CORRELATION OF CHEMICAL STRUCTURE AND PHARMACOLOGIC ACTION OF SOME NEW ANTICHOLINE AGENTS*

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(Received March 29, 1956. Presented by Active Member AMN SSSR Professor S.V. Anichkov)

Studies on the correlation of chemical structure and pharmacologic action were carried out on four groups of anticholine agents: 1) the pentaphen or diethylaminoethyl ester of phenylcyclopentane carboxylic acid group [9, 10, 1, 4, 3], 2) the diphazine or diethylaminoacetylphenothiazine group [8, 4, 3], 3) the alphamethyldiphazine group containing a methyl group in the alpha position with respect to the nitrogen of the aminoacetyl part of the molecule [7], 4) the arpenal or diethylaminopropylamide of diphenylacetic acid [10, 3].

Each group was composed of three preparations: the hydrochloride containing a tertiary nitrogen atom, and two alkyl iodides (methyl iodide and ethyl iodide) containing a quaternary nitrogen atom. In the pentaphen and diphazine groups there were also the methylsulfomethylates. The structure of all these compounds is shown in the table (see below). The majority of the substances were synthesized by N. B. Khromov-Borisov and A. M. Yanovitskaya (I LMI), the arpenal group was synthesized in Professor A. L. Mndzhoyan's Laboratory (Academy of Sciences of the Armenian SSR), while pentaphen hydrochloride was obtained from VNIKhVI.

EXPERIMENTAL METHODS

Experiments were performed on cats under urethane and hexenal anesthesia and on decerebrate animals. The vagosympathetic trunks were dissected in the animal's neck; the sympathetic nerve was isolated on the left, and the vagus on the right. Ligatures were applied to the nerves, the nerves were cut and introduced into cannula-like electrodes. During the experiment the preganglionic sympathetic nerve trunk was subjected to prolonged stimulation with square-wave pulses from an electronic stimulator at a frequency of 16 per second (duration of each pulse 0.1 millisecond). The preparations were injected intravenously. The effect of the substances on transmission in the superior cervical sympathetic ganglion was determined by their ability to lower the height of contraction of the nictitating membrane [6] (Fig. 1). In control experiments it was established that the preparations in similar doses did not affect contractions of the nictitating membrane elicited by stimulation of postganglionic fibers (Fig. 2) and adrenalin..

The peripheral segment of the vagus was subjected for 5 seconds with an interval of 3-5 minutes to periodic stimulation with induction current with a frequency of 35 impulses per 1 second. The effect of the compounds on conduction in the vagus was determined by their ability to abolish the fall of blood pressure caused by stimulation of this nerve (Fig. 1).

The effect of the preparations on the muscarine-sensitive choline-reactive systems was evaluated by their ability to abolish the fall of blood pressure occurring in response to intravenous administration of acetylcholine (Fig. 3).

The blocking effect of the preparations on the nicotine-sensitive choline-reactive systems of the adrenals and the carotid sinus zones was determined by their ability to abolish respiratory stimulation and rise of blood pressure following intravenous administration of nicotine (0.02-0.03 mg/kg) or of dicholine ester of suberic acid

* Communicated at the 603rd meeting of the I.M. Sechenov Society, Leningrad on April 19, 1955.

(0.01 mg/kg) (Fig. 3). The pressor effect of these preparations is determined chiefly by the action on adrenal medulla, while the respiratory stimulating effect-by the action on the chemoreceptors of the carotid sinus zones [5].

RESULTS

The results of the experiments are presented in the table. All the preparations being studied revealed anticholine action. In each group of substances the alkyl iodides containing a quaternary nitrogen atom showed much stronger anti-acetylcholine action than the corresponding hydrochlorides containing a tertiary nitrogen atom. In this respect the present data agree with the results obtained in studies on other anticholine preparations [7,11,13, 14]. Thus, as regards the ability to abolish the muscarine-like effect of acetylcholine, the alkyl iodides exert a 2-3 times stronger effect than the corresponding hydrochlorides. This feature is still more clearly shown by the determination of the ability of the preparations to prevent the depressor action of the vagus. Pentaphen and diphazine hydrochlorides block vagal conduction in doses of 1.0-2.0 mg/kg, arpenal and alphamethyldiphazine hydrochlorides – in doses of 0.3-0.5 mg/kg. All the alkyl iodides block vagal conduction when used in doses of 0.03-0.05 mg/kg, exceeding in strength of their action that of the corresponding hydrochlorides by 20-40 times for the penthaphen and diphazine groups, and by 6-10 times for the arpenal and alphamethyldiphazine groups. It was thus found that all the preparations being studied prevented the depressor effect of stimulation of the vagus in doses tens of times smaller than those required to abolish the depressor effect of acetylcholine on intravenous injection. The difference in the doses which block the depressor effects of the vagus and acetylcholine may also depend on the fact that on stimulation of the vagus this effect arises as the result of action on the heart only, while the depressor effect of intravenous acetylcholine is determined predominantly by action on the vessels. Consequently, the difference in the doses of the preparations which block these effects may depend on different sensitivity of the "M"-choline reactive systems of the heart and the vessels. However, administration of a purely anti-muscarine agent – adrenalin – is not associated with such a difference, the two doses being almost identical. This suggests that the preparations being studied may block vagal conduction at the level of the intramural ganglia of the end-organ. Nevertheless, it is impossible to dismiss the hypothesis that, unlike atropine, these substances may also differ in their ability to block muscarine-sensitive receptors of the heart and vessels.

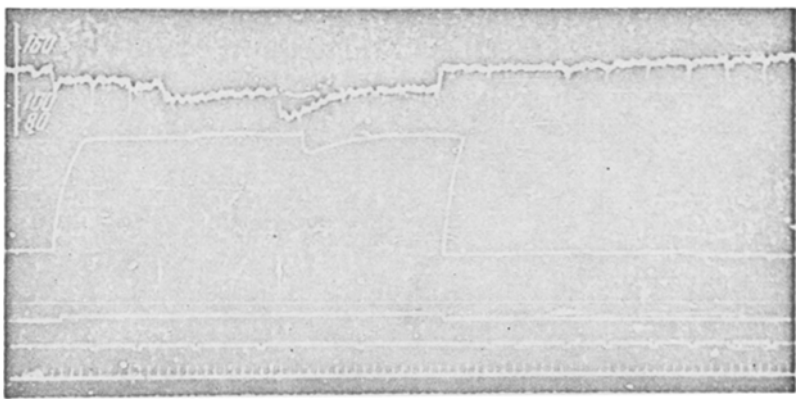


Fig. 1. The influence of diphazine methyl iodide on the depressor effects of vagal stimulation and on contraction of the nictitating membrane elicited by prolonged stimulation of preganglionic sympathetic fibers. Cat, 2.7 kg. Hexenal 150 mg/kg subcutaneously. Records from above down: blood pressure in common carotid artery, contractions of the nictitating membrane, marker for stimulation of sympathetic nerve, marker for stimulation of the peripheral segment of the vagus, time marker (1 minute). Arrows indicate intravenous injections of diphazine methyl iodide in doses of 0.5 and 10 mg/kg.

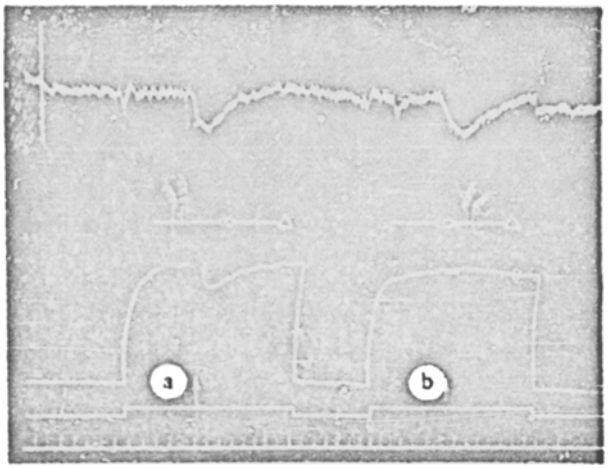


Fig. 2. The influence of pentaphen methyl iodide on contractions of the nictitating membrane elicited by stimulation of pre- and postganglionic sympathetic fibers.
Cat, 3.2 kg. Urethane 1 g/kg intraperitoneally. Records from above down: blood pressure, contractions of the nictitating membrane, marker for stimulation of preganglionic (a) and postganglionic (b) sympathetic fibers, time marker (1 minute). Arrows indicate intravenous injections of pentaphen methyl iodide in doses of 0.3 mg/kg.

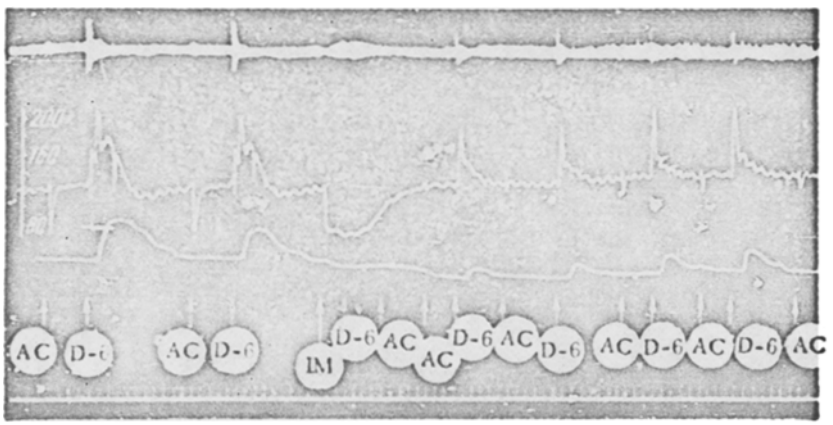


Fig. 3. The influence of penthaphen iodomethylate on the effects of acetylcholine and of dicholine ester of suberic acid.
Cat, 3 kg. Urethane 1 g/kg intraperitoneally. Records from above down: respiration, blood pressure, contractions of the nictitating membrane, time marker (1 minute). Arrows indicate intravenous injections: AC – acetylcholine $1 \cdot 10^{-6}$ in dose of 1 ml, D-6 dicholine ester of suberic acid in dose of 0.01 mg/kg, IM – pentaphen methyl iodide in dose of 3 mg/kg.

Larger doses of the preparations are required for diminution of transmission in the superior cervical sympathetic ganglion, but the relative strengths of action between the substances with tertiary nitrogen atoms and with quaternary nitrogen atoms in their molecules are preserved. Pentaphen and arpenal hydrochlorides exert this action in doses of 2.0-3.0 mg/kg, alpha-methylated diphazine hydrochloride – in doses of 5.0-7.0 mg/kg, and

Minimal Doses of Anticholine Substances (in mg/kg intravenously) and Their Action

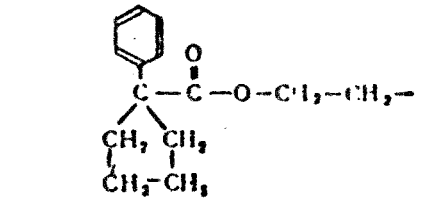
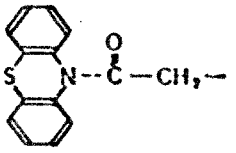
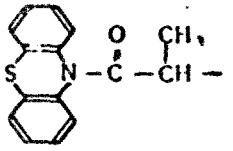
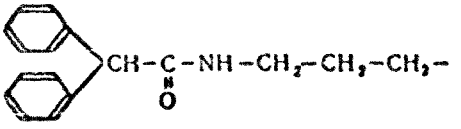
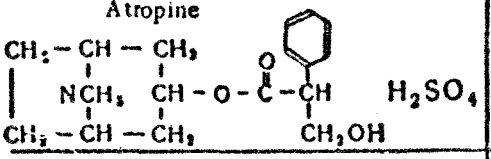
Chemical structure of the preparation		Molecular weight
R I	R II	
Pentaphen 	$-N(C_2H_5)_2(C_2H_5)\cdot HCl$	320.8
	$-N^{+}(C_2H_5)(CH_3)(C_2H_5)$	426.3
	$SO_4CH_3-N^{+}(C_2H_5)(CH_3)(C_2H_5)$	415.0
	$-N^{+}(C_2H_5)(C_2H_5)(C_2H_5)$	440.3
Diphazine 	$-N(C_2H_5)_2\cdot HCl$	341.8
	$-N^{+}(C_2H_5)(CH_3)(C_2H_5)$	446.3
	$SO_4CH_3-N^{+}(C_2H_5)(CH_3)(C_2H_5)$	438.0
	$-N^{+}(C_2H_5)(C_2H_5)(C_2H_5)$	460.3
Alphamethyl diphazine 	$-N(C_2H_5)_2\cdot HCl$	362.9
	$-N^{+}(C_2H_5)(CH_3)(C_2H_5)$	468.4
	$-N^{+}(C_2H_5)(C_2H_5)(C_2H_5)$	474.4
Arpenal 	$-N(C_2H_5)_2\cdot HCl$	360.9
	$-N^{+}(C_2H_5)(CH_3)(C_2H_5)$	446.4
	$-N^{+}(C_2H_5)(C_2H_5)(C_2H_5)$	480.4
Atropine 	—	339.4
Tetraethyl-ammonium CH_3-CH_2-	$Br^{-}\,N^{+}(C_2H_5)_4$	173.9

Table (continued)

Abolition of depressor effects on		Lowering of the hgt. of contrac. of nictit. memb. kept by prolonged stim. pregang. simpath. fibers	Abolition of Effects Elicited by Intrav. Injec. of Dicholine Ester of Suberic Acid		
intravenous injection of acetylcholine	stimulation of the vagus		Pressor effect	Respiratory stim.	Contrac. nictit. membrane
5.0	0.5—1.0	2.5—3.5	10.0	5.0	5.0
2.0	0.03	0.2—0.3	3.0	3.0	3.0
—	0.03	0.2—0.3		—	—
3.0	0.2	0.2—0 3	3 0	3.0	3.0
5.0	1.5—2.0	20.0	10.0	10.0	10.0
3.0	0.05	1.0—1.5	5.0	5.0	5.0
—	0.05	1 0—1.5	—	—	—
3.0	0 05	1.0—2.0	3.0	3.0	3.0
5.0	0.2—0.5	7.0—8.0	7.0—8.0	7.0—8.0	7.0—8.0
1 0	0.03	0 2—0.5	2.0	2.0	—
2.0	0.05	2.0—3.0	3.0—4.0	3.0—4.0	—
6.0	0.3	2.0	5.0	5.0	5.0
2.0	0.05	0.2	2 0	2.0	2.0
2.0	0.05	0.1	2.0	2.0	2.0
0.02	0.01	—	—	—	—
10.0	1.5	0.1	10.0	10.0	10.0

diphazine hydrochloride only in the toxic dose of 20 mg/kg. The alkyl iodide preparations in all the groups block sympathetic ganglionic transmission in doses 5-10 times smaller than the corresponding hydrochlorides (see table).

Abolition of pressor effects, respiratory stimulation and contractions of the nictitating membrane elicited by the dicholine ester of suberic acid was achieved by administration of large doses of the preparations, although in this case, too, the blocking activity proved to be more pronounced in compounds containing a quaternary nitrogen atom in their molecules.

The radical at the quaternary nitrogen atom is also of substantial importance. Among the alkyl iodides the iodomethylates showed stronger anticholine action in most cases as compared with iodoethylates.

The comparison of iodomethylates (methyl iodides) of pentaphen and diphazine with the corresponding methylsulfomethylates failed to reveal any difference in the action of these preparations. At the same time the the solubility of the latter is much higher than the solubility of methyl iodides.

Thus, the main consistent feature traced in all four groups of substances being studied is the manifold increase of peripheral anticholine effects on transition from hydrochlorides to alkyl iodides. In connection with this it is interesting to note that the central anticholine action of the same preparations (anticonvulsant action, ability to influence higher nervous activity) on the contrary either diminishes markedly or disappears completely on transition from hydrochlorides to alkyl iodides, and methyl iodides prove to be the least active [4, 3].

Another feature has been noted: introduction of a methyl group into the alpha position with respect to the nitrogen atom of the aminoacetyl part of the diphazine molecule increases considerably its anticholine action. This becomes particularly noticeable on comparison of the corresponding hydrochlorides (see table).

All the compounds studied showed most pronounced ability to block transmission in autonomic ganglia. Pentaphen and diphazine block conduction in the vagus in the same doses as tetraethylammonium [6, 2], ersenal and alpha-methyldiphazine – in doses which are 3-5 times smaller. Their alkyl iodide derivatives proved to be 20-30 times stronger than tetraethylammonium. The blocking action of the compounds under investigation on transmission in the superior cervical sympathetic ganglion proved to be markedly less pronounced than that of tetraethylammonium, although compounds with a quatenary nitrogen atom (alkyl iodides) approached tetraethylammonium in this respect. All the compounds studied thus show first of all, on intravenous injection, a blocking effect on conduction in the vagus, the, with increasing doses, a blocking effect on transmission in the superior cervical sympathetic ganglion, and in still larger doses exert a blocking effect on the muscarine-sensitive and nicotine-sensitive choline-reactive systems of the carotid sinus zones and the adrenals.

Some of the compounds studied, the methyl iodides in particular, may be of interest as substances exerting a selective blocking effect on conduction in the vagus. Consideration of the discovered correlations may facilitate further search for anticholine substances with selective action.

SUMMARY

Four groups of anticholine agents were studied. Each group consisted of three prepartions: the hydrochloride containing a tertiary nitrogen atom, and two alkyl iodides (methyl iodide and ethyl iodide) containing a quaternary nitrogen atom. All of the preparations with a quarternary nitrogen atom were several times more active than their tertiary analogue, blocking all peripherical choline-reactive systems. In respect to their sensitivity to these preparations, the choline-reactive systems may be grouped as follows: the most sensitive are the choline-reactive systems of the cardiac branches of the vagus nerve, then the superior cervical sympathetic ganglion, and last, the carotid sinus zones and the adrenals.

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