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TREATMENT OF MENTAL DISTURBANCES BY CHEMOTHERAPEUTIC MEANS

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This invention relates to the treatment of mental disturbances by chemotherapeutic means. More particularly, it relates to a new method of treating certain anxiety states and similar mental tensions by chemical means and a composition dosage form.

Mental disorders comprising the milder forms such as anxieties, hallucinations, and hyperactivity, as well as the severe states of manic depression and schizophrenia, are disturbances of the mind which only recently have been attacked by chemical means. In the last few years, a number of new drugs have been introduced to relieve the tension by which most of these disturbances are caused. These drugs, commonly called tranquilizers, are usually quite acceptable for certain types of disturbances, but in general, have very little effect on the severely disturbed mental patients. Furthermore, such tranquilizers very often cause objectionable signs and symptoms in the patient such as depressions, disinterest in the surroundings, retreat from reality, and withdrawal from activity.

A new method has now been found which, like the tranquilizers, relieves anxiety states and nervous disorders, but in contrast to the tranquilizers, has a calming effect without causing mental depressions. This new effect is called a "normalizing effect."

The new treatment consists in administering to a mentally disturbed subject, in dosage form, 4-propylpyridine or 2,4,6-trimethylpyridine, or the corresponding non-toxic, dissociable, acid addition salts thereof.

Improved behavior patterns in disturbed subjects may be produced by any dosage form, e.g., oral, intravenous, intramuscular, intraperitoneal, or subcutaneous administration of the above compound. In treatment of humans, the oral administration route is preferred due to its simplicity, whereas in animal studies, administration by various injection routes is sometimes easier to control.

The above two alkylpyridines are, chemically speaking, relatively strong bases which may form a number of acid addition salts. The basic compounds or their non-toxic, dissociable, acid addition salts may be pressed into tablet form or they may be processed into gelatin capsules. Tablets or capsules may include other non-toxic ingredients, ordinarily used for such preparations, e.g., fillers, adjuvants, carriers, flavoring agents, coloring agents, etc. or they may include other pharmaceutically effective compounds useful in the treatment of diseases or symptoms relating to mental disturbances. In case of tablets, any form of a tablet may be selected, but a sub-coating may be desirable in certain instances for the protection of the chemicals. The solid salts of the above alkylpyridines may also be used for the various injection routes together with physiologically acceptable solvents, diluents, carriers, etc. Solution concentrations from about 50–125 mg./cc. are best suited, although somewhat higher or lower concentrations are equally acceptable.

The effective dosage for treating mental disturbances and anxieties with 4-propylpyridine, 2,4,6-trimethylpyridine, or the corresponding non-toxic, dissociable, acid addition salts thereof varies, of course, with the degree of disturbance to be treated and the route of administration selected. The normal oral dosage range is from 0.3 g./day to about 5.0 g./day in an adult human, preferably between 0.5 and 3.0 g./day, these amounts referring to the free bases. The definite amount which is actually administered will be determined by the attending physician. He will be guided by the skills of his art in prescribing an amount sufficient to obtain normalization of the subject. These amounts are very substantially below the limits dictated by the toxicity of the above alkylpyridines. In contrast to treatment involving other chemicals for relief of mental disturbances, no sedation, dizziness, impairment of motor function and coordination, or hypnosis is observed at effective dosage levels. Furthermore, the subjects so treated, remain alert, have a general feeling of improvement, and show improved appetite and sleep.

The effect of the new treatment is that of calming with relief from anxieties and hallucinations. The new treatment normalizes the severly disturbed subjects and creates normal activity patterns for those subjects disturbed by hallucinations. The restlessness and hyperactivity of the patients are relieved, thus, permitting integration into normal life or full therapeutic programs.

These effects can be observed in animals by a series of tests such as initially developing mental stress by modifying previously trained habit patterns and thereafter administering the above pyridine derivatives or their non-toxic, dissociable, acid addition salts. Thus, a strain is placed on a habit pattern and is increased to a point at which certain objective signs of disquietude or other physical imbalance of the test animals can be observed and measured, and under such conditions, the new treatment method may be tried and studied.

To better illustrate the foregoing disclosure, reference is made to the following examples which are not to be considered the only applications and embodiments of the new method.

EXAMPLE 1

4-Propylpyridine

A master solution containing 5 g. of 4-propylpyridine in 100 cc. of water made under sterile conditions is used to study the acute toxicity of the compound in animals. From this master solution, a more dilute solution is made by adding sufficient water to obtain a 1% solution. Individual groups of mice are injected with this 1% solution at various dosages by intraperitoneal application. In this manner, an intraperitoneal LD_{50} of 350 mg./kg. is determined. This means that at a dosage of 350 mg./kg., half of the test animals to which this dosage is applied, survive.

The above master solution is used to determine the oral toxicity of the 4-propylpyridine in mice. The test animals are given various dosages of this 5% solution orally by forced feeding. In this manner, an oral LD_{50} of 750 mg./kg. is observed.

EXAMPLE 2

A group of rats is kept individually in activity measurement cages. These cages are constructed in such a manner that the animal's movements produce oscillations which are registered on a counter. The normal count of a healthy control rat averages about 100 oscillations in a five-minute period. After treating the rate with 5 mg./kg. of the hallucinogen N-methyl-3-piperidyl diphenylglycolate, the animals become confused and hyperactive; their oscillator count for equivalent time periods climbs from 100 to about 1000. After 15 minutes, the rats are injected with a neutral solution of 4-propylpyridine at a dose of 25 mg./kg. by intraperitoneal administration. This neutral solution is made by dissolving 5 g. of 4-propylpyridine in 100 cc. of water containing sufficient hydrochloric acid to produce a neutral solution. After 5 minutes, the confusion and hyperactivity of the rats reduces to an oscillator count of about 150, showing

the counter-effect of the 4-propylpyridine to the hallucinogen. Furthermore, the muscle tension, hyperirritability, and characteristic body movements produced by the administration of the hallucinogen are blocked by the 4-propylpyridine. The animals also seem somewhat less sensitive to outside stimuli.

EXAMPLE 3

Gelatin capsules containing 200 mg. each of the hydrochloride salt of 4-propylpyridine are made for clinical studies. One tablet each is given to a restless mental patient suffering from anxieties, and to a mental patient suffering from hallucinations and anxieties. Both patients exhibit, after a single dose, a much more normal pattern, showing a calming and quieting effect of the drug together with almost complete relief from anxities. One of the patients further comments on "having slept better than in weeks." In both patients, the effect of the normalizing drug lasts for a period of about 24 hours.

EXAMPLE 4

2,4,6-Trimethylpyridine

In the manner described in Example 1, the intraperitoneal and oral toxicity of this compound is studied by first making a 5% master solution of the 2,4,6-trimethylpyridine hydrochloride salt and diluting this solution further to a 0.5% solution. In mice, an intraperitoneal LD_{50} of about 90 mg./kg. is determined, whereas the oral LD_{50} is demonstrated to be about 900 mg./kg.

In the intraperitoneal study, no side effects are observed at levels below 50 mg./kg. and in the oral studies, no side effects are observed up to levels of about 500 mg./kg.

By replacing the above hydrochloride with the corresponding phosphate salt, substantially the same toxicity values are found, when the amounts are based on the same content of the free 2,4,6-trimethylpyridine.

By repeating the above toxicity studies with rats as test animals, both the intraperitoneal and oral LD_{50} levels are established to be higher than in mice. Rats injected intraperitoneally with 20 mg./kg. of 2,4,6-trimethylpyridine hydrochloride exhibit no autonomic changes. The effect of the injection lasts for about 3–4 hours.

EXAMPLE 5

To study possible side effects of 2,4,6-trimethylpyridine hydrochloride, some higher animals are treated with this compound. Two dogs given 200 and 300 mg./kg., respectively, of 2,4,6-trimethylpyridine hydrochloride orally show no symptoms like ataxia, emesis, mydriasis, miosis, ptosis, cyanosis, or decreased activity or respiratory rate. Another dog is treated intravenously with 10 mg./kg. of the hydrochloride salt of 2,4,6-trimethylpyridine as a 5% aqueous solution. The dog shows no symptoms except possibly some decreased inhibition and fear.

A monkey given 50 mg./kg. of 2,4,6-trimethylpyridine hydrochloride by intraperitoneal administration shows no signs of ataxia, cyanosis, and no change in activity and respiratory rate. At a dose of 200 mg./kg., the monkey shows some salivation, slight emesis, some ataxia, decreased activity and ptosis and shows definite signs of being tranquilized.

EXAMPLE 6

In the experiment described in Example 2 above, the rats are injected intraperitoneally with a neutral solution containing 25 mg./kg. of 2,4,6-trimethylpyridine 15 minutes after the application of 5 mg./kg. of N-methyl-3-piperidyl diphenylglycolate. The oscillator count in the test animals reduces from about 1000 to about 150 for an equivalent time period. The test animals also exhibit muscle relaxation and marked reduction in tension.

EXAMPLE 7

A group of four mental patients suffering from severe mental disturbances and schizophrenia, are given 175 mg. each of 2,4,6-trimethylpyridine hydrochloride in gelatin capsules. This dosage is administered three times per day for a period of two weeks. The patients show marked reduction of anxiety, decreased aggression and are observed to be much more quiet and calm. No effects are observed in the catatonic type patient in this group. None of the patients shows any toxic effects.

From the above examples, it will be seen that 4-propylpyridine and 2,4,6-trimethylpyridine have typical normalizing effects, as exhibited by the calmness produced and the relief of hallucinations in test animals and mental patients. Furthermore, the above compounds show some relaxing properties, as exhibited by the better sleep produced in the patients treated with these compounds. The compounds also reduce muscle tension and counter-act hallucinogenic agents and the behavioral changes produced by such agents.

Thus, the above alkylpyridines are of great value in the treatment of mental disturbances. For such treatment, the indicated oral dosage range for an adult human is about 0.3 g./day to about 5.0 g./day, preferably between 0.5 and 3.0 g./day, although excellent results may be obtained by the administration of a single dose of between 200 and 500 mg. to an adult human suffering from hallucinations and anxiety states.

In addition to the above basic compounds 2,4,6-trimethylpyridine and 4-propylpyridine, the corresponding non-toxic, dissociable, acid addition salts thereof are useful in the treatment of anxiety, hallucinations, hyperactivity, and mental disturbances. The above mentioned dosages remain the same where the dosages are calculated on the free bases, but increase proportionally to the molecular weights of the salts, e.g. a dose of 0.3 g. of 4-propylpyridine or 2,4,6-trimethylpyridine corresponds with a dose of 0.39 g. of the hydrochloride salt of either of these two compounds. The desirable salts of the compounds are those with the non-toxic acids, preferably those with those acids which are compatible with the body fluids, e.g., hydrochloric, sulfuric, phosphoric, succinic, tartaric, maleic, fumaric, ascorbic, citric and acetic acid as well as similar acids which possess the above limitations of being non-toxic and capable of dissociating from the basic alkylpyridines. Although all the above and similar acid addition salts are equally useful for the treatment of mental disorders and psychic disturbances in warm-blooded animals, those in which the acid is of lower molecular weight and/or is monobasic are preferred.

Others may practice the invention in any of the numerous ways which will be suggested by this disclosure to one skilled in the art. All such practice of the invention is considered to be a part thereof provided it falls within the scope of the appended claims.

We claim:

1. A method of reducing and in some cases eliminating the outward signs of hostility and paranoid tendencies evidenced by aggression, combativeness and belligerency and certain types of withdrawal and detachment engendered by hostility, without causing central nervous system depression or sedation, in mentally ill human subjects in whom the aforementioned signs are evidenced, comprising administering to said subject, in dosage form, a compound selected from the group consisting of 2,4,6-trimethylpyridine, 4-propylpyridine and the non-toxic, dissociable, acid addition salts thereof, in an amount sufficient to normalize said subject.

2. A method of reducing and in some cases eliminating the outward signs of hostility and paranoid tendencies evidenced by aggression, combativeness and belligerency and certain types of withdrawal and detachment engendered by hostility, without causing central nervous system depression or sedation, in mentally ill human sub-

jects in whom the aforementioned signs are evidenced, comprising administering orally to said human a composition containing a compound selected from the group consisting of 2,4,6-trimethylpyridine, 4-propylpyridine and the non-toxic, dissociable, acid addition salts thereof, and a non-toxic pharmaceutical carrier, said compound being administered in an amount of from about 0.3 g./day to about 5.0 g./day, said amount referring to the free base.

3. The method of claim 2 wherein said compound is 2,4,6-trimethylpyridine hydrochloride.

4. The method of claim 2 wherein said compound is 2,4,6-trimethylpyridine phosphate.

5. The method of claim 2 wherein said compound is 4-propylpyridine hydrochloride.

6. The method of claim 2 wherein said compound is 4-propylpyridine phosphate.

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