Gastroprotective Properties of 11-Deoxymisoprostol (Prostaglandin E_1 Analog) and Its Effect on the Level of Sialic Acids in Gastric Tissue of Rats with Peptic Ulcer

N. Zh. Baschenko, T. A. Sapozhnikova, S. F. Gabdrakhmanova, N. S. Makara, R. Yu. Khisamutdinova, F. S. Zarudii, N. A. Ivanova, and V. S. Nazarov

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 142, No. 10, pp. 451-453, October, 2006
Original article submitted January 31, 2006

11-Deoxymisoprostol (prostaglandin E_1 analog) exhibited a pronounced gastroprotective effect on various models of experimental ulcers induced by nonsteroid antiinflammatory drugs. A relationship between high resistance of the gastroduodenal mucosa under the effect of 11-deoxymisoprostol and changes in the level of sialic acid was detected.

Key Words: *prostaglandins; peptic ulcer; nonsteroid antiinflammatory drugs; sialic acids*

Decreased synthesis of endogenous prostaglandins resulting from therapy with nonsteroid antiinflammatory drugs (acetylsalicylic acid, diclofenac, butadion, *etc.*) leads to grave functional disorders, *e.g.* gastrointestinal diseases. Misoprostol (MP; Cytotec), a synthetic analog of prostaglandin E_1, is widely used in clinical practice for the prevention of gastric diseases of this origin. However, this drug has a number of side effects, and therefore extension of the range of prostaglandin applications necessitates creation of its new highly effective analogs with minimum side effects. Prostaglandins stimulate reparative processes in the gastric mucosa and normalize its secretory function by forming a protective mucopolysaccharide mucus; among its components are sialocontaining compounds providing resistance to the proteolytic action of the gastric juice [4,6,7]. We failed to find reports about the effects of synthetic prostaglandins on the mucus-producing function, specifically, on the content of sialic acid fractions in the gastric mucosa in humans and animals.

11-DMP (2-demethoxycarbonyl-2-ethoxycarbonyl-11-deoxymisoprostol) was synthesized at Laboratory of Low-Molecular Bioregulators, Institute of Organic Chemistry. This compound is an analog of natural prostaglandin E_1 and a derivative of MP widely used as a gastroprotective drug. Preliminary studies showed that 11-DMP is free from side effects typical of MP, is characterized by sufficient therapeutic range and 2-fold lower toxicity, it has no effect on morphological and biochemical parameters of the blood, diuresis and urina tests, does not influence liver function, does not suppress the CNS, and does not stimulate the small intestinal peristalsis in rats and mice.

We compared the antiulcerative activity of 11-DMP, a new synthetic analog of prostaglandin E_1, and MP in acute experiments on various models and their effects on the levels of gastric mucosal sialic acid fractions in a chronic experiment.

Department of Pharmacology No. 1, Bashkir State Medical University; Laboratory of New Drugs, Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences

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MATERIALS AND METHODS

Antiulcerative activity of 11-DMP was studied in autumn-winter on adult male Wistar rats (160-200 g) on models of acute experimental gastric ulcers induced by oral treatment with acetylsalicylic acid (300 mg/kg at 4-h interval), butadion (300 mg/kg), or diclofenac (50 mg/kg). 11-DMP and MP were used orally in a dose of 0.04 mg/kg (antiulcerative effect ED_{50}) 1 h before ulcer modeling. After 24 h the animals decapitated under ether narcosis, the stomachs were removed, and lesions in the gastric mucosa were counted visually.

The effects of 11-DMP and MP on mucus-producing function (levels of sialic acids) were studied on models of ulcers induced by indomethacin (single intraperitoneal dose of 20 mg/kg). 11-DMP and MP were used 1 h before ulcer reproduction and during 20 days. The lesions were counted on days 1, 5, 15, and 20. Freshly isolated gastric tissues were homogenized; the content of sialic acid fractions (mmol N-acetylneuraminic acid/kg dry free-from-fat tissue) was determined in the gastric wall homogenates by the calibration curve [5]. Analysis was carried out using Sialotest-80 commercial kits (Reachim). The data were processed by methods of variation statistics; the significance of differences was evaluated using Student's *t* test.

RESULTS

Inhibition of mucus production after acetylsalicylic acid injury to rat gastric mucosa was paralleled by enhanced reverse diffusion of protons into interstitial space, which was associated with histamine release and increased capillary permeability often leading to hemorrhages [1,3]. Pretreatment with 11-DMP prevented ulcer formation induced by acetylsalicylic acid. The number of lesions in rats treated with 11-DMP was 3.5 times lower than in the controls (Table 1) and 1.9 times lower than in animals treated with MP.

Intragastric treatment with 11-DMP and MP before butadion protected the gastric mucosa, which manifested by a significant (approximately 3-fold) reduction in the incidence and area of ulcer defects (Table 1).

Treatment with 11-DMP 1.4-fold reduced the mean number of gastric mucosal lesions induced by diclofenac in comparison with the control (Table 1). MP exhibited no gastroprotective effect in this type of ulcers, and the number of gastric mucosal lesions was at the level of the control group (Table 1).

Intraperitoneal injection of indomethacin to rats led to the formation of acute ulcers and punctate erosions of the gastric mucosa in the presence of its severe hyperemia. Edema and hyperemia of the gastric mucosa were detected in control animals 10 days after ulcer modeling. The mean number of lesions was 3.1 times lower in animals treated with 11-DMP in comparison with the control and 1.5 times lower than in animals treated with MP (Table 1).

Sialic acid metabolism in the gastric wall during the first days of ulcer formation was characterized by significant increased content of free and oligo-bound fractions in all groups and reduced content of protein-bound fraction. These changes in the sialic acid pool are known to be a result of their cleavage from sialoglycoproteins, which leads to reduction of mucus viscosity and its resistance to proteolytic enzymes [1]. On day 15 of treatment the level of sialic acids in the gastric wall in rats treated with 11-DMP was characterized by a significant reduction in the levels of free and oligobound sialic acid fractions (Table 2), virtually corresponding to the levels in intact animals, while in controls the levels of these fractions continued to increase and were 3.6 and 2.7 times higher than in intact animals, respectively. The level of protein-bound fraction in the stomach homogenates from animals treated with 11-DMP increased on day 15 and corresponded to the level in intact animals (Table 2).

In the control the concentration of protein-bound fraction continued to decrease and was almost 1.3

TABLE 1. Antiulcerative Activity of 11-DMP and MP in Ulcers Induced by Nonsteroid Antiinflammatory Drugs ($M \pm m$; n=6)

Drug, dose	Number of gastric mucosal lesions after treatment with		
	mineral oil (control)	11-DMP	MP
Acetylsalicylic acid, 300 mg/kg	29.5±2.6	8.5±1.2***	16.5±3.1**
Butadion, 300 mg/kg	16.5±3.1	5.3±1.9*	4.9±1.2**
Diclofenac, 50 mg/kg	19.8±3.1	14.2±1.4*	20.2±2.2
Indomethacin, 20 mg/kg	19.3±3.9	6.2±1.2***	9.50±0.68**

Note. Here and in Table 2: *p<0.05, **p<0.01, ***p<0.001 compared to the control

TABLE 2. Levels of Sialic Acids (mmol/kg) in Indomethacin-Damaged Gastric Wall during Treatment with 11-DMP and MP (*M*±*m*; *n*=6)

Sialic acid fraction	Day of study	Intact	Control	11-DMP	MP
Free	5	0.20±0.01	0.52±0.04	0.42±0.10	0.48±0.10
	15		0.72±0.04	0.32±0.67	0.46±0.09
	20		0.52±0.05	0.19±0.02***	0.22±0.06
Oligo-bound	5	1.70±0.10	2.52±0.04	2.13±0.10	2.09±0.10
	15		4.58±0.14	1.85±0.06	2.20±0.02
	20		3.02±0.02	1.65±0.07***	1.99±0.07
Protein-bound	5	8.56±0.20	6.80±2.34	7.76±1.01	8.00±2.30
	15		6.57±0.23	7.93±1.24	8.04±0.09
	20		7.58±0.11	8.30±0.24*	8.97±1.00

times lower than in intact animals. By day 20 of treatment the level of sialic acids in animals treated with 11-DMP and MP corresponded to that in intact animals. The effect was more pronounced in animals treated with 11-DMP. Hence, a pronounced gastroprotective effect of 11-DMP in comparison with MP was revealed, which was seen from significantly reduced incidence of large, small, and medium-sized ulcers, in lower incidence of ulcerative lesions, and more rapid normalization of the gastric mucosa bottom.

Mucus is an important component of the gastric mucosa protection. Peptic ulcer is associated with qualitative changes in the content of carbohydrate/protein components of the gastric mucosa and wall (a significant increase in the levels of free and oligo-bound sialic acid fractions and a decrease in the protein-bound fraction in the presence of total reduction in prostaglandin content). All this leads to disorders in the defense, selective transporting, and barrier functions of the gastroduodenal mucins [2]. Treatment with 11-DMP and MP stimulated reparative processes in the gastric mucosa: the volume of barrier mucus increased and the level of sialic acids normalized much sooner, which seemed to play an important role in stabilization of the defense properties of the gastric mucosa during treatment of peptic ulcer.

The study was supported by the Russian Foundation for Basic Research.

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