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SOLUBLE CORTISONE AND HYDROXYCORTISONE COMPOSITIONS

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The object of the invention is to provide solutions of the adrenosteroidal compounds cortisone acetate, cortisone base, hydroxycortisone acetate and hydroxycortisone base suitable for intravenous injection.

These products comprise true steroid hormones having certain characteristics that make them of great and in many ways unparalleled value in the treatment of numerous diseases, such for example as rheumatoid arthritis even in advanced form, acute rheumatic fever, acute disseminated lupus erythematosus, psoriatic arthritis, dermatologic conditions, sarcoidosis, berylliosis, bursitis, nephrotic syndrome and inflammatory eye diseases, and it has long been theorized that they might reasonably be expected to relieve if not actually cure these and other conditions and diseases more promptly if they could be prepared in soluble form, in order that they could be administered intravenously, as the most efficacious of all methods.

To understand the great value of the present discovery, certain fundamental principles of medicine must be appreciated and borne in mind. First, it is thoroughly established and widely recognized, that pharmaceutical products attain a much higher degree of effectiveness and resultingly enhanced therapeutic value in a substantially shortened period, when administered intravenously, as compared with intramuscular and subcutaneous injections and oral administration, in the descending scale of values.

More specifically, the effect of a pharmaceutical product administered intravenously can be expected within one minute or so after injection, while the entire quantity is potentially effective by direct entrance into the blood stream, whereas with intramuscular and subcutaneous injections only a part of the quantity administered reaches the blood stream, and the effect of the same is not felt for a half hour or thereabouts afterwards, and with oral administration only a small part of the product ultimately reaches the blood stream, after an average delay of from four to six hours in most cases.

It is also an elementary fact that solid particles, no matter how minutely subdivided, cannot be safely injected into the blood stream, and especially if they are not soluble therein, which means that at best they would have to be water-soluble, as well as of exceedingly small and perhaps of colloidal size, or otherwise soluble in a solvent that is itself soluble in the bloodstream. Finally, cortisone being a true steroid hormone has from the first been known to be incapable of being brought into aqueous solution and soluble only in oil, which it is well known is immiscible with the predominately aqueous fluid of the blood stream, and consequently cannot be injected therein without probably untoward results, depending upon the quantity used and even at that without conceivable benefit. Consequently, when it was introduced in medicine, it was featured as a suspension of the insoluble particles in water, and therefore recommended for intramuscular injection only.

More specifically, therefore, a further object was to dis-

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cover if possible some solvent, or group of solvents, in which cortisone would dissolve, and which would insure the desired prompt effectiveness with no dangerous or even undesirable results, realizing that in view of the unprecedented success of cortisone in certain fields, even when administered by intramuscular injection, and the great amount of research that has unquestionably been carried on by laboratories and personnel representing immense financial investments, a vast range of solvents of all kinds and types must certainly have been thoroughly explored, without producing a safely administrable product, as far as has been reported.

Accordingly, in attacking the problem all solvents having oil characteristics were eliminated from consideration at the start, and likewise all those having clearly toxic characteristics were rejected. This left a few that might or might not lead to the desired solution of the problem, which required delicate and painstaking tests from every angle, including the evaluation of relatively very small differences of solubility between solvents of the same chemical groups, coupled with their respective chemical, physical and potential therapeutic characteristics, and finally testing of the most promising solutions first with animals and then clinically.

With these facts as background, many classes or solvents were considered, most of which had to be rejected as incapable of dissolving cortisone acetate, or as potentially unsafe, or as incompatible for physiological reasons, until the field narrowed down to certain of the glycols, and then involved the checking of the results thus obtained with the same glycols as solvents of the derivative hydroxycortisone, initially known as Compound F, the original cortisone acetate having been initially known as Compound E by its discoverer, Dr. Edward C. Kendall of the Mayo Clinic.

After extensive consideration, a group of solvents was found, comprising (1) propyleneglycol, (2) hexenylglycol, (3) octyleneglycol, (4) ethyleneglycol monoethyl ether and (5) polyethyleneglycol #400. Due to its known toxicity, ethyleneglycol was not included in the study of the subject, but by contrast butyleneglycol, amyleneglycol and heptylglycol would have been tested had they been available, as there is every reason to believe from their known characteristics that they would also function satisfactorily, in view of the success obtained in varying degrees with those first mentioned. (1) Propyleneglycol and (2) hexenylglycol have a very low degree of toxicity and so are perfectly safe to use.

Throughout extensive experiments it was determined that (1) propyleneglycol is a very poor solvent for cortisone acetate. Hot propyleneglycol solution of cortisone acetate, containing 25 milligrams per cubic centimeter, will precipitate on cooling. Likewise, a hot solution of propyleneglycol containing 10 mgm. per cc., and containing 5 mgm. per cc. of cortisone acetate will precipitate upon cooling. Therefore, we were forced to the conclusion that propyleneglycol for all practical purposes is not to be considered a suitable solvent for cortisone acetate.

The remaining four solvents studied, namely (2) hexenylglycol, (3) octyleneglycol, (4) ethyleneglycol monoethyl ether and (5) polyethyleneglycol #400, were found to dissolve cortisone acetate when heated, and upon cooling retain approximately 10 mgm. of the latter per cc. in solution, or a strength of about 1%. This is suitable for intravenous injection and has been proved highly successful, as hereinafter described.

Hexenylglycol is apparently the least toxic of the solvents enumerated, and accordingly was the first tested both upon animals and clinically. All of the glycols possess a marked degree of viscosity. In order to decrease this viscosity, an appreciable proportion of water was included. Many different proportions were tried,

and as representative of them, and as being illustrative of the best results obtained, 80% hexenylglycol was mixed with 20% of water, in which solution 8 mgm. cortisone acetate was permanently held in solution, representing a strength of approximately 0.8%. Use of larger proportions of water causes a precipitation of the cortisone acetate.

As an initial step towards determining the efficacy of this solution, experiments with rabbits established its low toxicity and complete safety. The solution was then tried clinically with numerous persons suffering from arthritis and other conditions where cortisone acetate was indicated, and in every instance the results were reported as excellent. The response to the cortisone acetate was immediate, and in fact produced even better results than had been anticipated or were reasonably predictable. The dosage varied between 0.5 and 1.0 cc., or from 4 to 8 mgm. cortisone acetate.

Of further interest and entirely unexpected was learning the fact that the hexenylglycol solution possesses bacteriostatic properties, which while a secondary effect contributed to the overall beneficial results in all of the cases studied.

Also included in the study of the broad subject was the degree of solubility of hydroxycortisone, which was initially known as Compound F, whereas cortisone itself was initially identified as Compound E. Hydroxycortisone acetate, or Compound F, has been found by the medical profession to be effective when given orally, and also effective when injected directly into affected joints; but it is definitely ineffective if given intramuscularly or subcutaneously; and the suspension of said hydroxycortisone acetate can not under any conditions be given intravenously. By contrast, the solubility of hydroxycortisone acetate in the various glycols makes it possible to inject the same intravenously, which fact opens up new therapeutic possibilities such as have already been successfully demonstrated and fully established.

It was most encouraging to learn from our studies that hydroxycortisone is soluble to a higher degree in the glycols than is cortisone. For example, whereas cortisone acetate and base have a relatively low degree of solubility of only about 1 mgm. per cc. or 0.1% in propyleneglycol, it has been found that hydroxycortisone acetate and base possess a solubility of approximately 10 mgm. in the same solvent, or about 1.0%. In hexenylglycol the solubility of hydroxycortisone acetate and base is even greater, being approximately 16.6 mgm. per cc., or about 1.66%. Thus, hexenylglycol dissolves more hydroxycortisone acetate (1.66%) than it does cortisone acetate (1.0%). Likewise, the other glycols, namely, (3) octyleneglycol, (4) ethyleneglycol monoethylether and (5) polyethyleneglycol #400, dissolve considerably more of the hydroxycortisone acetate than of the Cortisone acetate.

With regard to the free base Cortisone, it was found, contrary to expectations, that propyleneglycol is an excellent solvent, by comparison with the fact that Cortisone acetate is but barely soluble therein. In fact, the free base cortisone has a solubility of approximately 20 mgm. per cc., or about 2.0% therein. Likewise, each

of the other solvents in this group, namely, (2) hexenylglycol, (3) octyleneglycol, (4) ethyleneglycol monoether and (5) polyethyleneglycol #400, dissolve free cortisone base to the extent of approximately 16.6 mgm. per cc. or approximately 1.66%.

Hydroxycortisone cannot be given in suspension intramuscularly, but it has been established by Dr. Joseph E. Hollander of the University of Pennsylvania Hospital that hydroxycortisone acetate when injected directly into the knee, or in fact any of the other potentially arthritic joints, exerts a beneficial action. Carrying this fact still further it has been found by numerous clinical tests, that the above mentioned solutions of hydroxycortisone acetate can similarly be administered both intravenously and into the joints direct with even greater and more prompt results than have heretofore been obtainable.

From this research work, it has been definitely established that for the first time since the discovery of cortisone acetate and hydroxycortisone acetate, they can be administered intravenously with entire safety and immediate improvement upon the part of the patient. However, the solubility of cortisone acetate and its base and hydroxycortisone acetate and its base has long been recognized as being greatly to be desired in a carrier solvent readily miscible with the fluids of the blood stream. The desired end was to give the solutions intravenously, but it was only by extended experiments and trial and rejection of many normal solvents not herein enumerated, and both animal and clinical tests, that the solutions herein mentioned were discovered and established as being both completely safe and immediately effective.

Having thus described our invention, what we claim and desire to protect by Letters Patent of the United States is:

1. A pharmaceutical product adapted for intravenous injection, comprising a clear solution of steroid hormones of the adrenal gland selected from the group which consists in cortisone, cortisone acetate, hydroxycortisone and hydroxycortisone acetate, dissolved in hexenylglycol.

2. A pharmaceutical product adapted for intravenous injection essentially comprising a clear solution of cortisone acetate containing about 0.8% of cortisone acetate, about 80% hexenyl glycol, and about 20% water.

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