Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 7586 – 7595
Received 05 March 2021; Accepted 01 April 2021.

The Effect of Fenkarole and Zaditen on the Intestinal Microflora of Rats in the Stages of Sensitization and Food Anaphylaxis of Passive Anaphylactic Reaction

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Abstract: It is known that the prevalence of allergic diseases is constantly growing in both developed and developing countries. Therefore, changes in the microeubiotic system of the rat intestine in the stages of passive anaphylactic reaction (PAR) and the influence of antihistamines on the observed disorders of intestinal microbiocenosis were studied in this work.

In experiments on white rats, changes in the microflora of the small and large intestine in the stages of sensitization and food anaphylaxis of passive anaphylactic reaction and the effect on the observed disorders of antihistamines fenkarole and zaditen were studied.

Based on the results of experiments, it was found that under the conditions of PAR, the most pronounced dysbiotic changes occurred in the microflora of the small and large intestine on the 6th day of sensitization and on the 3rd day of food anaphylaxis, and relatively more distinct dysbiotic shifts were observed in the large intestine. While studying the effect of antihistamines on these disorders, their ambiguous effect was established, although fenkarole and zaditen did not have a sufficient protective effect on dysbiotic changes in the intestinal microflora.

Key words: antihistamines, fenkarole, zaditen, sensitization, food anaphylaxis, intestinal microflora.

Introduction

It is known that the prevalence of allergic diseases is constantly growing in both devel-

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Received 05 March 2021; Accepted 01 April 2021.

oped and developing countries. According to a number of authors, the prevalence of these diseases in countries such as Germany, England, France, is 10-30% among urban and rural populations. In Europe and the United States, about 20% of the population suffer from allergies, and the first symptoms are registered in 40-50%, and in some environmentally unfavorable areas, their prevalence reaches 60% [10]. According to the data published by FSBI "SSC Institute of immunology" FMBA of Russia, the prevalence of allergic diseases in different regions of Russia is 19-40% among adults and more than 27% among children and adolescents [1].

Due to the existing contact of a larger area of the gastrointestinal tract with the external environment, its mucous membrane forms a microecological system consisting of many species of microorganisms [3, 9]. Intestinal microflora because of its antagonistic properties not only protects the body from the effects of pathogenic and opportunistic bacteria, but also widely involved in the synthesis of vitamins, enzymatic processes, metabolism and immunobiological activity [4, 5]. Therefore, changes in this system can lead to metabolic disorders, to a deficiency of micronutrients such as minerals, vitamins and microelements, and to a decrease in the immunological status of the body. If we consider the gastrointestinal tract the main "area" - the place of manifestation of allergic reactions in the sensitization of the body, then violations of digestive function and intestinal microecology in various allergic conditions are quite logical outcome. However, these functions of the gastrointestinal tract in various allergic conditions of the body have not been sufficiently studied.

As it is known, histamine and related biologically active substances play an important role in the origin and development of allergic reactions [6, 7]. Therefore, in everyday practice for the prevention and treatment of allergic diseases along with other remedies are widely used antihistamines [2, 8]. However, it remains poorly understood the diverse influence of these remedies on the intestinal microbiota in allergic conditions of the body.

Based on the above, in this work we studied changes in the microeubiotic system of the intestine of rats in the stages of passive anaphylactic reaction (PAR) and sought to reasonably assess the effects of antihistamines on the observed violations of the intestinal microbiocenosis in allergies.

Material and methods of research

The experiments were conducted on 294 white mongrel rats of both sexes weighing 120-200 g. An experimental model of the stages of sensitization and food anaphylaxis of PAR were called by the method of V.A.Shaternikov (1982). At the stage of sensitization, the state of microflora of the small and large intestine was studied on the 3rd and 6th days of sen-

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sitization, against the background of anaphylaxis-24 and 72 hours after it. Sensitization and food anaphylaxis were also caused against the background of antihistamines, which were administered in the morning hours daily orally from the first day of feeding the animals with egg protein. To determine the effect of the difunctional drug hifenadine (fenkarole, JSC "Olainfarm", Latvia) at a dose of 50 mg/kg and the polyfunctional remedy ketotifen at a dose of 1 mg/kg (zaditen, Novartis Pharma AG, Switzerland) on the observed disorders of the microflora of the small and large intestine against the background of sensitization and food anaphylaxis, the experiments were carried out on the 3rd and 6th days of sensitization, on the 24th and 72nd hours after anaphylaxis and on the 3rd and 7th days after it.

For bacteriological study after decapitation and opening of the abdominal cavity of rats we took 1 ml of material from the lower part of the small and large intestines and delivered in bacteriological seals to the bacteriological laboratory for 2 hours. Bacteriological study of the taken material was carried out by the method of F. Y. Garib et al. (1994). Identification of the seeded microorganisms was carried out according to the « The Shorter Bergey's Manual of Determinative Bacteriology» (1994). The number of bacteria in each species was expressed in log CFU / ml.

Statistical processing of the obtained results was carried out on a personal computer using a package of applied programs for IBM PC "Statgrafics" according to the Student's criteria with the calculation of arithmetic averages (M), their standard errors (m), indicators of reliability of differences in the compared values (P). The value $P < 0.05$ was considered as an indicator of significant differences.

Research results and their discussion

Analysis of the results showed that at the stage of sensitization of PAR there were no visible changes in the sensitized rats, but there were to a certain extent dysbiotic disorders in the microflora of the small and large intestines, starting from the 3rd day of the experiments, reaching its maximum by the 6th day. If the ratio of anaerobic flora of the small intestine to aerobic is normally 1:1.2, then by the 6th day of sensitization it was 1:2, which indicates a violation of the balance between them.

During the experiments, we were convinced that not all microorganisms occur completely in the intestine, even in rats of control groups. Staphylococci, Proteas and fungi were not sown in the small intestine in 17% of rats of these groups, streptococci-in 8%, in the large intestine, Proteus and fungi - in 17%. The studied microorganisms were determined in the small intestine of all rats on the 3rd day of sensitization, staphylococci were not sown in 14% of rats on the 6th day and fungus -in the large intestine of 14% of rats on the 3rd and 6th days

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of sensitization. It follows that the intestinal flora on the background of sensitization is also subject to violations.

Against the background of the experimental model of food anaphylaxis, violations in the behavior of animals in the form of increased aggressiveness, increased breathing, various seizures were observed, but no deaths were recorded. When opening the abdominal cavity after decapitation, there was hyperemia, swelling and multiple erosions in the mucous membrane of the stomach and small intestine, and there were no visible disorders in the pancreas. In this stage of PAR pronounced dysbiotic disorders in the intestinal microflora were observed (табл. 1). There was a significant decrease in anaerobic flora in the small intestine at the 24th hour after anaphylaxis, the ratio of anaerobic flora of the small intestine to aerobic was 1:1,9. There was a decrease in anaerobic flora in the large intestine due to lactobacilli and an increase in aerobic flora due to Proteus. In addition, the content of fungi in the large intestine increased by 1.3 times.

At the 72nd hour after it, the ratio of anaerobic flora of the small intestine to aerobic was 1: 2.5. There was an increase in streptococci by 36%. Also, the content of fungi was 1.3 times higher than the control indicators. Anaerobic flora decreased by 16% in the large intestine, enterococci from aerobic flora -by 21%, Proteus-by 22%. Fungi increased by 1.3 times. As can be seen from the above data, at the 72nd hour after anaphylaxis there were deeper dysbiotic disorders in the intestinal microflora compared to the 24th hour, this in some individuals led to diarrhea. Occurrence of microorganisms on the background of anaphylaxis: in the small intestine at 24-hour experiments, anaerobic bacteria – in 29% and streptococci-in 14% of rats, in the large intestine, anaerobic microorganisms and lactobacilli were not encountered in 14% of rats. At 72-hour anaphylaxis in the small intestine, Proteus-in 14% and fungi -in 29%, in the large intestine, bifidobacteria and fungi - in 14% of rats. Comparing the above with the data of the control and sensitized groups, we can say that against the background of anaphylaxis, not only deeper dysbiotic changes in the intestine are noted, but also the frequency of occurrence of microflora is also subjected to deeper violations.

Natural recovery of intestinal microflora after food anaphylaxis was studied on the 3rd and 7th days of experiments. There were no signs of recovery of intestinal microflora on the 3rd day of anaphylaxis, and there was a tendency to increase aerobic activity in the small intestine on its 7th day, which was 12% and a decrease in anaerobes by 30%, fungi increased by 21%. In the large intestine-anaerobes are 12% below the control indicators, and aerobes - at the level of. The reduction of lactobacilli was 15%. It should be noted that there was a significant recovery of intestinal flora on the 7th day after anaphylaxis compared to the 3rd day,

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Received 05 March 2021; Accepted 01 April 2021.

which has not yet been fully recovered.

Anaerobes and streptococci were not sown in 14% in the small intestine on the 7th day after anaphylaxis and in the large intestine, anaerobes were not also in 14% of rats.

Fenkarole and zaditen had a noticeable protective effect on the observed dysbiotic changes in the intestinal microflora caused by sensitization. Against the background of fenkarole on the 3rd day of sensitization in the small intestine, the content of lactosonegative forms of E. coli increased by 34%, in the large intestine, the content of lactosonegative forms of E. coli remained elevated by 59%. On the 6th day of experiments in the small intestine was determined an increased content of Proteus by 18% and lactosonegative forms of E.coli by 22%, in the large intestine-a decrease in the content of fungi by 18%. On the background of zaditen there was a decrease in anaerobic bacteria by 15%, streptococci-by 21%, fungi-by 16% in the microflora of the small intestine on the 3rd day of experiments. In the microflora of the large intestine, there was a decrease in staphylococci by 17% and an increase in Escherichia coli by 18%. On the 6th day of experiments there was an increase in aerobes by 14%, staphylococci-by 24%, Proteus-by 44% and a decrease in streptococci by 33% in the microflora of the small intestine. In the large intestine- a decrease in aerobic activity by 13% and an increase in lactosonegative forms of E. coli by 19%. When comparing the results with the data of the sensitized group, it can be noticed that fenkarole and zaditen on the 6th day of the experiments had a minor protective effect on dysbiotic disorders in the intestinal microflora.

When analyzing the frequency of occurrence of microorganisms in sensitized animals against the background of antihistamines, the following results were obtained: on the 3rd day of sensitization against zaditen in the large intestine, fungi were not found in 14% of rats, and the rest of all microorganisms against both remedies were found in all rats. On the 6th day of experiments on the background of fenkarole in the microflora of the small intestine Proteas were not sown in 29%, fungi and lactosonegative forms of E. coli – 14%, in the microflora of the large intestine – fungi 14% of rats; on the background of zaditen in the microflora of the small intestine E. coli, Proteus, fungi and lactosonegative forms of E. coli – 14%, in the microflora of the large intestine bifidobacteria, Lactobacillus and Proteus – 14% of rats. When comparing these data with control indicators and data of sensitized animals, it should be said that the incidence of intestinal microflora of sensitized rats against the background of antihistamines was slightly corrected, although it still remained impaired.

Antihistamines in food anaphylaxis had a more pronounced corrective effect on the noticed dysbiotic disorders of the intestinal microflora caused by anaphylaxis (table 1). Against the background of fenkarole 24 hours after anaphylaxis, there was a decrease in the content of

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anaerobes by 37%, an increase in aerobes by 33%, streptococci-by 28%, Escherichia coli-by 31% and fungi-by 19% in the microflora of the small intestine. In the microflora of the large intestine, the decrease of anaerobes by 18%, bifidobacteria – by 22%, enterococci – by 21%, the increase of fungi by 20%, lactosonegative forms of E. coli – by 73% of cases was determined. 72 hours after anaphylaxis in there was determined a decrease in anaerobes by 24%, increase in aerobes by 20%, Escherichia coli-by 29%, Proteus-by 58%, lactosonegative forms of E. coli-by 57% the microflora of the small intestine. In the microflora of the large intestine, the content of anaerobes was normalized by 37% compared to the control data. There was also an increase in Proteus content by 27%, lactosonegative forms of E.coli-by 63%. On the background of zaditen, 24 hours after food anaphylaxis, a decrease in anaerobes by 28%, an increase in aerobes by 31%, streptococci – by 34%, Escherichia coli – by 35%, fungi – by 47% was found in the microflora of the small intestine. In the microflora of the large intestine-a decrease in anaerobic bacteria by 16%, bifidobacteria-by 21%, enterococci-by 29%, an increase in Proteus by 20%, fungi-by 22% and lactosonegative forms of E.coli-by 74%. 72 hours after anaphylaxis there were determined a decrease in anaerobes by 28%, an increase in aerobes by 22%, Escherichia coli-by 26%, Proteus-by 60%, lactosonegative forms of E. coli-by 60% in the microflora of the small intestine. In the flora of the large intestine, there was a tendency to decrease anaerobes by 11%, a decrease in lactobacilli and enterococci by 17%, an increase in the content of Proteus by 28% and lactosonegative forms of E. coli by 56%. As it can be seen from the above data, on the background of antihistamines there was a noticeable protective effect on the intestinal microflora, because at the 72nd hour of anaphylaxis on the background of fenkarole and zaditen in the microflora of the small intestine, anaerobic bacteria were normalized by 37% and 24%, and in the large intestine-37% and 28%, respectively.

The study of the frequency of occurrence of microorganisms in the intestine showed that against the background of fenkarole and zaditen marked changes in the microflora of the small and large intestine markedly approached normal values, but full recovery to normal was not observed.

When studying the natural recovery of intestinal microflora after anaphylaxis on the background of fenkarole and zaditen on the 3rd day of experiments, the above-mentioned violations observed in rats in the stage of food anaphylaxis without the use of remedies were preserved. On the background of fenkarole on the 7th day of treatment, an increase in Proteus by 2.1 times and lactosonegative forms of E. coli by 2.2 times was revealed in the microflora of the small intestine. There was a decrease in lactobacilli by 14%, an increase in Proteus by 29% and lactosonegative forms of E.coli by 48% in the flora of the large intestine. On the

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background of zaditen in the microflora of the small intestine an increase in Proteus by 66% was determined on the 7th day of experiments. In the flora of the colon-there was a decrease in lactobacilli by 14%, an increase in Proteus by 31% and lactosonegative forms of E.coli by 24%.

Analysis of the incidence of microorganisms in the stage of anaphylaxis on the background of treatment with antihistamines showed that under the influence of fenkarole in the microflora of the small intestine on the 3rd day of anaphylaxis streptococci, Protei and fungi in 14% of rats were not sown, on the 7th day of staphylococci, Protei and fungi in 14%; and under the influence of zaditen on the 3rd day of experiments in the microflora of the small intestine, streptococci and fungi in 14% of rats, on the 7th day, staphylococci and streptococci- in 14% of rats were also not sown. In the microflora of the large intestine against the background of both remedies in all terms of this study, all microorganisms were found in 100% of cases.

Result

As a result of the conducted researches it was established that in the conditions of PAR the most expressed dysbiotic changes in microflora of small and large intestines occurred on the 6th day of sensitization and on the 3rd day of food anaphylaxis. Relatively more distinct dysbiotic shifts were observed in the large intestine. And when studying the effect of antihistamines on these disorders, their ambiguous effect was established. Fenkarole and zaditen did not have a sufficient protective effect on dysbiotic changes in the intestinal microflora.

Conclusion

1. At the stages of sensitization and food anaphylaxis of PAR, dysbiotic changes in the microflora of the small and large intestine are observed. These changes directly depend on the form and duration of allergic reactions. They are most pronounced on the 6th day of sensitization and on the 3rd day of food anaphylaxis. Relatively more distinct dysbiotic shifts are observed in the large intestine.

2. Fenkarole and zaditen in this pathology do not have sufficient corrective action on dysbiotic shifts in the intestinal microflora.

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Table 1.

The influence of fenkarole and zaditen on the intestinal microflora in food anaphylaxis (lg CFU / ml) (M±m, n=7)

№ s/i	Groups	Microflora of the small intestine							
		Total number of anaerobes	Total number of aerobes	Staphyla-coccus	Strept. fecalis	E.coli	Proteus	Fungi	Lactose (-) E.coli
1.	Control	3,16±0,14	3,78±0,14	2,54±0,37	3,36±0,33	3,24±0,08	1,01±0,16	1,88±0,32	0,98±0,05

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Received 05 March 2021; Accepted 01 April 2021.

2.	FA, 24 h	2,21±0,58	4,27±0,18*	2,58±0,15	3,57±0,62	3,60±0,16*	1,94±0,14*	2,22±0,11	1,61±0,16*
3.	Ph+FA,24 h	2,00±0,14*	5,03±0,37*	2,94±0,15	4,30±0,72	4,23±0,31*	1,95±0,37*	2,24±0,43	1,81±0,06*
4.	Z+FA,24 h	2,26±0,18*	4,94±0,21*	2,81±0,54	4,50±0,36*	4,37±0,17*	2,66±0,17*	2,76±0,20	2,07±0,15*
5.	FA, 72 h	1,97±0,10*	5,01±0,22*	2,91±0,14	4,56±0,30*	4,36±0,22*	2,13±0,40*	2,35±0,66	1,83±0,10*
6.	Ph+FA,72 h	2,41±0,16*	4,54±0,29*	2,45±0,51	2,96±0,56	4,19±0,19*	1,60±0,31	1,86±0,51	1,54±0,16*
7.	Z+FA,72 h	2,26±0,11*	4,60±0,31*	2,75±0,34	3,01±0,57	4,10±0,18*	1,62±0,30	1,89±0,51	1,57±0,19*

Continuation of table 1.

№s/i	Microflora of the large intestine									
	Total number of anaerobes	Bifidobacteriums	Lactobacillus	Total number of aerobes	Staphyla-coccus	Enterococcus	E.coli	Proteus	Fungi	Lactose (-) E.coli
1.	9,29±0,32	8,39±0,18	8,56±0,19	6,21±0,19	4,83±0,22	5,26±0,20	5,33±0,14	2,67±0,38	2,64±0,39	1,24±0,12
2.	8,21±0,39	8,01±0,17	7,44±1,28	6,80±0,30	4,79±0,30	5,30±0,23	4,62±0,29*	3,47±0,26	3,56±0,30	2,72±0,18*
3.	7,66±0,24*	6,53±0,28*	7,33±0,26*	6,66±0,26	5,51±0,31	4,17±0,22*	6,07±0,27*	3,10±0,23	3,16±0,13	2,14±0,14*
4.	7,77±0,18*	6,64±0,26*	7,63±0,19*	6,34±0,44	5,54±0,20*	3,72±1,03	5,52±0,19	3,21±0,23	3,21±0,12	2,16±0,27*
5.	7,84±0,33*	6,61±1,12	7,30±0,19*	6,77±0,32	4,59±0,22	4,04±0,12*	5,26±0,16	3,25±0,21	3,50±0,60	2,51±0,16*
6.	8,35±0,20	7,36±0,16*	7,35±0,33*	6,81±0,44	4,53±0,81	4,34±0,76	5,43±0,26	3,40±0,18	2,62±0,71	2,02±0,20*
7.	8,24±0,2	7,39±0,1	7,13±0,3	6,79±0,4	4,59±0,8	4,38±0,7	5,49±0,2	3,43±0,	2,59±0,6	1,93±0,1

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Received 05 March 2021; Accepted 01 April 2021.

	8*	8*	8*	8	2	7	9	17	9	8*

Note: FA – food anaphylaxis; Ph+FA, Z+FA – the group of animals treated in the process of summoning food anaphylaxis, respectively, fenkarole and zaditen; sign * – differences statistically significant in relation to control groups; the indicator was considered as reliable at $P < 0.05$.

SUMMARY

THE INFLUENCE OF FENKAROLE AND ZADITEN ON INTESTINAL MICROFLORA OF RATS IN THE STAGES OF PASSIVE ANAPHYLACTIC REACTION

It is known that the prevalence of allergic diseases worldwide is constantly growing both in developed and, especially, in developing countries. Therefore, in this work it was studied changes in microeubiotic system of the rat intestine in stages of passive anaphylactic reaction (PAR) and the influence of antihistamines on the observed violations of microbiocenosis of the intestine.

In experiments on white rats we studied the changes in the microflora of the small intestine and colon in sensitization and food anaphylaxis stages of passive anaphylactic reactions and the impact of antihistamines fenkarole and zaditen on the monitored violations.

Based on the results of the experiments, it was found that the most pronounced dysbiotic changes in the microflora of the small and large intestine on the 6th day of sensitization and on the 3rd day of food anaphylaxis occurred in PAR, and relatively more distinct dysbiotic changes were observed in the large intestine. And in the study of the effect of antihistamines on these disorders, their ambiguous effect was established, although fenkarole and zaditen did not have sufficient protective effect on dysbiotic changes in the intestinal microflora.

Key words: antihistamines, fenkarole, zaditen, sensitization, food anaphylaxis, intestinal microflora.