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Autor: Feldmeier, H. / Bienzle, U. / Döhring, E. DOI: https://doi.org/10.5169/seals-312976

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Department of Medicine, Bernhard-Nocht-Institut für Schiffs- und Tropenkrankheiten, Hamburg, Federal Republic of Germany

Flubendazole versus mebendazole in intestinal helminthic infections

H. Feldmeier, U. Bienzle, E. Döhring, M. Dietrich

Summary

In a double-blind study the vermicidal effect of flubendazole, a new benzimidazole derivative, was evaluated and compared to mebendazole. Both drugs were administered in a single dose of 600 mg. While in the treatment of Ascaris and hookworm infestations flubendazole and mebendazole showed a similar efficacy, mebendazole seemed to be slightly superior in the treatment of trichuriasis. Both drugs were well tolerated and no side effects were observed even in patients with a heavy worm load.

Key words: flubendazole; mebendazole; double-blind trial; intestinal helminthiasis.

Introduction

Flubendazole, methyl (5-[4-fluorobenzyol]-1-H-benzimidazol-2-yl) carbamate, the p-fluoro analogue of mebendazole has recently entered the stage of clinical trial. Previous studies in laboratory animals have shown that flubendazole is effective against a wide variety of nematodes and cestodes. It was also successfully used in infections with Chinese liver flukes (Duong et al., 1980). The drug has a low toxicity and no teratogenic properties have been discovered (Thienpoint et al., 1978). Flubendazole interferes with the vital uptake of glucose into the cells of the helminths leading to exhaustion of the glycogen reserves and consequently to a breakdown of the glucose metabolism (Van den Bossche and de Nollin, 1973). Absorption of the drug by the intestinal mucosa occurs only in unimportant quantities. Plasma concentration of flubendazole normally does not exceed 5 μ g/ml (Heykants et al., 1979). Maximal levels in

Correspondence: Prof. Dr. M. Dietrich, Department of Medicine, Bernhard-Nocht-Institut für Schiffs- und Tropenkrankheiten, Bernhard-Nocht-Strasse 74, D-2000 Hamburg 4

plasma are attained 1–4 h after drug intake, the average half life is 16 h (Heykants et al., 1979). The drug is well tolerated, even if an administration of 2000 mg per day is repeated over a period of two weeks and more (Quilici et al., 1979).

The present clinical study was undertaken in order to compare the therapeutic efficacy of flubendazole with that of mebendazole, the parent compound. A better or similar therapeutic efficacy of flubendazole would be of interest, as experimental data indicate a lower tolerance of mebendazole (Thienpoint et al., 1978).

Patients and Methods

Patients. Admission: admitted to the study were refugees from Vietnam, Laos and Kampuchea. They were all seen at the Outpatient Department of the Bernhard-Nocht-Institut within two weeks after their arrival. These patients were admitted to the study because they represented a homogeneous group, and because many of them were concomitantly infected with different intestinal helminths. Exclusion: children under six years of age as well as pregnant or lactating women were excluded from the study. Informed consent: consent was verbally obtained by means of an interpreter.

Examinations performed. For reasons of assessing the health status when entering Germany, all patients had a physical check-up, a chest X ray, and the following laboratory investigations: haemoglobin determination, red and white blood cell count, differential white blood count, protein electrophoresis, and determination of serum GOT and GPT. Malaria parasites were excluded by thick blood films. Stool examinations for intestinal helminths and protozoa were performed by the MIF concentration technique (Blagg et al., 1955), one immediately before, one 1 month after therapy.

Organization of the study. The trial was carried out as a double-blind study. During a three-month period all examined patients found to be infected with intestinal helminths were included in the trial. Sequential identification numbers were attributed to each patient and were noted with a pencil both on his right forearm and on a disposable plastic vial filled with 2 ml of a MIF solution. When the vial was returned with the stool sample, the identification numbers were cross-checked and the remedies administered under surveillance. 12 and 24 h after intake of the drugs, the patients were interrogated about side effects.

Administration of drugs. Mebendazole and flubendazole were prepared as indistinguishable tablets and packed in coded vials. Mebendazole was provided in an identical galenical preparation as the commercially available drug. Each patient received either 6 tablets (600 mg) of mebendazole or 6 tablets (600 mg) of flubendazole at once.

Evaluation. Patients were defined as cured when no worm ova were detected by stool examination four weeks after treatment. Statistical evaluation of the efficacy of the drugs was performed by the chi-square test.

Results

141 patients were admitted to the study, 70 patients received flubendazole (group F) and 71 mebendazole (group M). In group F the median age was 17.5 years and the male/female ratio was 45/70 (64%), in group M the median age was 20 years and the male/female ratio 32/71 (45%), respectively. In both groups 7 patients were not available for the follow-up and had to be removed from the study.

Table 1. Number and type of intestinal parasites found in the two treatment groups¹

Parasite species	Treatment group		
	Flubendazole (n = 70)	Mebendazole $(n = 71)$	Total
Ascaris	68	64	132
Hookworm	16	6	22
Trichuris	10	16	26
Strongyloides	2	3	5
Taenia	1	1	2

¹ 22 out of the 141 patients were simultaneously infected with 2 parasites, 9 with 3 parasites, and 2 with 4 parasites.

Table 2. Overall efficacy of flubendazole and mebendazole

	Flubendazole (n = 70)	Mebendazole $(n = 71)$	Total	Level of significance
Cured	$e^1 = 54.1$ $o^2 = 53$	56	109	n.s.
Not cured	10	8	18	n.s.
N.D. ³	7	7	14	-

¹ Expected frequency ² Observed frequency ³ Not done, patient could not be followed up after treatment

The types of parasites detected in the two patient groups are summarized in Table 1. The majority of the patients suffered from Ascaris, hookworm and Trichuris infestations. In 24% of the cases polyparasitism was found. Taenia and Strongyloides infestations were excluded from the evaluation due to the small number of cases.

Table 2 demonstrates the effect of flubendazole and mebendazole treatment on the overall worm load. A complete parasitological cure was obtained in 84.1% of the flubendazole group and in 87.5% of the mebendazole group. No statistical difference can be noted. When the effects of the two drugs on Ascaris, hookworm and Trichuris were analyzed separately, it could be shown that both medicaments acted similarly on Ascaris and hookworm (Tab. 3 A and B). Complete cure was obtained in 95.2% and 94.8% of Ascaris infection (flubendazole and mebendazole, respectively), and in 73.3% and 66.7% of hookworm infection. The differences are not significant. In patients infected with Trichuris, comparison of relative frequencies of obtained cure seems to show a slight superiority of mebendazole (87.5% cured) as compared with flubendazole

Table 3. Efficacy of flubendazole and mebendazole in the treatment of ascariasis (A), hookworm infection (B), and trichuriasis (C)

	Flubendazole	Mebendazole	Total	Level of significance
A. Ascariasis	(n = 68)	(n = 64)		
Cured	e = 58.9 o = 59	55 3	114 6	n.s.
Not cured	3	3	6	n.s.
N.D.	6	6	12	_
B. Hookworm infection	(n = 16)	(n = 6)		
Cured	e = 10.7 o = 11	4 2	15 6	n.s.
Not cured	4	2	6	n.s.
N.D	1	0	1	-
C. Trichuriasis	(n = 10)	(n = 16)		
Cured	e = 5.7 o = 4	14	18	p = 0.1
Not cured	3	1	4	p = 0.1
N.D	3	1	4	Anna

Abbreviations see above.

(57.1%) (Tab. 3 C), however, the difference is statistically not significant (p = 0.1).

No side effects were noted by the patients in both treatment groups, even in those individuals with a high worm load.

Discussion

Intestinal helminthiasis is still the most common medical finding in people living in the tropics. As in most conditions concomitant infection with different intestinal parasites occurs and the devastating effect of polyparasitism combined with heavy worm load on the health status of individual patients is well known, reliable drugs are required which integrate single-dose therapy with a broad-spectrum activity and low toxicity.

In the present study the therapeutic activity of flubendazole, the p-fluor analogue of mebendazole, was compared to that of the parent compound, a well known anthelminthic drug (Maqbool et al., 1975, Degrémont and Baumgartner, 1975). Both substances have the same pharmacological action as they interfere with the vital uptake of glucose into the cells of the helminths (Van den

Bossche and de Nollin, 1973). In experimental studies flubendazole appears to be active against a wide variety of nematodes and cestodes in a single dose (Thienpoint et al., 1978). We could show that flubendazole and mebendazole showed a similar efficacy in the treatment of Ascaris and hookworm infections. Interesting to note that the slight inferiority of flubendazole in the treatment of trichuriasis is comparable to a similar deficiency of another benzimidazole derivative, i.e., cyclobendazole (Guggenmoos et al., 1978). The apparently higher efficacy of the parent compound mebendazole in this infection should be approved in further studies, as the number of patients in our study is too small to allow definite conclusions. In contrast to experimental results, in the present study flubendazole and mebendazole were equally well tolerated. Even patients with a heavy worm load and polyparasitism did not claim about any side effects.

It can be concluded from our data that flubendazole and mebendazole are reliable drugs for the treatment of intestinal helminthiasis. As the chemotherapeutic efficacy is very similar, preferential use should be given to the drug with the lowest toxicity and the lowest incidence of side effects. The complete absence of side effects of flubendazole in our study should be verified in further investigations in patients with different intestinal helminths.

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