ADRENAL BLOCKING ACTION OF TROPINE ESTERS

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Many of the presently known esters of tropine have antichlorinergic actions. Atropine, homatropine, pseudotropine and other compounds of this group are commonly considered to be anticholinergic substances which act selectively on the m-cholinergic systems of the organism. A great deal of experimental material that has accumulated in the course of a number of years indicates, however, that the action of these esters, in particular, atropine, is not extremely selective. The works of Marrazi, Yu. I. Syrneva [4], Kontset [10], Fink [7] et al. show that atropine acts on the cholinergic systems and in appropriate doses decreases the reactivity of the autonomic ganglia and of the chromaffinic tissue of the adrenals. The data on the adrenergic blocking action of atropine are also of interest. As early as 1857, Bezold and Bluebaum [6] stated that large doses of atropine are capable of interrupting the passage of excitation along a sympathetic nerve. Okamoto [12], Wehland [14], Uhlmann [13] et al. later observed the antagonism between atropine and adrenaline in their effect on the uterus and the blood vessels. In recent times György and Porszasz [8] showed that atropine decreases the effect of adrenaline on the blood pressure and tonus of the nictitating membrane of cats.

By study of the pharmacological properties of various esters of tropine, we established that the ganglionic and adrenergic blocking actions of atropine may be considerably enhanced if the tropine molecule is esterified with carboxylic acids other than tropic acid. Thus, through studying the tropine ester of diphenylacetic acid (tropatsyn) we showed [2] that this compound has a pronounced effect on n-cholinergic systems and a considerably less pronounced effect than atropine on the m-cholinergic systems. We have recently established that tropine may serve as the basis for the preparation of esters having a strong adrenergic blocking action. The tropine ester of acetoxyphenyl-α-phenylpropionic acid (OF-717) and the tropine ester of methoxyphenol-α-phenylpropionic acid (OF-718) are such compounds. The hydrochlorides of these compounds were synthesized by O. Yu. Magidson and V. M. Fedosova and were the first compounds that we investigated.

Effect on Blood Pressure

We investigated the effect of preparations OF-717 and OF 718 on the blood pressure of cats and dogs. The cats were anesthetized by injecting urethane (1 g per 1 kg of weight) into the abdominal cavity. The blood pressure was recorded with a mercury manometer, connected by a cannula with the common carotid artery. The solutions of the preparations were injected into the femoral vein. The blood pressure of the dogs was measured by a sphygmomanometer, connected to a cuff placed on the common carotid artery which had previously been brought out into a flap of skin.

On injection of the preparations into the cats, it was established that both of them had a pronounced and persistent hypotensive action. No substantial difference was noted in their effect. With a dose of 0.5-1 mg/kg the blood pressure of the cats dropped 40-50 mm (in the first 20 seconds); stabilization proceeded very slowly as a rule; only after 1-2 hours did the pressure return to its initial level. Respiration did not change appreciably with these doses. With a dose of 2mg/kg the blood pressure dropped 50-70 mm and returned to the initial value after 3-4 hours. An even stronger hypotensive action was noted with a dose of 5 mg/kg: the pressure dropped 70-80 mm, and 5 hours after injection of the preparation it was 40-60 mm below the initial. Respiration was somewhat retarded with this dose. When 7-10 mg/kg was injected, the pressure dropped 80-120 mm. A dose of 15 mg/kg proved fatal in most of the experiments; death was attended by cessation of respiration and subsequent heart failure.

In dogs subcutaneous injection of 5 and 10 mg/kg of the preparations also brought about a marked drop in blood pressure: 10-15 minutes after injection, the pressure dropped 40-60 mm; toward the end of the day the pressure remained low. The following day it was the same as the initial value.

Subcutaneous injection of a dose of 5 mg/kg of preparation OF-717 in dogs with experimental renal hypertonia with an initial blood pressure of 200 mm caused the pressure to drop to 130 mm within 15 minutes: after an hour, the pressure was 115 mm, after 4 hours it was 140 mm. The following day the pressure rose again to 200 mm.

Thus, in different species of animals and with different methods of injection, preparations OF-717 and OF-718 showed a pronounced hypotensive action.

Adrenal Blocking Action

We determined the adrenal blocking action of preparations OF-717 and OF-718 by experiments on animals (cats and dogs) and on the vessels of isolated rabbit ears. In cats, anesthetized with urethane, we studied the effect of the preparations on the pressor action of adrenaline and on the contracting of the nictitating membrane that it causes. Adrenaline was injected intravenously in doses of 5-10 and 20 γ/kg. In some experiments nor-adrenaline (20 and 30 γ/kg) and mezatone (200 γ/kg) were injected.

In cats both preparations even in a dose of 0.1 mg/kg somewhat decreased the effect of adrenaline injection on the nictitating membrane, blood pressure and respiration. It was established by repeated adrenaline injections that, with this dose, the adrenal blocking action persisted for one to three hours. Upon injection of 0.5-1 mg/kg, the pressor effect of adrenoline was considerably reduced, the reaction of the nictitating membrane also diminished sharply or completely disappeared. In a number of experiments these changes persisted for more than three hours. When the dose was increased to 2 mg/kg and more, they almost disappeared and, in a number of experiments, the pressor effect of adrenaline was also distorted. The adrenergic blocking action persisted for 5 hours and more (Figure 1).

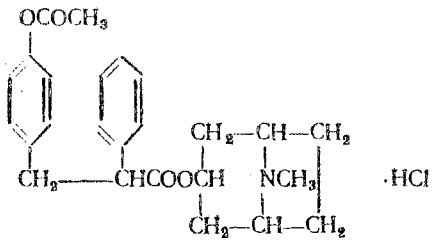
In those experiments in which the blood pressure was recorded simultaneously with renal oncometry, we noted a considerable decrease or complete disappearance of the vasoconstrictor action of adrenaline on the kidney.

In a dose of 0.1 mg/kg the preparations decreased the pressor action of mezatone and its effect on the nictitating membrane. With a dose of 0.5 mg/kg we noted an almost complete absence of pressor effect and contraction of the nictitating membrane. In experiments with injection of both adrenaline and mezatone restoration of the pressor reaction preceded restoration of the nictitating membrane reaction.

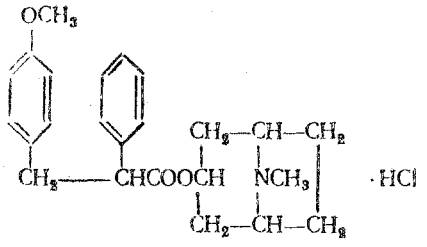
The action of nor-adrenaline under the influence of preparations OF-717 and OF-718 was considerably reduced, although their influence on the pressor effects of nor-adrenaline was less pronounced than on the pressor effects of adrenaline. Even when OF-717 and OF-718 were injected in doses of 5 and 7 mg/kg, the pressor reaction of nor-adrenaline not only was undistorted but it was completely present. Restoration of the initial pressor reaction of nor-adrenaline also took place much more rapidly than that of adrenaline (Figure 2).

The adrenal blocking action of preparation OF-717 was also checked on dogs. In an anesthetized dog (anesthesia: 10 mg/kg premedol subcutaneously and 1 g/kg urethane in the abdominal cavity) we observed a reduction in the action of adrenaline, similar to that observed in cats. Intravenous adrenaline (20 γ/kg) injection into an unanesthetized dog brought about a rise of 90 mm in blood pressure. After intravenous injection of a dose of 5 mg/kg of preparation OF-717, the same dose of adrenaline brought about a blood-pressure rise of only 30 mm.

Well-defined adrenal blocking action was noted upon passage of solutions of the preparations through the vessels of isolated rabbit ear. The preparations themselves showed a vasodilator action. In 1:10,000 concentration they brought about a 16-18% increase in the dilation of the blood. Under the influence of the preparations the vasoconstrictor action of adrenaline was sharply reduced Thus, in one of the experiments passage of adrenaline (concentration 1:1,000,000) through the aural vessels reduced the number of drops from 60 to 6 per minute: upon passage of adrenaline (same concentration) with preparation OF-717 (concentration 1:500,000)



OF-717



OF-718

the number of drops was only reduced to 46. In another experiment passage of adrenaline (concentration 1:10,000,000) reduced the number of drops from 78 to 24, and upon passage of adrenaline (same concentration) with preparation OF-717 (concentration 1:10,000), the number of drops increased to 108. Analogous results were obtained in other experiments.

Effect on Reactions that are Caused By Stimulation of Sympathetic Nerves.

We investigated the effect, in cats, of preparation OF-717 on pressor reactions caused by stimulation of a coeliac nerve and on contraction of the nictitating membrane caused by stimulation of the cervical section of the sympathetic trunk.

When a dose of 1 mg/kg was injected intravenously, the pressor reaction, caused by stimulation of the sympathetic nerve, was reduced for one hour after injection of a dose of 1 mg/kg of preparation. To suppress the effect of stimulation completely, the preparation had to be administered in considerably larger doses — — up to 5 mg/kg.

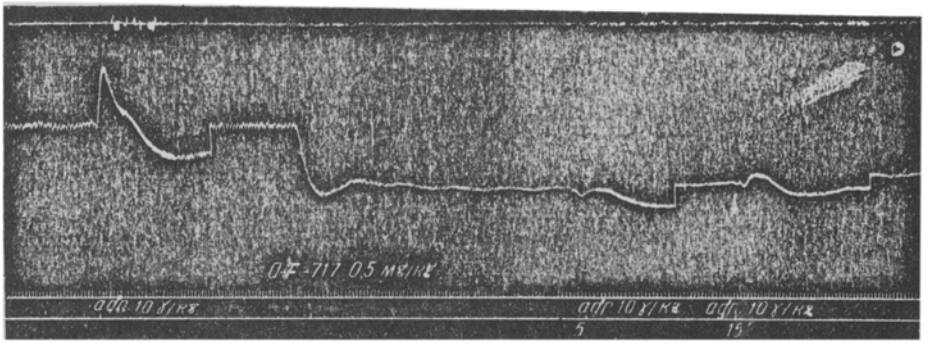


Figure 1. Experiment on cat (weight 3 kg; urethane 1 g/kg).
1) Key to curves (top to bottom): respiration, blood pressure, indications of time, indications of injection of adrenaline (adr.) and OF-717.

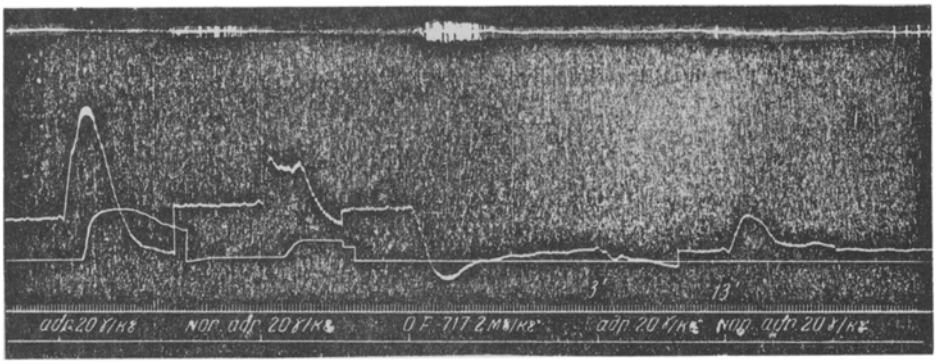


Figure 2. Experiment on cat (weight 2.4 kg; urethane 1 g/kg).
1) Key to curves (top to bottom): respiration, blood pressure, contraction of nictitating membrane, indications of time, indications of injection of adrenaline (adr.), nor-adrenaline (nor. adr.) and OF-717.

Effect on cholinergic systems

The effect of preparations OF-717 and OF-718 on m-cholinergic systems was investigated in whole animals and in isolated organs. The criterion of the activity of the preparations in whole animals (anesthetized cats) was the change in the blood circulation after induction-current stimulation of the ramus of the vagus nerve and intravenous injection of acetylcholine. In these experiments it was established that the preparations have a weak effect on m-choline receptors. In doses of 0.5 to 1-3 mg/kg they had no appreciable effect on the blood-circulation change caused by stimulation of the nerve and acetylcholine injection. Only with a 5 mg/kg dose did we observe a decreased hypotensive reaction.

The weak anticholinergic action of the preparations was also noted on sections of rabbit intestine. The intestinal spasm, caused by acetylcholine (concentration 1:500,000) did not disappear under the influence of preparations OF-717 and OF-718 (concentration 1: 1,000,000-1:50,000); only at a concentration of 1:100,000-1:10,000 did the intestinal musculature show signs of relaxation. At the latter concentration the preparations showed, however, a general antispasmodic action on the intestinal musculature.

The criteria of the effect of the preparations on n-cholinergic systems were the changes in blood circulation, respiration and tonus of the nictitating membrane in anesthetized cats after injection of cytisine (20-40 γ/kg intravenously). The results showed that even in a dose of 0.5-1 mg/kg the preparations markedly reduced the action of the cytisine: with a dose of 1-2 mg/kg we observed a prolonged and persistent anti-cytisine action (Figure 3). After intravenous injection of a dose of 1 mg/kg of OF-717 in atropinized cats, we noted a distortion of the nicotinic action of acetylcholine. The pressor reaction, observed upon injection of acetylcholine in a dose of 2 mg/kg, after injection of the preparation, was superceded by a decrease in blood pressure.

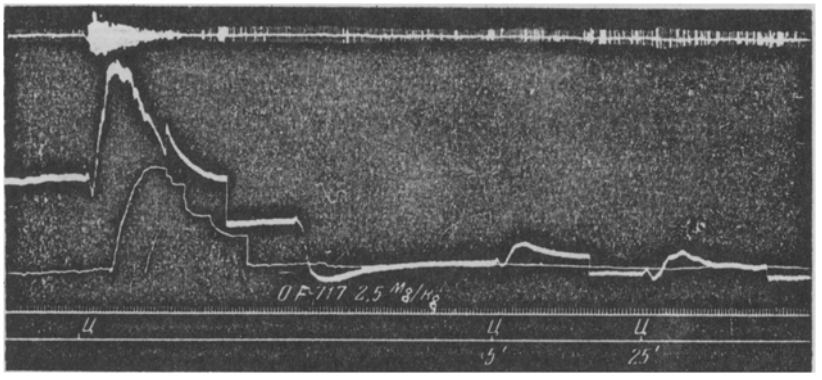


Figure 3. Experiment on cat (weight 2.7 kg: urethane 1 g/kg).
1) Key to curves (top to bottom): respiration, blood pressure, contraction of nictitating membrane, indications of time, indications of cytisine (C) and OF-717 injection.

The strong action on n-cholinergic systems was detected also in experiments on the abdominis rectus muscle of the frog. At a concentration of 1:10,000,000 the preparations decreased the reaction of the muscle to acetylcholine (concentration 1:5,000,000 - 1:1,000,000) and at a 1:100,000 concentration of the preparations muscular contraction was not observed after injection of acetylcholine.

DISCUSSION OF RESULTS

The foregoing data indicate that the compounds we investigated differ considerably in pharmacological properties from previously known tropine esters. Unlike atropine and compounds analogous to it that act predominantly on m-cholinergic systems, the tropine esters of acetoxy- and methoxyphenyl-α-phenylpropionic acid show only an extremely weak effect on these systems of the organism. Compared to atropine, the compounds we investigated show a considerably stronger effect on n-choline receptors and in the quality and strength of action, in this respect, they approach tropatsyn. The most interesting pharmacological characteristic of these new compounds is their active effect on adrenergic systems, namely, their adrenal blocking action, which

is many times greater than the adrenal blocking actionof atropine. While atropine, according to the data of Gyorgy and Porszasz, in a dose of 2 mg/kg only slightly weakens the action of adrenaline, the compounds we investigated show a well defined adrenal blocking action even in a 0.1 mg/kg dose.

At present we have a great deal of literature on numerous adrenal blocking agents (dihydrogenated alkaloids of ergot, derivatives of benzodioxane, chloroethylamine, imidazoline etc.). Our own literature devotes the most attention to benzolin [1, 3] and sympatolitin [5]. On comparing the adrenal blocking action of the compounds we investigated with the properties of the latter preparations, it is apparent that preparations OF-717 and OF-718 are less active than simpatolitin; however, they are less toxic and do not irritate tissues. Preparations OF-717 and OF-718 are considerably more active than benzolin.

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