Original Article

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Pharmacology Section

The Patients' Adherence and Adverse Drug Reactions (ADRs) which are Caused by *Helicobacter pylori* Eradication Regimens

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ABSTRACT

Background: *Helicobacter pylori* is a major cause of upper gastrointestinal disorders. The eradication of *H. pylori* has been recommended for the treatment of different gastrointestinal diseases. Notwithstanding, a combination therapy is needed for *Helicobacter pylori* eradication, but using these medications can be the cause, the incidence risk of patients' adherence to treatment regimens reduction and probably increase risk of Adverse Drug Reactions (ADRS), so, it is seem that evaluation the out come of combination therapy is need more than the past.

Aim: The aim of present study was to determine the patients' adherence to the treatment and the ADRs with five eradiation regimens.

Setting and Design: A cross sectional study was done in a well known referral clinic of gastrointestinal disorders in Tehran, Iran.

Methods and Materials: Ninety patients were evaluated the study (18 in each of the five regimens). The adherence to the treatment and the ADRs of the patients were asked during the treatment, twice, by doing telephone assays.

Statistical Analysis Used: The data were analyzed by using the SPSS, 17 software and the statistical significance was accepted for the P values of 0.05.

Results: 81% of the patients had a good adherence and there was no significant difference between the types of regimens (triple or quadruple therapy) and the adherence to the treatment regimens by the patients (p=0.6). Also, we found that there was no significant relationship between the types of regimens and the sex (p=0.99), education level (p=0.99), accommodation (p=0.93), an existence of underlying disease (p=0.86) and the concurrent use other medications (p=0.93). But there was a significant relationship between the patients' age and adherence to the treatment regimens (p=0.008). The most reported ADRs belonged to gastrointestinal (GI) disorders (an abnormal taste had the most prevalence (36.6%) among the GI disorders). There was no significant relationship between the regimen type and the GI ADRs, (p=0.48).

Conclusion: The findings of this study showed that the patients' adherence to the treatment regimens and the ADRs did not have a significant relationship with the various eradication regimens for *H. pylori*. It seems that the type of *H. pylori* eradication regimen may not be an important factor in the patients' adherence to the treatment regimens and the ADRs.

Key Words: Adherence, Adverse drug reactions, *Helicobacter pylori*, Patients

INTRODUCTION

Adherence to treatment regimens is generally defined as the degree of correctly following medical by patient that based on therapeutic advices that established alliance or contracted between the patient and the physician [1]. Adverse drug reactions (ADRs) are important factors which decrease the adherence to the treatment regimens by the patients with regards to the pharmacotherapy. According to the WHO's definition, an ADR is "a response to a drug that is noxious and unintended and which occurs at doses which are normally used in man for the prophylaxis, diagnosis or the therapy of a disease, or for the modification of the physiological functions" [2]. Several methods are used for measuring the adherence to the treatment regimens; and also, selecting the measurement approach is dependent on the type of intervention, the patients' health conditions and also, ethical and legal considerations [3].

The *Helicobacter pylori* infection is a major cause of upper gastrointestinal diseases and it is highly prevalent worldwide [4]. The eradication of the *Helicobacter pylori* infection is one of the indicators in a number of medical diseases, which include PUD (peptic ulcer Disease) [5,6]. The consensus guideline with extension indicators in the *H. pylori* eradication had been recommended in 1996 (Maastricht I) for the first time and so, a combination therapy for the eradication of Helicobacter is a worldwide consensus [7].

The current *Helicobacter pylori* eradication regimens focus on different pharmacologic therapies which range from the identification of the target population and the appropriate use of the existing treatment regimens [8]. The different aspects of the *Helicobacter pylori* eradication regimens such as the duration and composition of the drugs exist in the available guidelines [9,10].

ADRs can affect the patients' adherence to the treatment regimens in the patients who undergo the *H. pylori* eradication regimens. For example, Martines et al reported the lowest compliance proportions for the regimens which contained imidazoles. These drugs have a higher incidence of side effects (such as a metallic taste) [11].

It is a fact of concern that adverse effects affect the quality of the *H. pylori* eradication therapy. The aim of present study was to determine the ADRs and the patients' adherence to treatment with respect to five eradiation regimens in a Gastrointestinal and Liver Diseases referral centre of Tehran, Iran.

PATIENTS AND METHODS

This prospective observational study was done in the gastrointestinal and liver clinic of the Talighani Hospital in Tehran, Iran. This clinic is a well known referral centre for gastrointestinal and liver diseases in Tehran, Iran. The study period was between May 2011 and January 2012.

As a criterion for their inclusion in the study, the patients who were admitted for an endoscopy test (upper gastrointestinal) and a 13C-Urea Breathe Test (UBT) (IRIS, Wagner Analysen- Technik, Germany) were included. Those patients with a delta value above the baseline of 4 per mil (DOB‰) were considered to be infected with *H. pylori* and they were selected for receiving any of the eradication regimens of *H. pylori*. In this clinic, the physicians usually administered five different *H. pylori* eradication regimens [Table/Fig-1]. The inclusion criteria had to have one type of these eradication therapies prescribed and agreed on to be followed-up for 14 days after finalizing the therapy. The reasons for the exclusion were a history of a previous treatment for the *H pylori* infection, non compliance to the treatment, an allergy to salicylate and mental disability.

Triple medication regimens	Regimen 1	PPIs*	Standard dose
		Amoxicillin	1000 mg BD
		Clarithromycin	500 mg BD
	Regimen 2	PPIs	Standard dose
		Metronidazole	500 mg BD
		Clarithromycin	500 mg BD
Quadruple medication regimens	Regimen 3	PPIs	Standard dose
		Amoxicillin	1000 mg BD
		Clarithromycin	500 mg BD
		Metronidazole	500 mg BD
	Regimen 4	PPIs	Standard dose
		Amoxicillin	500 mg QID
		Metronidazole	250-500 mg QID
		Bismuth Subcitrate	120 mg QID
	Regimen 5	PPIs	Standard dose
		Tetracycline	500 mg QID
		Metronidazole	250-500 mg QID
		Bismuth Subcitrare	120 mg QID

[Table/Fig-1]: *Helicobacter pylori* eradication regimens in studied patients
*PPIs used in the regimens were either omeprazole 20 mg BD or panthoprazole 20 mg BD

The demographic data of the patients, which included age, sex, the educational level and the address were taken. After receiving a drug regimen, all the patients received preliminary counseling by the pharmacist, which usually lasted for 10-15 minutes, about the duration of the treatment and the correct medication usage. The pharmacist trained the patients to note on a calendar, every dose of medication which was taken. The subjects were asked to give every telephone number at which they could be contacted. All the patients were referred to the outpatients office or the clinic. The local ethical committee of the Shahid Beheshti University of Medical Sciences approved the study and all the subjects were entered into the assessment after they gave their written informed consents; also, there was no added cost to the patients.

The patients completed the regimens in 14 days. After 1 week and at the end of the treatment course, an educated pharmacist called the patients and asked them regarding their adherence to the regimen and the occurrence of any adverse drug reactions during the pharmacotherapy course. Also, an investigator used a questionnaire for evaluating the patients' adherence to the therapy. Although no gold-standard questionnaire currently exists for measuring the patients' adherence to the treatment regimens, the other part of the questionnaire was dedicated to all the ADRs that were related to the *H. pylori* eradication regimens.

Indeed, the self-reported patients were used to assess the adherence regarding the regimens. This was done by asking the patients if he or she had ever forgotten to take any medication or if he or she had ever not taken it by his/her own initiative; how many pills he/she had taken per day, at what time and if he/she had always taken it at the right time. The questionnaire was filled by the investigator. Also, the patients were asked whether they had experienced any adverse drug reactions during the 14 days of treatment against *H. pylori*. All the patients were asked about all the adverse reactions which were related to the eradication regimens such as abnormal taste, nausea, vomiting, stomachache, constipation, anorexia, diarrhoea, headache, drowsiness, sleepiness and skin eruption, one by one. These ADRs were categorized as gastrointestinal and non gastrointestinal related, as has been mentioned in [Table/Fig-2].

Adverse Effect		Number of Patients (%)
Gastrointestinal	Abnormal taste	31 (34.4)
	Nausea	23 (25.5)
	Stomachache	17 (18.9)
	Constipation	10 (11.1)
	Anorexia	9 (10)
	Vomiting	8 (8.8)
	Diarrhea	7 (7.7)
Non Gastrointestinal	Headache & Drowsiness	19 (21)
	Sleepiness	10 (11.1)
	Skin eruption	4 (4.44)

[Table/Fig-2]: Reported ADRs of HP eradication regimens in the study

The data were analyzed by using the SPSS, 17 software. All the data are given as mean ± SD. A statistical significance was accepted for *P* values of 0.05.

RESULTS

90 patients who were infected with *H. pylori* were enrolled in this study, with 18 patients in each therapeutic regimen. The demographic characteristics of the patients have been demonstrated in [Table/Fig-3].

In the clinic, the *H. pylori* eradication regimens were prescribed by the gastroenterologists for all the patients. An investigator effectively measured the adherence from the patients' self-reports; if the patients had followed the orders correctly without missing even one dose and if they stated that they had taken all the medicines in the right doses and at the right time, it was considered as a proper adherence, although no severe adverse drug effect was reported by these patients. In this study, 73 of the 90 observed patients (81%) had a good adherence; but

other patients (19%) didn't fully comply to the physicians' order. 7 of 17 (41%) of the non-compliant patients expressed that the frequency of dosing had influenced their capability to comply with the regimen, whereas 5 of 17 (29.4%) of them proposed that the number of medications affected their adherence. Chi-square analysis demonstrated no correlation between the type of eradication regimens (5 different regimens) and the patients' adherence (p=0.6).

Parameters		Number of Patients	Percentage (%)
Age	< 30	24	26.66
	30 - 60	49	54.44
	>60	17	18.88
Sex	Female	53	58.88
	male	37	41.11
Educational level	Illiterate	16	17.78
	Under Diploma	27	30
	diploma	34	37.78
	BA and MA	13	14.44
Accommodation	Tehran	59	65.56
	Other places	31	34.44
Existence of Concomitant Disease	Yes	28	31.11
	No	62	68.89
Concomitant Use of Other medications	Yes	29	32.22
	No	61	67.78

[Table/Fig-3]: Demographic characteristic of patients

In assessing the variables which were assumed to affect the patients' adherence, there were no statistically significant correlations between the patients' adherence to the treatment regimens and the sex (p = 0.99), educational level (p = 0.99), accommodation (p = 0.93), existence of underlying diseases (p = 0.86) and the concurrent usage of the other medications (p = 0.78) But there was a significant relationship between the patients adherence and their ages (p= 0.008). In other words, only the patients' ages affected their adherence in this study. Those who were aged < 30 years were more compliant.

[Table/Fig-2] shows the most common ADRs which were reported by the patients. The ADRs of different regimens were evaluated and categorized as gastrointestinal and non gastrointestinal side effects. An abnormal taste (a bitter taste and a metallic taste) and nausea were the main gastrointestinal tract findings (34.4% and 25.5% respectively).

As most of the ADRs were GI related, we analyzed the relationship between the adherence and the GI ADRs. [Table/Fig-4] shows the distribution of the GI ADRs in the studied patients who were under the triple or quadruple therapies. There was no statistically significant difference between the regimen type (triple or quadruple regimens) with respect to the gastrointestinal side-effects (p= 0.48).

	Triple regimens	Quadruple regimens
Patients with at least 1 GI ADRs	39	23
Patients without any GI ADRs	15	13
Total	54	36

[Table/Fig-4]: Distribution of reporting GI ADRs in studied patients

DISCUSSION AND CONCLUSION

The *Helicobacter pylori* infection is still extremely widespread; the incidence of Peptic Ulcer Disease (PUD) in the developed countries is 10% and it is associated with different outcomes that range from asymptomatic gastritis to more serious conditions such as PUD and stomach cancer [12,13]. Several regimens are prescribed to the infected patients and an optimal compliance has been recognized as an essential factor for achieving the maximum effectiveness of the treatment, and it is obvious that ADRs can affect the extent to which the patients take medications [11].

An indirect technique of the adherence measurement, self-reported patient by questionnaire was used in this study; the investigator asked all the questions exactly and filled in all parts of the questionnaire. The advantages of this method are that it was simple and inexpensive, and also, it was the most useful method in the clinical setting [14]. With this method, the patients could get information about their regimen and ask questions about their problems. So they could maintain more compliance with their regimens.

This study evaluated the adherence to the therapy and the prevalence of ADRs in 90 *H. pylori* infected patients who were referred to a well known GI clinic in Tehran. Among the patients, 81.11% had proper adherence. The same study, by using 2 methods of compliance measurements (an electronic method and the patients' reports) in Portugal, showed a mean compliance of 56% to the H. pylori eradication regimens by the electronic method; they also reported a 52% non consistency between the patients' self reports by the electronic information. This might be due to forget the omitted dosages; it can also be theorized that such a performance might be deliberate [11]. The electronic methods have been described as the most suitable adherence measurement for chronic diseases, but we couldn't use that in our study for the evaluation of the *H. pylori* regimens; the main disadvantages of the indirect method are that it was susceptible to error and that the results could be easily distorted by the patients.

Some studies showed that 5 days after and prior to the physicians' visits, the patients adhered more to their treatment. This phenomenon is called as 'white-coat adherence' [14,15] and a randomized controlled trial demonstrated that the techniques such as a received medication counseling (written and oral) from a pharmacist, as well as a telephone call follow-up after the initiation of the therapy, increased the number of patients who took more than 90% of the medications; we performed both the pharmacist counseling and the telephone call follow-up for evaluating the patients' compliance. This could be the major source of the motivation for the greater compliance rate of our study [16]. In the randomized study, to evaluate the efficacy of the *H. pylori* eradication regimes, 90% of the patients used 100% of the prescribed medications correctly, and it seemed that the results of this study were similar to those of our study [17].

The inverse relationship between the number of dosages and the adherence had been demonstrated in a review article in 2001 [18]. The main reason of our patients' non-compliance was the frequency of the dosing; the complexity of the *H. pylori* eradication regimens, the frequency of dosing and the number of pills were reported as the most important factors that affected the measure of the administration of the therapy, exactly as was prescribed in a randomized control trial that was carried out on *H. pylori* infected patients [19].

In Martines et al's studies, women patients who were aged between 46 and 64 years and the less literate were found to be more compliant [11], but in our research, there was no statistically significant correlation between the patients' adherence to the treatment regimens and sex. Also, the education level didn't affect the patients adherence, although it appeared that it was affecting the patients' adherence. But according to the results of a review which was done in 1998, factors such as age, education, gender, intelligence and race had only a limited effect on the adherence to the treatment [3]. The patients' age was the only factor that influenced the adherence in our investigation and those who were aged < 30 years were more compliant. This could be because they had more knowledge about the medications, or may be their lifestyles were less busier.

Some of the patients who were included in this study suffered from chronic diseases and they had used other medications for a long time. So we assessed the effect of these issues on the patients' adherence; there wasn't any significant relationship between two factors (the chronic disease and other medications) and adherence. In a study which was done on independently living adults who were aged 55 years and older, in the southeastern United States, on evaluating the compliance rates, no relationship was found between the compliance and the number of illnesses, age, or sex [19].

Our results suggest that there was no significant relationship between the type of regimens and the patients' adherence to the treatment regimens or the ADRs. It seems that the type of *H. pylori* eradication regimen may not be an important factor in the patients' adherence to the treatment regimens and the ADRs.

Another objective of this study was evaluation of the relationship between the type of *H. pylori* eradication regimens and the ADRs. In several studies, the ADRs of different drug regimens were compared. We couldn't detect a statistically significant difference between the regimen types (triple or quadruple regimens) with respect to the gastrointestinal side-effects. In one meta-analysis which was done in 2004, it was found that the occurrence of adverse events was consistently similar for the triple or quadruple regimens in the 10 controlled trials [20].

An abnormal taste in the mouth, a bitter taste and a metallic taste, especially that which was caused by metronidazole, was the main gastrointestinal tract finding in our study. In Lee et al's study, 36% of the patients had experienced a gastrointestinal intolerance, which included nausea, vomiting, diarrhoea, stomach cramps, and constipation; taste disturbance was the more frequent GI ADR, as in our study [16]. This bothering effect of metronidazole can be explained as the reason for the noncompliance to the regimens. 67% of the patients in our study experienced different severities of GI intolerances. The investigator in this study asked exactly about each possible side effect of the *H. pylori* eradication regimens, and this may be the cause of the greater rate of reported ADRs. In Sanches et al's study, 84% of the patients presented with adverse effects. Among these, 95% were mild; a bitter taste, nausea and abdominal pain were the more observed GI ADRs. Dizziness had been reported as a main non GI intolerance effect. The patterns and frequencies of the adverse effects in the above research were more comparable to our investigations [17].

A noncompliant behaviour is multifactorial; a poor adherence to the medication regimens is widespread, leading to worsening of the disease, resistance to the antibiotics and increased health care costs; evaluating the reasons of the noncompliance and classifying methods to support the patients, such as modifying regimens to reflect the patient preferences, amending the patients' attitudes toward the therapeutic regimens and enhancing their knowledge may improve the health care outcomes. Pharmacists obviously have a role in enhancing the patient adherence.

REFERENCES

[1] Ralph I, Sarah M. Adherence to Treatment and Health Outcomes. *Arch Intern Med.* 1993; 153(16):1863-68.

[2] Brunton LL, Parker KL, Blumenthal DK, Buxton ILO. Goodman and Gilman's Manual of Pharmacology and Therapeutics. 11th ed. New York: McGraw-Hill. 2007; 623-32.

[3] Boudes P. Drug Compliance in Therapeutic Trials: A Review. *Control Clin Trials*. 1998; 19(3):257-68.

[4] Selgrad M, Malfertheiner P. New strategies for *Helicobacter pylori* eradication. *Curr Opin Pharmacol.* 2008; 8(5):593-97.

[5] Vakil, N. *Helicobacter pylori* eradication: Sequential and traditional therapy. *Gastroenterology and Hepatology.* 2009; 5(1):59-64.

[6] Stewart DJ, Ackroyd R. Peptic ulcers and their complications. *Surgery -Oxford*. 2008; 26 (11):452-57.

[7] Malfertheiner P, Mégraud F, O'Morain C, Hungin AP, Jones R, Axon A, et al . Current concepts in the management of *Helicobacter pylori* infection the Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther.* 2002; 16(2):167-80.

[8] Qasim A, O'Morain CA, O'Connor HJ. *Helicobacter pylori* eradication: role of individual therapy constituents and therapy duration. *Fundam Clin Pharmacol.* 2009; 23(1):43-52.

[9] Howden CW, Hunt RH. Guidelines for the management of *Helicobacter pylori* infection. Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. *Am J Gastroenterol.* 1998; 93(12):2330-38.

[10] Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, et al. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. *Gut.* 2007; 56(6):772-81.

[11] Martines AP, Ferreira AP, Costa F, Cabrita J. How to measure (or not) compliance to eradication therapy. *Pharmacy Practice.* 2006; 4(2): 88-94.

[12] Suerbaum S, Michetti P. *Helicobacter pylori* infection. *N Engl J Med.* 2002; 347(15):1175-86.

[13] Sonnenberg A, Everhart JE. The prevalence of self-reported peptic ulcer in the United States. *Am J Public Health* 1996; 86(2):200-05.

[14] Osterberg L, Blaschke T. Adherence to Medication. *N Engl J Med*. 2005; 353(5):487-97.

[15] Schwartz GF. Identifying and Measuring patient adherence and Persistency. *Adv Stud Ophthalmol*. 2007; 4(3):68-71.

[16] Lee M, Kemp J, Canning A, Egan C, Tataronis G, Farraye F. A Randomized Controlled Trial of an Enhanced Patient Compliance Program for *Helicobacter pylori* Therapy. *Arch Intern Med.* 1999; 159(19):2312-16.

[17] Sanches B, Coelho L, Moretzsohn L, Vieira Jr. Failure of *Helicobacter pylori* Treatment After Regimes Containing Clarithromycin: New Practical Therapeutic Options. *Helicobacter.* 2008; 13(6):572-76.

[18] Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther.* 2001; 23(8):1296-310.

[19] Coons SJ, Sheahan SL, Martin SS, Hendricks J, Robbins CA, Johnson JA. Predictors of medication noncompliance in a sample of older adults. *Clin Ther.* 1994; 16(1):110-17.

[20] Fischbach LA, van Zanten S, Dickason J. Meta-analysis: the efficacy, adverse events, and adherence related to first-line anti-*Helicobacter pylori* quadruple therapies. *Aliment Pharmacol Ther.* 2004; 20(10): 1071-82.

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