health.

A followup of 15 patients following treatment with mycoheptin after 10, 30, and 60 days showed that in the majority (13) a stable clinical and mycological cure had been achieved.

In five patients with chronic granulomatous candidiasis, an improvement was noted during treatment. The ineffectiveness of the treatment in these patients could be due to the characteristics of pathogenesis in this condition, which require further investigation.

According to the observations from all the clinics, the overwhelming majority of the patients tolerated the drug well. Of 83 patients receiving the drug in the clinics, nine exhibited side effects in the form of nausea and slight pain in the epigastric region, and in one patient vomiting occurred. In five patients the blood residual nitrogen level was raised to 45.7-70.8 mg%. One patient displayed individual intolerance in the form of an allergic reaction, which also occurred on treatment with other drugs. In two patients, towards the end of treatment with mycoheptin, protein appeared in the urine together with individual casts and fresh erythrocytes. The results of the clinical tests have shown mycoheptin to be well tolerated in most patients on internal administration. The rare side effects consequent upon treatment with the drug do not usually require its withdrawal.

The unique nature, broad antifungal spectrum, and the effectiveness of mycoheptin in the oral treatment of deep-seated mycoses, which has been established clinically, enable it to be recommended for use in general medical practice.

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TSIKLOBUTONII — A NEW SOVIET CURAREMIMETIC AGENT

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The curaremimetic substances existing at the present time do not fully satisfy the demands of anesthesiologists. Consequently, the necessity for seeking new drugs of this group differing in the duration and breadth of their myoparalytic action still exists. Particular interest is presented by antidepolarizing curaremimetic agents blocking nerve–muscle transfer without preliminary excitation. In contrast to drugs with a depolarizing action they have no effect on the distribution of potassium ions and therefore do not disturb cardiac activity and do not cause muscular pains. A substantial advantage of antidepolarizing (competitive) drugs is the presence of antagonists which, where necessary, permit a rapid restoration of nerve–muscle conduction. Such antagonists are anticholinesterase agents.

One of the new antidepolarizing curaremimetic drugs is tsiklobutonii ["cyclobutonium"],

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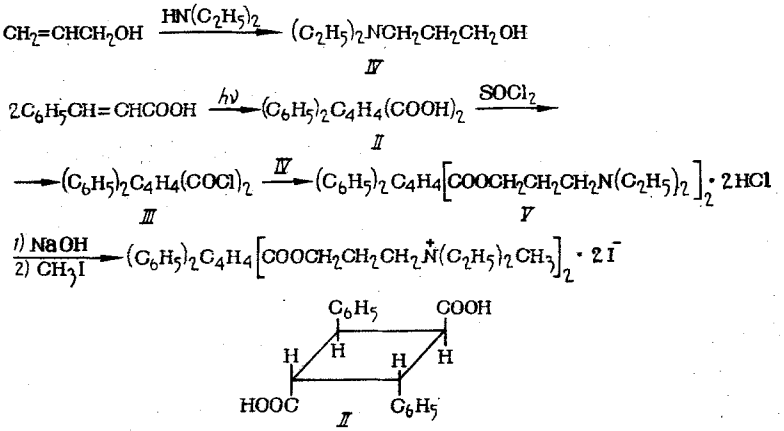
which has been obtained as the result of a study of the relationship between structure and myoparalytic activity for a large number of bisquaternary derivatives of stereoisomeric diphenylcyclobutanecarboxylic acids [1-3]. The search for curaremimetic drugs in this series was of interest, since the alkaloid thesine, which is a derivative of α-truxillic acid, has shown high curaremimetic activity, and, moreover, the structure of the compounds under construction permitted a wide variation of the stereoconfiguration of the acid, of the structure and length of the aminoalkyl chain, of the substituents in the aromatic nuclei and attached to the quaternary nitrogen atoms, and also of other structural parameters. It was particularly important that by the mechanism of their action all the compounds obtained belonged to the antidepolarizing myorelaxants. One of the most active compounds of this series – the dimethiodide of bis(diethylaminopropyl) α-truxillate, which has been called tsiklobutonii [4] – has been subjected to a further detailed pharmacological and clinical study.

The starting material for the synthesis of tsiklobutonii is cinnamic acid [1] which, under the action of sunlight or certain artificial light sources, undergoes photodimerization to α-truxillic acid (II). In a number of investigations performed together with the All-Union Scientific-Research Institute of Illumination Technology, artificial sources of light have been selected the spectral composition of the radiation of which has enabled the optimum yields of the photodimer – α-truxillic acid – to be obtained. It must be mentioned that the reaction takes place in the solid phase when an aqueous suspension of crystalline cinnamic acid is irradiated, because of which crystal structure of the latter has decisive importance. Irradiation of the metastable β-form of cinnamic acid forms only the stereoisomeric β-truxillic acid, and since commercial cinnamic acid is frequently the β form or a mixture of the α and β forms, a method has been developed for converting the β forms of cinnamic acid into the α-form of



α-Truxillic acid can be converted into tsiklobutonii in various ways, of which we have used the reaction of the dichloride of α-truxillic acid (II) with 3-diethylaminopropan-1-ol (IV). The latter was obtained by the addition of diethylamine to allyl alcohol by heating a mixture of them in an autoclave at 100-105°C in the presence of caustic potash; in this process it is necessary to take care that the reaction mixture is not overheated, since, according to the literature, at 130-140°C the spontaneous decomposition of allyl alcohol, accompanied by a sharp rise in the pressure in the autoclave, is possible. The dichloride (III) is formed smoothly by the reaction of the acids (II) with the thionyl chloride in dichloroethane; its isolation in the individual state is not essential, and the bis(3-diethylaminopropyl) α-truxillate (V) is formed by the reaction of dichloroethane solutions of 2 moles of the dichloride (III) with 2 moles of the amino alcohol (IV); the hydrogen chloride liberated in the reaction is bound by the amino groups of the diester (V). The diester (V) is separated from the residue of unchanged amino alcohol (IV) by fractional alkalinization since the latter has a higher basicity. The isolated diester (V) is converted into the dimethiodide tsiklobutonii – by heating it with methyl iodide in methanol.

The method of obtaining tsiklobutonii and, in particular, the performance of the most complex part of the process – the photodimerization of cinnamic acid into α-truxillic acid – was developed in the "Farmakon" factory; the tsiklobutonii so obtained corresponded to the requirements of VMRTU [All-Union Interrepublican Technical Specification 42 No. 3733-69.

Tsiklobutonii forms a white crystalline powder sparingly soluble in water (1:100 at 20°C), slightly soluble in 95% ethanol, and very slightly soluble in acetone, chloroform, and ether. It turns yellow in the light.

A medicinal form of tsiklobutonii was developed in the laboratory for the preparation of medicinal forms, and methods for analyzing tsiklobutonii and its medicinal form were worked out in the analytical laboratory of the Institute of Pharmacology of the Academy of Medical Sciences of the USSSR.

Tsiklobutonii is supplied in the form of a 0.7% aqueous solution in 2 ml ampuls. Trilon B (the disodium salt of ethylaminediaminetetraacetic acid) is used as stabilizer. The solution is sterilized with live steam.

A solution of tsiklobutonii consists of a colorless clear liquid with a pH of 4.5-5.5. It is stored in a place protected from the light (list A).

Reaction for Authenticity.* 1) With heating, 0.03 g of the substance is dissolved in 5 ml of water; to 0.5 ml of this solution is added 3 drops of Congo Red solution, whereupon a voluminous red precipitate insoluble on heating is formed. 2) Reaction for iodide ion with silver nitrate.

Melting point 203-208°C.

Test for Purity. A solution of 0.3 g of the substance in 30 ml of carbon-dioxide-free water must be clear and colorless and have a pH of 5.5-6.5. The preparation must contain not more than 0.03% of sulfates, its loss of weight on drying at 100-105°C must not exceed 0.5%, the sulfated ash must not exceed 0.1%, and the heavy metal not more than 0.001%.

Quantitative determination is performed by nonaqueous titration with 0.1 N perchloric acid in formic acid (97.7%, 3 ml), acetic acid (15 ml), and a solution of mercuric acetate (10 ml) with Crystal Violet as indicator.

1 ml of 0.1 N perchloric acid corresponds to 0.04033 g of tsiklobutonii, the amount of which in the sample must not be less than 99%.

EXPERIMENTAL - PHARMACOLOGICAL SECTION

The properties of tsiklobutonii were studied in experiments on rabbits and cats. The myoparalytic activity of tsiklobutonii on its investigation in experiments on rabbits (head inclination symptom) proved to be approximately three times greater than the activity of tubocurarine chloride under the same conditions; the mean effective dose of the tsiklobutonii was 37.5 (32.4-43.3) mg/kg. In experiments on cats we investigated the influence of tsiklobutonii on the contraction of the gastrocnemial muscle (semiisometric conditions) caused by electric discnarges of the peripheral segment of the sciatic nerve (single supramaximum pulses lasting 0.5 msec). It was found that in its capacity for completely blocking nerve–muscle transfer in cats tsiklobutonii was somewhat superior to tubocurarine chloride (130-180 and 180-230 µg/kg, respectively). The duration of the nerve–muscle block in these experiments was 3-8 min. In the doses mentioned, tsiklobutonii generally suppressed respiration to the extent of complete cessation. From the mechanism of its myoparalytic action, tskilobutonii must be assigned to the substances of the antidepolarizing competitive types. In favor of this are the following facts. On intravenous administration to chicks (15-20 µg/kg) the drug caused flaccid paralysis, like tubocurarine chloride. In experiments on cats (recording of nerve–muscle transfer) proserine [neostigmine] constantly decreased and shortened the myoparalytic effect of tsiklobutonii. In an investigation of the drug in experiments on the musculus rectus abdominis of the frog, it was established that it had no stimulating effect on the muscle and decreased or prevented the stimulating action of acetylcholine on the muscle. In experiments on rabbits, after the administration of the drug muscle relaxation set in without preceding muscular fibrillations. The antidepolarizing nature of the action of tsiklobutonii is also confirmed by experiments in which the interaction of the drug with ether was investigated. On a background of ether narcosis in cats, tsiklobutonii had a suppressive influence on nerve–muscle transfer which was considerably greater than normal and more prolonged. In analogous experiments, hexenal [hexobarbital] and thiopental

*VMRTU 42 No. 3733-69.

sodium did not affect the action of the drug.

Of the other effects of tsiklobutonii the slight and brief hypotensive action must be mentioned, which is apparently due to a weak ganglion-blocking activity of the drug (tsiklobutonii obviously does not exhibit a myotropic spasmolytic action, since it does not eliminate in an experiment the spasm of isolated rat intestine caused by barium chloride).

Furthermore in muscle-relaxing doses tsiklobutonii exhibits a distinct suppressive action on the m-cholinoreceptors of the heart which is shown in the experiments on cats in the elimination of the bradycardia caused by acetylcholine. Here the magnitude of the depressor reaction to acetylcholine does not change substantially.

The cardiotropic m-cholinolytic action of tsiklobutonii is apparently the cause of the tachycardia that may arise after the administration of the drug.

The m-cholinolytic action of tsiklobutonii is expressed to a smaller degree on the muscle of the bronchi (reduction in the reaction of the bronchi to acetylcholine). In experiments on cats, tsiklobutonii had no effect on the contraction of the intestine and urinary bladder caused by acetylcholine [5].

Tsiklobutonii possesses no antihistamine properties. In concentrations of $2 \cdot 10^{-6}$-$1 \cdot 10^{3}$ M the drug does not eliminate the contraction of isolated intestine caused by histamine ($2 \cdot 10^{-7}$ M), and in muscle-relaxing doses it does not influence the depressor effect of histamine on its intravenous administration in a dose of 5 μg/kg.

When a 1% solution of the drug was introduced into the conjunctival sac in experiments on cats, no anesthetizing or irritant properties of the preparation were shown.

Experiments on the influence of the drug on the blood system performed on cats under artificial respiration (the results of M. F. Runova) showed that tsiklobutonii in doses of 500-1000 μg/kg intravenously did not change the concentrations of hemoglobin, erythrocytes, reticulocytes, and leucocytes of the differential blood count.

The toxicity of the drug was studied on cats and rabbits under artificial respiration with recording of the arterial pressure and ECG. It was found that intact rabbits did not die after the intravenous administration of tsiklobutonii in doses of 200-400 mg/kg and cats (under narcosis due to urethane and chloralose) even after the administration of 600 mg/kg. A comparison of these doses with the myoparalytic doses indicates the low toxicity and considerable therapeutic breadth of tsiklobutonii.

Clinical trials of tsiklobutonii [6-9] have shown the high efficiency and more prolonged action of the new muscle relaxant. After the intravenous administration of tsiklobutonii weakening of the skeletal muscle arises in a few minutes and continues for 1-3 h, depending on the dose. The sequence of the switching off of the skeletal muscles is similar to that for the majority of muscle relaxants, and it is possible to achieve satisfactory weakening of the muscles of the lower extremities and the abdominal wall without substantial disturbance of respiration. However, it must be noted that at the beginning of the action of the muscle relaxant, particularly when it is used in high doses, suppression of respiration is possible which requires auxiliary or artificial ventilation of the lungs.

In the use of tsiklobutonii on patients, tachycardia is found not infrequently which is due to the vagolytic properties of the drug. According to the ECG, tsiklobutonii does not affect conductivity and compactability of the myocardium.

Some reduction in arterial pressure, more pronounced in patients with increased arterial pressure, is also observed. In large doses, tsiklobutonii may cause dilation of the pupils. These effects are apparently connected with the ganglion-blocking action of the drug.

In the clinical trials of tsiklobutonii it showed no effects on EEG and the tendon and corneal reflexes.

These properties of tsiklobutonii permit its use for the relaxation of skeletal muscles in operative interventions. It is particularly desirable to use tsiklobutonii in those cases where there is no need for the switching off of spontaneous respiration. At the same time, in view of the possible suppression of respiration at the beginning of the action of the drug, it should be used only under conditions ensuring intubation of the trachea and the performance

of artificial respiration. Tsiklobutonii is unsuitable for ensuring intubation itself since the muscular relaxation necessary for this purpose develops only some minutes after the administration of the drug and only with fairly high doses of it. Consequently, intubation is generally performed against a background of the action of ditiline, and then the patient is given tsiklobutonii.

On a background of ether anesthesia, for relaxing the abdominal muscles for 1-3 h tsiklobutonii is administered in doses of 0.1-0.12 mg/kg, which leads to the relaxation of the muscles after 2-5 min. After the initial brief suppression, spontaneous respiration continues in adequate volume. To switch it off, the dose of the drug must be increased to 0.18-0.2 mg/kg.

In nitrous oxide anesthesia, larger doses of tsiklobutonii are required than in ether anesthesia — about 0.25 mg/kg.

Where the effect after the first injection of tsiklobutonii is inadequate, the dose is increased gradually (in steps of 0.01-0.02 mg/kg at intervals of 5-10 min). After the muscular relaxation caused by the first injection of the drug has died away, repeat doses of not more than 1/3-1/2 of the original dose are administered.

To stop the muscle-relaxing action of the drug, proserine (2-4 mg intravenously or intramuscularly) or similar anticholinesterase drugs are used.

Side effects that have been observed in the clinical use of tsiklobutonii include tachycardia, a slight fall in the arterial pressure, and dilation of the pupils. When large doses of tsiklobutonii are used, recurarization is possible

A contraindication for the use of tsiklobutonii is myasthenia. The drug must not be used when conditions for intubation of the trachea and the performance of complete artificial respiration do not exist.

Thus, tsiklobutonii is an effective-long-acting muscle relaxant of the antidepolarizing type with a great width of myoparalytic action. The drug has a weak ganglion-blocking action and shows pronounced m-cholinolytic activity in relation to the heart and the bronchi. These properties of the drug permit it to be recommended for muscular relaxation in operative interventions, particularly in those cases where the switching off of spontaneous respiration is not required. The lowering of the tonus of the blood vessels and of the smooth muscles of the bronchi under the action of tsiklobutonii make its use particularly desirable in patients with hypertonic disease, obliterating endarteritis, bronchial asthma, nephrolithic disease, etc.

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