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2,781,291

MAGNESIUM CHELATE OF ETHYLENEDIAMINE-TETRAACETIC ACID FOR TREATMENT OF HYPERTENSION

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This invention relates to medical preparations and their use in the treatment of high blood pressure, and has for its object the provision of medical preparations for use in the treatment of high blood pressure.

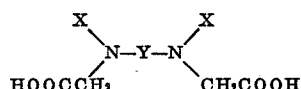
An object of the invention is to provide organo-metallic compounds which may be injected intravenously or subcutaneously to be effective in lowering the blood pressure in the human body.

More particularly the object is to provide an organo-magnesium compound which may be injected intravenously or subcutaneously or absorbed through the skin, and which will be effective in lowering the blood pressure in the human body.

A further object is to provide medical preparations containing such organo-magnesium compound suitable for injection intravenously or subcutaneously or which may be absorbable through the skin.

Other objects will be apparent as the invention is more fully hereinafter disclosed.

We have found that certain organo-metallic compounds, such as magnesium compounds, in the form of the alkali metal salts of their chelates are effective in the lowering of high blood pressure, the compounds being those which correspond to the chelates of the following fundamental structure:



wherein Y is an alkali radical which places two or three carbon atoms in the chain between the nitrogens and may be substituted with other alkyl radicals, including within the scope thereof such materials as ethylene, propylene, methylethylene and cyclohexylene, and X in the formula represents CH_2COOH or an alkali metal salt thereof or a β -hydroxy ethyl radical. Typical compounds corresponding to the above formula are ethylenediaminetetraacetic acid, mono- β -hydroxyethylethylenediaminetetraacetic acid, di- β -hydroxyethylethylenediaminediacetic acid, cyclohexylene diamine tetraacetic acid and mono- and di- β -hydroxyethyl derivatives thereof.

Since the invention is useful through the application of the magnesium chelates of compounds corresponding to the general formula indicated above, and the evaluation of the compounds is directly parallel, in order that the discussion thereof may be simplified it will be oriented about the administration of the magnesium compounds.

In accordance with these objects we have ascertained that magnesium-disodium ethylene diamine tetra acetate, which is the magnesium-chelated salt of ethylene diamine tetraacetic acid disodium salt possesses the chemical property of base exchange reaction with calcium ions contained in the blood stream thereby removing the calcium ions from the blood stream in soluble chelate combination and releasing magnesium ions into the blood stream thereby lowering the calcium ion content of the blood stream and increasing the magnesium ion concentration in the blood stream.

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Heretofore in the art, it has been recognized that in certain types of high blood pressure the calcium and magnesium ion concentration in the blood stream have opposite effects. In cases where high blood pressure is directly due to an unbalance in the Ca and Mg ratios in the blood stream resulting in an abnormal contraction in the blood vessels, the addition of magnesium ions to the blood stream substantially immediately results in a lowering of the blood pressure. As an example, certain types of high blood pressure, as in the toxemia of pregnancy, have been treated by injection of massive doses of magnesium ions in the form of the sulfate. Under such conditions a fall in the blood calcium level can be determined. The use of magnesium sulfate, however, is disadvantageous for the reason that calcium forms a sulfate of low solubility in the blood stream and the elimination of this calcium sulfate from the body is exceedingly slow and of doubtful completion.

The magnesium and calcium chelate compounds of the present invention are each soluble and the elimination of both compounds from the body in fluid excretions is complete and relatively rapid, with the result that excess amounts of either chelate cannot long remain in the system.

The great advantage of the disodium magnesium chelate compound over the magnesium sulfate in the treatment of high blood pressure is apparent from the fact that tests have shown that only one one-hundredth ($\frac{1}{100}$) of the magnesium ion dosage with magnesium sulfate is required when the magnesium chelate is used to obtain equivalent results in blood pressure fall.

The introduction of this magnesium chelate into the human system by subcutaneous or intravenous injection or by absorption through the skin has been achieved as hereinafter described. The chelate compound itself must be absolutely chemically pure and must be used in pyrogen-free isotonic solution having a pH of approximately 7.4.

The preparation of the chemically pure magnesium chelate of ethylene diamine tetraacetic acid disodium salt is best effected by dissolving the repeatedly precipitated chemically pure ethylene diamine tetraacetic acid in a pyrogen-free aqueous solution of chemically pure sodium hydroxide containing two (2) molar weights of NaOH for each molar weight of the acid. The solution of the tetraacetic acid normally will occur with agitation and gentle heating. To this solution is then added a water-soluble chemically pure magnesium salt, such as the chloride or acetate, or a basic magnesium compound, such as the oxide or hydroxide (freshly precipitated) or carbonate compound, in an amount providing one (1) molar weight of the magnesium salt or compound for each molar weight of the tetraacetic acid.

The resulting pyrogen-free solution of the magnesium ethylene diamine tetraacetic acid disodium salt then is concentrated by boiling off the excess water of solution to a desired concentration of magnesium ions per cc. of solution and the pH of the solution is adjusted to a pH within the range 7.2 to 7.4 by appropriate additions of hydrochloric, acetic or citric acid on the one hand or of sodium hydroxide on the other hand, as may be required.

In place of the sodium salts of this magnesium chelate or complex, potassium or non-toxic salts may be employed without departure from the invention and the term "sodium" as it hereinafter appears in the specification and claims is meant to include such equivalent substituents.

In the use and application of this pyrogen-free aqueous solution medically, it is essential to employ isotonic solutions of the magnesium chelate when the compound is to be injected subcutaneously or intravenously. By the term "isotonic" is meant that the solution of the salt that is injected into the body must be compatible with the

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blood stream and must not substantially change or alter the osmotic pressure of the blood stream. In general, it has been found that isotonic solutions containing glucose and this magnesium chelate, are the most satisfactory to employ. The amount of glucose present may vary widely without essential departure from the invention within the range 5 percent to 10 percent.

This isotonic solution is formed by adding a known quantity of the above described pyrogen-free solution of the magnesium chelate containing a known quantity (in milligrams) of the chelate to a pyrogen-free aqueous glucose solution containing 5 percent glucose.

As one specific example of the use and utility of the pyrogen-free isotonic solution of the magnesium chelate in the treatment of high blood pressure the following clinical tests are given:

Four normotensive patients and eight hypertensives were studied in this series. In each case blood pressure determinations were made prior to hospitalization and blood pressures were taken three to four times daily during the hospital stay. The patients were admitted one to several days prior to administration of the compound. Control blood pressure after bed rest was thus obtained. In addition, complete blood counts, including platelets, were taken. Serum calcium, phosphorus, alkaline phosphatase and total proteins, with albumin-globulin ratio were also determined. In each case the magnesium chelate dissolved in 250 cc. of five percent aqueous glucose was given in the form of an intravenous drip. The initial sterile solution of (pH 7.2 to 7.4) magnesium disodium ethylene diamine tetraacetate was prepared to contain one milligram of magnesium ion per cubic centimeter. The dose was calculated so that 10 milligrams of magnesium ion in the 250 cc. glucose solution was administered by intravenous drip in one to two hours. Blood samples were taken before and immediately after the treatment and also 24 hours later. In some patients the treatment was repeated two or more days later. While the intravenous drip was in progress blood pressure readings were made every five minutes for the first half hour and then every fifteen minutes until completion. Thereafter readings were every four hours during the time the patient was awake for the remainder of the hospital stay.

When there was a marked drop in blood pressure, the pressure was taken every minute until the flow of the drip could be controlled to the desired level. During the treatment and 24 hours after, all hypertensive patients had a feeling of increased well-being. They were relaxed. The pulse rate was taken simultaneously with every blood pressure reading. Usually a slight increase in the pulse rate was followed by bradycardia. Two patients among the normotensive controls complained of weakness, and in one this persisted 24 hours after the treatment, and then disappeared. Two patients with moderate hypertension had headache and one patient, a control with normal starting pressure, complained of a transient faintness which accomplished a rapid fall in blood pressure. The patients lost weight on an average of five pounds each during their week or so of hospital stay. The blood pressure changes were similar in all cases receiving ten or more milligrams of magnesium ion as magnesium chelate. The systolic pressure was lowered almost immediately (in two cases after a transient initial rise lasting several minutes) and continued to drop until the drip was discontinued. The fall in the systolic pressure reached as much as 80 mm. of mercury. The drop in diastolic pressure was equally definite. The fall which approached a maximum of 40 mm. of mercury occurred gradually, at times with a short latent period.

The changes in blood calcium and phosphorus were marked in some cases. Serum calcium levels were lowered from about 10 mg. percent (the normal level) to 7.4 to 8 mg. percent. Phosphorus levels were also diminished.

No significant change was observed in the blood count except in the platelets.

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Following hospitalization the blood pressure of the treated hypertensive patients was followed with readings two to three times weekly for several months. The blood pressure remained depressed for two to six weeks in most cases with a gradual return to pre-existing high levels. No toxic manifestations were observed in these cases.

On the basis of these clinical tests the following conclusions and observations have been made:

Magnesium chelate in the form of magnesium disodium ethylene diamine tetraacetate in isotonic solution can be utilized by intravenous drip to lower the blood pressure of hypertensive individuals. The dose of the compound, calculated in terms of magnesium ion, used was 10 to 15 mg. usually repeated once after several days, and given in 200 cc. of 5 percent glucose as an intravenous drip over a period of an hour and a half to two hours. In the eight hypertensive individuals reported all showed a fall of both systolic and diastolic pressures. The fall in systolic pressure reached as much as 80 mm. and the fall in diastolic as much as 40 mm. of mercury. Usually the fall in blood pressure was accompanied by bradycardia. It is believed that the magnesium chelate released magnesium ion in the process of combining with calcium since this form of chelate used has this action in vitro. This interpretation is also supported by the fall of serum calcium which follows the administration of the compound. In general, the serum calcium values fell from 1 to 3 mg. percent during the administration of the intravenous drip. The fall is transient and normal calcium values were observed in 24 hours. The depression of serum calcium values were too small to produce symptoms of hypocalcemia. The hypotensive effect persisted for days or weeks following the intravenous administration with a gradual tendency to return to pre-existing levels. The hypotensive effect, therefore, was not correlated with the hypocalcemic effect of the chelate compound. No other form of therapy was administered.

For subcutaneous administration tests have indicated that the pyrogen-free solution of the magnesium complex may be used directly when the concentration of the magnesium ion in the solution approximates one (1) milligram per cc. of solution and where the dosage employed does not exceed about 15 cc. The rate at which the magnesium complex passes into the blood stream after subcutaneous injection varies widely between individuals and the determination of the maximum concentration of the complex and the maximum dosage permissible requires careful individual control.

On the other hand, the introduction of this magnesium chelate into the blood stream by absorption through the skin appears to be readily and effectively obtained without substantial isotonic disturbance in the blood stream by mixing the pyrogen-free solution of the magnesium chelate in a water miscible ointment base common in the art and applying the mixture to the skin.

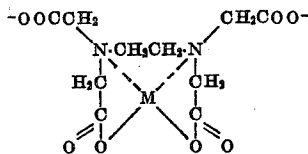
In general, it has been found best to limit the amount of the magnesium chelate thus introduced into the ointment to a low percentage, preferably within the range one percent to five percent to avoid the danger of the individual absorbing too much of the complex and to limit the skin area covered with the mixture to a few square inches, with the dosage to be repeated frequently until full relief has been obtained.

From the above disclosure it is believed apparent that the magnesium complex described is highly effective in the treatment of the high blood pressure due to a calcium magnesium unbalance in the blood stream and that due to the extreme solubility of both the magnesium and calcium chelate compounds and the ease of elimination of the chelate from the system in the body fluids, the use of the magnesium complex for this purpose in the low amounts required is advantageous.

In similar fashion the administration of magnesium chelates of any of the compounds defined may be carried out. Apparently basic to the proper functioning of the compound is the use of a chelating agent which will form

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a five-membered or six-membered ring with the alkaline earth metal chelated. Thus, represented graphically, the generic formula given above calls for the inclusion of two carbon atoms in the chain between the nitrogen atoms. The chelate compound formed with alkaline earth metals, such as magnesium which serve as a replenishment of physiological calcium, has the following structure:



wherein M represents the metal which serves to displace physiological calcium; the rest of the molecule takes up the calcium released. Apparently the five-membered ring formed is of a stability such that calcium can be replaced by magnesium and thereby eliminated from the body. A further desirable characteristic of the chelating agent is that it be of this class of non-metabolizable synthetic amino acids.

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This application is a continuation-in-part of our pending application Serial No. 216,259, now abandoned.

The foregoing description is not to be considered as limiting the invention since variations may be made without departing from the spirit or scope thereof.

What is claimed is:

1. A medical preparation consisting of a pyrogen-free aqueous solution of chemically pure disodium magnesium chelate compound of ethylenediamine tetraacetic acid having a pH within the range 7.2 to 7.4
2. The medical preparation of claim 1 in isotonic solution.
3. An isotonic pyrogen-free aqueous solution containing a known amount of the disodium magnesium chelate of ethylenediamine tetraacetic acid per milliliter, from 5 percent to 10 percent glucose, and having a pH within the range 7.2 to 7.4.

References Cited in the file of this patent

- Sollmann, "A Manual of Pharmacology," W. B. Saunders Co., Philadelphia, 1948, pp. 744-750. (Copy in P. O. S. L.)