

Original article



FACTORS LIMITING THE EFFECTIVENESS OF INTESTINAL PARASITOSSES' PHARMACOTHERAPY

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ABSTRACT

The effective etiological antiparasitic treatment fulfils two major goals - to cure the infected patient and to terminate its role as an epidemiologically relevant source of infection.

The **purpose** of this study is to evaluate the effectiveness of the pharmacotherapy against the most common intestinal helminthic and protozoal infections diagnosed in Varna region.

Material and Methods: 879 patients with laboratory confirmed intestinal parasitoses were treated etiologically with the established anthelmintic and antiprotozoal agents. Mandatory and active post-treatment laboratory monitoring served as the basis for the assessment of the therapy effectiveness.

Results: *Enterobiasis* has the highest prevalence of the intestinal parasitic infections with estimated treatment success of 94,7% at the end of the mandatory period and nearly 100% at the end of our monitoring. The significantly greater rate of relapses was registered among the patients with the two most common protozoal invasions – *Giardiasis* (9,5%) and *Blastocystosis* (6,7 %). Our analysis established that the main factors limiting the effective antiparasitic pharmacotherapy are extraneous, i.e. independent of the pharmacological properties of the agent or parasite's biology. The most prominent reasons for therapy failure were poor or missing compliance to the therapy regimen, inadequate dosage of the medication or unrecognized source of reinvasion in close family contacts.

In **conclusion**, the collaboration between the general-practitioners, clinical parasitologists and respectively the patients themselves is crucial for achieving an effective therapy and the effective control of the intestinal parasitoses.

Keywords: intestinal parasitic diseases, *Enterobiasis*, *Giardiasis*, antiparasitic agents, treatment effectiveness

INTRODUCTION:

Etiological therapy and chemoprophylaxis play pivotal role in the control of parasitic diseases in the modern

medicine age. In the developed countries parasitic invasions of the gastrointestinal system are a complex and often underestimated clinical and epidemiological problems, among children and adults [1-4]. From a clinical point of view, the accurate diagnosis of the parasitic pathogen allows for the timely application of radical, etiological therapy, thus healing the patient and preventing potential complications. The epidemiological sequel of the etiological treatment, in both clinically relevant cases and asymptomatic carriers, eliminates the source of invasion, restricts the epidemiological process and eradicates the epidemic focus [5].

The **purpose** of this study is to evaluate the effectiveness of the pharmacotherapy of the most common intestinal helminthic and protozoal infections diagnosed in Varna region and to reveal the primary reasons for treatment failure.

MATERIAL AND METHODS:

A total number of 55 856 patients were examined for intestinal parasites on prophylactic and clinical grounds for a 10-year period (2007-2016) in one of the Parasitology laboratories of Varna city, Bulgaria. For the identification of the intestinal parasites 171 311 morphological tests were performed with the following standardized methods - Lugol's Iodine wet mount preparations for the detection of intestinal protozoa, modified Ziehl-Neelsen stain for coccidian protozoa, Graham's (scotch tape) test for detection of *E.vermicularis* eggs, concentration by sedimentation for helminth's eggs. Overall 879 infected persons were identified (table 1). The etiological treatment was conducted according to the pathogenic organism with the internationally standardized treatment agents, doses and regimens [6-9] and in accordance with the national register of authorized pharmaceutical products registered for use in the Republic of Bulgaria [10].

The evaluation of the pharmacotherapy effectiveness was based on the regulated controls– for the contact parasitoses (enterobiasis, giardiasis and hymenolepiasis) on the

10th and 20th day after the treatment. The same regimen was applied to the opportunistic parasites with a similar mechanism of transmission (*Blastocystis spp.*, *Cryptosporidium spp.*). For ascariasis and taeniarhynchosis the control parasitological tests were performed at first, third, sixth, and 12 months.

The control tests were actively documented and analysed, as was the effect of the prescribed treatment and the compliance of the patients with the medication's regimen. If a positive result in the control tests (relapse) was observed, the probable causes of treatment failure were further investigated after which the therapeutic courses was repeated, changed or supplemented with immunomodulatory therapy.

Descriptive statistics and classical epidemiological analysis were performed using specialized software "R system for statistical computation and graphics" v.3.3. [11, 12] Effect sizes of the different treatment regimens were compared by odds ratio analysis. All confidence intervals in the text and table are computed at $p=0,05$.

RESULTS AND DISCUSSION:

Table 1 shows the total number of diagnosed patients with intestinal parasitoses for a 10-year interval among the investigated part of the population of Varna District in Northeastern Bulgaria. The established prevalence for all intestinal parasitoses is $1,57\pm 0,09\%$.

Table 1. Number of cases with intestinal parasitoses and prevalence (2007-2016)

	Children	Adults	Total
• Giardiasis	224	103	327
<i>Giardiasis' prevalence</i>	0,70% $\pm 0,08\%$	0,43% $\pm 0,02\%$	0,58% $\pm 0,06\%$
• Blastocystosis	40	49	89
• Cryptosporidiosis	6	0	6
• Commensal amoebas	10	21	31
➤ Intestinal Protozoal Infections	280	173	453
• <i>Prevalence</i>	0,88% $\pm 0,09\%$	0,72% $\pm 0,05\%$	0,81% $\pm 0,10\%$
• Enterobiasis	332	73	404
<i>Enterobiasis' prevalence</i>	1,04% $\pm 0,10\%$	0,30% $\pm 0,06\%$	0,72% $\pm 0,08\%$
• Hymenolepiasis	9	1	10
• Ascariasis	4	2	6
• Taeniarhynchosis	1	4	5
➤ Intestinal Helminthic Infections	346	80	426
➤ <i>Prevalence</i>	1,08% $\pm 0,09\%$	0,33% $\pm 0,11\%$	0,76% $\pm 0,10\%$
➤ Intestinal Parasitic Infections	626	253	879
➤ <i>Prevalence</i>	1,96 $\pm 0,09\%$	1,06% $\pm 0,12\%$	1,57 $\pm 0,09\%$

I. Antiprotozoal pharmacotherapy and causes for treatment failure.

Giardiasis. *G. duodenalis* infection has highest prevalence among the protozoal pathogens - $0,58\% \pm 0,06\%$. This result corresponds with the data for the average prevalence of the region ($0,56 \pm 0,05\%$) found in the Annual reports of the Regional Health Inspectorate –Varna [13-16].

In the first year of the study, etiological treatment with metronidazole (one tab.250 mg three times daily for five days or the equivalent paediatrics' dose of 15 mg/kg) was given in 37 (11,3%) of the patients with giardiasis. In nearly

¼ of them (nine patients) a second positive result in one of the two controls was established. The targeted investigation found that all discontinued their treatment before the end of the five-day period. In all of, the children, difficulty in swallowing of the tablet was reported, which resulted in choking or/and vomiting immediately after ingestion. Among the adults, treated with metronidazole the disruption of the treatment was attributed to the emerged gastro-intestinal adverse effects ("bitter taste in the mouth", "regurgitation", "heart-burn") and the recommendation to stop alcohol consumption (Disulfiram-reaction). The administration of metronidazole could also be limited by the additional adverse reac-

tions as- increased risk of peripheral neuropathies, photo dermatitis, decreased seizure threshold and clinically significant drug interactions with oral anticoagulants.

This led to a general change in the giardiasis therapy for the rest of the period with a single dose tinidazole regimen (2 g for adults and 40-60 mg/kg for children/per intake). Afterwards, a much lower percentage (9,7%) of treatment failure was recorded. In other words, the likelihood for relapses in the tinidazole treated patients is nearly five times lower than those treated with metronidazole- OR=0,27 (0,09-0,9; p=0,016; Fisher's Exact test). The reason for this outcome we attribute to the single dose therapy, which determines much better patient's compliance. The effective therapeutic dose in the tissues is acquired with the single intake, and the frequent but mild gastrointestinal adverse effects usually appear post factum and cannot lead to the interruption of the pharmacotherapy.

For tinidazole treated patients (n=29) the enquiry of the treatment failure causes revealed the several problems. The lack of a correct medicinal form for the youngest patients (in 15 children-age between one and four) led to positive control results in 4,5%. This required a repetition of the treatment, and after the accurate intake, no further relapses were observed. The ineffective treatment in 13 more cases (3,9%) was attributed to the inadequate or inaccurate application of the prescribed by the parasitology expert therapy. In seven of the relapses, we established that tinidazole was replaced by the General practitioner (GP) with more familiar and inaccurately considered as "universal" treatment course with a single dose of anthelmintic drug (albendazole or mebendazole). In 2 children, the daily regimen was replaced by the GPs with a significantly reduced dose (1/2 and 1/3 of the required). In four cases the patients or their parents deliberately refuse to administer the antiprotozoal therapy.

Due to the frequent gastrointestinal adverse effects of antiprotozoal drugs in the last 3 years of the study, in parallel with the etiologic treatment, we recommended therapy with agents that stimulate local intestinal mucosal immunity (various probiotic strains). A faster resolving of the gastro-intestinal symptoms and reduced etiologic agents' adverse effects were observed in all patients in this group.

In only one (0,3%) of the patients with giardiasis, a possible drug resistance was observed. The patient was registered for the first time in 2011 and tested positive for more than five times over the next five years. The administration of tinidazole regimen led to the clearing of *Giardia* cysts for different periods (the longest interval was eight months), but the symptoms usually reappeared. Some additional measures included testing and treating of the infected contacts in the family, proper sanitation of the environment, purification of the drinking water. The prolonged metronidazole treatment (for ten days) in combination with immunomodulatory therapy prompted continuous negative results in 2015. As in the other described in the literature chronic giardia patients [17] for the successful treatment outcome an individual approach and prolonged monitoring are essential.

Blastocystosis.

For the period of the survey on the basis of internationally accepted criteria [3, 18] clinically significant blastocystosis was confirmed in 40 children and 49 adults. In all, a five days' regimen with metronidazole was recommended. As with giardiasis, the ineffective treatment results (in 6,7 %) were attributed to the discontinuation of therapy by the patient or the replacement of the treatment regimen with ineffective one by GPs. Further course with Sulfamethoxazole/Trimethoprim and immunomodulatory probiotic agents were prescribed only in patients with residual high parasite density.

Cryptosporidiosis.

Cryptosporidiosis was included in our study at the beginning of 2016, and those are the first and preliminary results regarding the distribution of cryptosporidiosis in Varna region. Of the six diagnosed cases, four were young children (one to three years old, without immune deficits) with acute diarrhea. Although there is not a standardized treatment for cryptosporidiosis [7] in addition to the symptomatic rehydration therapy we recommended and applied an antibiotic (Azithromycin) with established antiprotozoal effect. Due to the lack of clinical manifestation the other two immunocompetent individuals were recognized as asymptomatic carriers and only probiotic therapy was recommended. In all six patients, the consecutive control test remained negative. This could also be attributed to the generally self-limiting course of the Cryptosporidiosis in immunocompetent patients.

II. Anthelmintic pharmacotherapy and causes for treatment failure.

Enterobiasis.

Of the intestinal helminthic infections traditionally, for both the country and the region the highest prevalence was estimated for the enterobiasis (0,72% ± 0,08%). Our results are comparable with the mean prevalence of 0,68± 0,10% for the whole District reported by Regional Health Inspectorate -Varna for the same time interval [13-16].

In 140 (34,7%) of the patients with *E. vermicularis* etiologic treatment with the drug of choice - mebendazole was recommended. The single 100 mg dose had to be followed by a re-administration after a 20 days' interval. The discontinuation of the mebendazole' supply in the national drug-store network in 2014 led to the conversion of the therapy to albendazole-400 mg tab. The single dose course followed by a second intake in 20 days was administered in the rest 65,3% (n=264) of the infected. On the ground of socio-epidemiological indications (poor social conditions, institutionalized children, minority groups) a preventive third and fourth intake in 20-day intervals were recommended in some of the patients [5].

The successful treatment was established in 389 of the patients (96,3%), all adults and a sizable percentage of the children. There was no difference in the success rates between the two types of drug therapy (96,2% success rate with mebendazole vs. 96,4% with albendazole).

The assessments of treatment failure in 15 patients

(3,7%) (only children) revealed the following problems: In five cases the extended range of sampling among the closest contacts established at least one more parasitized family member and a preventive pharmacotherapy course was applied to the whole household. In other four children (0,98%) (age between two and four years) difficulty in swallowing the tablet form was recorded. The re-admission of the therapy was recommended, and no subsequent relapses were recorded. In two cases the daily prescription was replaced with a significantly reduced (1/4th of the required) dose by the family's GP. In the remaining four patients (0,98%), the recurrent positive findings were a result of the complete absence of anthelmintic drugs in the pharmacy network during various periods of 2014, 2015 and 2016. Only after the renewal of albendazole supply, the radical cure of enterobiasis was possible and accomplished.

Ascariasis.

Varna district is one of the provinces of the country without local distribution of ascariasis, and all of the cases are accidental and "imported" for the region [4, 13, 16]. Only six patients with *A. lumbricoides* were diagnosed during the 10-year interval of our investigation. All of them were treated with mebendazole –one tab.100mg twice a day for three days' period or a daily pediatrics' dose of 10 mg/kg divided into twice daily. All of the control tests at first, third, sixth, and 12 months after the treatment remained negative and we report a 100% curative rate.

Hymenolepiasis.

During the investigated period, 9 children and one adult (contact of an infected child) were infected with *H. nana*. A major obstacle to the timely and effective treatment of hymenolepiasis was the complete lack of anticestodal drugs in the pharmacy network of the country [10]. In three of the patients, the effective treatment with praziquantel (10 mg/kg in two intakes with ten days' interval) was established by negative control tests. In three patients the anticestodal drug niclosamid was used in combination with immunomodulant - isoprinosin (50 mg / kg daily for two weeks) [5]. All of the control tests, on the 10, 20 days and after one month remain negative. In the remaining three patients (children from a large roma family living in extreme poverty), due to the lack of alternative, treatment with albendazole was prescribed. The control samples were not provided, and we cannot determine the effect of this treatment regimen.

Taeniarhynchosis.

During our study, four of the five cases diagnosed with taeniarhynchosis were assessed as "imported" for the region. Two of the patients were residents of Shumen and Dobrich city, and two were foreign nationals (one Syrian and one patient from Russia). Only one was a resident of a village in Varna region. As in hymenolepiasis the complete lack of anticestodal pharmaceuticals lead to delay of the treatment. Two of the patients were treated with

Praziquantel (10 mg / kg once) and one with niclosamid (2 g once). A saline purgative was supplemented in the therapy in order to facilitate the evacuation of the taenia [5]. The dispensary observation for one year of all Bulgarian patients revealed effective treatment. Due to leaving the country, there was no data collected on the effect of the treatment prescribed for the two foreigners.

CONCLUSION:

The common intestinal parasitic infections are an important health problem in both children's and adults' population of Varna district and correspondingly through all the regions of Bulgaria as well.

Our analysis established that the factors reducing the effectiveness of antiparasitic pharmacotherapy are mostly extraneous, i.e. independent of the pharmacological properties of the therapeutic agent or the parasite's biology. In antiprotozoal therapy, a better compliance and a more effective treatment outcome are observed when the long-term therapy with metronidazole is substituted by the single-dose courses with tinidazole. The former should be reserved and recommended mainly in complex cases - chronic infections or immunocompromised patients. In nematode infections, the proper effect of the etiological therapy with both agents - albendazole and mebendazole, is established. The shortage of these medications or the irregularity of their supply in the country and the region, however, causes a delay in therapy and prolongation of the period in which those persons are epidemiologically active sources of infection. The complete absence of anticestodal drugs on Bulgarian market is another cardinal problem that needs solving for years. Thus, the necessity to obtain a proper medication from neighbouring countries leads to unnecessary delay in radical therapy. A practical problem in the treatment of the most common intestinal infections in children (enterobiasis and giardiasis), is the absence of a different than a tablet form in the pharmacy network, although such do exist on the international market, and some are even registered in Bulgaria.

We confirm the beneficial effect of the supplementary immunomodulating probiotic therapy in the treatment of intestinal parasitic infection (faster recovery of gastrointestinal symptoms, decreased adverse effects) and we recommend its use in all such patients.

To achieve radical and effective anti-parasitic treatment a rational and individual approach is needed which requires active co-operation between parasitologists, GPs and the patients themselves.

In conclusion, although the antiparasitic drugs are among the earliest discovered etiological agents in medicine, their variety in our country is extremely limited, and this obstructs the timely and effective etiological therapy of the most common intestinal parasites.

Abbreviations:

IP – intestinal parasites

GP – general practitioners

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Conflict of Interest: No conflict of interest to declare

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