

Original Research Article

How do metronidazole drawbacks impact patient compliance and therapeutic outcomes in treating amoebiasis in Rwanda

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 and attitude, 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 40% of respondents were judged noncompliant, stopping taking medicine. For patients' attitudes towards the use of metronidazole, 47.8% ranked metronidazole as a bad medicine to withdraw from the market. However, there was a strong association between patient compliance and clinical improvement levels ($p < 0.001$). 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.

Key words: amoebiasis, metronidazole resistance, side effects, compliance

Introduction

Amoebiasis, also called amoebic dysentery, is an intestinal illness caused by a parasite, *Entamoeba histolytica*. This parasite lives in the intestines and produces eggs (cysts) which are passed from the body in the stool ^[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 last three years (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.

73 **Methods**

74 *Study design*

75 This was a descriptive cross-sectional survey conducted from January to April 2013 among
 76 registered students who have had used before or were taking oral metronidazole (Flagyl®) at the
 77 time for treatment of mild to severe amoebiasis. Respondents were selected randomly and those
 78 who satisfied criteria for inclusion and agreed to participate were recruited. Candidates with
 79 known hypersensitivity to azoles have been excluded. A standardized questionnaire form was
 80 designed to self report side effects experienced, use practice, attitudes and improvement. The
 81 therapeutic outcome was assessed in terms of improvement (relief of symptoms) and non
 82 improvement as self-evaluated by the participants. One of the following requirements had to be
 83 fulfilled in order to define a case as noncompliance to treatment: stopping or interrupting the
 84 treatment, not use medicines as instructed for dose and the duration of treatment less than 5 days.
 85 Respondents whose questionnaire forms were not satisfactory filled were not included for
 86 analysis. Finally, 115 students were retained for analysis.

87 *Data analysis*

88 Data was treated with SPSS v18 software for Windows and Microsoft Excel. The descriptive
 89 statistics and cross tabulation analysis were performed. Chi-square test was applied for
 90 significant tie between compliance and therapeutic outcome at 95% ($p=0.05$).

91 **Results**

92 Table-1 summarizes the frequencies of measurement variables. The sample included 62 (53.9%)
 93 males and 53 (46.1%) females. Ten (10) participants were taking metronidazole during the
 94 survey and 105 had taken it before. Concerning the number of treatment, 43 (37.4%) respondents
 95 were naive (first time); the others had used it more than once. The relapse-free time varied from
 96 one month (6.1%) to more than three months (52.2%). Respondents were asked to tell whether
 97 they stopped taking metronidazole and shifted to another treatment or interrupted treatment and
 98 then resumed later. Those who said no were classified as compliant (62.6%) and those who said
 99 yes were considered noncompliant (36.5%). Taking medicine for less than 5 days is considered
 100 inappropriate compliance (43.5%). Respondents self-evaluated the outcome as improvement or
 101 good (66.7%) or bad improvement (33%). Of 42 respondents with bad improvement, about
 102 38.1% attributed the failure to drug inefficacy; some thought the bad therapeutic outcome
 103 observed could be due to the fact they did not finish the cure.

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

Variables	Class	N	%
Gender	Female	62	53.91
	Male	53	46.09
Under treatment	Currently	10	8.70
	Before	105	91.30
Treatments	one	43	37.39
	two	20	17.39
	three or more	42	36.52
Relapse –time	one month	7	6.09
	two months	6	5.22
	three months	24	20.87
	> three months	60	52.17
	Unknown	18	15.65
Taking drug	non stop	72	62.61
	stop and shift	39	33.91
	stop and retake	3	2.61
Duration	<3 days	8	6.96
	3 to 5 days	42	36.52
	> 5 days	64	55.65
Associated drugs	None	74	64.35
	Vitamin	21	18.26
	Paracetamol	11	9.57
	Herbal	8	6.96
Compliance	Good complier	72	62.61
	Bad complier	42	36.52
Improvement	Good	76	66.70
	Bad	38	33.04
Cause of failure (N=42)	Dose not finished	16	38.10
	Drug inefficacy	16	38.10
	I do not know	9	21.43
User Opinion	Good medicine	56	48.70
	Bad medicine	56	48.70

108 NB. Missing cases are not indicated.

109 The majority of good compliers judged metronidazole as a good medicine and recommended it
 110 for further use. However, the majority of bad compliers judged it bad medicine to be withdrawn
 111 from the market and suggested using another medicine in place. Respondents were also asked to
 112 indicate any medicines they were using concomitantly with metronidazole. The majority (64.9%)
 113 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.

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.

Figure 1 shows the association between level of compliance and level of therapeutic outcome. There is strong association between patient compliance and therapeutic outcome ($p=0.000$). The p -value indicates that higher the compliance better the therapeutic response expected.

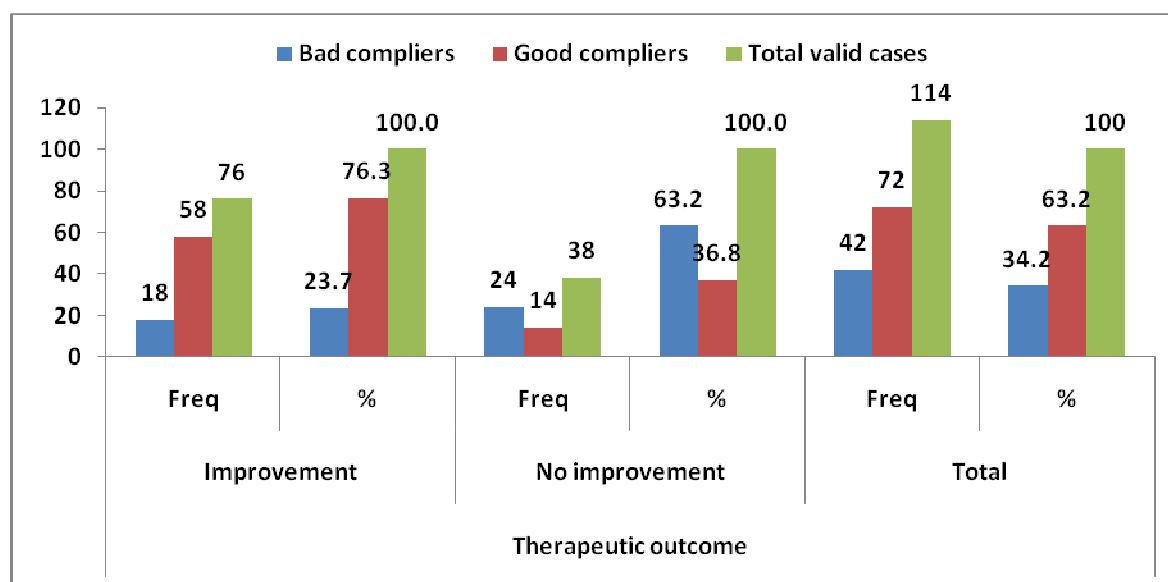
Discussion

This work 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 and both sexes were represented almost equally (53.9% men vs 46.1% females). Data analysis showed that a number of more predictable common side effects were experienced with some differences in importance compared to other studies. Nausea (70.4%), appetite loss (58.3%), fatigue (56.5%) and dizziness (40%) are dominant in our population. One study^[7] comparing the tolerability and adverse events of vaginal vs peroral administration of metronidazole to treat giardiasis found that nausea was the most common adverse event reported in 10.2% i.vag. vs. 30.4% p.o. of all cases ($p < 0.001$), abdominal pain in 16.8% i.vag. vs. 31.9% p.o. ($p < 0.01$), a "metallic taste" in 8.8% i.vag. vs. 17.9% p.o. ($p < 0.05$).

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			

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142 **Figure 1 Association between patient compliance and therapeutic outcome (p-value=0.000)**

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144 We used the duration of treatment as measure of compliance. For acute intestinal amoebiasis
 145 (acute amoebic dysentery) the recommended dose is 750 mg orally three times daily for 5 to 10
 146 days. The usual adult *oral* dosage is 7.5 mg/kg every six hours (approx. 500 mg for a 70-kg
 147 adult). A maximum of 4 g should not be exceeded during a 24-hour period. The usual duration of
 148 therapy is 7 to 10 days; however, infections of the bone and joint, lower respiratory tract, and
 149 endocardium may require longer treatment^[5,6,10,11]. The result showed that 63.2% of respondents
 150 were compliant vs 36.8% who were noncompliant, meaning either they stopped or interrupted
 151 taking medicine for some days. The analysis of respondents' answers showed that only 56.1% of
 152 respondents complied with the duration of 5 to 10 days, the remaining took less than 5 days of
 153 treatment. This is consistent with another study designed to determine which patients had been
 154 compliant with i.v. metronidazole in periodontitis which indicated that only 56% of patients were
 155 considered compliant in their usage^[12].

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157 Looking insight the data, it clearly appeared that 50.9% out of 63.2% of compliant respondents
 158 had good improvement vs 12.3% who declared bad improvement. In other terms, the majority of
 159 noncompliant respondents (21% out of 36.8%) did not get good improvement. The compliant
 160 group experienced a significantly greater benefit from the metronidazole than did the
 161 noncompliant group (p=0.01). However, the question arising are to explain why 15.8% of
 162 noncompliant reported good improvement and why 12.3% among compliant respondents did not
 163 get good improvement. One can say that the improvement is related to the severity of infection
 164 and to drug regimens given. In mild infection, good improvement may mean disappearance of
 165 diarrhoea and abdominal pain relief which generally occur in three days. Bad improvement

despite good compliance may be related to incomplete treatment or to Metronidazole resistance strains. According to respondents thinking, the causes of bad clinical response is either they stopped taking medicine or the medicine is not working.

For patients' attitudes towards the use of metronidazole, 47.8% of them consider metronidazole as a bad medicine that needs withdrawal from the market.

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 diloxantide furoate [13,14]. 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.

Treatment with metronidazole is usually very effective. However, metronidazole resistance is well documented for various bacteria and protozoan species [15-19]. Metronidazole resistance in the protozoan parasite *Entamoeba histolytica* is associated with increased expression of iron-containing superoxide dismutase and peroxiredoxin and decreased expression of ferredoxin 1 and flavin reductase [15]. *Helicobacter pylori* resistance to metronidazole has only been induced *in vitro* [16]. Metronidazole resistance in *Helicobacter pylori* is due to null mutations in a gene (*rdxA*) that encodes an oxygen-insensitive NADPH nitroreductase [17].

Similar findings have been reported for metronidazole-resistant strains of *Trichomonas vaginalis* [18,19].

Conclusion

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. In medical 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-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.

Ethical issues

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

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