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THERAPEUTIC COMPOSITIONS OF CYANACETIC ACID HYDRAZIDE AND ACID ADDITION SALTS THEREOF, AND PROCESSES EMPLOYING THE SAME

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My invention relates to therapeutic compositions of cyanacetic acid hydrazide and acid addition salts thereof, and processes employing the same. More particularly, my invention relates to such compositions in which the active ingredient is cyanacetic acid hydrazide or an acid addition salt thereof, such as hydrochloride, hydroiodide, phosphate, sulfinate.

Having studied the pharmacological action of the hydrazide of isonicotinic acid, I have reached the conclusion that its action cannot be compared to that of nicotinic acid, as several authors have contended. I have refuted this comparison (see Tórax, Montevideo, vol. I, pages 5–16, May 1952), basing myself on the works of MacKenzie (J. Lab. and Clin. Med. 33, 1249, 1948) as well as on those of Brun and Vellier (Lyon Médical, 4–8, 1946), or Morellini and Montani (Réf. Min. Med. 37, 442, 1946) and of Jouin and Buu-Hoi (Ann. Inst. Pasteur, 72, 580, 1946).

On the contrary, I have established that the superiority of the hydrazide of isonicotinic acid must be sought for in the highly advantageous structure of the molecule of this compound, in which certain atoms are arranged and bound together according to a configuration which gives an intensive and efficacious pharmacological effect.

In fact, the properties of a substance do not only depend on the number of its atoms, but rather on their position in the molecule, on the distances separating them, on the angles formed by their valencies, all data which it is easy to determine accurately by means of to-day's refractometric techniques.

Basing myself on my above-mentioned theory, I have searched for the compounds possessing active groupings similar to those of the hydrazide of isonicotinic acid, situated at the same spatial distance and not presenting the drawbacks of the pyridine ring. I have found that the hydrazide of cyanacetic acid fulfilled the desired conditions, taking into account the distance existing between its nitrogen atom (corresponding to that of the pyridine ring of the hydrazide of isonicotinic acid) and its nitrogen atom of the hydrazinic group. The linear chain of carbon atoms that binds these two atoms replaces the pyridine ring (which only plays the part of a simple support) and situates these two atoms at the same distance as that existing in the case of the hydrazide of isonicotinic acid between the two analogous nitrogen atoms.

The clinical tests have fully confirmed my hypothesis and shown that the hydrazide of cyanacetic acid has an action similar to that of the hydrazide of isonicotinic acid while being better tolerated.

The molecular weight of the hydrazide of cyanacetic acid (99) being lower than that of the hydrazide of isonicotinic acid (137.15), a larger quantity of active functional groups is administered at even weight. Moreover, the substitution of the pyridine ring by an aliphatic chain decreases the toxicity and facilitates the diffusion of the product in the organism.

The hydrazide of cyanacetic acid has already been synthetized at the end of the last century (R. von Rothenburg: Berichte des Deutschen Chem. Gesellsch. 27, 687, 1894) but has not heretofore been the object of any therapeutic application.

The hydrazide of cyanacetic acid has proved active against the *Mycobacterium tuberculosis* in laboratory as well as clinically.

In vitro, the product inhibits the growth of the *Mycobacterium tuberculosis* in concentrations of 1×10^{-6} in Löwenstein and Youmans medium. In solution, the hydrazide of cyanacetic acid is extremely unstable and loses its activity after a short time owing to various chemical transformations. Moreover, it is very quickly destroyed under the influence of heat. It follows, as a consequence, that the values of the antibacillary activity obtained in vitro are necessarily much lower than the real abilities of the product.

The toxicity has been studied on white mice by intraperitoneal injection and "per os"; the lethal dose LD_{50} (which kills 50% of the animals) has been 283.4 mg./kg. and respectively 350 mg./kg. These doses are higher than those obtained in the case of the same tests with the hydrazide of isonicotinic acid, thus resulting in a wider tolerance margin in favor of the hydrazide of cyanacetic acid.

The therapeutic tests on animals show the efficiency of the hydrazide of cyanacetic acid against the *Mycobacterium tuberculosis* "in vivo." Batches of six guinea-pigs infected in the thigh according to the Steenken and Wolinsky technique and simultaneously treated with hydrazide of cyanacetic acid showed no tuberculous lesions after having been sacrificed at the end of 50 days. All control animals showed tuberculous lesions.

In clinic, the action of hydrazide of cyanacetic acid on patients suffering from pulmonary tuberculosis may be summarized as follows:

Improvement of subjective state, disappearance of fever, cough and expectoration, recovery of appetite, progressive and regular increase in weight, decrease or disappearance of bacilli in sputum, lowering of erythrocyte sedimentation rate, radiological improvements have been observed in certain cases. Tolerance, at therapeutic doses, is perfect, even with certain patients who do not stand the hydrazide of isonicotinic acid. Moreover, the hydrazide of cyanacetic acid is efficacious even with certain patients who have become "resistant" to hydrazide of isonicotinic acid (F. G. Valdecasas, J. A. Salva, P. Puig Muset; Medicina clinica No. 4, Tome XIX, page 275 (1952).

The hydrazide of cyanacetic acid is also active in extrapulmonary tuberculosis, such as tuberculosis of the skin, genital and urinary tuberculosis.

My invention may be applied to the treatment of tuberculosis in veterinary medicine as well as to man. the product may take the form of tablets, sterile powder, capsules or of any other way of administration by oral route. For parenteral route, the hydrazide of cyanacetic acid may take the form of sterile powder to be diluted at the time of use, or possibly in solution. In veterinary medicine, in addition to the above-mentioned forms, the product may take the form of animal feed, in which there will be not less than 1‰ (one part per thousand) of active ingredient.

The hydrazide of cyanacetic acid may be mixed with various substances in order to facilitate administration. The quantities of active product going into the various compositions may vary according to need; they may be comprised between 10 mg. and 100 mg. per dosage unit (tablet) for human medicine, and between 20 mg. and 200 mg. per dosage unit for animal medicine. The active product may be used under the form of its acid addition salts (hydrochloride, hydroiodide, phosphate, sulfinate, etc.)

The excipients used may be all those which are generally used in the preparation of pharmaceutical specialities, such, for instance, as lactose, starch, stearin, magnesium stearate, calcium carbonate, aluminum silicate, gum, etc.

Here are a few preparations that may be used in therapeutics, of which the active principle is the hydrazide of cyanacetic acid. It is well understood that I do not limit my invention to these preparations, which are only given by way of example and may be modified in taking into account the aim of the invention.

Example 1

Composition of tablet dosage for human medicine:

	G.
Hydrazide of cyanacetic acid	0.051
Lactose	0.170
Starch	0.030
Stearin	0.004

Example 2

Composition of a tablet dosage for human medicine:

	G.
Hydrazide of cyanacetic acid	0.101
Lactose	0.120
Starch	0.030
Stearin	0.004

Example 3

Composition of tablet dosage for animal medicine:

	G.
Hydrazide of cyanacetic acid	0.151
Calcium carbonate	1.200
Aluminum silicate	1.800
Starch	0.500

The method for preparing tablets in accordance with the above Examples 1 and 2 is the following:

The lactose is mixed with starch paste, then granulated by means of a 2 mm. mesh sieve and afterwards dried and screened. The other components are then added to the granule; the mass thus obtained is mechanically stirred during at least one hour and compressed into 0.255 g. tablets. Within the 24 hours which follow the compression, the tablets disintegrate in 15 to 20 seconds when put into water. Exposing the active substance to dampness or to a temperature exceeding 30° C. must be avoided.

Example 4

Preparation of ampules of hydrazide of cyanacetic acid in sterile powder for injections.

All the material which will be used for the various following manipulations must be perfectly dry and sterile.

A concentrated solution (20%) of hydrazide of cyanacetic acid in distilled water is prepared. This is filtered under vacuum through a sterilizing filter (Chamberlain bougie or porous glass G5). The filtered liquid is collected in a sterile container.

1 liter of this solution is poured, immediately after having been prepared and filtered, into 5 liters of absolute alcohol which has also been filtered by means of a bougie and kept in a sterile container. The hydrazide of cyanacetic acid precipitates. It is left at rest for two hours, in order that the product should precipitate to the maximum, then the solution is filtered through a sterilized porous glass.

The precipitate is collected and placed in a sterile crystallizer. The latter is placed in a desiccator under vacuum in the presence of phosphoric anhydride.

The hydrazide is removed from the desiccator after 48 hours and is aseptically pulverized in a sterile glass mortar. The powder is placed in a dry and sterile flask.

The quantity required for filling the ampules is taken from the flask and the filled ampules will be sealed by means of a blow-pipe or closed with a sterile rubber stopper.

All these manipulations must be performed aseptically and preferably under sterilizing rays.

What I claim is:

1. The method of combatting tuberculosis which comprises the step of administering to a human being infected with tubercle bacilli a compound selected from the group consisting of cyanacetic acid hydrazide and acid addition salts thereof.

2. The method for combatting tuberculosis which comprises the step of adminstering to a human being infected with tubercle bacilli a composition comprising not less than ten percent of a compound selected from the group of cyanacetic acid hydrazide and acid addition salts thereof as an active ingredient.

3. The method for combatting tuberculosis which comprises the step of administering to a human being infected with tubercle bacilli a composition containing as an active ingredient not less than twenty percent of a compound selected from the group consisting of cyanacetic acid hydrazide and acid addition salts thereof.

4. The method for combatting tuberculosis which comprises the step of adminstering to a human being infected with tubercle bacilli a composition containing as an active ingredient between ten milligrams and one hundred milligrams per dosage unit of a compound selected from the group consisting of cyanacetic acid hydrazide and acid addition salts thereof.

5. The method for combatting tuberculosis which comprises the step of administering to a human being infected with tubercle bacilli a composition containing as an active ingredient between twenty milligrams and two hundred milligrams per dosage unit of a compound selected from the group consisting of cyanacetic acid hydrazide and acid addition salts thereof.

6. A therapeutic composition in dosage unit form comprising between ten milligrams and one hundred milligrams per dosage unit of an active ingredient selected from the group consisting of cyanacetic acid hydrazide and acid addition salts thereof, and a solid pharmaceutical carrier.

7. A therapeutic composition according to claim 6, in which said solid pharmaceutical carrier is at least partly starch.

8. A therapeutic composition according to claim 6, in which said solid pharmaceutical carrier is at least partly lactose.

9. A therapeutic composition according to claim 6, in which said solid pharmaceutical carrier is at least partly stearin.

10. A therapeutic composition in dosage unit form comprising between twenty milligrams and two hundred milligrams per dosage unit of an active ingredient selected from the group consisting of cyanacetic acid hydrazide and acid addition salts thereof, and a solid pharmaceutical carrier.

11. A therapeutic composition according to claim 10, in which said solid pharmaceutical carrier is at least partly starch.

12. A therapeutic composition according to claim 10, in which said solid pharmaceutical carrier is at least partly lactose.

13. A therapeutic composition according to claim 10, in which said solid pharmaceutical carrier is at least partly stearin.

14. A veterinary feed for combatting tuberculosis comprising not less than one part per thousand of a compound selected from the group consisting of cyanacetic acid hydrazide and acid addition salts thereof.

15. A solid and sterile preparation in dosage unit form intended for dissolving in a suitable quantity of sterilized and buffered water in order to prepare a liquid for treating, by parenteral route, human tuberculosis, comprising between ten milligrams and one hundred milligrams per

dosage unit of a member selected from the group consisting of cyanacetic acid hydrazide and acid addition salts thereof, as an active ingredient.

16. A solid and sterile preparation in dosage unit form intended for dissolving in a suitable quantity of sterilized and buffered water in order to prepare a liquid for treating, by parenteral route, animal tuberculosis, comprising between twenty milligrams and two hundred milligrams per dosage unit of a member selected from the group consisting of cyanacetic acid hydrazide and acid addition salts thereof, as an active ingredient.

17. The new composition of matter comprising a veterinary feed admixed with a compound selected from the class consisting of cyanacetic acid hydrazide and the acid addition salts thereof.

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