giving rise to an oil embolism which retards, or in some cases even completely inhibits, the desired physiological absorption of the medicament, and also impairs normal fluid movement through and between tissues adjacent to the site of the embolism; (*b*) the androgenic solute is comparatively easily absorbed from such a solution with the result that the physiological action is undesirably transient rather than prolonged, thus necessitating an objectionable increase in the frequency of injections required to obtain optimum therapeutic results; (*c*) the oily character of such a preparation creates a special problem with respect to the cleaning and sterilizing of hypodermic equipment.

A second method for the parenteral administration of androgenic materials consists in the implantation of a pallet of the active substance in a cavity especially prepared for receiving it by surgical means. In addition to demanding a certain amount of skill on the part of the operator, this method of administration possesses the further disadvantages: (*a*) that the patient is exposed to the risk of infection involved in the preparation of the cavity, and (*b*) that such an implant is not infrequently so thoroughly and efficiently encapsulated by one or another of nature's mechanisms of dealing with foreign insoluble bodies that the desired continuous absorption and the resultant continuous therapeusis are seriously inhibited and often completely prevented.

A third method of administering androgenic materials consists in the injection of a suspension of the medicament dispersed in a liquid in which it is comparatively insoluble. While prolonged action is sometimes secured in this manner, nevertheless the method is characterized by several disadvantages, particularly: (*a*) the precision with which the suspension must be prepared if the individual particles are to be of uniform and proper size in order to permit uniform and prolonged physiological utilization, (*b*) the difficulties

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attendant the preparation of such a product with positive assurance that it is free of contamination with insoluble foreign particles, (*c*) problems associated with rendering such a product absolutely sterile by processes which will not cause a change in size of the suspended particles, and (*d*) the care which must be exercised by the technician if uniform doses are to be continuously withdrawn from multidose vials.

A fourth method of administering androgenic materials is by injecting a true solution of the medicament in a physiologically-inert, water-miscible solvent such as propylene glycol and glycerin. This method is disadvantageous in that: (*a*) greater dilution with tissue fluid is required in case quantitative precipitation of the medicament is desired, (*b*) the particles of medicament which precipitate on dilution of such solutions are not uniform in size thus making impossible uniform physiological absorption from the individual particles, and (*c*) such solutions are commonly hygroscopic in character and give rise to irritational effects on administration, presumably through their property of abstracting water from adjacent tissues.

The main object of this invention is to provide a new and novel method of administering testosterone and other androgenically active materials whereby the previously described disadvantages associated with methods of administration in current use are overcome.

In general, the novel method of administration herewith invented consists in the preparation of a solution of the androgenic material in a specially constructed vehicle, the finished solution being such that when injected, dilution with tissue fluid soon causes a practically quantitative precipitation of the testosterone or other androgenic material in macroscopically uniform particles. The specially constructed vehicle is composed of two parts: (1) a physiologically-inert, water-miscible organic solvent for the androgenic material such as propylene glycol, diluted with water if necessary to obtain optimal precipitation characteristics on further dilution with tissue fluid, and (2) a physiological-inert solute such as a polyoxyalkylene sorbitan monolaurate in an amount sufficient to regulate the precipitation characteristics of the solution so that on dilution with tissue fluid the testosterone or other androgenic material is precipitated in particles of uniform size.

By varying the concentration of the precipitation regulator in relation to the concentration of the androgenic material, the time required

for precipitation of the androgenic material when the solution is diluted can be varied within wide limits, thus making possible the preparation of products which will precipitate quickly in a limited region near the site of injection or products which will precipitate more slowly over a more extended region.

While the advantages inherent in the novel method of administration provided by this invention can be deduced from the hereinbefore given description of the disadvantages characteristic of the ordinary methods of administration in current use, nevertheless, for convenience, these advantages are specifically set forth in the following.

Because the vehicle is miscible with water and tissue fluid, products formed by the processes of this invention are free from the undesirable characteristics of oil solutions of androgenic materials. This means particularly: (*a*) freedom from any danger of oil embolism, (*b*) freedom from any effect of oil on the rate of physiological absorption, and (*c*) freedom from contamination of syringe, sterilizer and accessory equipment with difficultly removable oil or grease.

Products prepared by the processes of this invention are obviously free from the disadvantages associated with pellet implantation. Being true solutions, these products are administered by means of a hypodermic syringe thus eliminating the need for unusual skill on the part of the operator for the preparation of a pellet cavity, and thus also avoiding exposing the patient to the risk of infection associated with the preparation of such a cavity. Furthermore, the tendency toward pellet encapsulation is eliminated since the precipitated particles are relatively small in size and are distributed throughout local tissues near the site of injection.

Because they are true solutions at the time of their preparation and administration, the products prepared by the processes of this invention are free from the disadvantages common to suspension types of products. No precautions need be taken to assure uniform and proper particle size. No danger of contamination with foreign insoluble bodies exists because the products are true solutions and can be filtered by conventional processes to render them absolutely free of such foreign bodies; furthermore, by virtue of the fact that the products are true solutions, they can be subjected to the usual visual or physical methods commonly employed in the art for the detection of such foreign materials. No difficulties are encountered in the sterilization of products produced by the processes of this invention, either filtration or heat sterilization methods being adaptable for the purpose without incurring the risk of causing any undesirable change in the products. The homogeneity of the products produced by the processes of this invention automatically eliminates the need for precautions on the part of the technician in order to be certain that continuous doses withdrawn from the same multidose container provide the same quantities of active ingredient.

Products formed by the processes of this invention are superior to similar preparations consisting of a solution of the androgenic material in a pure solvent in various respects. Properly prepared, they require less dilution with tissue fluid in order to secure quantitative precipitation of the medicament. When precipitation does occur on administration, the particles so produced are uniform in size thus making for uniform physiological absorption and utilization. Finally, the specially constructed vehicle contains an amount of water sufficient to eliminate the possibility of irritational effects caused by abstraction of water from surrounding tissues due to hygroscopicity of the organic solvent.

The products of this invention and the processes by which they are produced will be apparent from the examples which follow. It is to be appreciated, however, that the materials used in describing the products formed in these examples have been selected as typical members of groups of related substances which could be employed in similar fashion. It is obvious that those who are skilled in the art of preparing parenteral medicinal products will recognize at once that other agents can function in the place of those used in the examples, but recognition of the possibility of employing substitute materials shall in no way detract from or limit the broad claims of this invention.

Instead of testosterone, other androgenic materials such as testosterone esters and androgenic substances derived from various sterols by chemical processes may be employed.

The choice of solvents is not limited to propylene glycol. Glycerin, or any other physiologically-inert, water-miscible solvent may function in its place provided that the androgenic material is sufficiently soluble in it and that said androgenic material will precipitate practically quantitatively when the solution is diluted with an equal volume of physiological saline solution or tissue fluid.

Similarly, although polyoxyalkylene sorbitan monolaurate is employed in the illustrative examples as the precipitation regulator, actually the agent to be used for this purpose can be selected from a wide variety of chemical compounds. It is well recognized that both physical and chemical precipitation reactions can often be controlled through the inclusion of an additional ingredient in the reaction mixture. Inhibiting colloids such as proteins and polysaccharides can function in this manner. So also can traces of fats, waxes and high fatty acids and their related alcohols. Many of the synthetic organic detergents, emulsifying agents, solubilizing agents, and surface active agents can also function as precipitation regulators; included among these are polyhydric alcohols and many of their derivatives such as their partial esters and their polymeric condensation products. It is thus evident that there are very many agents which can function as precipitation regulators, and any of these which are therapeutically-inert and do not otherwise confer undesirable characteristics on the product may be used in the processes of this invention.

Example No. 1

Two grams of testosterone and five-tenths of one gram of chlorobutanol, the bacteriostatic agent, are dissolved in seventy seven and one-half cubic centimeters of propylene glycol with the aid of gentle heat, precautions being taken to avoid volatilization of the chlorobutanol. After solution is complete, twenty cubic centimeters of water and two and one-half cubic centimeters of polyoxyalkylene sorbitan monolaurate are added. The mixture is agitated and warmed if necessary until solution is again complete, after which it is sterilized by filtration under pressure and transferred aseptically into sterile containers

from which it is later withdrawn for therapeutic administration.

When one cubic centimeter or more of this solution is mixed with an equal volume of physiological sodium chloride solution, blood serum or tissue fluid, there results an immediate faint opalescence due to the commencement of precipitation of testosterone. As the testosterone continues to precipitate, the mixture acquires a deep white opacity and the colloidal particles of testosterone begin to coalesce into individually discernible masses interspersed by clear vehicle. Within five minutes after mixing, eighty five per cent or more of the total testosterone contained in the original sample has precipitated in the form of macroscopically uniform particles of dimensions suitable for therapeutic purposes.

Example No. 2

This differs from Example No. 1 with respect to the per cent of precipitation regulator present. The ingredients and quantities are the same as in Example No. 1 except that the quantity of polyoxyalkylene sorbitan monolaurate is increased to five cubic centimeters and that of the propylene glycol is reduced to seventy five cubic centimeters. The compounding procedure remains the same.

When the solution of Example No. 2 is mixed with physiological sodium chloride solution, blood serum or tissue fluid, the same general phenomena are observed as described previously under Example No. 1 except that the times required for the initial and successive changes to take place are noticeably and measurably increased.

Example No. 3

This differs from the preceding examples in that the per cent of precipitation regulator is still further increased. In this instance, ten cubic centimeters of polyoxyalkylene sorbitan monolaurate and seventy cubic centimeters of propylene glycol are employed, and the testosterone, chlorobutanol and water contents are kept the same as in the preceding examples. The compounding procedure remains the same as in the preceding examples.

When the solution of Example No. 3 is mixed with physiological sodium chloride solution, blood serum or tissue fluid, the same general phenomena are observed as described under Example No. 1 except that the times required for the initial and successive changes to take place are very noticeably and measurably increased beyond those observable in Example No. 2.

Example No. 4

This example is illustrative of the versatility of the processes of this invention with respect to sterilization of the final products. In the previous examples, a thermally unstable bacteriostatic agent, namely chlorobutanol, was employed, and hence sterilization of the final product was effected by filtration. If for any reason a thermally stable bacteriostatic agent such as phenol or cresol is desired in the final product, such can also be accommodated in the processes of this invention through appropriate changes in the compounding procedure as described in the following.

The testosterone and the phenol or cresol are dissolved in the propylene glycol, and the water and polyoxyalkylene sorbitan monolaurate are added as in Example No. 1. The finished solution is then filtered and placed in the containers in which it is to be marketed. It may then be heat sterilized by any of several processes common to the industry.

I claim:

1. A clear solution for intramuscular administration in human therapy formulated to effect a substantially quantitative precipitation of its therapeutically active ingredient when injected, comprising an androgenic material selected from the group consisting of testosterone and testosterone esters, propylene glycol, water up to forty per cent, and approximately two and one-half to ten per cent of a polyoxyalkylene sorbitan fatty acid ester.

2. The composition of claim 1 containing a bacteriostatic agent.

3. A clear solution for intramuscular administration in human therapy formulated to effect a substantially quantitative precipitation of its therapeutically active ingredient when injected, consisting of two grams of testosterone, one-half gram of chlorobutanol, seventy seven and one-half cubic centimeters of propylene glycol, twenty cubic centimeters of water, and two and one-half cubic centimeters of polyoxyalkylene sorbitan monolaurate.

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