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GANGLIOLYTICS IN THE THERAPY OF ULCEROUS DISEASES

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- USSR -

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GANGLIOLYTICS IN THE THERAPY OF ULCEROUS
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Following is the translation of an article entitled "Gangliolitiki v Lechenii Yazvennoy Bolezni" (English version above) by S. M. Ryss in Vrachebnoye Delo (Physicians Affairs), Vol 42, No. 4, Kiev, April 1960, pages 351-354.

Ganglion-blocking substances or gangliolytics, block selectively vegetative ganglia and thus temporarily shut off central impulses transmitted through the vegetative nervous system. Such shut-offs provide - on the one hand - rest for the corresponding organ (or even for the whole physiological system) that happens to be in a pathological state.. On the other hand, by effecting quantitative and qualitative changes in the central impulsation, they condition considerable shifts in the functional activity of individual organs. Soviet pharmacologists (S.V. Anichkov and associates, M.D. Mashkovskiy and associates) and chemists (A.L. Mdzhoyan and associates) have contributed tremendously to the doctrine of ganglion-blocking substances and have supplied concrete substantiation for the use of gangliolytics in clinical practise.

This present report is devoted to application of domestic synthetic ganglion-blocking preparations in the therapy of ulcerous disease.

The following preparations were used in the didactic clinic of internal medicine of the Leningrad medical institute (A.T. Povalya'yev's): tetamonum I, hexonium, gangleron, difacil, and arpenalum.

Tetraethylammonium -- tetamon (T Ae A) -- an iodido of the former, synthesized in the Ukranian institute of ex-

perimental endocrinology, acts selectively upon -N-choline-reactive systems.

The pharmacology of the preparation has been studied in detail by Z.I. Vedeneyeva, T.A. Mel'nichkova and M.L. Tarakhovskiy. Z.I. Vedeneyeva showed that the greatest sensitivity with respect to the preparation is demonstrated by N-choline-reactive systems of parasympathic ganglia. T.A. Mel'nikova established experimentally the sharp suppression of stomach and intestine secretion when tetamon was taken.

Donald and Smith had observed that tetamon inhibits the movements of a hungry stomach.

L.P. Flanchik, I.G. Simon, Ae. S. Reynes and S. A. Bagen have noted analgesic effect of the preparation in those afflicted by ulcerative disease. V.M. Kogan-Yasnyy observed an instantaneous termination of pain in such patients when tetamon was introduced, as well as a decrease in heightened indexes of acidity and the secretion of stomach fluids (gastric juice).

We employed tetamon I. The preparation was administered in a 10% solution intramuscularly - 1 millilitro twice daily over a period of 2-3 weeks. A total of 90 persons with ulcerous disease were subjected to tetamon treatment. The majority of them had a decrease in pains from the very first days of the treatment. A number of patients noted a sharpening of pain after the first 2-3 injections. Complete termination of pain was experienced by 50% of the patients in the course of the first 10 days of treatment. Thus there is created a relatively favorable impression of the effect of the preparation on the acid-producing secretory functions of the stomach - with respect to their normalization; so far as its effect on the motility function of the stomach is concerned, observation shows that waves of contraction disappear and the gastric motility chart curve becomes considerably straightened after the preparation has been introduced.

Röntgonologically, the niche symptom was present prior to treatment in 83 patients. After the tetamon treatment the niche became indistinguishable in 63 patients and inconstant in 5.

Hexonium (C6). The pharmacological action of hexonium was studied in detail by P.P. Denisenko, who showed experimentally that hexonium possesses cholinolytic effects on all N-choline-reactive systems; it lowers the lability of vegetative ganglia.

According to the author's data, hexonium acts predominately in a suppressive way upon the function of the gastro-intestinal tract. By means of a proper choice of dosages (small dosages), lowered gastric function can be successfully enhanced.

Hexonium manifests high properties of warning and therapy in cases of reflex trophic disturbances of the stomach wall. I.S. Zavodskaya has shown that, in instances of experimental ulcers in guinea pigs, a delay in the synthesis of proteins in the gastric mucosa is observed, which presents one of the early signs of disruption in the trophic activity of the gastric mucosa.

A suppression of gastric secretion was obtained by Grossman and Robertson in experiments with dogs into whose veins 4 ml/kg of hexonium were injected.

P.A. Tepper and A.N. Kamenskiy noted the suppression of excessive secretion, the lowering of increased motor activity of irritated stomach, as well as the analgesic effect of hexonium in therapy of ulcerative disease.

Kay and Smith point out that hexomethonium treatment (1) led to elimination of pains in patients with ulcerative disease, to normalization of secretion, to suppression of motor activity of the stomach.

We used hexonium - C6 - diiodide -- 1.6 hexamethylenbis (ammonium trimethyl), synthesised in the Institute of experimental medicine in the A.S. Anichkov laboratory. It was injected intramuscularly: 1.5 ml of 2% solution twice daily, i.e. 30-60 milligrammes of hexonium in 24 hrs. Course of treatment -- about 2 weeks. We strove to achieve only partial ganglion blocking, because complete blocking by means of large dosages of hexonium affects metabolic processes adversely -- tissues are denied the trophic influences of the nervous system.

Hexonium was used in the treatment of 150 patients with ulcerative disease.

(1) Hexomethonium = foreign analogy of hexonium.

The pain-stilling effect of hexonium was felt, essentially, on the fourth to sixth day of treatment, without any preceding phase of increased acuteness. Hexonium exerted a normalizing influence upon the secretory and acid-producing functions of the stomach, while the motility function of the stomach - in cases where it was excited -- was suppressed, as precise observation showed. Of the 126 patients with the finding of a niche, 108 (85.7%) had none left after the treatment.

Gangleron. --- chloralhydrate-of-diethylaminoalcalic ester-paraisobutylate of oxybenzoinic acid, synthesised by A.L. Mndzhoyan in the Institute of fine organic chemistry at the Academy of Sciences of the Armenian SSR.

Pharmacological properties of gangleron were studied by M. Ya. Mikhel'son, Ya. R. Savinskiy, Yu. G. Fedorchuk and others.

Gangleron is a cholinolytic substance capable of blocking not only the N-choline-reactive systems of peripheral ganglia, but also the choline-reactive systems of central interneutonal synapses, i.e. it has both central and peripheral pharmacological action.

We used gangleron intramuscularly: 2 ml of a 1.5% solution three times daily, i.e. 90 mg. in 24 hrs. The preparation was injected for 2 weeks and then gradually the gangleron injections were changed to orally taken identical dosages of the same preparation, continuing for 14-30 days.

Ninety-five

^ patients with ulcerative disease were subjected to gangleron treatment. An overwhelming majority of them felt the pain-stilling effect of gangleron in the course of the first week of treatment. After the treatment a tendency towards normalization of secretional and acidity-producing functions of the stomach became distinguishable.

Prior to the treatment, a positive niche sign was found in 79 patients, but after the treatment no niche was discovered in 65 patients, it had decreased in 12, and remained unchanged in two.

The peptic factor, i.e. an enhanced digestive ability of the gastric juice relates to the final link of the pathogenetic mechanism of the ulcerative disease. Ulcers -- the destruction of the stomach wall -- are the direct result of heightened digestive action of the gastric juice.

Members of our clinic staff (Ts. G. Masevich), using the method of paper electrophoresis to determine stomach-fluid proteins, have shown that - under the effect of gangleron - persons with ulcer disease have a lessening of the heightened digestive activity of the gastric juice.

Arpenal. The use of yet another new gangliolytic has recently been commenced by us. The new preparation is arpenal synthesized by A.L. Mdzhoyan in the Institute of fine organic chemistry of the Academy of Sciences of the Armenian SSR.

Arpenal -- is a salt-acidic salt of diethylamino-propylamide of diphenyl-acetic acid. Its pharmacological properties were studied by M. Ya. Mikhel'son. Arpenal possesses expressly manifested spasmolytic properties.

Twenty-eight

A ulcer patients were given arpenal intramuscularly: 20-40 mg three times daily over a period of 2-3 weeks. It is as yet difficult to come to any conclusions, but one may say that pronounced spasms of the upper part of the small intestine were quickly eliminated by arpenal. A quicker elimination of the pain syndrome was achieved when arpenal was combined with gangleron. Constipation, which - as a rule - accompanies ulcers, can be affected by arpenal, but only under the condition that any one employed dosage of the preparation should not be less than 40 mg. The finding of a niche, noticed prior to treatment in 21 patients, was not found in 21 patients after the treatment.

Difacil (spasmolytin), synthesized by M.D. Mashkovskiy, belongs to cholino-reactive substances which block mainly the cholino-reactive systems of central interneuronic synapses, affecting to a considerably lesser degree the transmission of impulses through peripheral ganglia.

S.V. Anichkov had proposed to call such substances central cholinolytics. Dyfacil was used by us either internally - 0.25 grammes twice daily in gelatinous capsules or in the form of paravertebral segmental intracutaneous blockade (50 ml of 0.25% solution). Dyfacil was prescribed as an adjunct in hexonium treatment. This led to a quicker elimination of pains -- of telling consequence for the general morale of the patient -- and the normalizing effect on the secretory and acid-producing functions of the stomach was enhanced. The inclusion of dyfacil into the complex of therapeutic means did not have any influence on the change of the roentgenological picture.

Comparing the therapeutic properties of the gangliolytics employed, we must give preference to hexonium and gangleron. Their use leads to a quicker disappearance of pain, a high percentage of healing of the ulcerous niche is observed, a more beneficial influence on the general condition of the patient is noted.

Of particular therapeutic value is gangleron for those patients whose ulcer disease is combined with hypotensive disease and with a disruption of coronary blood circulation, as well as for people well-advanced in age.

We cannot share the existent apprehension that hypotension, commonly accompanying ulcerous disease, serves as an argument against the use of gangliolytics. Due to their hypotensive action (especially hexonium), the patient is put in bed half-an-hour before the injection, and he remains there in the same position for 1-2 hrs. after the preparation has been injected. If these precautionary rules are followed, no side-effects -- even in case of low arterial-pressure initial figures -- develop in gangliolytic therapy with dosages mentioned.

Comparison of therapeutic effectiveness of gangliolytics with some other modern methods of treatment (the control group consisted of 224 patients), in particular -- with the application of thymine, serum of A.N. Filatov, or insulin, -- it appears that gangliolytics have advantages in all basis indexes. The niche, as the most telling sign of the direct positive result of the ulcer disease, disappeared: in 16% of patients treated with thymine; in 3

out of 35 when Filatov's serum was used; 0% for insulin; tetamon -- 75%; hexonium -- 85.5%, gangleron -- 82.2%.

Thus the direct results of treatment of persons with the ulcer disease with ganglion blocking substances are more favorable in comparison with other current methods of treatment.

Long-range results have so far been studied in 45 patients. Seven persons have been under observation since 1955, 12 since 1956, 14 - 1957, and the remaining ones, since 1958.

Duration of remission after the first course of treatment with gangliolytics was as follows: 4-6 months in 7 persons, 7 to 12 months -- 11, year-and-one-half -- 8 persons, over 2 years -- 4 persons.

A repeat course of treatment with gangliolytics in the in-patient ward was ordered for 13 to 45 patients in the period of new exacerbation of the disease. Twelve persons were called and hospitalized in the period of remission, prior to the emergence of exacerbation, for the purpose of carrying out a prophylactic course of treatment with gangliolytics.

After the repeat-course of treatment (during the period of exacerbation as well as during the period of "well-being" the subsequent remission usually became of longer duration -- up to one year, 2 years, and longer. Only five out of the 25 persons subjected to the course of repeat-treatment with gangliolytic substances had a remission of 8-11 months. Especially good results were obtained with that group of patients which had been subjected to the prophylactic course of treatment prior to the occurrence of exacerbation (the majority had experienced no relapse from 1957 till today). This latter circumstance points at the feasibility and purposefulness of repeat-courses of prophylactic gangliolytic treatment during the remission period of the ulcer disease.

Thus our observations - in toto - give us a basis for regarding the use of ganglia blocking substances (hexonium, gangleron, tetamon) as creating a good immediate therapeutic effect: elimination of pains in ulcer

patients, a tendency towards a normalization of the secretory and acidity-producing functions of the stomach emerges, removed is also (gangleron) the heightened digestive action of gastric acid, a high percentage of remission in the ulcerous niche is achieved, the over-all general condition and morale of patients is improved, ability to work is restored.

Account of subsequent long-range results of treatment requires further observation; the effectiveness of repeat-courses of gangliolytic therapy during the remission period of the ulcerous disease demands further continuous study.