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Project

USE OF ANTI-HYPERTENSIVE AND ANTI-CHOLINE COMPOUNDS FOR THE CONTROL OF STRESS REACTIONS

Object of Investigation

The object of the present project is to find the most effective method of inhibiting the alarm reaction stimulated through the autonomic nervous system in individuals under stress. The method of approach is to devise chemical blocking agents or drugs which may be administered at the proper time to prevent both cholinergic and adrenergic manifestations of the autonomic nervous system.

General Considerations

In individuals under stress both cholinergic and adrenergic responses occur. "The sympatho-adrenal system frequently discharges as a unit and this occurs especially under circumstances of rage and fright (Cannon, 1932). The autonomic structures all over the body are affected at the same time. The heart is accelerated; the blood pressure rises; red blood cells are poured into the circulation from the spleen; the blood redistributes itself from the skin and splanchnic bed to the skeletal muscles; the blood sugar rises; the palpebral fissures widen; the pupils dilate; and, on the whole, the organism is better prepared for fight or flight." (Goodman & Gilman)

The splanchnic innervation of the adrenal medulla which liberates epinephrin into the system is triggered by the release of acetylcholine. This release of acetylcholine is a prime motivator of the alarm response

in both the sympathetic and parasympathetic divisions of the autonomic nervous system. The acetylcholine release therefore affects all the categories of fibers of the parasympathetic system and also all autonomic preganglionic nerves, whether sympathetic or parasympathetic, the splanchnic (preganglionic) fibers to the adrenal medulla, the "sympathetic" fibers to sweat glands and certain blood vessels, and the somatic motor nerves to skeletal muscles.

Plan of Procedure

It is obvious that to arrive at the objective of these investigations, suitable facilities for clinical testing must be provided. It is understood that these will be available elsewhere, but that preliminary clinical screening will be performed by the principal investigator to determine the most effective combination of anti-cholinergic and anti-adrenergic compounds for inhibiting alarm responses.

At present the standard anti-cholinergic and anti-adrenergic drug preparations usually combine phenobarbital and belladonna with or without the addition of xanthine derivatives or hyoscyamine. Among the available preparations marketed by drug concerns, the following may be listed:

BELLADONAL	
The alkaloids of belladonna leaf	.25 mg.
Phenobarbital	50 mg.
BELBARB	
Phenobarbital	1/4 gr. (16 mg.)
Hyoscine Hydrobromide	0.0072 mg.
Atropine Sulfate	0.0240 mg.
Hyoscyamine Hydrobromide	0.1280 mg.

PUROBARB	
Phenobarbital	1/6 grs.
Theobromine Calcium	3.25 grs.
NEMBUTAL AND BELLADONNA	
Nembutal Sodium	1/4 gr. (15 mg.)
Extract Belladonna	1/6 gr. (10 mg.)
DONNATAL	
Hyoscyamine sulfate	0.1037 mg.
Atropine sulfate	0.0194 mg.
Hyoscine hydrobromide	0.0065 mg.
Phenobarbital (1/4 gr.)	16.2 mg.

It is planned to administer these preparations first, in order to get a base line to determine how far beyond these presently available materials the researchers must go to produce satisfactory results. The methods that we will use here to screen the effectiveness of these compounds will be the control of blood pressure in hypertensive patients, in patients under excitement, and also the effect of these compounds on the palmar sweating test. This test is performed by placing the palm of the subject's hand on filter paper previously dipped in tannic acid and dried. The amount of the imprint left by the hand is a measure of palmar sweating. The best of these preliminary compounds will be given the grade "10", and new experimental preparations will have their effectiveness expressed numerically according to their relative effectiveness as compared to the best of these compounds.

The use of new compounds, available either commercially or synthesized by the investigator, will fall into two groups: The first group will be labeled "Anti-hypertensive Agents." The second group will be labeled "Anti-cholinergic Agents."

The anti-hypertensive agents will include phthalazine derivatives, a group of magnesium salts of alkylamino phthalates and of the double amine derivatives of propanol. A number of these compounds have been prepared by the chief investigator. Others will be obtained from leading pharmaceutical companies, such as priscoline, which is a sympatholytic agent marketed by CIBA, and Dihydroergocornine available from Sandoz.

Among the anti-cholinergic preparations, some of the 6-methoxy quinoline derivatives prepared by the principal investigator will be tested along with blocking agents devised for pilocarpine and eserin. These are an outgrowth of anti-asthmatic therapeutic agents devised by the principal investigator.

In addition, from commercially available supplies, such compounds as Banthine will be investigated.

The object, as previously stated, is to find the most effective combination of anti-cholinergic and anti-adrenergic compounds which will prevent the release under stress of the chemical effectors which produce the alarm response in individuals.

The principal investigator will conduct both acute and chronic toxicity studies on all compounds submitted for clinical investigation. In addition to this, preliminary pharmacological studies on the relative anti-hypertensive and anti-cholinergic effects of these compounds will be carried out.

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The following budget is proposed for these investigations:

Administration, office overhead and travel	$ 3,000.00
Chemical Assistants and Consultation part-time	3,600.00
Laboratory technician for pathologic sections, chronic toxicity, etc.	2,400.00
Clinical technician for clinical laboratory determination	3,000.00
Equipment, supplies and chemicals	3,000.00
	$ 15,000.00

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Typical Materials to be Evaluated in Project

Atropine

Syntropan

Benthine

Other standard synthetic Atropines

Bistrium

Veraloid

Apresaline (CIBA)

Experimental compounds will be tried only after evaluation of acute and chronic toxicity data (and other pertinent data) by the responsible Medical Officer on the project.