Choleretic Activity of 2-Demethoxycarbonyl-2-Ethoxycarbonyl-11-Deoxymisoprostol on the Model of CCl_4-Induced Hepatitis

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

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Therapeutic administration of 11-deoxymisoprostol had a hepatoprotective effect, which manifested in a decrease in the content of alanine transaminase and aspartate transaminase in blood plasma, and produced a choleretic effect in rats with CCl_4-induced toxic hepatitis.

Key Words: *11-deoxymisoprostol; choleretic and hepatoprotective activity; carbon tetrachloride; hepatitis*

Natural and synthetic prostaglandins improve hepatocyte function during hepatitides of different etiology. For example, prostaglandin E_1 analogue misoprostol (MP) is used as a hepatoprotector in patients with hepatobiliary diseases [4,6].

Here we studied hepatoprotective and choleretic activity of MP analogue 2-demethoxycarbonyl-2-ethoxycarbonyl-11-deoxymisoprostol (11-deoxymisoprostol, 11-DMP), which was synthesized at the Laboratory of Low-Molecular-Weight Bioregulators (Institute of Organic Chemistry, Ufa Research Center of the Russian Academy of Sciences). Toxicity of 11-DMP is 2-fold lower than that of MP. Hence, 11-DMP has a wider range of therapeutic activity than MP.

MATERIALS AND METHODS

Experimental toxic hepatitis was induced by subcutaneous injection of 50% CCl_4 in oil (0.4 ml/100 g) for 4 days [1]. Experiments were performed on 30 male and female Wistar rats weighing 160-200 g and obtained from the Rappolovo nursery of laboratory animals (Russian Academy of Medical Sciences). The animals were kept under similar conditions and fed a standard diet. The rats were divided into groups of 6 specimens each. These specimens were of the same age. Body weight variability did not exceed 10%. Group 1 rats were intact. Hepatitis was induced in the remaining animals. Group 2 rats received vegetable oil (control) [2]. Group 3 rats received 11-DMP. Group 4 and 5 rats received MP and Carsil, respectively (reference drugs).

11-DMP and MP were given perorally (therapeutic administration) for 7 days before the induction of hepatitides. We used the effective doses (ED_{50}) of 11-DMP (0.04 mg/kg, 1/1000 of LD_{50} perorally), MP (0.04 mg/kg; Cytotec, Pharmacia), and Carsil (50 mg/kg, Sopharma). The study was conducted with oil solutions of 11-DMP and MP and aqueous solution of Carsil. ED_{50} of 11-DMP was selected from preliminary screening on the model of indomethacin-induced ulcer. After the experiments the animals were euthanized with chloroform.

*Department of Pharmacology No. 1, Bashkirian State Medical University; Laboratory of New Medicinal Agents, Institute of Organic Chemistry, Ufa Research Center of the Russian Academy of Sciences, Ufa. ***Address for correspondence:*** newpharm@anrb.ru. F. S. Zarudii

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TABLE 1. Effect of 11-DMP on the Rate of Secretion and Total Amount of Bile Flow in Rats on Day 7 of CCl_4-Induced Hepatitis (n=6, $M\pm m$)

Group	Dose, mg/kg	Bile flow (amount of bile over 4 h, mg/100 g)	Rate of secretion, mg/100 g/1 min
1	—	850.9±59.7	4.1±0.5
2	—	740.0±73.0	3.5±0.2
3	0.04	1078.0±63.1**+	4.5±0.4*
4	0.04	975.9±66.8*	4.1±0.5
5	50	847.9±61.1	3.5±0.2

Note. +p<0.05 compared to group 1. Here and in Table 2: *p<0.05, **p<0.01, and ***p<0.001 compared to group 2.

Hepatoprotective activity of 11-DMP was estimated from the content of marker enzymes alanine transaminase (ALT) and aspartate transaminase (AST) in the serum.

Choleretic activity of the compound was estimated from bile secretion and bile flow in hepatocytes (total amount of bile over 4 h) [1]. The bile was collected from urethane-anesthetized rats using a cannula. This cannula was inserted into the duodenum. Both ends of the cannula were ligated.

The results were analyzed by Student's t test. Intergroup differences were significant at p<0.05.

RESULTS

CCl_4 poisoning was accompanied by hepatic dysfunction. Bile secretion decreased under these conditions. On day 7, the total amount of 4-h bile flow in group 2 rats was lower than in intact animals (Table 1). The rate of bile secretion decreased. 11-DMP increased bile secretion and flow into the duodenum. The total amount of 4-h bile flow in group 3 rats was higher than in group 2 and 5 animals by 1.5 (p<0.001) and 1.3 times (p<0.001), respectively. The rate of bile secretion in group 3 rats was 1.4-fold higher than in group 5 and 2 animals (p<0.05, Table 1).

CCl_4 stimulates the release of transaminases AST and ALT (marker enzymes of liver damage) into the blood by 5.1 and 3.2 times, respectively, compared to intact animals. Published data show that MP has hepatoprotective properties and significantly decreases the content of transaminases on this model of acute hepatitis [3,5]. 11-DMP therapy was followed by a significant decrease in transaminase content in CCl_4-poisoned animals. The content of ALT and AST in treated rats decreased by 2.9 (p<0.001) and 5.6 (p<0.001), respectively, compared to the control. Hence, the effect of 11-DMP was similar to that of MP (Table 2).

TABLE 2. Effect of 11-DMP on Parameters Charac-terizing Hepatocyte Damage in Rats with CCl_4 Poisoning (n=6, $M\pm m$)

Group	Dose, mg/kg	ALT, μmol/liter/h	AST, μmol/liter/h
1	—	0.9±0.1***	1.9±0.3***
2	—	4.7±0.2	6.2±0.1
3	0.04	1.6±0.01***	1.1±0.03***
4	0.04	1.8±0.01***	1.3±0.02***
5	50	2.3±0.5**	3.5±0.5***

Our results indicate that hepatoprotective activity of 11-DMP is similar to that of MP. 11-DMP reduces the degree of hepatocyte cytolysis, modulates bile secretion in the liver, and increases the rate of bile secretion and total amount of 4-h bile flow. We conclude that 11-DMP stabilizes the structural and functional resistance of cell membranes and, therefore, maintains bile production in hepatocytes.

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