Doxycycline in Eradication Therapy of *Helicobacter pylori* – A Systematic Review and Meta-Analysis

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Key Words

Doxycycline · *Helicobacter pylori* · Eradication · Gastritis

Abstract

Background: Since resistance of *Helicobacter pylori* is developing very fast all over the world, new treatment regimens for eradication are urgently needed. **Aim:** To compare eradication success rate of *H. pylori* treatment regimens with and without doxycycline. **Methods:** English medical literature searches were conducted for regimens including doxycycline for eradication of *H. pylori*. Searches were performed up to August 31, 2015, using MEDLINE, PubMed, EMBASE, Scopus and CENTRAL. Meta-analysis was performed by using comprehensive meta-analysis software. Pooled ORs and 95% CIs were calculated comparing treatment regimens for eradication of *H. pylori* infection with and without doxycycline. **Results:** The OR for eradication success rate in a fixed model was in favor for treatment regimens with doxycycline: 1.292, 95% CI 1.048–1.594, $p = 0.016$. There was no significant heterogeneity in the included studies: $Q = 15.130$, d.f. (Q) = 8, $I^2 = 47.126$, $p > 0.10$. When treatment regimens with doxycycline were compared only with treatment regimens with tetracycline, no significant difference was found in eradication success rate: OR 0.95, 95% CI 0.68–1.32, $p = 0.77$. But when treatment regimens with doxycycline were com-

pared with treatment regimens without tetracycline, the OR in favor of doxycycline was even higher: OR 1.59, 95% CI 1.21–2.09, $p < 0.001$. **Conclusion:** In this meta-analysis, we confirmed doxycycline efficiency in the eradication of *H. pylori*. Thus, triple, quadruple or even high dose dual therapy with regimens containing doxycycline should be considered.

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Introduction

Since resistance of *Helicobacter pylori* is developing very fast in many countries all over the world, new treatment regimens for eradication are urgently needed. Amoxicillin is a very effective part of every regimen, and resistance to this antibiotic is very rare. Patients, who are allergic to penicillin, cannot take amoxicillin and a substitute is needed. Tetracycline has a similar therapeutic range as amoxicillin, and may be active against *H. pylori*. Substitution of doxycycline for tetracycline HCL offers advantages of less frequent dosing and extra renal excretion. Doxycycline was first demonstrated to be effective drug against *H. pylori* in 1992, with a MIC 0.25–8.0 µg/ml [1]. The first reports of doxycycline substitute for tetracycline were disappointing in this regard [2, 3].

But the results of the paper by Realdi et al. [3] were somewhat confusing because of the high resistance rate not only to doxycycline (33.3%), but also to amoxicillin (26%). In contrast, Usta et al. [4] found a higher eradication rate in a second-line quadruple therapy including doxycycline than 2 first-line triple therapies in children, 64.6 versus 60.5 and 55.8%, respectively. Recently, a combination of esomeprazole, levofloxacin and doxycycline was tried as a third-line therapy with a low eradication efficacy that was somewhat enhanced with probiotics [5].

In this meta-analysis, we looked at studies that compared the eradication success rate of *H. pylori* treatment regimens with and without doxycycline. A high rate of successful eradication will give legitimation to use doxycycline instead of amoxicillin in cases of penicillin allergy or as a rescue quadruple therapy.

Methods

Search Strategy

English medical literature searches were conducted for treatment regimens which included doxycycline for eradication of *H. pylori*. Searches were performed through August 31, 2015, using MEDLINE, PubMed, EMBASE, Scopus and CENTRAL. Search terms were: ('doxycycline'(MeSH Terms) OR 'doxycycline'(All Fields)) AND ('Helicobacter pylori'(MeSH Terms) OR 'Helicobacter'(All Fields) AND 'pylori'(All Fields)) OR 'Helicobacter pylori'(All Fields)). Hand searches of articles were performed after the initial search, and included article bibliography. Only fully published human studies in English were included (fig. 1).

Study Selection

Case-control studies comparing treatment regimens for eradication of *H. pylori*, with and without doxycycline, were included. *H. pylori* infection should be diagnosed with ¹³C-urea breath test, stool antigen, rapid urease test or histology and successful eradication with one of the same tests, at least a month after treatment, and at least 2 weeks without antibiotics, bismuth or proton pump inhibitor therapy. We selected only randomized, prospective, controlled studies that used intention to treat method to express the results.

Data Extraction

Successful eradication rates were extracted for treatment regimens with and without doxycycline. In studies where sub-studies were performed, such as comparison of first and second regimens, gender, treatment specification such as triple, quadruple, concomitant or sequential regimens, their results were compared in innate studies.

Meta-analysis was performed by using comprehensive meta-analysis software (version 3, Biostat Inc., Englewood, N.J., USA). Pooled ORs and 95% CIs were calculated comparing eradication success rate in individual studies by using the fixed effects model.

Fig. 1. Flow chart of the articles identified for the meta-analysis.

Heterogeneity between studies was evaluated using the Cochran Q test, and it was considered to be present if the Q test p value was <0.10. I² statistic was used to measure the proportion of inconsistency in individual studies, with I² >50% representing substantial heterogeneity. We also calculated a potential publication bias.

Results

All together we found 53 eligible studies. Twenty-one studies were rejected because of language, for being performed in animals or not having full text. Twenty-four papers were excluded being editorials, review articles or because of duplications. We were left with 8 case-control studies from 8 countries, comparing eradication treatments of *H. pylori* with or without doxycycline, that fulfilled the inclusion criteria, published till August 31, 2015 [2, 3, 6–11] (fig. 1; table 1). There are 15 sub-studies (innate studies, stratifying data according to treatment regimen or duration). In the study from Texas [3], 5 sub-studies have been performed, comparing the same doxycycline regimen with 5 different regimens without doxycycline. The studies from Italy, Iran and New York [6, 8, 10] include 2 sub-studies each. Since Texas and New York are big states in the USA, with different demographic characteristics (many black people in New York,

Table 1. Case-control studies comparing *H. pylori* eradication treatment regimens with and without doxycycline

Author	Year	Site	Regimen with D, mg/day	n	Men	Mean age, years	Duration, days	SE, %	Regimen without D, mg/day	n	Men	Mean age, years	Duration, days	SE, %	p value
Borody et al. [2]	1992	Australia	D 200 B 432 M 800	34	18	Unknown	10	64.7	T 2000 B 432 M 800	39	22	Unknown	10	92.3	0.01
Realdi et al. [3]	1999	Texas	O 40 M 1000 D 300	60	35	51	7	55	O 40 M 1000 T 2000	56	50	50	7	91	0.001
Realdi et al. [3]	1999	Texas	O 40 M 1000 D 300	60	35	51	7	55	O 40 M 1000 C 1500	62	50	50	7	53.2	0.84
Realdi et al. [3]	1999	Texas	O 40 M 1000 D 300	60	35	51	7	55	O 40 A 2000	65	29	53	15	36.9	0.04
Realdi et al. [3]	1999	Texas	O 40 M 1000 D 300	60	35	51	7	55	O 40 C 1500	63	36	52	15	36.5	0.04
Realdi et al. [3]	1999	Texas	O 40 M 1000 D 300	60	35	51	7	55	O 40 M 1000 A 2000	63	34	48	7	98.4	0.03
Perri et al. [6]	2002	Italy	A 2000 D 200 L 60	87	43	50	14	35.6	A 2000 T 2000 L 60	89	42	49	7	34.8	0.91
Perri et al. [6]	2002	Italy	A 2000 D 200 L 60	87	43	50	14	35.6	A 2000 T 2000 R 800	88	39	47	7	20.4	0.03
Sanches et al. [7]	2008	Brazil	R 40 B 240 D 200 F 400	29	13	46	10	82.7	R 40 L 1000 F 200	31	16	46	10	77.4	0.61
Taghavi et al. [8]	2009	Iran	D 200 CO 1875 O 40	67	Unknown	Unknown	14	61.1	A 2000 C 1000 O 40	53	Unknown	Unknown	14	66	0.16
Taghavi et al. [8]	2009	Iran	D 200 CO 1875 O 40	67	Unknown	Unknown	14	61.1	A 2000 O 40 F 200 B 480	69	Unknown	Unknown	14	49.2	0.58
Akyildiz et al. [9]	2009	Turkey	R 800 A 2000 D 200	57	23	44.4	14	36.8	R 800 A 2000 T 2000	58	20	44	14	34.4	0.79

Table 1. (continued)

Author	Year	Site	Regimen with D, mg/day	n	Men	Mean age, years	Duration, days	SE, %	Regimen without D, mg/day	n	Men	Mean age, years	Duration, days	SE, %	p value
Basu et al. [10]	2011	New York	LE 250 O 40 N 1000 D 100	90	52	37	7	88.8	L 30 A 2000 C 1000	90	53	37	10	73.3	0.01
Basu et al. [10]	2011	New York	LE 250 O 40 N 1000 D 100	90	51	36	10	90	L 30 A 2000 C 1000	90	53	37	10	73.3	0.01
Wang and Wu [11]	2012	China	E 40 B 440 A 2000 D 200	44	21	47.65	10	68.1	E 40 B 440 M 800 T 3000	41	18	46.07	10	58.5	0.36

D = Doxycycline; B = bismuth subcitrate; M = metronidazole; T = tetracycline; O = omeprazole; A = amoxicillin; C = clarithromycin; L = lansoprazole; R = ranitidine; F = furazolidone; CO = co-amoxylav; N = nitroxanide; LE = levofloxacin; E = esomeprazole.

and many Hispanic in Texas), we preferred to separate the results. The regimens used were different, and the studies from Texas and New York were published 12 years apart.

Out of 15 sub-studies, the results of 8 reached significance (table 1) [2, 3, 6, 10]. In 5 sub-studies, treatment regimens with doxycycline had significantly higher eradication rate than treatment regimens without doxycycline (table 1) [3, 6, 10]. In 3 sub-studies, treatment regimens without doxycycline have done better (table 1) [2, 3]. In 6 sub-studies, treatment regimens with doxycycline were compared with treatment regimens containing tetracycline (table 1) [2, 3, 6, 9, 11]. In 2 sub-studies tetracycline was better [2, 3], in 1 sub-study doxycycline was better [6] and in the other no difference between them was demonstrated (table 1) [6, 9, 11].

The OR for eradication rate in a fixed model was in favor for treatment regimens with doxycycline: 1.292, 95% CI 1.048–1.594, $p = 0.016$ (fig. 2). Funnel plot denies a significant publication bias (fig. 3). There was no significant heterogeneity in the included studies: $Q = 15.130$, d.f. (Q) = 8, $I^2 = 47.126$, $p > 0.10$.

When only treatment regimens with doxycycline were compared with treatment regimens with tetracycline, no significant difference was found in eradication success rate: OR 0.95, 95% CI 0.68–1.32, $p = 0.77$ (fig. 2a). But when treatment regimens with doxycycline were compared with treatment regimens without tetracycline, the OR in favor of doxycycline was even higher: OR 1.59, 95% CI 1.21–2.09, $p < 0.001$.

Discussion

Doxycycline was clinically developed in the early 1960s and approved by the FDA in 1967 [12]. It belongs to the tetracycline group of antibiotics, with improved stability and pharmacological efficacy. Tetracycline and doxycycline have therapeutic range similar to penicillin, thus, theoretically could replace amoxicillin in the treatment regimen for *H. pylori*. This may be especially important in patients allergic to penicillin. Both drugs, tetracycline and doxycycline, act systemically after absorption from the upper gastrointestinal tract. The main advantage of doxycycline over tetracycline is its longer activity, and it can be taken twice or once a day. The peak concentration of both drugs is similar, but in the case of doxycycline the time to peak concentration is shorter, and half life is significantly longer [13].

Fig. 2. Meta-analysis of studies comparing eradication success rate of treatment regimens, with and without doxycycline (8 papers and 15 studies). **a** Meta-analysis of studies comparing eradication success rate of treatment regimens with doxycycline and those with tetracycline (5 papers and 6 studies). **b** Meta-analysis of studies comparing eradication success rate of treatment regimens with

doxycycline and those without tetracycline (4 papers and 9 studies). D = Doxycycline; B = bismuth subcitrate; M = metronidazole; T = tetracycline; O = omeprazole; A = amoxicillin; C = clarithromycin; L = lansoprazole; R = ranitidine; F = furazolidone; CO = co-amoxylav; N = nitanoxanide; LE = levofloxacin; E = esomeprazole; d = days.

Fig. 3. Funnel plot for publication bias.

In this meta-analysis, we confirmed doxycycline efficiency in the eradication of *H. pylori*. Treatment regimens containing doxycycline had a similar eradication success rate as regimens containing tetracycline, but better than those without a representative of the tetracycline family of antibiotics. When treatment regimens with tetracycline HCL were excluded, the OR for doxycycline containing regimens reached 1.59 and is very significant ($p < 0.001$).

I believe that according to this meta-analysis, triple, quadruple or even high dose dual therapy with regimens containing doxycycline will be considered as a therapeutic option. This observation is particularly important in the era of drug resistance and the increasing need for alternative eradication regimens and rescue therapy [14].

This study is limited by the lack of many trials with treatment regimens containing doxycycline, reporting only 8 case-control studies. In addition, some of the studies described first-line therapy and some rescue therapy, thus eradication success varied and was $<85\%$. Thus, the results should be taken with caution, and more randomized controlled studies are needed for final conclusions.

Summary

In this meta-analysis, we looked at studies that compared the eradication success rate of *H. pylori* treatment regimens with and without doxycycline. The OR for eradication rate in a fixed model was in favor for treatment regimens with doxycycline: 1.292, 95% CI 1.048–1.594, $p = 0.016$. There was no significant heterogeneity in the included studies: $Q = 15.130$, d.f. (Q) = 8, $I^2 = 47.126$, $p > 0.10$. When treatment regimens with doxycycline were

compared only with treatment regimens with tetracycline, no significant difference was found in eradication success rate. But, when treatment regimens with doxycycline were compared with treatment regimens without tetracycline, the OR in favor of doxycycline was even higher. Thus, triple, quadruple or even high dose dual therapy with regimens containing doxycycline should be considered.

Disclosure Statement

Professor Y. Niv has no conflict of interest to declare.

Data Sharing Statement

Technical appendix, statistical code and data set available from the corresponding author at nivyaron80@gmail.com. No additional data are available.

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