

[54] TREATMENT OF MENTAL DEPRESSION

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[56] References Cited**UNITED STATES PATENTS**

3,361,773 1/1968 Wieckert..... 260/239.55 R

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[57] ABSTRACT

Mesterolone and its 17-esters possess neuropsychotropic activity and are administered to persons in a mentally depressed state to treat the depression.

11 Claims, No Drawings

TREATMENT OF MENTAL DEPRESSION

BACKGROUND OF THE INVENTION

This invention relates to medicinal agents comprising mesterolone and the 17-esters thereof and to their use.

Mesterolone (1α -methyl-5 α -androstane-17 β -ol-3-one) and its esters are known, for example, from U.S. Pat. No. 3,361,773.

Several steroids are known to exert a depressant effect on the central nervous system and possess hypnotic and/or anesthetic effects. These steroids are not useful as psychotropic drugs because, for example, they produce a marked depression of the central nervous system.

It is known that it is possible, in case of a lack of steroidal sexual body hormones, e.g., androgen deficiency, to eliminate also the psychic disturbances connected with the deficiency by the administration of endocrin-active steroids.

Testosterone was reported to delay a drop in functional capacity in certain psychological testing processes upon infusion into healthy persons (W. Vogel et al., *Electroenceph. Clin. Neurophysiol.* 1971, 400). However, these effects have no significance for the utilization according to this invention, either, since testosterone shows such effect only when administered as an alcoholic infusion. Additionally, testosterone leads, due to its gonadotropin-inhibiting activity, to atrophy of the testes and a reduction in the body androgens. Androgens having an improved oral effectiveness, such as methyltestosterone, can moreover lead to serious liver damage.

It is known that psychopharmacological agents with antidepressant effectiveness contain, as the active components, the so-called tricyclic antidepressants, such as amitriptyline, imipramine, and desipramine, and monoamine oxidase inhibitors, such as nialamide and pargyline, as well as stimulants of the amphetamine type. These active agents have in common that they possess a high toxicity. Furthermore, they have the disadvantage that the antidepressant effect occurs only after weeks of administration. These disadvantages represent a high risk, especially in case of suicide-prone persons. Furthermore, these effective agents show a number of side effects. Particularly undesired side effects of the tricyclic antidepressants are neurological and vegetative symptoms, such as, for example, visual disturbances, heart rhythm disturbances, dry mouth, consciousness changes, as well as, in some instances, dangerous alterations of the blood picture. Undesirable side effects of the monoamine oxidase inhibitors are, in particular, liver damage and dangerous hypertonic crises upon the ingestion of tyramine-containing foods. In case of amphetamines, the strong central-stimulating and dependency-forming effect of these substances has led to the result that for all practical purposes, they are no longer used as antidepressants.

It has now been found that mesterolone and its esters exhibit a psychostimulating effect at lower doses and a pronounced antidepressant effect at higher doses. This result has been obtained for the first time with a substance having a steroid structure.

SUMMARY OF THE INVENTION

According to this invention, mesterolone or a 17-ester thereof is administered to a patient in a mentally depressed state in an amount effective to evoke at least

one of a psychostimulating and an antidepressant effect.

DETAILED DISCUSSION

Mesterolone and its 17-esters exhibit neuropsychotropic effects, especially antidepressant, mood-elevating and efficiency-raising properties. At lower dosages, e.g., about 0.1–10 mg. per dose, they evoke a psychostimulating effect and at higher dosages, e.g., about 25–300 mg. per dose, an antidepressant effect.

The preferred 17-esters of mesterolone are esters of hydrocarbon carboxylic acids of 1–8 carbon atoms, preferably 2–8 carbon atoms, e.g., a monobasic alkanic acid, e.g., formic, acetic, propionic, butyric, isobutyric, α -ethylbutyric, valeric, isovaleric, α -ethylvaleric, trimethylacetic, 2-methylbutyric, 3-ethylbutyric, hexanoic, diethylacetic, triethylacetic, enanthic, octanoic, a cyclic acid, preferably a cycloaliphatic acid, e.g., cyclopropylideneacetic, cyclobutylcarboxylic, cyclopentylcarboxylic, cyclopentylacetic, β -cyclopentylpropionic, cyclohexylcarboxylic, cyclohexylacetic, a carbocyclic aryl or an alkaryl acid, e.g., benzoic, 2-, 3- or 4-methylbenzoic acid.

A preferred class of acyl groups are those of straight or branched chain monobasic alkanic acids, preferably 2–8 carbon atoms, e.g., acetyl, propionyl, butyryl, isobutyryl, of which acetyl is most preferred.

Since the exact chemical nature of the acyl radical of the 17-ester group is not critical, as long as it is not physiologically toxic and it can be formed on mesterolone 17-hydroxy group, contemplated equivalents of the preferred esters described above, insofar as they can be formed, are those formed with other aliphatic and aromatic unsubstituted and substituted and monobasic, dibasic and polybasic carboxylic acid, saturated or unsaturated aliphatic, araliphatic and aromatic carboxylic acids containing up to 18 and preferably up to 8 carbon atoms, e.g., undecylic, palmitic, β -cyclohexylpropionic acid, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethylbenzoic, ethylbenzoic, 2,4,6-trimethylbenzoic, cinnamic, naphthoic, 3-methyl- α -naphthoic, β -phenylpropionic, diphenylacetic, biphenylacetic or α -naphthylacetic acid, or a dibasic alkanic acid, e.g., oxalic, maleic, fumaric, succinic, malonic, glutaric, α -methylglutaric, β -methylglutaric, β,β -dimethylglutaric, adipic, pimelic and suberic acid, a dibasic aryl acid, especially those capable of forming a cyclic anhydride, e.g., phthalic acid, or a carbamic acid, e.g., carbamic acid, phenylcarbamic, *n*-butylcarbamic, dimethylcarbamic, diethylcarbamic and allophanic acid; or of a heterocyclic acid, e.g., β -furylcarboxylic pyrrolecarboxylic, β -pyrrolidylpropionic, *N*-methylpyrrolidyl-2-carboxylic, α -picolinic, nicotinic, indole-2-carboxylic, 6-hydroxylindolyl-3-acetic and *N*-methylmorpholyl-2-carboxylic and pyrrolyl-2-carboxylic acid, or a sulfonic acid of 1–18, preferably 1–12, carbon atoms, including alkanesulfonic, e.g., methane- and ethanesulfonic, and aryl sulfonic, e.g., benzene- and *p*-toluenesulfonic acid.

Such contemplated equivalents can also be esters with an acid containing one, two or more simple substituents in the molecule, e.g., hydroxy, halo, alkoxy, acyloxy, sulfonyloxy, amido, sulfato, nitro, mercapto and cyano, in the molecule, e.g., glycolic, lactic, citric, tartaric, *d*-maleic, *d*-glyceric, mannoic, gluconic and salicylic acid; of an amino acid, e.g., glycine, aminopropionic, diglycollamic, triglycollamic, methylglycine,

dimethylglycine, diethylglycine, para-aminosalicylic, paraaminobenzoic, ethylmercaptoacetic, benzylmercaptoacetic, chloroacetic, fluoroacetic, trichloroacetic, trifluoroacetic, thioglycolic, m-nitrobenzoic, 2,3,4-trimethoxybenzoic, phenoxyacetic and α -naphthoxyacetic acid.

Mesterolone and 17-esters thereof were tested on humans in several, respectively independent, placebo-controlled double blind experiments by quantitative pharmaco-electroencephalography (CEEG) and by the method of evoked potentials (EP). The effects and side effects were also recorded by means of various rating scales, for example for neurological and psychosomatic symptom spectra, by self-rating scales for sedation, fear and depression, as well as by interviews with physicians. In clinical tests, the effect determined in the CEEG and EP was confirmed in low as well as high doses. During the clinical investigations, detailed case reports on the therapeutic success were conducted and placed into an objective form in rating scales, e.g., Hamilton Depression Scale.

In the practical application of mesterolone and the esters thereof, the desired effect occurs shortly, e.g., about 2-3 hours, after administration. This is surprising, since it is generally known from endocrine-active steroids that the effect manifests itself only after a longer treatment period. In case of mesterolone, in its conventional applications, it is known per se that the effect occurs only after weeks of treatment. Whereas, the desired psychotropic and CNS-stimulating effects of mesterolone occurs within hours after administration.

The advantage of use of medicinal agents based on mesterolone or a 17-ester thereof resides particularly in that even a huge individual oral dose, on the order of 2 g., no neurological, vegetative, or other side effects are ordinarily evoked. Therefore, a large overdose is not inevitably lethal.

Furthermore, it is also advantageous that even in case of a long-term use of mesterolone and its esters, no dependency is created, as is possible in case of the conventional antidepressants.

In its method of use aspect, this invention relates to a method for the treatment of mental depressions and disturbances in mood, behavior and functional capacity employing mesterolone or a 17-ester thereof. Among these are, in particular, endogenic, neurotic and reactive depressions, depressions of the aging, climacteric and involutional depressions, as well as the conditions related to the climacteric depressions with changes and disturbances in the affective region, waning functional power and concentration, and increased irritability, with and without a lack of body hormones.

Moreover, the medicinal agents of this invention are also suitable for the treatment of weaknesses of concentration and memory, also in persons without androgen deficiency, as well as of psychophysiological illnesses, such as a drop in general functional capacity, fatigue, loss of interest, and in case of sleep disturbances, such as loss of sleep during the night with tiredness during the day, disturbances in sexuality, such as loss of libido and potency in younger patients without steroid hormone deficiency.

The compositions of this invention are thus useful for the treatment of mental depressions generally and the amelioration of and relief from the symptoms thereof, the term "mental depression" as used herein meaning

any mental state which is abnormally depressed for that individual (as opposed to congenital-defect or trauma- or physical disease-related reduced mental capacity), including both depressed mood and mental outlook and depressed level of mental activity or function.

The term "antidepressant effect" is used in the conventional sense. It is associated with a reversal of or a reduction in the severity of a depressed mood or state of mind. Subclassification of the patients with depressions to be treated are manic depressive psychoses depressive type, neurotic depression, reactive depression as well as involutional depression, climacteric depression and depression of the old aged. The term "psychostimulating effect," as the term implies, is associated in an increase in the overall level of mental activity. It is related to patients with lack of energy, drive and desire as well as lack of concentration and memory.

In the medical practice, the drugs based on mesterolone or a 17-ester thereof according to this invention can be administered systemically, including parenterally, e.g., subcutaneously and intramuscularly, and orally. The daily dosage is 0.1 - 1000 mg. In the lower daily dosage range of 0.1 - 20 mg., a psychostimulating effect is predominant among the components of the above-mentioned spectrum of effectiveness, whereas, in the upper daily dosage range of 25 - 1000 mg., a specifically antidepressant activity can be determined in addition to the psychostimulating effect. The dosage can be administered at once or in several doses of a pharmaceutical composition containing 0.1 - 200 mg., preferably 1-50 mg., per unit dosage.

The formulation of the medicinal agents of this invention comprising mesterolone or a 17-ester thereof can be conducted in a conventional manner by processing mesterolone or a 17-ester thereof with the vehicles, diluents, flavor-ameliorating agents, etc., customary in galenic pharmacy, and converting these formulations into the desired form of application, such as, for example, tablets, dragees, capsules, solutions, etc. Suitable for injections are, in particular, oily solutions, such as, for example, solutions in sesame oil, castor oil and cottonseed oil. If desired, it is possible to add diluents or solubilizers, such as, for example, benzyl benzoate or benzyl alcohol to increase the solubility. To obtain a protracted effect, mesterolone and the 17-esters thereof can also be utilized in microencapsulated form. For oral application, especially suitable are tablets, capsules, dragees, pills, suspensions and solutions.

The desired effects of mesterolone and its 17-esters according to this invention occur not only by injection but equally well in case of oral administration, which is preferred. The amount of effective agent in the thus formulated medicinal agents is 0.1 - 200 mg., preferably 1 - 50 mg., per day in a single or in divided doses. The above-mentioned dosage range is related to oral administration. Among the parenteral administrations the intramuscular administration is preferred. If a prolonged release is desired, the mesterolone is intramuscular administered as 17-Ester, e.g., as mesterolone cypionate, in a dosage range between 10 and 500 mg per 2 weeks, preferably in a dosage of 10 to 200 respectively 50 to 500 mg per two weeks, according to the desired effect.

For oral administration divided dosages are preferred.

Dosages will be given, preferably in the morning and in the noon.

For special purposes and in depressed patients it may be given in addition to this in the evening. The intramuscular form is normally given in one dosage.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever.

EXAMPLE 1

10.0 mg. of 17 β -hydroxy-1 α -methyl-5 α -androstane-3-one (mesterolone) having a specific external surface of 20,000 cm²/g. and an average particle diameter of 7 μ is homogeneously mixed with:
36.0 mg. lactose (DAB [German Pharmacopoeial] 6; USP XVII),
66.565 mg. corn starch (USP XVII),
1.4 mg. gelatin (DAB 6; USP XVII),
0.024 mg. methyl parahydroxybenzoate (DAB 6, USP XVII),
0.011 mg. propyl parahydroxybenzoate (DAB 6, USP XVII),
4.8 mg. talc (DAB 6, USP XVII), and
1.2 mg. magnesium stearate (USP XVII),
and compressed into tablets without previous granulation, these tablets having a dividing notch and a weight of 120 mg., with a diameter of about 7 mm. and a thickness of 2.7–2.9 mm.

EXAMPLE 2

25.0 mg. of mesterolone is compressed, analogously to Example 1, into tablets having a final weight of 120 mg. with:
60.5 mg. lactose (DAB 7, USP XVII),
32.165 mg. corn starch (DAB 7, USP XVII),
2.0 mg. poly-N-vinylpyrrolidone 25,
0.024 mg. methyl parahydroxybenzoate (DAB 7, USP XVII),
0.011 mg. propyl parahydroxybenzoate (DAB 7, USP XVII), and
0.3 mg. magnesium stearate (USP XVII).

EXAMPLE 3

In order to prepare an injection solution,
20.0 mg. of mesterolone is dissolved in:
618.6 mg. benzyl benzoate (USP XVII) and
353.4 mg. castor oil (DAB 7, USP XVII);
the solution is filtered aseptically and filled into 1-ml. ampoules under sterile conditions.

EXAMPLE 4

Analogously to Example 3,
25.0 mg. of 17 β -cyclopentylpropionyloxy-1 α -methyl-5 α -androstane-3-one (mesterolone cypionate) is dissolved in:
152.3 mg. benzyl benzoate and
86.4 mg. castor oil,
and filled into 1-ml. ampoules.

EXAMPLE 5

Respectively 0.5 mg. of mesterolone (micronized, particle size 2–8 μ) is mixed homogeneously with 150 mg. of lactose (USP XVII) and filled into hard-gelatin capsules (5 \times 15 mm.).

EXAMPLE 6

Five male depressive patients in the age range of 20–25 (two patients with psychoneurotic depressive reaction, two patients with reactive depression, and one patient with bipolar depressive illness) were included in this study. Except for one, it was a first-time illness for all other patients. None, but one, was treated before with any psychotropic drugs. The one occasionally received different anxiolytics and antidepressive drugs.

With daily dosages of 25–200 mg (mean daily dosages ranged from 102–131 mg. and the total dosages from 2,440–3,150 mg.) two of the patients showed complete remission in symptomatology, two showed nearly complete remission, and one showed slight degree of remission (the length of treatment ranged from 2½–3 weeks).

EXAMPLE 7

Five male subjects in the age range of 20–23 with a diagnosis of depression (one patient with psychoneurotic depression, four patients with reactive depression) were included in this study. All patients with the exception of one had never been treated with any psychotropic drug. All patients had, in addition to typical depressive symptoms, psychomotor retardation, apathy, lack of energy and drive.

With daily dosages of 2–6 mg (mean daily dosage ranged from 3.7–4.2 mg and total dosages from 91–101 mg), three of the patients showed complete remission in depressive symptomatology and two of the patients almost complete remission. The length of the treatment was 24 days.

The preceding examples can be repeated with similar success by substituting the generically and specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A method for the treatment of mental depression in an affected person which comprises administering systemically to the affected person an amount of mesterolone or a 17-ester thereof with a hydrocarboxylic acid of 1–8 carbon atoms effective to evoke at least one of a psychostimulating and an antidepressant effect.
2. A method according to claim 1 wherein mesterolone is administered.
3. A method according to claim 2 wherein the mesterolone is administered orally.
4. A method according to claim 1 wherein mesterolone cypionate is administered.
5. A method according to claim 4 wherein the mesterolone cypionate is administered parenterally.
6. A method according to claim 1 wherein the mental alteration is a depressed mood.
7. A method according to claim 6 wherein the amount administered is 25–1,000 mg. daily, for oral administration.

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8. A method according to claim 6 wherein the amount administered is 50-500 mg per two weeks, for parenteral administration.

9. A method according to claim 1 wherein the mental alteration is reduced mental activity.

10. A method according to claim 1 wherein the

amount administered is 0.1 - 20 mg. daily, for oral administration.

11. A method according to claim 1 wherein the amount administered is 10 - 200 mg per two weeks, for parenteral administration.

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