POSSIBLE MECHANISMS OF THE ULCEROSTATIC ACTION OF SILATRANES

M. M. Rasulov, I. G. Kuznetsov, S. K. Suslova, M. V. Velikaya, and M. G. Voronkov

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KEY WORDS: silatranes; ulcerostatic action; mechanism; lipid peroxidation.

Particular interest has been shown in recent years in a new class of biologically active silicon compounds, the silatranes. We showed [3, 5] that various silatranes have an antiulcerogenic effect and accelerate wound healing. However, the mechanism of the ulcerostatic action of silatranes has not yet been explained.

An important role in the development of pathological states of varied genesis is played by products of lipid peroxidation (LPO). LPO products affect membrane permeability, enzyme activity, mitotic activity of cells, and so on [2, 4], so that it is essential to study LPO because this may provide the key to the molecular and cellular mechanisms of formation of pathological states and also for the more effective pharmacologic correction of various diseases. The aim of this investigation was to compare the effects of a series of silatranes on the course of healing of experimental gastric ulcer and on the intensity of LPO.

EXPERIMENTAL METHOD

Noninbred albino rats weighing 160-180 g were anesthetized by the open ether method, and a gastric ulcer was produced by the acetate method [6]. The animals were divided into the following groups: 1) intact, 10 standard individuals; 2) animals with an untreated ulcer (40 control animals); 3) rats with a gastric ulcer treated with oxyferriscorbone (OFS) (1st comparison preparation, 28 animals); 4) animals with gastric ulcer treated with methyluracil (MU, 2nd comparison preparation, 28 animals); 5) rats with gastric ulcer treated with methylethyl(silatrane-1-ylmethyl)sulfonium iodide (MESI, 28 animals); 6) animals with gastric ulcer treated with 1-chloromethylsilatrane (CMS); 28 rats); 7) rats with gastric ulcer treated with 1-ethoxysilatrane (ES, 28 rats). Starting with the 1st day after the operation the experimental animals received the following medication daily: OFS intraperitoneally in a dose of 30 mg/kg, MU perorally in a dose of 500 mg/kg, MESI intraperitoneally in a dose of 5 mg/kg, CMS perorally in a dose of 5 mg/kg, and ES intraperitoneally in a dose of 5 mg/kg. Treatment continued for 10 days. Groups of rats were killed on the 3rd, 7th, and 10th days, the stomach was inspected, and the area of the ulcer defect measured. The tissue of the ulcerated part of the stomach was transferred into liquid nitrogen in order to prepare it for further investigation.

Blood was taken from the caudal vein in a volume of 0.02 ml from animals with an untreated ulcer (10 rats from the control group) and with an ulcer treated by each of the different substances (seven rats from each group of experiments), before the operation and 1, 2, 6, and 24 h and 3, 7, and 10 days after the operation. The blood was mixed with 1 ml of physiological saline and then centrifuged for 30 min at 3000 rpm, and the plasma was separated and used for further investigations. The intensity of LPO was determined by chemiluminescence (ChL) method on an apparatus described previously [2]. During work with blood plasma LPO was initiated by 10% H_2O_2 solution, whereas during work with gastric tissue homogenates 1 ml of a 10^{-2} M solution of ferrous sulfate was added to the system. The samples of plasma and tissue homogenates were incubated in medium containing 105 mM KCl and 20 mM KH_2PO_4 at 37°C and pH 7.4. The antioxidative action of the substances studied

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TABLE 1. Changes in Area (in mm^2) of Acetate-Induced Gastric Ulcer in Rats Following Treatment with Silatranes and Control Preparations ($M \pm m$)

Type of ulcer	Days of observation		
	3	7	10
Ultreated (control)	31,8±3,1 (10)	28,6±2,15 (10)	7,4±0,75 (10)
Treated with OFS	21,7±2,5*** (7)	7,8±0,8* (7)	0* (7)
With methyluracil	25,8±3,2 (7)	9,2±1,1* (7)	1,2±0,2* (7)
With MESI	22,8±2,5*** (7)	8,6±0,75* (7)	0* (7)
With CMS	21,1±2,6** (7)	5,4±0,7* (7)	0* (7)
With ES	24,1±2,7*[4] (7)	8,8±0,8* (7)	0* (7)

Legend. Number of animals in each series of observations shown in parentheses. $*p < 0.001$, $**p < 0.01$, $***p < 0.02$, $****p < 0.05$ compared with control.

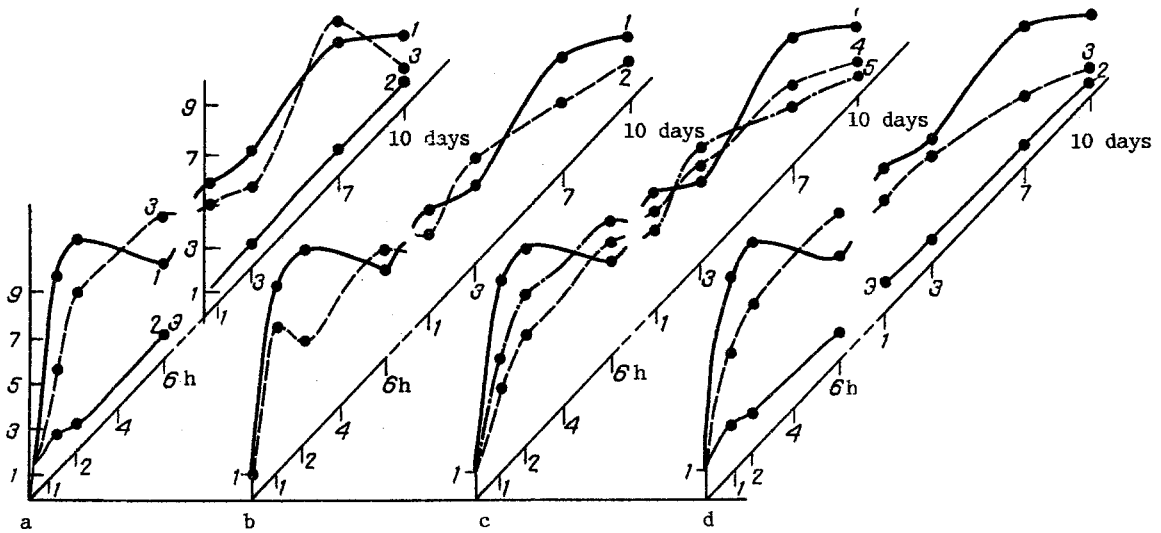

Fig. 1. Photodynamic effect of silatranes in blood plasma. Here and in Figs. 2 and 3: ordinate, intensity of chemiluminescence (in relative units); abscissa, time of observations. 1) Time course of ChL in rats with untreated gastric ulcer (control); 2) time course of ChL in intact rats (standard); 3) effect of test substances on intensity of ChL: a) action of OFS, b) action of methyluracil, c) action of MESI (4) and CMS (5), d) action of ES.

was determined by measuring their effect on the kinetics of all stages of Fe^{2+}-induced ChL in an in vitro system containing a suspension of multilayered liposomes, prepared from hen's egg yolks.

EXPERIMENTAL RESULTS

The experiments showed that the use of all the substances accelerated healing of an acetate ulcer. The morphologic data are summarized in Table 1 and they show that the effects of both silatranes and control preparations appeared as early as 72 h after the operation. Methyluracil was the least active and CMS the most active substance.

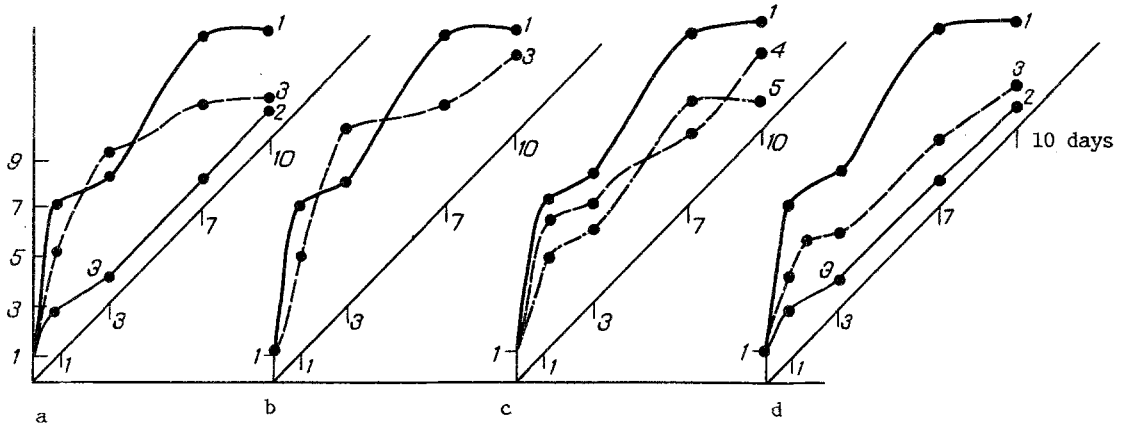

Fig. 2. Photodynamic effect of silatranes in gastric tissue homogenates. Legend as to Fig. 1.

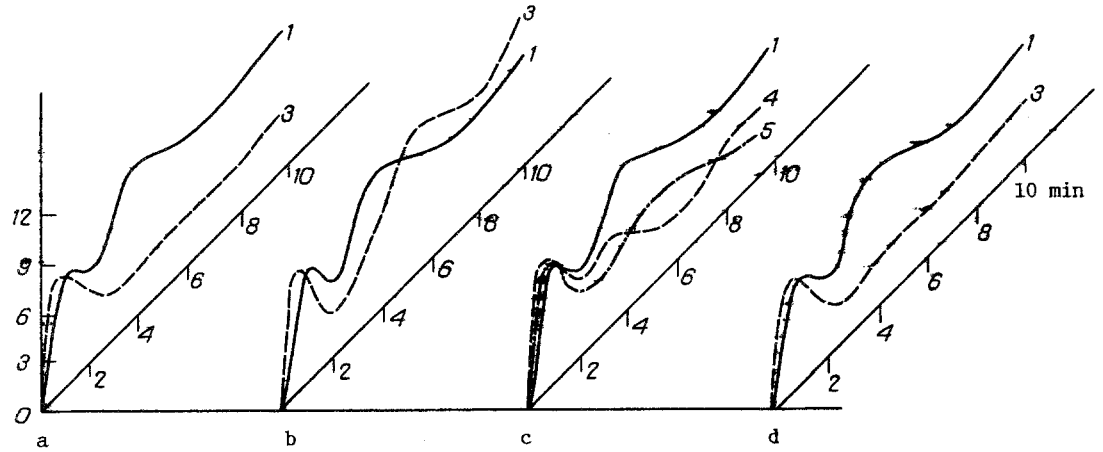

Fig. 3. Photodynamic effect of silatranes in suspension of liposomes. Legend as to Fig. 1.

The next experiments showed that in the initial stages of development of the ulcer (especially in the first 2 h after the operation) marked activation of LPO took place in the blood plasma, followed by lowering of its intensity and stabilization at a lower level in the later stages. Administration of all the test compounds and preparations led to reduction of the photodynamic effect of lipid peroxidation in the blood plasma and stabilization of LPO at the control level. Maximal inhibition of LPO was observed on the 1st day after the operation (Fig. 1).

The study of LPO in gastric tissue homogenates showed that on the 3rd-10th day after the operation repair processes were accompanied by reduction of very weak luminescence. Administration of the test substances and comparison preparations to the animals led to slowing of LPO inhibition in the gastric tissues on the 7th-10th day of development of the ulcer defect (Fig. 2).

A study of the antioxidative action of silatranes and of the comparison preparations on different stages of Fe^{2+}-induced LPO on a liposome model showed that all the substances gave rise to an inhibitory effect at the stage of the slow flash of ChL, i.e., at the stage of branched-chain reactions. The strongest of the dose-dependent effects is illustrated in Fig. 3. In this case, the following substances were added to 1 ml of the liposome suspension: OFS in doses of 0.2, 0.6, and 1 mg; methyluracil in doses of 0.2 and 1 mg, MESI in doses of 0.2 and 0.4 mg, CMS in doses of 0.2 and 0.5 mg, and ES in doses of 0.2 and 0.5 mg.

Thus the induced very weak luminescence of the test tissues had a definite time course, reflecting LPO in different stages of development of the acetate gastric ulcer in the different groups of rats. The test substances modified LPO processes and accelerated healing of the gastric ulcer. The kinetics of LPO has been studied in adequate detail [1]. In accordance with these views the stage of the slow flash of ChL is accompanied by a chain reaction of free radicals of the RO'_2 type, modifying the structure of various biological substrates. The phenomenon of LPO activation in the very early stages (before 2 h) of development of gastric ulcer may lie at the basis of further changes in the relations between destructive and proliferative processes in the stomach at the later stages of development of the ulcer focus. This suggests that the ulcerostatic action of the comparison preparations and silatranes is due to their ability to inhibit LPO in the early stages of ulcer development, i.e., it can be tentatively suggested that one step in the mechanism of the ulcerostatic action of the test substances is their antioxidative effect.

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EMOXYPINE DURING REPERFUSION OF THE ISCHEMIC DOG MYOCARDIUM: EFFECT ON INFARCT SIZE AND PLASMA CREATINE KINASE ACTIVITY

E. A. Konorev, V. Yu. Polumiskov, O. A. Avilova, and A. P. Golikov

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Determination of activity of the enzyme creatine kinase (CK), penetrating from necrotic tissue into the systemic blood flow, is one of the principal methods of quantitative assessment of heart damage in myocardial infarction. Meanwhile, restoration of the coronary blood flow in the ischemic myocardium, which is increasingly used in the treatment of acute myocardial infarction, leads to a sharp rise in the plasma CK level and may be the cause of a change in the ratio between plasma CK activity and the size of the infarct [15]. Release of intramyocardial proteins, linked with reperfusion, is due not so much to the flushing out of CK that has accumulated in the ischemic tissue as to damage to cardiomyocytes occurring during reperfusion [11]. It will be evident that this damage is determined by the supply of oxygen to the ischemic tissue, since reoxygenation after anoxic perfusion of the heart also causes CK release, but anoxic reperfusion of ischemic tissue, on the contrary, is not accompanied by any such release of CK into the perfusion fluid [10, 11]. Recent studies have shown that reperfusion damage can be diminished by means of antioxidants [12].

Laboratory of Bioenergetics, Institute of Experimental Cardiology, All-Union Cardiologic Scientific Center, Academy of Medical Sciences of the USSR. N. V. Sklifosovskii Emergency Aid Research Institute, Moscow.

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