

Efficacy Of Macmiror[®] In The Therapy Of Giardiasis Invasion In Children With Chronic Hapatitis B

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ABSTRACT

Application of three-stage therapy of giardiasis in 250 children with CHB, using MACMIROR[®], Albendazole, and Metronidazole at the second stage of effecting the parasite and its elimination from the organism, provided achievement of clinical-biochemical remission in 91.1%, 72.5% and 52,5% cases, and parasite elimination in 93.3%, 32.5% and 60.0% cases, respectively. It should be noted, that in the conditions of administration of Trichopolium, in spite of the high rate of G.Lambliia elimination, the therapy was associated with the expressed hepatic toxicity, making recommendation of it for that category of children impossible. Thus, the first line agent for a specific therapy of giardiasis in children with CHB is MACMIROR[®], due to its efficacy and safety.

Key words: chronic viral hepatitis, giardiasis infection, antiparasitic agents, therapy, children.

1. INTRODUCTION.

In spite of vaccination against hepatitis B and achievements in the field of diagnostics and treatment of chronic viral hepatitis in children, the problem is still topical one for the world and local health care system. According to WHO, up to 2 million deaths are registered annually only due to liver cirrhosis, conditioned by chronic hepatitis B (CHB), ranking that pathology to be the 9th in the world mortality structure [3;7;10;11]. It is proven, that any associate pathology with infectious and non-infectious origin often predetermine unfavorable progressing of the basic disease. Parasite intestinal diseases, among which the most significant one is giardiasis with involvement of children reaching 40-60%, have a notable effect on the progression of CHB [4;5;6;8;9]. As a result there is a global problem of mixed infections with viral-parasite etiology with resulting pending issues. The complexity of the problem is conditioned by both insufficient number of scientific researches in the field and absence of therapeutic approaches in its therapy. In the conditions of viral-parasite infection

the therapy of giardiasis is complex due to a sudden decrease in the immune protection, conditioned by pathological processes in liver, limitation in the choice of antiprotozoal agents because of their hepatic toxicity, high re-infection rate, and, in some cases, strains of the agents gaining resistance to medication [1;2;5]. All the aforesaid determined the necessity of the choice and performance of pharmacological correction in the therapy of giardiasis invasion in children suffering CHB, taking into accounts agents' hepatic toxicity, biological availability, and efficacy.

The objective of the study was assessment of the efficacy of antiparasitic agents from various pharmacological groups with the background three-stage anti giardiasis therapy of children suffering CHB with intestinal giardiasis.

2. METHODS AND DATA.

We observed 250 children with combined HBV+G.Lambdia infection in the age from 3 to 18 years old, where 66.4% were boys, and 33.6% were girls. Average duration of CHB was 4.1 ± 0.2 years. Distribution according to CHB activity demonstrated that 38.4% of the children had a moderate, 32.0% expressed, and 29.6% had a minimal degree of CHB activity. Diagnosis of CHB was based on the history data, clinical examination, biochemical and instrumental tests. Etiological diagnosis was confirmed on the basis of detection of HBsAg, HBsAb, HBeAg, HBeAb, HBcorAb by means of EIA and detection of HBV-DNA by means of PCR. Diagnostics of giardiasis was performed using EIA for detection of G. Lambdia antigen in feces, PCR qualitative analysis for detection of DNA G. Lambdia in blood and feces, EIA for detection of G. Lambdia antibodies class IgM and IgG in blood serum, and triple microscopic test of sedimentation components of feces. We calculated the positivity coefficient by the ratio of optic density to critical one. As a result of specific markers study it was determined, that the majority (75.5%) of children had an activation stage of giardiasis invasion (DNA G. Lambdia and G.Lambdia antigen with positivity coefficient > 6 in feces). Giardiasis therapy was performed step-by step, adopted for the patients with CHB (I – preparation, II – effecting the parasite, III - rehabilitation), where at the second stage together with the basic therapy as a specific therapeutic agents we applied Metronidazole 20 mg/kg/day for 10 days in 80 children (I group), Albendazole 10 mg/kg/day for 7 days in 80 children (II group), and 90 children received MACMIROR[®] 15 mg/kg/day for 10 days (III group). Criteria of efficacy assessment were: prevalence of clinical, biochemical, and parasite elimination, which was performed at the end of the therapy course. Statistical processing was done by means of variation statistic method using Student's t-criterion. Differences were considered to be reliable with $p < 0.05$.

3. RESULTS AND DISCUSSION.

Comparative analysis of the application of various anti giardiasis agents showed, that administration of MACMIROR[®] had a greater effect on the progression of CHB compared to Albendazole and Metronidazole (Table1). Particularly, clinically 91.1% of the children (versus 52.5% and 72.5% respectively in the I and II groups, $p < 0.05$) responded positively, which was reflected in the improvement of feeling, stop of complaining about increased fatigability, weakness, nausea, and stomachache. There was leveling of flatulence, rumbling in stomach, and stool disorders, appetite recovered. Obviously icteric skin and sclerae disappeared in the majority of the patients (77.7%, $p < 0.05$). Reliably less often we registered symptoms of hemorrhagic syndrome such as nasal bleeding and ecchymosis (11.1% versus 39.7% and 21.1% respectively to the I and II groups, $p < 0.05$). There was apparent decrease of the expression of hepatosplenomegaly ($p < 0.05$ to comparison group). Extra hepatic signs

such as palmar erythema, spider veins and venous collaterals on stomach preserved only in 12.8% of the patients, and that was 2.6 and 4.2 times less than among the children administering Albendazole and Metronidazole, respectively.

Table 1. Prevalence of clinical symptoms in children with combined viral-parasite infection after the therapy (%)

Clinical symptoms	Metronidazole n=80 (I)	Albendazole n=80 (II)	MACMIROR® n=90 (III)
<i>Asthenovegetative syndrome:</i>			
Fatigability, weakness	60.0±7.8*	32.5±7.5**	4.4±1.5***
Sleep disorder	47.5±8.0*	20.0±6.4**	4.4±1.5***
Headache	52.5±8.0*	25.0±6.9**	0.0±0.0***
Pale and dry skin	57.5±7.9*	32.5±7.5**	6.7±3.8***
<i>Dyspeptic syndrome:</i>			
Nausea, vomiting	20.0±6.4*	10.0±4.8	0.0±0.0
Stomachache	52.5±8.0*	25.0±6.9**	4.4±1.5***
Bad appetite	57.5±7.9*	27.5±7.1	11.1±4.7***
Tongue coating	57.5±7.9*	32.5±7.5	11.1±4.7***
Flatulence	60.0±7.8*	35.0±7.6**	6.7±3.8***
Stool disorder	47.5±8.0*	25.0±6.9**	4.4±1.5***
<i>Cholestatic syndrome:</i>			
Sub-icteric skin	17.5±6.1	10.0±4.8	6.7±3.8***
sclerae	52.5±8.0	32.5±7.5	11.1±4.7***
<i>Hemorrhagic syndrome:</i>			
Nasal bleeding	52.5±8.0	32.5±7.5	11.1±4.7***
Ecchymosis	27.5±7.1	10.0±4.8**	0.0±0.0***
<i>Extra hepatic symptoms:</i>			
Palmar erythema	60.0±7.8	42.5±7.8	20.0±6.4***
Capillary net	77.5±6.7	52.5±8.0**	22.2±6.3***
Spider veins	20.0±6.4*	7.5±4.2	0.0±0.0***
Venous collaterals	57.5±7.9*	32.5±7.5	8.9±4.3***
<i>Hepatolienal syndrome:</i>			
Enlargement of liver up to 3cm	52.5±8.0	72.5±7.1	95.6±3.1***
3-5cm	22.5±6.7	17.5±6.1	4.4±1.5***
Above 5cm	25.0±6.9	10.0±4.8	0.0±0.0***
Enlargement of spleen	27.5±7.1	12.5±5.3**	0.0±0.0***

Note: * - reliability of differences between the studied values
*- between I and II; ** - II and III; *** - I and III groups (p<0.05-0.001).

Among the symptoms pathognomic for giardiasis in children with CHB, who received Nifuratel, manifestations such as bruxism, teaks, and hyperkinesis like biting nails, sucking a finger, and biting lips, reliably more often disappeared (p<0.05 to comparison group). Enuresis was not observed in any of the children (versus 4.0% and 20.0% respectively in the I and III groups, p<0.05). Dermal manifestations such as depigmentation and hyperkeratosis leveled off in 73.3% of the children, while in the rest of the cases (20.0%) there was a tendency for decrease in visible expression. None of the children had a red margin of lips and peeling around the mouth (p<0.05). At the same time, it should be noted, that application of Metronidazole was accompanied by side-effects such as hyperenzymemia, enlargement of

liver, and so on, testifying hepatic toxicity of the agent. Mostly these were children with expressed activity of CHB, and that, apparently, excludes the possibility of its recommendation for the treatment of giardiasis in that category of children.

Similar situation was observed in the dynamics of biochemical parameters (Table 2). Thus, in the III group of children at the end of the therapy most of the parameters reached normal values, and it was reliable in relation to the comparison group, where intermediate position was taken by the children receiving Albendazole ($p < 0.05$). Less expressed dynamics was noted among the children, who received Metronidazole ($p < 0.001$).

Table 2. Biochemical parameters in children with CHB and giardiasis (after the therapy)

Parameters	Metronidazole n-80 (I)	Albendazole n-80 (II)	MACMIROR [®] n-90 (III)	Control
ALT, mkmol/L	1.2±0.26	0.99±0.2**	0.59±0.1***	0.68±0.02
AST, mkmol/L	0.60±0.1	0.48±0.1**	0.36±0.1***	0.38±0.02
Total bilirubin, mkmol/L	19.1±2.7	17.9±1.0**	15.7±1.0***	14.8±0.57
GGTP, u/L	25.7±1.0	24.1±1.0**	21.1±0.8***	33.3±1.28
Alkali phosphatase, U/L	179.8±14.2	174.8±12.3**	138.4±9.9***	177.0±12.0
Thymol test, u.	7.3±0.9	6.9±0.6	5.1±0.4	3.6±0.2
γ-globulin, %	25.0±0.7	24.4±0.7	21.9±0.6	15.7±0.47
Albumin, %	45.5±2.6	46.3±2.0**	51.4±1.0***	54.4±0.72
PTI %	70.2±1.1	70.7±1.1**	74.9±1.5***	75.0±0.66

Note: * - reliability of the differences between the studied parameters

*- between I and II; ** - II and III; *** - I and III groups ($p < 0.05-0.001$).

The activity of ALT in blood serum was average 2 times higher, and AST 1.7 times higher in the patients of the I group, than in the children of the III group. Ideal situation was revealed in the analysis of the expression of cholestatic syndrome. Thus, total bilirubin in the I group of the patients was increased up to 19.1±2.7 mkmol/L, in the II up to 17.9±1.0 mkmol/L ($p < 0.001$ in both cases in relation to the III group). In the patients of the III group the parameter varied within the range 15.7±1.0 mkmol/L and did not differ from the control. Similar changes could be seen in the analysis of the composition of alkali phosphatase and GGTP: in the I group of the patients average amount of AP in blood serum varied in the range 179.8±14.2 u/l ($p < 0.01$ compared to the III group). In the III group of the patients the amount of AP was in the normal limits (138.4±9.9 u/l). Intermediate position was taken by the patients of the II group with 174.8±12.3 u/l ($p < 0.05$ compared to the III group). The greatest rise of GGTP was observed in the I group (up to 25.7±1.0 u/L, $p < 0.01$ in relation to the III group).

Activity of mesenchymal inflammatory syndrome conditioned by immune inflammation, was the greatest one in the I group. So, the average value of thymol test was equal to 7.3 u. ($P < 0.01$ in relation to the III group). In the II and III groups that values in the dynamic therapy tended for decrease and its average value were 6.9 u. and 5.1 u. ($p < 0.01$ in relation to the I). Reliable differences in the values were revealed in the analysis of the expression of hyper-γ-globulinemia in the compared groups, which was observed in the patients after the treatment with Metronidazole and Albendazole (up to 25.0% and 24.4% respectively, $p < 0.05-0.001$ in relation to the III group), than in the patients, who received MACMIROR[®] (up to 21.9%). At the same time, it should be noted that, administration of Metronidazole was accompanied by side-effects such as hyperenzymemia, enlargement of liver, testifying hepatic toxicity of the agent. Mostly these were children with expressed activity of CHB, and that, apparently, excludes the possibility of its recommendation for the

treatment of giardiasis in that category of children. The “soft” effect of MACMIROR[®] on children’s body suffering CHB was apparently linked with the specificity of its pharmacokinetics, where elimination of the agent occurred exclusively via kidneys and did not involve detoxificative reservoirs of liver, different from the other two studied agents.

The study of HBV marker spectrum showed that, though the studied viral agents had positive dynamics, statistically confirmed one was registered in the production of antibodies to HBsAg (by 18.9%) and HBeAg (by 29.7%) in children receiving MACMIROR[®], while in the other groups the values were at the level of initial parameters. That makes it possible to conclude that complex therapy did not have any effect on viral elimination, but at the same time it had some immune modulating effect.

The study of the spectrum of giardiasis markers demonstrated high efficacy of MACMIROR[®] in the eradication of G.Lambliia. After the therapy from the whole spectrum only 6.7±3.8% (p<0.05 to comparison group) of the patients had specific antigen, which was combined with cystic forms of G.Lambliia in sedimentation components of feces detected by means of microscopy in one case (4.4±1.5%). The second effective drug for elimination of G.Lambliia was found to be Metronidazole, with which the situation after the therapy confirmed the decrease of the number of patients with positive DNA-G.Lambliia in blood up to 7.5±4.2% (versus 17.5±7.1% of the children receiving Zentel), in feces up to 25.0±6.9% (versus 40.0%, p<0.05) and antigen in feces up to 20.0±6.4% of the cases (versus 40.0±7.8%, p<0.05).

In relation to coproscopy, the number of patients with positive results of the analysis (presence of trophozoids) after the therapy was 5.0±3.5% and 10.0±4.8%, of those who received Trichopolium and Zentel. Obtained results allowed us to state various degrees of eradication of G.Lambliia dependently on the used specific agents (figure 2), where the first place was taken by MACMIROR[®] (93.3%), intermediate one by Metronidazole (60%), and the last place by Albendazole (32.5%).

Analysis of catamnestic one-years follow-up of the children, who administered MACMIROR[®] in the composition of three-stage anti-giardiasis therapy showed, that preservation of CHB remission was stated in 6 months in 75.5% of the patients, and in 12 months in 62.2% of the patients. Obviously, that phenomenon was linked with the rise of immunological properties of an organism promoting elimination of Giardia during the therapy. Repeated isolation of G.Lambliia was observed in 8.9% and 15.5% of the cases respectively, which was considered as a new infection. Explanation we saw in the presence of familiar foci, which were not liquidated due to several reasons.

4. CONCLUSION.

Application of three-stage giardiasis therapy in children with CHB using MACMIROR[®], Albendazole, and Metronidazole at the second stage of effecting the parasite and its elimination from the organism, provided achievement of clinical-biochemical remission in 91.1%, 72.5% and 52.5% cases, and parasite elimination in 93.3%, 32.5% and 60.0% cases, respectively. It should be noted, that in the conditions of administration of Trichopolium, in spite of the high rate of G.Lambliia elimination, the therapy was associated with the expressed hepatic toxicity, making recommendation of it for that category of children impossible. Thus, the first line agent for a specific therapy of giardiasis in children with CHB is MACMIROR[®], due to its efficacy and safety.

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