EFFECT OF TOTALLY SYNTHETIC RACEMIC PROSTAGLANDINS $F_{2\alpha}$ AND OF 15α-OH-11-DEOXYPROSTAGLANDIN E_1 ON SMALL INTESTINE MOVEMENTS IN RABBITS WITH DYNAMIC ILEUS

J. F. Freimanis, M. M. Veveris,
J. K. Gauens, and A. M. Engelis

UDC 616.34-007.272-092.9-02:
577.175.859]-07

KEY WORDS: dynamic ileus; intestinal movements; prostaglandins.

Natural prostaglandins (PG) of the E and F groups play an important role in the regulation of movements of the gastrointestinal tract [1, 11]. PG of these groups usually stimulate contractions of the longitudinal muscle, whereas PG of the F group contract, and PG of the E group relax the circular muscle [14]. In experiments on whole animals both PGE_1 and $PGF_{2\alpha}$ increased the intraluminal pressure of the small intestine [7, 8]. Clinical investigations have shown that PGE_1, after enteral administration to healthy volunteers, induces spastic colic [9] and raises the intraluminal pressure in the small intestine [10]. Both PGE_1 and $PGF_{2\alpha}$ stimulate onward movement of the contents along the small intestine [8, 10, 13]. PG have a stimulating action on dynamic ileus (DI) in clinical practice [11]. Meanwhile considerable species-specificity of the action of prostaglandin compounds and differences in the response of different parts of the gastrointestinal tract of the same animal to them have been noted [1, 15]. For example, in experiments on isolated organs PGE_1 slowed the onward movement of the contents along a segment of the guinea pig small intestine [7], whereas $PGF_{2\alpha}$ had a stimulating action in this respect [12].

In the investigation described below the action of the following synthetic prostanoids on movements of the ileum was studied under conditions of DI [4]: the natural PGE_1 analog racemic 15α-OH-11-deoxyprostaglandin E_1 — (±)DPGE$_1$ [2] — and the racemic analog of natural $PGF_{2\alpha}$ — (±)$PGF_{2\alpha}$ [4]. These compounds are either more convenient or chemically more stable than natural PG. Their action was compared with that of known stimulators of intestinal movements, viz. aceclidine, neostigmine, galanthamine, and pituitrin [3, 6, 11], for which purpose the method of creation of DI and recording the intraluminal pressure of the intestine was used, as being closer to real clinical conditions, and in addition, sensitization of the animal before the creation of peritonitis was used.

METHODS

Two series of experiments were carried out on 38 male rabbits weighing 2.1-4 kg; with postoperative DI (PODI) and with DI caused by peritonitis (DICP). In the PODI series, unlike in the method recommended previously [3, 5, 7, 8], during combined anesthesia (30 mg/kg hexobarbital intravenously + 0.5% procaine solution locally), under aseptic conditions a right-sided laparotomy was performed on the rabbits, followed by cecotomy. A rubber balloon (capacity 1 ml), filled with distilled water, was then introduced transcecally into the distal part of the ileum to a distance of 15-20 cm from the ileocecal angle, and a polyvinyl connecting catheter was brought out into the wound. Ileus develops as a result of trauma from the operation. The course of the postoperative period, during which antibacterial therapy was given, was studied. The times of investigation ranged from 20 to 50 h after the operation, when neither narcotics or sedatives were given. For the DICP series, rabbits of the PODI series were used. On the 3rd day after the operation, artificial peritonitis was induced in them by injection of a fresh 30% suspension of feces of the same animal into the peritoneal cavity in a dose of 1 ml/kg body weight. The rabbits were sensitized 20-24 h before provocation by 1/10 of the provocation dose (fecal suspension from the same animal). At the end of the DICP series the rabbits were killed and the degree of development of peritonitis was

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Department of Pediatric Surgery, Riga Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Kanepa.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 101, No. 6, pp. 712-714, June, 1986. Original article submitted May 11, 1985.

 0007/4888/86/0006-0796$12.50

TABLE 1. Comparative Effectiveness of the Compounds Tested

Series of experiments	Preparation	Dose per kilogram body weight		Pituitary extract	Number of injections	Duration of action of compounds, min	Increase in Frequency of positive response, %	Increase in amplitude of contractions, %	Latent periods, min
PODI	(±)DPGE$_1$	10	μg	8	50	6,25±2,04	126,34±28,31	108.69±16,57	5,52±2,16
	(±)PFG$_{2\alpha}$	10		11	81,8	15,57±4,78	189,30±25,04	100,57±11,78	5,25±3,79
	Aceclidine	60		10	60,0	14,00±6,82	211,85±45,33	147,69±64,52	1,38±0,62
	Neostigmine	9		14	57,1	11,08±3,75	227,01±30,99	131,40±39,91	1,71±1,44
	Galanthamine	150		10	80,0	13,58±5,33	194,23±54,40	114,78±23,36	2,25±1,44
		0,1	U	9	66,7	8,12±3,04	196,33±41,26	96,41±15,04	0,75±0,50
DICP	(±) DPGE$_1$	10	μg	8	37,5	8,00±4,92	130,71±32,25	110,76±27,12	5,33±2,70
	(±) PGF$_{2\alpha}$	10		10	60,0	11,25±3,25	223,00±48.26	118,91±32,77	3,13±0,88
	Aceclidine	60		10	60,0	14,00±7,04	223,09±50,82	126,17±17,26	0,83±0,33
	Neostigmine	9		10	80,0	13,33±7,29	210,89±39,89	123,44±27,93	1,79±1,06
	Galanthamine	150		8	62,5	26,67±7,20	302.69±54.28	168,72±23,77	1,50±0,76
	Pituitary extract	0,1	U	9	66,7	7,00±2,19	178,00±32,26	116,73±38,76	1,00±0,50

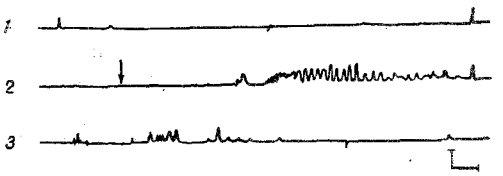

Fig. 1. Effect of (±)PGF$_{2\alpha}$ on intraluminal pressure in rabbit small intestine 24 h after induction of peritonitis. 1, 2, 3) Consecutive fragments of continuous trace (1, background period). Arrow indicates time of intravenous injection of (±)PGF$_{2\alpha}$ in dose of 10 μg/kg. Calibration: 150 Pa, 1 min.

assessed. Peritonitis developed in 100% of cases. Only one of the test compounds was injected (intravenously) into each rabbit, once or twice a day. Before administration of the compound the background activity of the intestine was recorded for 1 h. Each compound was given to at least five rabbits. Movements of the small intestine were assessed by recording changes in its intraluminal pressure by a balloon graphic method on the DMP-4B physiograph (from Narco BioSystems, USA), in conjunction with a P23B electromanometer (Statham, USA). The curves obtained were compared with background traces. The increase in frequency and amplitude of the peristaltic waves, the latent period after injection of the compound, and the duration of its action were calculated. The numerical results were subjected to statistical analysis with calculation of confidence limits at the P = 0.05 level of significance.

RESULTS

In some cases (Table 1) in the PODI series the action of previously known preparations was ineffective or even nonspecific. For instance, intestinal atony was observed in two cases immediately after injection of aceclidine. After specific action, atony developed in one case when neostigmine was used, in one case with galanthamine, and in three cases after injection ofpituitary extract. In this series of experiments, (±)PGF$_{2\alpha}$ had a stimulating action which was not weaker in degree than that of known stimulators, but the action of (±) DPGE$_1$ was weaker. The nonspecific effect of the compounds (intestinal atony) was observed in eight cases in the DICP series: immediately after injection of neostigmine (one case) and of pituitary extract (two cases), and in one case after the specific action, following injection of (±)PGF$_{2\alpha}$ and galanthamine and in three cases when pituitary extract was given (±)PGF$_{2\alpha}$ was similar to neostigmine and aceclidine in the duration of its action and the increase in the frequency of intestinal contractions recorded (Fig. 1), whereas (±)DPGE$_1$ was ineffective in this series also.

In these investigations galanthamine was found to be fairly active, especially in the DICP series, so that it can be recommended for more frequent use in the treatment of dynamic

ileus, especially when associated with inflammation in the peritoneal cavity. The action of pituitary extract was rather short in duration and weak in these experiments, and often it had an opposite action.

As regards the prostaglandin compounds, their optical inactivity is evidently not a serious obstacle for the effectiveness of these preparations. For example, the effect of (±) $PGF_{2\alpha}$ was found to be similar to the action of certain pharmacopeal preparations (see above), and it exhibited a nonspecific action less frequently. The reason why (±)$DPGE_1$ is less effective is probably the absence of the 11-hydroxyl group in the molecule of this compound. This substituent is preserved in the $PGF_{2\alpha}$ molecule.

LITERATURE CITED

1. I. S. Azhgikhin (ed.), Prostaglandins [in Russian], Moscow (1978).
2. M. M. Vereris and A. A. Kimenis, in: Science for Agriculture [in Russian], Riga (1979), p. 85.
3. Yu. M. Gal'perin, Pareses, Paralyses, and Functional Obstruction of the Intestine [in Russian], Moscow (1975).
4. A. A. Kimenis, M. M. Vereis, Z. A. Atare, et al., in: Synthesis and Study of Physiologically Active Substances [in Russian], Vilnius (1984), p. 67.
5. S. Z. Kletskin, L. D. Shekhvatov, and V. S. Shirokov, Methods of Recording Intestinal Motor Function [in Russian], Moscow (1980).
6. N. N. Timofeev, in: Abdominal Adhesions [in Russian], Leningrad (1977), p. 59.
7. A. Bennet, K. G. Eley, and G. B. Scholes, Brit. J. Pharmacol., 34, 639 (1968).
8. L. Fiedler, in: Advances in Prostaglandins and Thromboxane Research, Vol. 8, New York (1980), p. 1609.
9. E. V. Horton, I. H. M. Main, C. J. Thompson, et al., Gut, 9, 655 (1968).
10. J. J. Misiewicz, S. L. Waller, N. Kiley, et al., Lancet, 1, 648 (1969).
11. L. Nadrovski, Curr. Surg., 40, 260 (1983).
12. R. Radomirov, V. Petkov, and S. Yanev, Experientia, 39, 754 (1983).
13. M. J. Rudwart, M. S. Klepper, and B. D. Rush, Prostaglandins, 19, 415 (1980).
14. S. L. Waller, Gut, 14, 402 (1973).
15. D. E. Wilson and H. Kaymakcalan, Med. Clin. N. Amer., 35, 773 (1981).