ETPENAL, A NEW NEUROTROPIC DRUG

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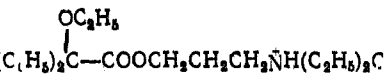
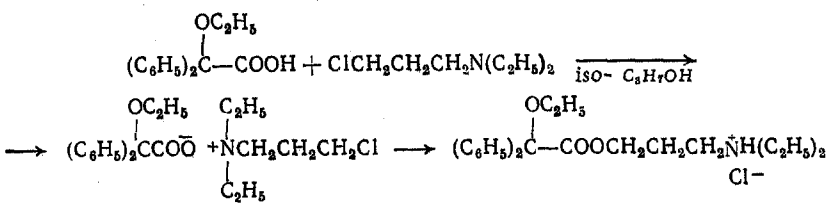
Etpenal (I) is a new home-produced drug which has high blocking activity on the choline receptors of the central and peripheral nervous systems. Chemically speaking, it is γ-diethylaminopropyl α-ethoxydiphenylacetate hydrochloride:



Etpenal (I) was obtained as a result of the joint work of chemists (O. L. Mndzhoyan and E. R. Bagdasaryan) and a pharmacologist (V. A. Samvelyan) at the Institute of Fine Organic Chemistry of the Academy of Sciences of the Armenian SSR under the leadership of A. L. Mndzhoyan.

The rationale for the synthesis of (I) was provided by a study of the relationship between chemical structure and physiological activity in aminoesters (substituted acetic acid derivatives), taking into account the two conformations of acetylcholine. It was established that the extended conformation resulted in an increase in the activity of the aminoesters of substituted acetic acids on the cholinergic structures of the central nervous system, in particular on the nicotine-sensitive receptors [1-11]. These observations provided the groundwork for new studies which led to the synthesis of (I) [12].

The synthesis of (I) is effected by the reaction between α-ethoxydiphenylacetic acid and γ-diethylaminopropyl chloride in isopropyl alcohol



It was found that the salt of γ-diethylaminopropyl chloride and α-ethoxydiphenylacetic acid was formed first, which on heating underwent rearrangement to form the aminoester hydrochloride.

Etpenol (I) is a colorless, crystalline powder, mp 132-134°C, soluble in water, alcohol, and chloroform, sparingly soluble in acetone, and insoluble in ether.

General Pharmacological Properties of (I). Studies of the pharmacological effects of (I) were carried out in several animals using standard methods. It was found that (I), at a dose of 2-3 mg/kg, induced brief and slight reduction in the arterial pressure. At higher doses, the hypotensive effect was extended and increased. Only when high doses were given was there reflex deepening and increased frequency of respiration due to the drop in arterial pressure.

The effects of (I) on the choline-reactive systems of the body were studied in isolated organs and in the intact animal. The effects on muscarine-sensitive choline receptors were examined in Straub isolated frog hearts, sections of isolated cat intestine, and narcotized cats treated with cholinomimetic compounds (acetylcholine and carbocholine). It was found that in concentrations of $1 \cdot 10^{-8}$-$5 \cdot 10^{-7}$ g/ml, which had no inhibitory effects on cardiac con-

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tractions, (I) had a cholinolytic (muscarinolytic) effect, eliminating or reducing the effects of acetylcholine by 50-85%. In the same concentrations, (I) had cholinolytic activity in the cat intestine. Myotropic activity was also shown by (I), since it caused 50% inhibition of the $BaCl_2$-induced contraction of isolated intestine in a concentration of $1 \cdot 10^{-7}$ g/ml.

In cats immobilized by diacetylcholine (ditiline), in a proserine model of bronchospasm the therapeutic effects of (I) were apparent at 0.5 mg/kg, and at 0.6 mg/kg total cessation of bronchospasm induced by stimulation of the peripheral terminus of the vagus nerve [8] was noted. Muscarine-sensitive formations in the central and peripheral nervous and cardiovascular system were blocked by doses of 3-5 mg/kg.

The effects of (I) on the sympathetic ganglia were studied by their ability to modify the contraction of the third eyelid of the cat caused by intravenous administration of the cholinomimetic drug subecholine, and by stimulation with a pulsed current of the pregangliar trunk of the sympathetic nerve. It was found that (I) eliminated these effects in doses of 1-3 mg/kg. In experiments on narcotized cats, the nicotinolytic effects of (I) on the choline receptors of the carotid ganglia and the medullary layer of the adrenals were apparent at doses of 0.5 mg/kg. In doses of 1-2 mg/kg, the excitatory effects of subecholine on the arterial pressure and respiration were eliminated completely. From doses of 0.1 mg/kg, (I) exerted a blocking effect on nicotine-sensitive formations (the cardiac parasympathetic ganglia). In doses of 0.4-0.5 mg/kg, (I) completely eliminated the effect of the vagal nerve on the heart These experiments demonstrated the high peripheral nicotine-sensitive activity of (I). No curariform effects were shown by (I), even in high doses (10-15 mg/kg), nor did it have any effect on the adrenergic biochemical systems.

In experiments on rabbit eye cornea, the frog sciatic nerve, and the intact animal, the ability of (I) to induce terminal, conductive, and spinal anesthesia was assessed. These experiments showed that (I) possessed local anesthetic properties. A 0.1% solution of (I) totally prevented the conduction of nerve impulses along the sciatic nerve of the frog, the effect commencing after 8 min and lasting for 15 min. In a 0.25% solution of (I), anesthesia commenced after 2 min and lasted for 35 min. In a 0.5% solution, terminal anesthesia was equal to 150 Renier units (moderate anesthesia).

The central effects of (I) were studied in a variety of experimental models of convulsive states, induced by arecoline, nicotine, corazole, and strychnine. The results of these experiments showed that in a dose of 0.1 mg/kg, (I) reduced the severity of nicotine convulsions from 2.6 to 1.2 points, and in a dose of 1 mg/kg, in most of the experiments, it completely prevented the development of convulsions. Arpenal, which was used as the standard of activity, was similarly effective in this model [13] only at a dose of 3.2 mg/kg.

In a model of tremor and convulsions induced by arecoline, (I) was again active, and in a dose of 1 mg/kg it considerably reduced the duration of tremor and completely protected the animals from a lethal outcome. In doses of 5-6 mg/kg, symptoms of intoxication by arecoline were totally absent [14]. Thus, (I) has considerable anticonvulsive activity, in low doses blocking the nicotine-sensitive formations of the central nervous system, and in higher doses blocking the muscarine-sensitive centers. The occurrence of central effects is also shown by its ability to potentiate the hypnotic effects of narcotics.

In acute and chronic experiments on rabbits and cats, the effects of (I) were studied on the biopotentials of the cortex and subcortex and the mesencephalic reticular formation, with mono- and bipolar electrode leads. In a dose of 4 mg/kg, (I) affected the EEG, but the desynchronization reaction was blocked only at doses of 7-9 mg/kg. Etpenal (I) mainly blocked the nicotine-sensitive choline receptors of the cerebral cortex, and it had little effect on the conduction of impulses in the reticular system [15-16].

There are indications [17] that there is a relationship between the nicotinolytic activity of a drug and its capacity to produce a favorable clinical effect in hyperkineses of varied origin and Parkinsonism. The nicotinolytic activity of (I) is greater than that of **spasmolytin, tropacin, arpenal,** and other antiparkinsonian drugs.

Etpenal (I) was highly effective in models of pulmonary edema induced by adrenalin and ammonium chloride [18]. Of the compounds studied in [12] for their central and peripheral cholinolytic properties, the best results in both models of pulmonary edema were obtained with (I), probably as a result of its combination of central and peripheral, **predominantly** nicotinolytic and partially muscarinolytic, properties.

A good effect was also obtained with (I) in the treatment of experimental myocardial infarction. Its mode of action is due to its ability to rectify processes occurring in the cellular membranes. Etpenal (I) is actively involved in the metabolism of phospholipids, has a stabilizing effect on the myocardial membranes under the experimental conditions, and improves the condition of the actomyosin contractile system, as shown by the general and intracardiac hemodynamic parameters [19].

A study of the acute and chronic toxicities of (I) showed that the LD_{50} following intraperitoneal administration to mice was 87.5 mg/kg. Toxic effects were noted at doses from 20 mg/kg following intravenous administration to rabbits and cats.

A study of its chronic toxicity (administration over a period of 30 days in a dose of 10 mg/kg) showed that (I) was without significant effects on the blood, urine, and behavior of the animals, and that the body temperature was reduced only slightly.

On the basis of these findings on its pharmacological effects and toxicity, (I) was recommended for clinical trials as an antispasmodic and spasmolytic drug in hyperkineses of extrapyramidal origin, the Parkinsonism syndrome, to reduce muscle tonus in spastic pareses, in various convulsive states, for nicotine poisoning, etc., i.e., in those cases in which it was necessary to block reversibly the cholinergic synapses of the central and peripheral nervous systems, and also to treat diseases in the pathogenesis of which a substantial part was played by spasms of the smooth musculature and hypersecretion (ulcerous conditions, bronchial asthma, etc.).

Results of Clinical Trials with (I). The drug was tested in a number of neurological and therapeutic clinics. In the neurological clinics, (I) was used in the treatment of Parkinsonism, extrapyramidal rigidity, a variety of hyperkineses, and pyramidal spasticity. The therapeutic activity of (I) was investigated at doses of 40-60 mg/kg 2-3 times daily, or sometimes the single dose was increased to 80-100 mg.

In most cases, the therapeutic effects of (I) became apparent within 8-10 days of the commencement of treatment. In some cases, however, improvement was observed at an earlier stage, with reduction in muscle constraint, hyperkinesis, tremor, greasiness of the face, etc. The reduction in hyperkinesis enables the patients to look after themselves, muscle pain is eliminated, the appetite improves, and insomnia disappears. In patients treated with (I), speech modulation improves, movement becomes more plastic, the patients feel better, and the drug is taken willingly. Combined treatment is recommended for treatment of extended duration with the drug being first administered by intramuscular injection, and subsequently perorally.

Significant improvement was obtained in 53.8% of patients, partial improvement in 18.7%, and no effect was observed in 3.1% of the patients.

In most of the clinical studies, the therapeutic effect of (I) was found to be superior to those of artan, tropacin, and spasmolytin.

Thus, preliminary clinical trials have shown (I) to be effective in the treatment of extrapyramidal rigidity, spastic pareses following transferred insults, choreal tremor, mixed hyperkineses, and typical Parkinsonism. Treatment of the patients with the drug was not accompanied by undesirable side effects, complications, or allergic reactions.

In therapeutic clinics, (I) was studied in hospitals and polyclinics, the drug being prescribed for patients with gastric and duodenal ulcers, myocardial infact, in preinfarct conditions in which fibrillar arrhythmia and supraventricular asystole were present, in stenocardial attacks, and in attacks of bronchial asthma. Treatment was continued for 2-3 weeks. Treatment was initiated with the recommended 20 mg dose (three times daily), and the daily dose was then gradually increased to 80-100-120 mg.

In these conditions, a steady reduction in pain was observed, usually commencing from the 3rd-4th day of treatment. In localized foci of irritation in the gastrointestinal tract with accompanying viscerocoronary reactions, the patients first of all noted a disappearance of pericardiac pain. Conversely, when stenocardia was resistant and accompanied by hypertonia, dyspeptic disturbances and accompanying dyskinetic symptoms in the gastrointestinal tract were the first to disappear. The drug had a stable hypotensive effect. Examination of the ECG showed an improvement in the terminal region of the electrocardiographic complex (S–T interval T wave), and the ballistocardiogram became normal. The best results were obtained in patients with stenocardia of primarily viscerocoronary origin, more particularly in the exacerbation

stage. Acute myocardial infarct and various arrhythmias are not contraindications to treatment with the drug.

Etpenal (I) was found to be particularly effective in patients with gastric and duodenal ulcers. It was found that in patients with excited peristalsis and acceleration of the motor-evacuatory function of the stomach, a quietening effect was obtained. In patients with flaccid peristalsis and retarded gastric motor-evacuatory function, some improvement in peristalsis was noted. Thus, treatment with (I) resulted in normalization of functional disturbances of gastrointestinal motor function. From the earliest days of treatment, patients with ulcerative disease and spastic colitis experienced cessation of pain and dyspeptic symptoms. X-ray examinations showed the disappearance of "pits" in 60% of patients and a substantial reduction in the remainder, and pylorospasm ceased.

In many instances, (I) was effective when other antiulcer drugs had failed. In all the clinics, (I) was found to have a stable analgesic effect, and its therapeutic value was confirmed by x-ray examinations, with normalization of the tonus of the gastrointestinal tract and gastric evacuatory function, elimination of edema of the mucous membranes, and the disappearance or substantial reduction of "pits."

Etpenal (I) was found to be effective in bronchial asthma. The drug is recommended for use in conjunction with other broncholytic drugs, in patients with nonchronic forms of asthma, without pneumosclerosis.

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