THE EFFECT OF AMINO ALCOHOLS OF THE ACETYLENE SERIES ON THE CENTRAL NERVOUS SYSTEM

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Numerous preparations possessing cholinolytic properties are used clinically in Parkinsonism, hyperkinesias of central origin, and in disorders associated with various spastic conditions. Certain of these compounds, belonging to the class of complex esters of the aromatic acids and amino alcohols, not only yield a therapeutic effect but also evidence side reactions (they disturb higher nervous function, produce lowered awareness, sleepiness "drunkenness," vertigo, etc.). In animal experiments it has also been established that aminoalkyl esters in small doses, close to the therapeutic dose, inhibit conditioned reflex activity [3, 5, 9].

In using other cholinolytic substances, particularly amino alcohols derived from 1,3-aminopropanol (preparations of the Artane type), a good therapeutic effect was obtained and they evidenced comparatively weaker side reactions [1, 8]. The effective therapeutic activity of these compounds may be associated with their blocking action on the central M- and N-choline reactive systems [8, 11].

The successful union of pharmacological effectiveness with comparatively minor side effects on the central nervous system permitted the application of compounds from this group, like Artane, Kemadrin, Pagitane, Akineton, and others in clinical practice [12-15].

The present investigation is a study of the effect of the acetylene series of amino alcohols on the central M- and N-choline reactive systems and on the conditioned reflex activity of healthy animals; the purpose was to identify preparations eliciting the least side effects and having a sufficiently strong M- and N-cholinolytic activity, so that the union of these properties would react favorably in the therapy of hyperkinesias of central origin [7, 8].

The acetylene amino alcohols differ from the previously studied amino alcohols which are derived from 1,3-aminopropanol in that they contain the triple bond. M. M. Libman of the Toxicological Institute synthesized the aminobutynol and aminoethynol derivatives [6].

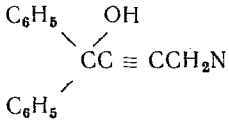
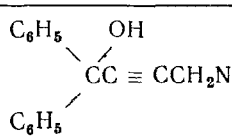
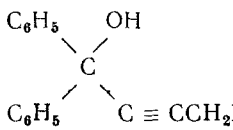
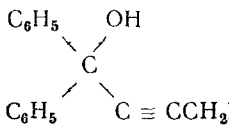
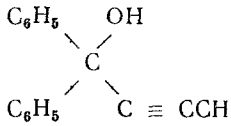
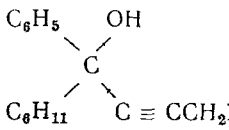
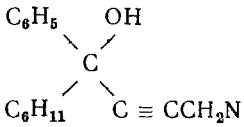
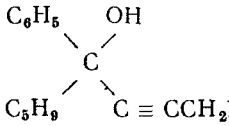
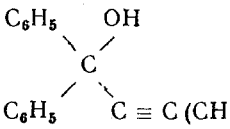
Nine compounds in all were studied.

METHODS

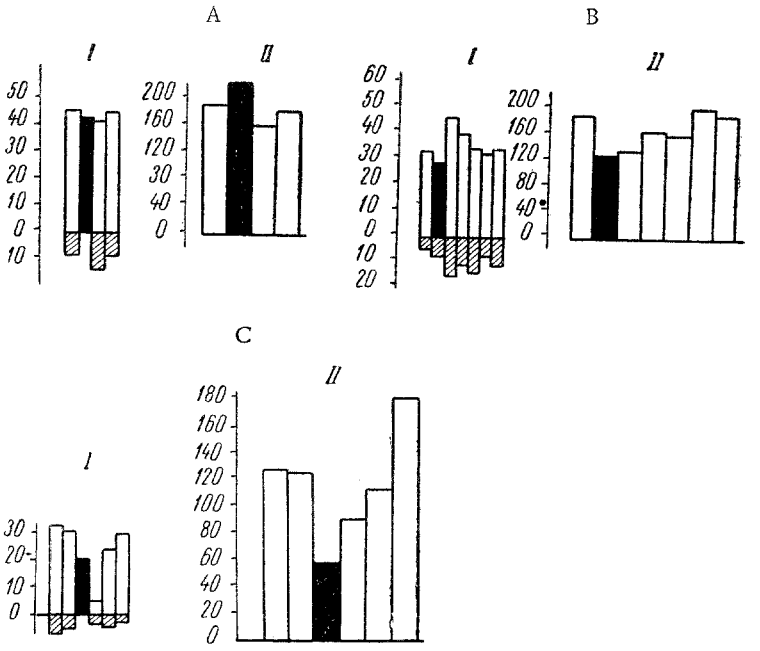
The experiments were carried out on 770 mice, 110 rabbits, and 5 dogs. Central M-cholinolytic activity was determined by the ability of the preparations to prevent arecoline tremor in mice (the S. N. Golikov method); central N-cholinolytic activity was assessed through the ability of the preparations to prevent nicotine hyperkinesia in rabbits (Bovet-Longo method).

The conditioned reflex activity was studied in 5 dogs. In 3 animals positive motor conditioned reflexes were established to 120 beats per min on the metronome (M_{120}) and to sound and light according to the method by P. S. Kupalov with situational conditioned reflexes. Differentiation was developed with a buzzer. Pieces of meat 20 g in weight were used for unconditioned reinforcement. In two dogs the salivary conditioned reflex was established to the bubbler, M_{120}, light, and differentiation to M_{60} according to the method of I. P. Pavlov. The unconditioned reinforcement was 20 g of meat-sucrose powder mixed with water in a ratio of 2:1.

Effect of Acetyleneic Amino Alcohols on the Central Nervous System of Animals

Preparation no.	Chemical structure	Dose (in mg/kg) effective in suppressing arecoline tremor in mice ED_{100}	Dose (in mg/kg) effective in suppressing arecoline tremor in mice ED_{50}	Dose (in mg/kg) effective in suppressing nicotine hyperkinesis in rabbits	Dose (in mg/kg) producing disturbance in conditioned reflex activity in the dog
1		12,0	5,5	—	6,5
2		4,0	2,6	3,0	3,0
3		2,1	1,0	2,5 — 3,0	2,0
4*		>100,0	—	—	10,0
5*		18,0	10,0	8,0	5,0
6		12,0	7,0	—	6,0 — 7,0
7*		>100,0	—	—	12,0
8*		9,0	5,0	7,0	4,0
9		5,0	2,6	3,0	3,0

* The substances were synthesized in a manner similar to that used on like compounds according to N. M. Libman and S. G. Kuznetsov [6].



Effect of preparation No. 3 (dipheridine) at a dose of 0.1 mg/kg (A) and 0.5 mg/kg (B) on the secretory conditioned reflexes in the dog Piskla and at the 2 mg/kg dose level (C) on the secretory conditioned reflexes in the dog Dzhim. The white columns show the average amount of conditioned (I) and unconditioned (II) secretions on each day of experiment (one scale division equals 0.01 ml); the black columns show the average amount of secretion on the day the material was administered; the shaded columns show the average amount of secretion with the differentiating stimulus.

The substances under study were given subcutaneously 15-20 min before the experiment at intervals of not less than 10 days.

RESULTS

The experiments on mice and rabbits showed that the unsaturated amino alcohols, especially preparations Nos. 2, 3, and 9, exhibit rather marked central M- and N-cholinolytic activity (see table). Preparations Nos. 1, 5, 6, and 8 were less active.

The quarternary compounds (Preparations Nos. 4 and 7) displayed the weakest central M-cholinolytic activity: even at doses of 100 mg/kg they failed to suppress the arecoline tremor in all the test animals (of 10 mice the tremor did not develop in 1 or 2, in the others it was merely diminished).

After treating dogs with small doses of the unsaturated amino alcohols (0.5-1 mg/kg) some improvement in conditioned reflex activity was observed. Higher doses within 15-30 min after administration subcutaneously produced a release of the differentiators, increasing the latent period in some positive conditioned reflexes (frequently to light and M_{120}). The time taken to consume the food was somewhat increased (by $1\frac{1}{2}$ times the normal 2-3 sec).

An hour after giving the preparations the maximum disturbance in conditioned reflex action was observed, although no visible signs of intoxication were noted.

Full inhibition of the conditioned reflex activity took place only when the drugs were given at 5-10 times the minimum effective dose. When giving the amino alcohols in high dosage (5-8 mg/kg) some animals vomited, the shaking reflex was strengthened, and excitability for food decreased, which indicated the action of the preparations on subcortical organization of the brain; this was the more evident since at that time the structure of the

motor conditioned reflex was not disturbed. In addition to the above symptoms a limited disorder in movement (muscular weakness, disordered motor coordination when jumping up on the table) was noted. When the minimal effective dose was given the conditioned reflex activity returned to normal within 24 h.

The quarternary compounds (Nos. 4, 7) in doses of 6-8 mg/kg elicited peripheral disturbances in the course of 2-4 h; these were evidenced in dryness of the mucous membrane, difficulty in swallowing food, dilatation of the pupils. The conditioned reflexes were not substantially altered under these conditions. When compounds Nos. 4 and 7 were administered at the 10-12 mg/kg level a disturbance was produced in the conditioned reflexes in addition to the peripheral disorder; the character of the reflex disturbances resembled those produced by the tertiary analogues (Nos. 3, 6).

After administering preparation No. 3 (dipheridine) in doses of 0.1-0.25 mg/kg a small increase in unconditioned secretion was observed. At the 0.5 mg/kg dose level this preparation elicited a prolonged depression (2-3 days) of unconditioned salivary secretion while the conditioned secretion remained unchanged or even increased (see figure). In doses of 1-2 mg/kg the drug suppressed conditioned salivation and in greater measure the unconditioned secretion, with consequent refusal of food by the animal. The other preparations behaved similarly. On the basis of the information given above it may be concluded that the unsaturated amino alcohols evidence marked activity on the subcortical structures, so that when these drugs are administered, food motivation is decreased, the unconditioned salivary secretion is inhibited, while the conditioned connections are retained and the animals react to the effect of the conditioned stimulus. Differentiation of the stimuli is not disturbed, although the general tonus of the activity is decreased (the volumes of saliva in the secretory conditioned reflexes are decreased).

According to data we have presented previously, the potency of effect on the higher nervous activity shown by the aminoalkyl esters (of acetic and glycolic acid) depends on the intensity of the N- and M-cholinolytic activity. The influence on the higher nervous function was greatest when the central M-cholinolytic activity was increased; the influence was decreased if the compound displayed a sufficiently potent central N-cholinolytic activity.

The investigation which has been made into the action of new cholinolytic substances reveals that, compared with the amino esters and with the amino alcohols of the 1,3-aminopropanol series, the unsaturated amino alcohols produce a brief and weaker disturbance of the conditioned reflex activity at considerably higher doses (about 5 to 10 times).

Consequently, the effect of the amino alcohols derived from acetylene upon the conditioned reflex activity becomes apparent when much higher doses are employed (compared with the amino esters); this is accounted for by the decreased central M-cholinolytic activity and the increased nicotinolytic effect.

Thus, the potency with which the cholinolytic substances affect conditioned reflex activity depends, also in this group of amino alcohols, upon the relative magnitudes of their central M- and N-cholinolytic effects. From this point of view the amino alcohols are of definite clinical interest because they simultaneously combine a sufficiently potent central M- and N-cholinolytic activity to be therapeutically effective with a weak influence on the conditioned reflex activity; therefore, these compounds (especially preparations Nos. 2 and 3) may be recommended for Parkinsonism and other hyperkinesias of central origin. Preliminary trials in the clinic of the S. M. Kirov Army Medical Academy showed that preparations from the group of acetylenic amino alcohols, especially preparation No. 3 (dipheridine which was confirmed by the Pharmacological Committee and recommended for use in medical practice) produce a favorable therapeutic effect in Meniere's syndrone, bronchial asthma,and other illnesses.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
