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COMPOSITIONS AND METHOD FOR REDUCING BLOOD SUGAR CONCENTRATION

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5 Claims. (Cl. 167—65)

The invention of this application is a pharmaceutical compound for effecting a reduction in the percentage of sugar in the blood. The product is particularly useful in the treatment of diabetes but the compound is effective for its purpose when administered to persons not suffering from diabetes and is therefore useful whenever it is desired to reduce the blood sugar—for example, when the load on the kidneys must be relieved.

The great value of the application of insulin in the treatment of diabetics permitting them to live reasonably normal lives utilizing rather liberal diets cannot be overestimated.

Although the mechanism of insulin action is to a large extent unknown, a few empirical facts have been established as to its mode of operation. When insulin is injected into a normal or diabetic subject the blood sugar drops perceptibly and the glycogen content of the liver increases in the diabetic while decreasing in the normal. The effect of insulin in increasing muscle glycogen is universally recognized today. Insulin does not stimulate carbohydrate combustion but plays a role in the redistribution of glucose and the formation of muscle glycogen as well as control of liver glycogen.

The use of insulin is, however, attended with certain disadvantages. Care must be exercised in its use, for an excess will cause hypoglycemia and rally the sugar-producing factors of the adrenals and pituitary to overcome the induced shock. Since insulin effects are temporary, it is necessary to inject its solutions daily. There are certain types of diabetes where insulin alone induces only slight responses, and also occasionally side reactions occur at the site of the insulin injection. Its daily use, the care with which it must be applied, its failure at times to produce desired effects, and the fact that its use may, due to its interference with the normal metabolic cycle, produce shock.

These disadvantages are largely overcome by the use of a composition consisting of adenosine 5-monophosphoric acid and diphosphopyridine nucleotide (COI). The adenosine 5-monophosphoric acid when injected intramuscularly will increase adenosine triphosphate in the blood of a normal person at least 100% and even show a greater increase in a diabetic. It is a very efficient phosphorylating agent. However, its use alone does not cause any reduction in blood sugar and sometimes causes a slight but perceptible rise. By injecting the adenosine 5-monophosphoric acid together with the diphosphopyridine nucleotide a rapid and consistent reduction in blood sugar is effected in normals as well as diabetics. While the mechanism is not fully established, it is believed that muscular glucose is phosphorylated to glycogen and also to the triose carbohydrate forms whence the diphosphopyridine nucleotide acts to complete the metabolic cycle.

A suitable grade of diphosphopyridine nucleotide may be made by the known method described in the Jour. Biol. Chem. 138:305–9 (1941) and the adenosine

5-monophosphoric acid can be made by the method described in J. Chem. Soc. 1947; 648–51.

In the treatment of diabetes an aqueous solution containing 1 milligram of diphosphopyridine nucleotide and 20 milligrams sodium salt of adenosine 5-monophosphoric acid per milliliter is prepared. One milliliter of this composition is injected intramuscularly three or four times a week. After each injection there occurs a reduction of blood sugar of 15–40% and an apparent increase in kidney thresholds as evidenced by markedly lowered urinary excretions of sugar. Even though the blood sugar may remain fairly high the diphosphopyridine nucleotide-adenosine 5-monophosphoric acid will in the diabetic and the non-diabetic thoroughly metabolize sugar and accelerate turnover of the muscle glucose and glycogen, thus effectuating considerable relief to the kidneys in its sugar load.

In recent animal experiments rabbits were given intramuscular injections of a mixture of diphosphopyridine nucleotide and an acid salt of adenosine 5-monophosphoric acid prepared as described above. The dosage was calculated on the body weight of the animal as compared with the above stated one milliliter dose for a human adult of average weight. Doses were administered daily until the blood sugar was reduced to 20% of the concentration at the beginning of the experiments. No symptoms of convulsions were observed. For comparison a second group of rabbits were injected with five units of insulin, subcutaneously. In every case the injection was followed by convulsions and shock and more than half of the rabbits died within six hours. In no case was the blood sugar reduced to below 40% of normal.

Another group of rabbits was injected subcutaneously with five units of insulin and also were given intramuscularly injections of a mixture of diphosphopyridine nucleotide and adenosine 5-monophosphoric acid. No shock or convulsions resulted in this group of rabbits. In another group of rabbits five units of insulin were injected subcutaneously and at the first signs of convulsions the rabbits were given, by intramuscular injection, an appropriate dose of the above mentioned mixture of diphosphopyridine nucleotide and adenosine 5-monophosphoric acid which checked the development of shock.

Similar experiments were tried with appropriate doses of diphosphopyridine nucleotide alone and adenosine 5-monophosphoric acid alone. The latter was found quite effective in reducing the severity of the shock, but the results were not as good as obtained when a mixture of the two substances were used. The diphosphopyridine nucleotide used alone was not as effective as the adenosine 5-monophosphoric acid alone.

The above described mixture as administered in the stated dosage constitutes the most effective method known to me of reducing the blood sugar concentration. I have found, however, that certain other compounds are effective to a lesser degree for that purpose. For example, I have found that adenosine triphosphate may be substituted for adenosine 5-monophosphoric acid, as may also the diphosphate form of that compound. Also I have found that nicotinic acid or nicotinamide may be substituted for diphosphopyridine nucleotide. Compounds involving such substitutions when injected intramuscularly significantly reduce the blood sugar content, but not to the extent of the preferred compounds above mentioned.

The reason why shock is not induced by the administration of my improved therapeutic agents and the reason why shock induced by insulin is relieved in the manner above described is not altogether clear. It is generally accepted that the shock which frequently follows the administration of insulin is due to the fact that the nor-

mal metabolic cycle, particularly the combustion of carbohydrates, is disrupted, and it is my belief that the action of the compounds above enumerated which I have found effective in reducing blood sugar without shock does so without significantly disrupting the normal metabolic cycle. That is to say, the transfer of glycogen to the muscle cells and its oxidation continue at a rate sufficiently near normal, notwithstanding the action of the insulin, to avoid shock.

In the accompanying claims I have designated the action of these compounds in preventing shock as "maintaining the metabolic cycle."

Further research will doubtless develop other related compounds which may be substituted for those above mentioned and it will be understood that my invention is not limited to the particular compounds found to be most effective, but covers all such modifications thereof as fall within the scope of the appended claims.

I claim:

1. The method of reducing blood sugar concentration which comprises administering a therapeutic agent comprising a compound taken from the class consisting of adenosine 5-monophosphoric acid, adenosine diphosphoric acid and adenosin triphosphoric acid and a compound from the class consisting of diphosphopyridine nucleotide, nicotinic acid and nicotinamide.

2. The method of reducing blood sugar which consists in administering insulin and a compound taken from the class consisting of adenosine 5-monophosphoric acid, adenosine diphosphoric acid, adenosine triphosphoric acid and a compound taken from the class consisting of diphosphopyridine nucleotide, nicotinic acid and nicotinamide.

3. A composition of matter for the reduction of blood sugar comprising a compound from the class consisting of adenosine 5-monophosphoric acid, adenosine diphosphoric acid and adenosine triphosphoric acid and a compound from the class consisting of diphosphopyridine nucleotide, nicotinic acid and nicotinamide.

4. A composition of matter for the reduction of blood sugar comprising adenosine 5-monophosphoric acid and a compound from the class consisting of diphosphopyridine nucleotide, nicotinic acid and nicotinamide.

5. A composition of matter for the reduction of blood sugar comprising adenosine 5-monophosphoric acid and diphosphopyridine nucleotide.

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