International Journal of TROPICAL DISEASE & Health
17(3): 1-7, 2016, Article no.IJTDH.27075
ISSN: 2278–1005, NLM ID: 101632866

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How do Metronidazole Drawbacks Impact Patient Compliance and Therapeutic Outcomes in Treating Amoebiasis in Rwanda

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Authors' contributions

This work was carried out in collaboration between both authors. Authors ED and JNK did the study design, wrote the protocol and did statistical analysis. Author ED conducted field work. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2016/27075
Editor(s):
(1) Janvier Gasana, Department of Environmental & Occupational Health, Robert Stempel College of Public Health & Social Work, Florida International University, USA.
Reviewers:
(1) Sai Wah Cheung, Tuen Mun Hospital, Hong Kong.
(2) Gunnar Sandström, Karolinska University Hospital, Huddinge, Sweden.
(3) Luis Enrique Jerez Puebla, Tropical Medicine Institute "Pedro Kour´ı", Habana, Cuba.
Complete Peer review History: http://sciencedomain.org/review-history/15248

Original Research Article

Received 17th May 2016
Accepted 24th June 2016
Published 1st July 2016

ABSTRACT

Amoebiasis is a parasitic disease with significant public health concerns in the Tropics. Metronidazole which is the first line most common prescribed medicine has shown a number of side effects difficult to tolerate by some patients, and many cases of true or erroneous treatment failure or frequent relapses have been observed among students of the University of Rwanda. This study aimed to evaluate how metronidazole side effects impact patients' compliance, misuse practice, and therapeutic outcomes. A cross-sectional survey was conducted using a self-administered questionnaire to 115 students who had used before or were on metronidazole treatment for amoebiasis at the time of study. The data showed almost all respondents experienced at least one of the known metronidazole side effects including nausea, vomiting, headache, dry mouth or metallic taste, stomach upset, loss of appetite, dizziness, fatigue, somnolence, constipation, diarrhoea, rash, dysuria, itching and fever. About 36.8% of respondents were judged noncompliant,

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stopping taking medicine. There was a significant association between the number of side effects experienced per respondent and the status of patient compliance; and also between compliance status and clinical improvement ($p<0.001$). Notwithstanding patient's noncompliance and a possible actual metronidazole resistance, some of relapses could be due to incomplete prescribing regimen which does not associate lumen (anti cysts) molecules and metronidazole. Prescribers are invited to seriously address this issue for a better achievement of amoeba eradication.

Keywords: Amoebiasis; metronidazole side effects; patient compliance; efficacy.

1. INTRODUCTION

Amoebiasis is an intestinal illness caused by a parasite, *Entamoeba histolytica*. This parasite lives in the intestines and produces cysts which are passed from the body in the stool [1,2]. The infective cyst form migrates to the bowel lumen to form motile and potentially invasive trophozoites. In most infections, the trophozoites aggregate in the intestinal mucin layer and form new cysts, resulting in a self-limiting and asymptomatic infection. Many individuals infected with *Entamoeba histolytica* are asymptomatic; the trophozoites remain confined to the intestinal lumen (noninvasive infection) of these individuals who are asymptomatic carriers, passing cysts in their stool.

In some patients the trophozoites invade the intestinal mucosa (intestinal disease) with resulting colitis and bloody diarrhea (amebic dysentery), or, through the bloodstream, extra-intestinal sites such as the liver where they establish an amebic liver abscess, brain, and lungs (extra-intestinal disease), with resultant pathologic manifestations. It has been established that the invasive and noninvasive forms represent two separate species, respectively *E. histolytica* and *E. dispar*. These two species are morphologically indistinguishable unless *E. histolytica* is observed with ingested red blood cells (erythrophagocystosis) [1,2].

Metronidazole (Flagyl) has been proven to be effective against a wide range of microorganisms including *Entamoeba histolytica* [3-6] as it has excellent penetration into almost all body tissue and fluids, including saliva, vaginal seminal fluids, and cerebrospinal fluid. Currently, metronidazole is on the formulary at most hospitals for treatment of antibiotic-associated colitis caused by *Clostridium difficile*, for treatment of wound abscess, and for prophylaxis against anaerobic infection after bowel surgery. In combination with other agents it is frequently used to eradicate *Helicobacter pylori*, a bacterium which is the cause of gastric ulcer and a risk factor for stomach cancer [5]. In addition metronidazole is cheap and hence affordable to patients. For these reasons, metronidazole is the medicine of first choice and the most prescribed in case of amoebiasis [5].

However, metronidazole induces a number of common side effects or adverse drug reactions (ADRs) including fatigue, nausea, vomiting, diarrhoea, appetite loss, constipation, dizziness, headache, stomach upset, metallic taste, etc. Severe ADRs have also been reported; these include severe allergic reactions (rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips or tongue), bloody stools, decreased motor coordination, increased or decreased urination, numbness, speech problems, stiff neck, sore throat, vision loss or other vision changes, etc. [5-7]. Consuming alcohol while taking metronidazole causes a disulfiram-like reaction with effects that can include nausea, vomiting, flushing of the skin, tachycardia (accelerated heart rate), shortness of breath and even death; it has been advocated that consumption of alcohol should be avoided by patients during systemic metronidazole therapy and for at least 24 hours after completion of treatment. Studies also showed carcinogenic potential related to Metronidazole hydroxy metabolite in animals and not proven in human [8].

These side effects seriously impair the tolerability of Metronidazole by many patients and affect their everyday life and activities within a couple of days. Because of that, some patients taking oral Metronidazole to cure amoebiasis often stop or interrupt medication by their own or upon the prescriber's instruction. This is a serious problem of compliance as it may increase persistence of amoebiasis and induce drug resistance especially in developing countries where repeat episodes are frequent.

Data collected in the period 2011-2013 at the student medical centre of the University of Rwanda (former NUR) showed the prevalence of

amoebiasis to be 92% of students examined over diarrhoea or gastrointestinal disturbances [9]. This prevalence may be the consequence of treatment failure that can result from bad compliance or from acquired parasite resistance to the drug. So, the question of whether metronidazole should be discontinued arises. Up to now, to our knowledge, no study has been undertaken to correlate the impact of these side effects to the patients' compliance and therapeutic outcome before questioning about metronidazole resistance. It was hence worth conducting this study to lighten what is going on and what action should be brought about. The hypothesis of our study was that the seemingly exaggerated prevalence of amoebiasis is due to a bad adherence to the treatment which is caused by the occurrence of intolerable side effects to metronidazole obliging patients to alter the course of treatment, rather than acquired resistance.

2. METHODS

2.1 Study Design

This was a descriptive cross-sectional survey conducted from January to April 2013 among registered students who have had used before or were taking oral metronidazole (Flagyl®) at the time for treatment of mild to severe amoebiasis. We should make difference between a SURVEY study assessing patients' point of view and a CONTROLED CLINICAL TRIAL. The clinical markers limited to symptoms of amoebiasis, particularly, diarrhea, dysentery, colic. Laboratory test was limited to stool examination. Bacterial infections were excluded. We are far from doing identification of strains in this study.

Respondents were selected randomly and those who satisfied criteria for inclusion and agreed to participate were recruited. Only symptomatic cases were considered because that is when patients are sick and consult. Candidates with known hypersensitivity to azoles have been excluded.

A standardized questionnaire form was designed to self report on side effects experienced, use practice, and improvement of symptoms. One of the following requirements had to be fulfilled in order to define a case as noncompliance to treatment: stopping or interrupting the treatment, not use medicines as instructed for dose and the duration of treatment less than 5 days. The therapeutic outcome was self-evaluated by the participants in terms of improvement (relief of symptoms) and non improvement (persistence of symptoms or frequent relapse episodes). Respondents whose questionnaire forms were not satisfactory filled were not included for analysis. Finally, 130 students were contacted and 115 students were retained for analysis.

2.2 Data Analysis

Data was treated with SPSS v18 software for Windows and Microsoft Excel. The descriptive statistics and cross tabulation analysis were performed. Chi-square test was applied for significant tie between compliance and therapeutic outcome at 95% ($p=0.05$). Not all items were absolutely filled, leaving some missing cases.

3. RESULTS

Table 1 summarizes the frequencies of measurement variables. The sample included 62 (53.9%) males and 53 (46.1%) females. Ten (10) participants were taking metronidazole during the survey and 105 had taken it before. Concerning the number of treatment, 43 (37.4%) respondents were naive (first time) and others had used it more than once. The relapse-free time varied from one month (6.1%) to more than three months (52.2%). Respondents were asked to tell whether they stopped taking metronidazole and shifted to another treatment or interrupted treatment and then resumed later. Those who said no were classified as compliant (62.6%) and those who said yes were considered noncompliant (36.5%). Taking medicine for less than 5 days is considered inappropriate compliance (43.5%). Respondents self-evaluated the outcome as improvement or good (66.7%) or bad improvement (33.3%). Of 38 respondents with bad improvement, about 42.1% attributed the failure to drug inefficacy; another 42.1% thought the bad therapeutic outcome observed could be due to the fact they did not finish the cure.

Respondents were also asked to indicate any medicines they were using concomitantly with metronidazole. The majority (64.9%) did not use any other medicine. The remaining used multivitamins, paracetamol and herbal preparations. No lumen or anti-cystic drug was mentioned. Few admitted taking some alcohol during treatment (2%).

Table 2 reports more common, less common and rare side effects encountered in our study. Over 115 students surveyed, almost all predicted side

effects were encountered with frequencies from 70.4% to 3.5%. These are nausea, vomiting, headache, dry mouth or metallic taste, stomach upset, loss of appetite, dizziness, fatigue, somnolence, constipation, diarrhoea, rash, dysuria, itching and fever.

Fig. 1 shows the association between the number of side effects experienced and the level of compliance. There appears strong association (p=0.001). Respondents who experienced one or two side effects were likely more compliant (76%) than those who reported more side effects (50% to 40%).

Fig. 2 shows also that there was strong association between level of compliance and level of therapeutic outcome (p=0.000).

Table 1. Frequencies of measurement variables (n=115 cases)

Variables	Class	N	%	Variables	Class	N	%
Gender	Female	62	53.91	Stopping drug	non stop	72	62.61
	Male	53	46.09		stop and shift	39	33.91
Under treatment	Currently	10	8.70		stop and retake	3	2.61
	Before	105	91.30	Duration	<3 days	8	6.96
Treatments	one	43	37.39		3 to 5 days	42	36.52
	two	20	17.39		> 5 days	64	55.65
	three or more	42	36.52	Associated drugs	None	74	64.35
Relapse –time	one month	7	6.09		Vitamin	21	18.26
	two months	6	5.22		Paracetamol	11	9.57
	three months	24	20.87		Herbal	8	6.96
	> three months	60	52.17	Compliance	Good complier	72	62.61
	Unknown	18	15.65		Bad complier	42	36.52
				Improvement	Good	76	66.70
					Bad	38	33.04
				Cause of failure	Dose not finished	16	42.10
				(N=38)	Drug inefficacy	16	42.10
					I do not know	6	15.80

Missing cases not indicated

Table 2. Types of metronidazole side effects reported by the user respondents

More common	Frequency	Percent	Less common	Frequency	Percent
Nausea	81	70.4	Visual disturbance	15	13.0
Appetite loss	67	58.3	Pain	12	10.4
Fatigue	65	56.5	Itching	9	7.8
Dizziness	46	40.0	Stomach upset	8	7.0
Headache	31	27.0	Flushing	7	6.1
Vomiting	28	24.3	Fever	7	6.1
Diarrhoea	23	20.0	Rash	5	4.3
Constipation	22	19.1	Smelly sweet	4	3.5
Metallic taste	20	17.4	Yellowish urine	4	3.5
Somnolence	18	15.7			
Stomach pain	18	15.7			
Dysuria	18	15.7			

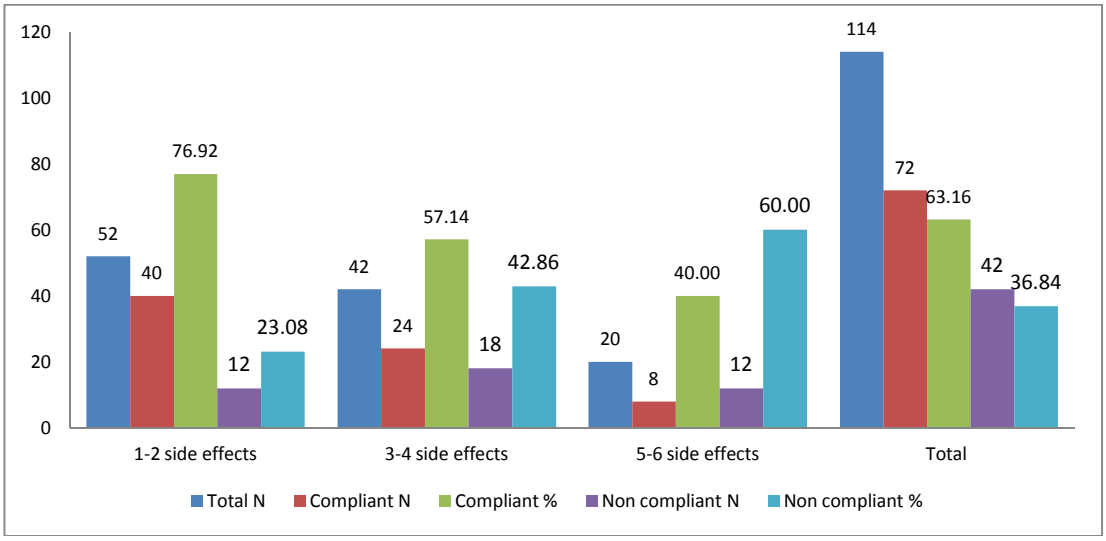

Fig. 1. Association between patient compliance and therapeutic outcome (p-value=0.001)

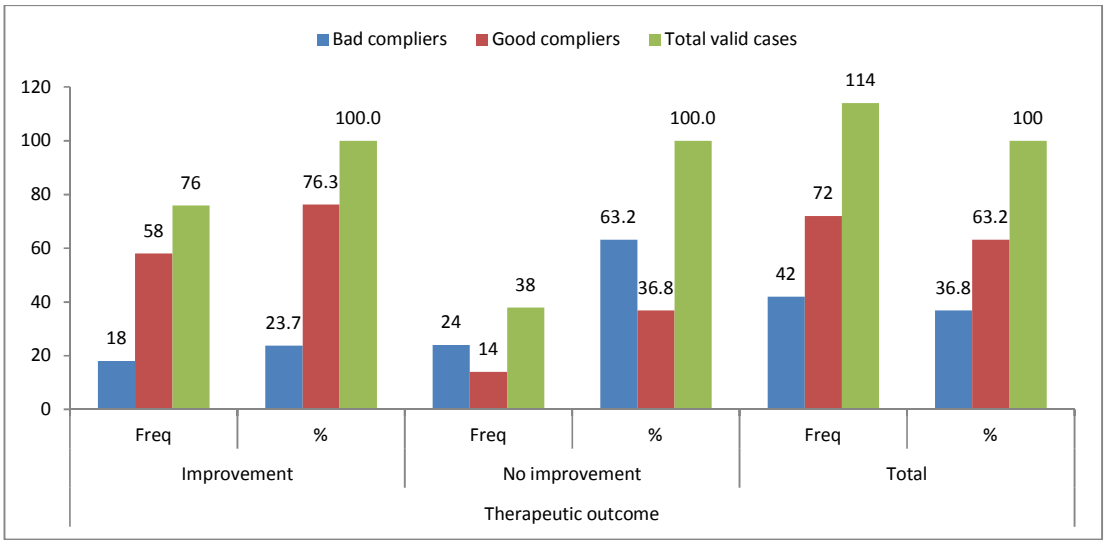

Fig. 2. Association between patient compliance and therapeutic outcome (p-value=0.000)

4. DISCUSSION

This work was a survey aimed at ascertaining the impact of side effects of metronidazole on the patients' compliance and the therapeutic outcome in treating amoebiasis to find factors associated with high prevalence of amoebiasis episodes observed in Rwanda. Students at the University of Rwanda constituted the target sample. All students were subjected to a standard regimen of 500-750 mg orally three times daily for 5 to 10 days [5].

Data analysis showed that most predictable common side effects reported in literature were experienced with some differences in importance compared to other studies [3]. Nausea (70.4%), appetite loss (58.3%), fatigue (56.5%) and dizziness (40%) are dominant in our population.

We used the duration of treatment as measure of compliance. The analysis of respondents' answers showed that only 56.1% of respondents complied with the duration of 5 to 10 days, the remaining took less than 5 days of treatment. Globally 63.2% of respondents were compliant vs 36.8% who were noncompliant, meaning either they stopped or interrupted taking medicine for some days. The status of non compliance was significantly related to the number of side effects experienced (p=0.001).

It is known that patient compliance or adherence to treatment protocol is the key factor to therapeutic success or improvement [10]. In this survey, it clearly appeared that 50.9% of compliant respondents had good improvement vs 12.3% who declared bad improvement out of 63.2%. In other terms, the majority of noncompliant respondents (21% out of 36.8%) did not get good improvement, or the compliant group experienced a significantly greater benefit from the metronidazole than did the noncompliant group.

However, the question arising are to explain why 15.8% of noncompliant reported good improvement and why 12.3% among compliant respondents did not get good improvement. One can say that the improvement is related to the severity of infection and also to drug regimens given. In mild infection, good improvement may mean disappearance of diarrhoea and abdominal pain relief which generally occur in three days. Bad improvement despite good compliance may be related to inadequate patterns or to some unknown factors such as re-infection or resistance. According to respondents thinking, the causes of bad clinical response is either they stopped taking medicine or the medicine is not working.

When respondents were asked to list other medicines taken in association with metronidazole, only paracetamol, multivitamins and herbal preparations were cited. We could not find lumen antiamebics that are active against cysts like iodoquinol, paromomycine or diloxanide furoate [5,11]. If the cysts are non cleared, re-infection is almost to resume in a short time. This has been shown in this survey indicating that respondents had to retake cures after one month to a few months. Any metronidazole drawback may significantly affect the compliance of patients pushing them to abandon the treatment at mid-way. Normally metronidazole is a prescription medicine, but in many circumstances in developing countries it is sold as OTC-drug, a practice that can lead to misuse and drug-resistance.

5. CONCLUSION

In practice, it has been observed that the treatment does not include lumen medications aimed at killing cysts. This may be one of the causes for treatment failure and needs to be advocated to the prescribers and the users. Notwithstanding the emergence of some cases of resistance to metronidazole, its efficacy is still proven. A seven-to-ten day course of treatment in association with lumen molecules may minimize re-infection by protecting the patient long enough. Stopping alcohol should also be emphasized. Thorough laboratory diagnosis is also needed to tackle cases of multiple co-infections by intestinal parasites.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study protocol was approved by the locally ethics committee. All participants were informed and agreed to participate in the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
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