PHARMACOLOGY

EXPERIMENTAL THERAPY OF PROSERINE-INDUCED BRONCHOSPASM•

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(Received March 2, 1955. Presented by Acting Member of the Acad. Med. Sci. USSR M. V. Chernorutsky)

The increase in the tonus of the smooth musculature of the bronchi (manifestation of bronchospasm) is seen in a number of diseases and plays an important part in the course of the disease and in the development of complications.

The preparations of the adrenalin and atropine groups usually applied to relieve bronchospasm cannot completely satisfy clinical requirements. The effect of adrenalin is of very short duration. Atropine is insufficently effective in the usual doses which do not produce manifestations of intoxication. In connection with this, research into new effective medicinal preparations with a different mechanism of action is of great importance.

For this purpose, four groups of new synthetic medicinal preparations with a cholinolytic effect have been studied: the pentaphen group (diethylaminoethyl ester of phenylcyclopentane carboxylic acid [10, 8, 1], the dyphasin group (diethylaminoacetyl-N-phenothiazine [9, 2]), the diethylaminoacetyl-diphenylamide group, and the arpenal group (diathylaminopropylamide of diphenylacetic acid [12, 2]). In each of these groups, three preparations were tested: the hydrochloride and two iodoalkylates (methyl and ethyl iodides).

Most of the investigated substances were synthesized in the laboratory of the Department of Organic Chemistry (Chairman N. V. Khromov-Borisov) of the First Leningrad Medical Institute, the pentaphen in the All-Union Scientific Research Chemical Pharmaceutical Institute, and the arpenal group preparations in the Laboratory of Pharmaceutical Chemistry of the Academy of Sciences of the Armenian SSR (Director A. L. Midshoyan).

Study of the relationship between the structure and pharmacological effect of these substances [5] showed that all the preparations possess a marked cholinolytic effect. The blocking effect of the investigated substances on N-cholinoreceptors manifests itself in considerably smaller doses than does the effect on M-cholinoreactive systems, i. e., all the preparations more easily remove the nicotine-like effect of acetylcholine than its muscarine-like effect. The blocking effect on the parasympathetic ganglia (disturbance of conduction of nerve impulses through the vagus to the heart) was manifest upon introduction of considerably smaller doses of the preparations than was necessary for production of the effect on the sympathetic ganglia (disturbance in conduction of the impulses in the upper cervical sympathetic ganglion). In each group of substances studied, upon transition from a preparation containing trivalent nitrogen atoms (hydrochloride) to preparations having quaternary nitrogen (iodoalkylate), the capacity of the substances to block N-cholinoreceptors of the vegetative ganglia was sharply increased and in this connection their influence on the central nervous system perceptibly fell (the anticonvulsive effect decreased, the influence on the higher nervous activity sharply diminished [4, 5, 2]).

• Presented at the 490th Session of the I. M. Sechenov Physiological Society, December 23, 1952.

Proceeding from the concept that in the development of asthmatic spasm with human bronchial asthma, the essential role is played by a spasm of the smooth musculature of the bronchial tree connected with the entry of an intensified stream of impulses through the vagus, we used as experimental models of an asthmatic state, the bronchospasm induced in a cat by intravenous injection of proserine.

Proserine-induced bronchospasm involves suppression of the cholinesterases and accumulation of a surplus of acetylcholine in various sections of the nervous system involved in innervation of the bronchial muscles, in particular in the vagal system; in its pathogenesis, it is thus, to a certain degree, akin to bronchospasm observed in the asthmatic condition in man.

EXPERIMENTAL METHODS

The experiments were conducted on decerebrated cats. In order to record the fluctuations in the tonus of the bronchial musculature, three methods were applied: 1) parallel recording of tracheal respiration and fluctuations in intrapleural pressure; 2) bronchography; and 3) recording of bronchospasm in artificial respiration by means of the so-called piston-recorder. A comparative study of these methods showed the most sensitive and convenient to be the method of recording the bronchospasm with the aid of the piston-recorder proposed by Konzett and Rössler [11], as modified by T. M. Turpaev [7], and it was therefore used by us in most of the experiments.

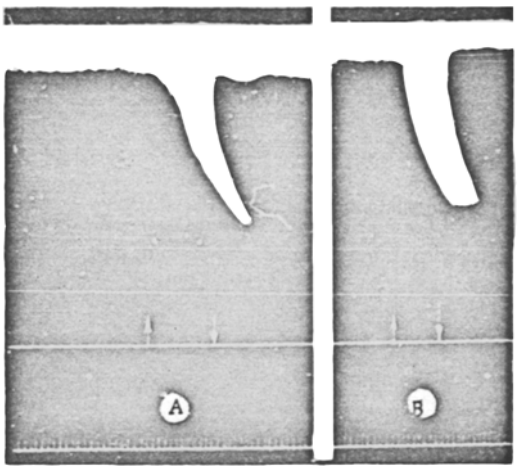

Fig. 1. Relief of proserine bronchospasm by pentaphen (A) and by pentaphen methyl iodide (B).
Significance of tracings (top to bottom): recording of tonus of bronchial musculature (indices of piston-recorder), indication of intravenous introduction of preparations, indication of time (20 seconds).
a – ↑ proserine 0.1 mg/kg; ↓ pentaphen 2.0 mg/kg;
b – ↑ proserine 0.1 mg/kg; ↓ pentaphen methyl iodide 0.1 mg/kg.

This method is based on an accurate graphic recording of the surplus of air not entering the lungs of the animal upon artificial respiration with constant pressure and constant volume of forced-in air. Involuntary respiration of the animal was suppressed with the introduction of the curare-like preparation dithiline [6]. Proserine and the new preparations under test were introduced into the femoral vein.

The strength of the medicinal effect of the substances was evaluated by the minimum dose of the preparation removing the bronchospasm, induced by introduction of 0.1 mg/kg body weight proserine (Fig. 1). In the conditions of our method such a spasm without treatment proved fatal.

For a more exact comparative appraisal of the strength of the effect of the preparations, the prophylactic effect of these substances and their capacity to prevent the development of proserine-induced bronchospasm were also studied. In these experiments, the preparation being tested was introduced intravenously in the dose of 3.0 mg/kg body weight, and then at brief time intervals (from 2 to 5 minutes) proserine was introduced into the animal at the rate of a single lethal dose at a time. The number of doses of proserine causing a 25% decrease in the lung capacity was noted in the experiment, i. e., reduction of the respiratory volume to 75% of the original value (Fig. 2).

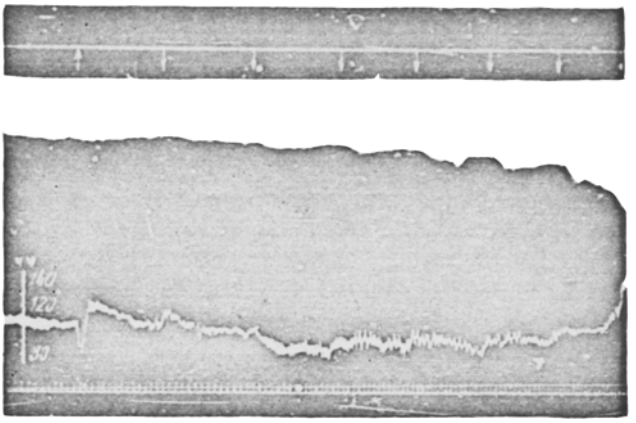

Fig. 2. Prevention of proserine bronchospasm by pentaphen. Significance of tracings (top to bottom): indication of intravenous injection of preparations (↑pentaphen 3.0 mg/kg, ↓ proserine 0.1 mg/kg), recording of tonus of bronchial musculature (indices of piston-recorder), blood pressure (in mm Hg), indication of time (20 seconds).

EXPERIMENTAL RESULTS

The medicinal and prophylactic effects of the new preparations with experimental bronchospasm were compared with the effects of some already known medicinal means (novocain, diphasil, tetraethyl ammonium hydroxide, atropine and adrenalin).

The results of the experiments are presented in the table.

It is clear from the table that in each group of new preparations the hydrochlorides containing trivalent nitrogen possess a less marked medicinal and prophylactic effect than either of the iodoalkylates having a quadrivalent nitrogen atom. The minimal medicinal dose for the hydrochloride in each group of preparations is considerably higher than the minimal doses of either of the iodoalkylates. Thus, the minimal medicinal dose with proserine bronchospasm for the methyl iodide of pentaphen is 20 times less than for pentaphen hydrochloride (Fig. 1, a and b).

Of the investigated new preparations with tertiary nitrogen, the most effective was arpenal, a somewhat less marked effect was shown by pentaphen, and least effective were diphasin and diethylaminoacetyldiphenylamide.

Of the preparations with quaternary nitrogen, the most effective were the arpenal and pentaphen methyl iodides.

Novocain, diphasil and tetraethyl ammonium hydroxide proved to be considerably less effective in their capacity to relieve and prevent the proserine bronchospasm than the majority of tested new preparations.*

* Two years after our work was presented to the I. M. Sechenov Physiological Society, findings [5] were published, according to which diphasil (spasmolytin) and pentaphen are uniformly effective in their capacity to relieve proserine-bronchospasm. It is possible that the authors reached such a conclusion because the method which they used (recording of pressure in the trachea) was less convenient for the quantitative evaluation of the effect of the preparations than was ours.

Medicinal and Prophylactic Effect of Cholinolytic Preparations on Proserine Bronchospasm.

Name of preparation	Medicinal effect	Prophylactic effect
	Minimum dose (in mg/kg) relieving an already developing lethal proserine broncospasm	Number of lethal doses of proserine producing a 25% reduction in lung capacity after prophylactic introduction of 3.0 mg/kg of preparation
Pentaphen hydrochloride	1.5—2.0	3—6
Pentaphen Iodomethylate	0.05—0.1	34—36
Pentaphen Iodoethylate	0.5	16
Diphasin hydrochloride	10.0	Less than
Diphasin Iodomethylate	0.2	22
Diphasin Iodoethylate	0.2	6
Diethylaminoacetyl-d iphenylamido hydrochloride		Less than
Diethylaminoacetyl-diphenylamido Iodomethylate		4
Arpenal hydrochloride	0.5	13
Arpenal Iodomethylate	0.05	34
Arpenal Iodoethylate	0.1	24
Novocain	5.0—10.0	Less than
Diphasil	5.0—6.0	Less than
Tetraethylammonium hydroxide	10.0	Less than
Atropine	0.03	

For atropine, which quickly and completely eliminates the bronchospasm, the minimal medicinal dose is also considerably higher than the medicinal doses applied clinically (with conversion to 1 kg of body weight). Adrenalin in our experiments proved to be of little effect. The minimal medicinal doses removing the bronchospasm for the majority of the preparations coincided with the doses preventing the depressor effect upon stimulation of the peripheral segment of the vagus, and were considerably smaller than doses exerting an atropine-like (muscarinolytic) effect, i. e., removing the depressor effect of intravenously introduced acetylcholine [5].

These observations give grounds for considering that the effect of the investigated preparations on bronchospasm depends primarily on the effect of these substances on the ganglia of the pulmonary branches of the vagus. By blocking the passage of nervous impulses in the ganglion synapses, these substances temporarily remove the influence of the vagus on the bronchi.

Such a concept is in good agreement with the findings we obtained in analyzing the mechanism of proserine bronchospasm.

It was established that for the development of the bronchospasm by introduction of proserine, the preservation of the vagal centers and the presence of links of the muscular elements of the bronchi with these centers are of great importance. Decapitation, vagotomy, or introduction of tetraethyl ammonium hydroxide, which ensure the "pharmocological intersection" of the vagus nerves, hinder or speedily eliminate bronchospasm already in progress.

Thus, in preparations with a cholinolytic effect which selectively block the transmission of the nerve impulse in the ganglia of the vagus, we have a new group of medicinal substances basically distinguishable in terms of their mechanism of action from the earlier applied preparations of the atropine and adrenalin groups for elimination of bronchospasm and excelling these substances in their efficacy in experimental therapy of proserine-induced bronchospasm.

The clinical testing of one of the new preparations— pentaphen— showed its high efficacy in removal of bronchospasm and in treatment of patients with bronchial asthma.

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