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# DIMETHYL PHENYL PIPERIDINIUM IODIDE COMPOSITIONS FOR STIMULATION OF THE AUTONOMIC GANGLION SYSTEM

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4 Claims. (Cl. 167—84.5)

This invention relates to compositions useful for stimulating the autonomic ganglia containing as the effective ingredient 1,1-dimethyl-4-phenyl-piperidinium iodide. I have discovered that the latter compound 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 sympathetic 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-phenylpiperidinium iodide in water, isotonic saline or isotonic glucose and sterilizing the resulting solution 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-phenylpiperidinium iodide give the same degree of response as 5 micrograms per kg. of epinephrine acting through the effector cells. The effects of 1,1-dimethyl-4-phenylpiperidinium 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-phenylpiperidinium iodide. In this test it only required 10 to 20 micrograms per kg. of 1,1-dimethyl-4-phenylpiperidinium 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-phenylpiperidinium iodide is 17 milligrams per kg. in mice given intraperitoneally.

The invention is illustrated by the following examples.

*Example 1*

6 g. of 1-methyl-4-phenylpiperidine is dissolved in 100 ml. of absolute alcohol and treated with 10 g. of methyl iodide. The solution is allowed to stand for one hour at room temperature and is then concentrated to approximately 75 ml. in a steam bath. The residue is diluted with ether and chilled. The crystals are filtered off and recrystallized in a mixture of ethanol and ether. The product is 1,1-dimethyl-4-phenylpiperidinium iodide having a melting point of 167–169° C.

100 mg. of 1,1-dimethyl-4-phenylpiperidinium iodide is dissolved in 100 ml. of isotonic salt solution which contains a total of 850 mg. of sodium chloride. 1 ml. portions of the solution are placed in 2 ml. glass ampoules and the ampoules sealed. The ampouled material is sterilized in a steam autoclave for twenty minutes at 115 to 125° C. The material in the ampoules is assayed by determining its effect on the sympathetic and parasympathetic ganglia using the methods described above. Each ampoule should contain approximately 1 milligram of 1,1-dimethyl-4-phenylpiperidinium iodide.

*Example 2*

50 milligrams of 1,1-dimethyl-4-phenylpiperidinium iodide is dissolved in 100 ml. of distilled water. One milliliter portions of the solutions 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 above. Each ampoule should contain 0.5 milligram of 1,1-dimethyl-4-phenylpiperidinium iodide.

This application is a division of my co-pending application Serial No. 318,761 filed November 4, 1952, now U.S. Patent No. 2,778,772.

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-phenylpiperidinium 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 - phenylpiperidinium iodide.

3. A composition for the simulation of the sympathetic

and parasympathetic ganglia consisting of a sterile, aqueous solution containing 0.5 milligram per milliliter of 1,1-dimethyl-4-phenylpiperidinium iodide.

4. The method of testing the effectiveness of ganglionic blocking agents, comprising administering to an experimental animal 1,1-dimethyl-4-phenylpiperidinium iodide for the laboratory determination of the effectiveness of potential ganglionic blocking agents.

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