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# DIMETHYL PHENYL PIPERAZINIUM IODIDE COMPOSITIONS AND PROCESS FOR STIMULATION OF THE AUTONOMIC GANGLION SYSTEM

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This invention relates to compositions useful for stimulating the autonomic ganglia containing as the effective ingredient 1,1-dimethyl-4-phenylpiperazinium iodide. I have discovered that this previously known compound, Chemical Abstracts 29, 4013 (1935), has the physiological property of exerting a stimulating effect on both the sympathetic and parasympathetic ganglia. This newly discovered property makes it possible to use the compound for the laboratory determination of the effectiveness of potential ganglionic blocking agents.

The autonomic ganglion system is composed of the sympathetic ganglia and the parasympathetic ganglia. Stimulation of the sympatthetic ganglia causes release of an epinephrine-like substance by the postganglionic fibers while stimulation of the parasympathetic ganglia causes release of acetyl choline by both the pre- and post-ganglionic fibers.

In many clinical conditions the normal functions of the autonomic ganglion system are impaired or stimulated and it is of great value to the practitioner to be able to ascertain whether this is due to the ganglion system itself or some other cause. In order to test the functioning of the autonomic ganglion system it is necessary to utilize some substance which will disturb in a controllable fashion the normal operation of the sympathetic and parasympathetic ganglia. It is known that nicotine is capable of stimulating both the sympathetic and parasympathetic ganglia. However, nicotine is a relatively weak stimulant and is unsatisfactory and dangerous to use clinically due to the depressive, toxic and paralyzing effects which it produces. Epinephrine and norepinephrine exert a stimulating effect upon the effector cells but they do not act on either the sympathetic or parasympathetic ganglia.

The compositions of the present invention are prepared by dissolving 1,1-dimethyl-4-phenylpiperazinium iodide in water, isotonic saline or isotonic glucose and sterilizing the resulting solutions by heat or by Zeitz filtration. It will also be appreciated that the compositions can be prepared under aseptic conditions using sterile ingredients. The solutions which are the most useful in the detection of ganglionic disorders are those containing 0.5 to 5 milligrams of the quaternary halide compound in each milliliter of the solution. These solutions are administered by the parenteral route and preferably intravenously.

The physiological effect of the compositions of the invention can be demonstrated on the sympathetic ganglia using pentobarbitalized cats and measuring the contraction of the nictating membrane caused by injection of a measured quantity of the composition. When tested in accordance with this method 200 micrograms per kg. of 1,1-dimethyl-4-phenylpiperazinium iodide give the same degree of response as 5 micrograms per kg. of



epinephrine acting through the effector cells. The effects of the 1,1-dimethyl-4-phenylpiperazinium iodide are completely blocked by the administration of 10 milligrams per kg. of the ganglionic blocking agent, triethylammonium chloride. Under these same conditions the stimulating effect of epinephrine was not blocked because it does not act upon the ganglia.

The physiological effect on the parasympathetic ganglia can be demonstrated by the increase in bladder pressure of female dogs under pentobarbital anesthesia following intravenous injection of a solution of 1,1-dimethyl-4-phenylpiperazinium iodide. In this test it only required 10 to 20 micrograms per kg. of 1,1-dimethyl-4-phenylpiperazinium iodide in order to bring about a change in bladder pressure and it was possible to block this pressure change completely by the administration of 10 milligrams per kg. of triethylammonium chloride.

The compositions of the invention exert a stimulating effect upon the ganglion-like material of the adrenal medulla and are therefore useful in determining the ability of the adrenal medulla to produce epinephrine. In utilizing the compositions for this purpose one injects a measured quantity of the ganglionic stimulating agent and measures the amount of stimulation obtained with and without a ganglionic blocking agent. The difference in the response obtained under these two conditions is a measure of the adrenal medulla's ability to produce epinephrine.

The compositions of the invention are relatively nontoxic. For example, the $LD_{50}$ of 1,1-dimethyl-4-phenylpiperazinium iodide is 27.5 milligrams per kg. in mice given intramuscularly and 1 milligram per kg. in rabbits intravenously.

The invention is illustrated by the following examples:

*Example 1*

100 milligrams of 1,1-dimethyl-4-phenylpiperazinium iodide is dissolved in 100 ml. of an isotonic salt solution containing 850 milligrams of sodium chloride. 1 ml. portions of the solution are placed in 2 ml. ampoules and the ampoules sealed. The ampouled material is sterilized by heating the ampoules in an autoclave for twenty minutes at 125° C. The material in the ampoules is assayed for its effect upon the sympathetic and parasympathetic ganglia by the methods mentioned above. Each ampoule should contain approximately one milligram per milliliter of 1,1-dimethyl-4-phenylpiperazinium iodide.

*Example 2*

50 mg. of 1,1-dimethyl-4-phenylpiperazinium iodide is dissolved in 100 ml. of distilled water. 1 ml. portions of the solution are placed in glass ampoules and the ampoules sealed. The ampouled material is sterilized by heating in a steam autoclave for fifteen minutes at fifteen pounds pressure steam. The material in the ampoules is assayed by the methods mentioned in Example 1. Each ampoule should contain 0.5 milligram of 1,1-dimethyl-4-phenylpiperazinium iodide.

What I claim is:

1. A composition for the stimulation of the sympathetic and parasympathetic ganglia comprising an aqueous solution containing 0.5 to 5 milligrams per milliliter of 1,1-dimethyl-4-phenylpiperazinium iodide.

2. A composition for the stimulation of the sympathetic and parasympathetic ganglia consisting of a sterile, aqueous, isotonic, saline solution containing 1 milligram per milliliter of 1,1-dimethyl-4-phenylpiperazinium iodide.

3. A composition for the stimulation of the sympathetic and parasympathetic ganglia consisting of a sterile, aqueous solution containing 0.5 milligram per milliliter of 1,1-dimethyl-4-phenylpiperazinium iodide.

4. The method of testing the effectiveness of ganglionic blocking agents, comprising administering to an experimental animal 1,1-dimethyl-4-phenylpiperazinium iodide



for the laboratory determination of the effectiveness of potential ganglionic blocking agents.

**References Cited in the file of this patent**

Howard: Modern Drug Encyclopedia, fifth ed. Drug Publications 1952, New York, pages 113–114.