Lack of Association between First Myocardial Infarction and Past Use of Erythromycin, Tetracycline, or Doxycycline

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To evaluate the association of prior treatment with antibiotics active against *Chlamydia pneumoniae* with the risk for incident myocardial infarction, we conducted a population-based case-control study. We found that use of erythromycin, tetracycline, or doxycycline during the previous 5 years was not associated with risk for first myocardial infarction. These results suggest little or no association between the use of these antibiotics and the risk for first myocardial infarction in the primary prevention setting.

Chlamydia pneumoniae has been associated with atherosclerotic cardiovascular disease in seroepidemiologic studies, by detection of the organism in atherosclerotic plaque, and in animal model studies (1-4). Two small clinical trials to assess the effect of treatment with antibiotics active against *C. pneumoniae* on cardiovascular disease outcomes have indicated a possible effect of azithromycin (5) or roxithromycin (6) in the secondary prevention of coronary heart disease. To evaluate whether past use of antibiotics active against *C. pneumoniae* is associated with decreased risk for first myocardial infarction (MI), we conducted a retrospective, population-based case-control study of patients enrolled at Group Health Cooperative of Puget Sound (GH), Seattle, WA, USA.

The Study

Case-patients were GH enrollees, ages 30 to 79 years, in whom an incident fatal or nonfatal MI was diagnosed during July 1986 through December 1995. Controls were a stratified random sample of GH enrollees frequency-matched with the case-patients by age (within decade), sex, calendar year, presence of treated hypertension, and menopausal status (post versus peri and premenopausal). The case-patients and controls had been identified for two previous cardiovascular studies, one of persons with pharmacologically treated hypertension (7) and one of postmenopausal women (8,9), by using methods previously reported. Therefore, men and women with treated hypertension and women without hypertension were included as both case-patients and controls, but men without hypertension were not included in the study population. Medical records were reviewed for all study participants to confirm the diagnosis of incident MI (case-patients) and obtain information on other cardiovascular risk factors.

All study participants had an index date. For the hospitalized case-patients, it was the date of admission for the first MI; for out-of-hospital case-patients who died, it was the date of death; and for the controls, it was a computer-generated random date within the calendar year for which they had been sampled as controls. We excluded persons who had been enrolled for fewer than 5 years or had fewer than four visits to a GH provider before their index date.

The GH computerized pharmacy database, which contains records of all prescriptions dispensed at GH pharmacies, was used to assess prescriptions for antibiotics. A survey conducted

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in conjunction with the previous study of postmenopausal women determined that 95% of study participants filled all their prescriptions at a GH pharmacy (9). During the period of interest to this study, newer macrolidelike antibiotics such as azithromycin and clarithromycin were not routinely available at GH; thus, we selected erythromycin, tetracycline, and doxycycline, antibiotics available for routine use during this period, for evaluation because of their in vitro activity against *C. pneumoniae* and their indication for treatment of *C. pneumoniae* respiratory infections. To determine duration of use for each agent, we defined 1 day of use as equivalent to 2 g erythromycin, 2 g tetracycline, or 100 mg doxycycline. The total duration of therapy with these drugs was calculated by using the sum of the quantities dispensed during the 5 years before the index date.

The Findings

We identified 1,796 eligible case-patients with an incident fatal or nonfatal MI and 4,882 eligible controls during the study period (Table 1). At least one prescription for erythromycin, tetracycline, or doxycycline was recorded for 775 (43%) of the case-patients and 2,061 (42%) of the controls. In multivariate logistic regression models controlling for the matching variables (age, sex, hypertension status, menopausal status, and index year) or the matching variables and known cardiac risk factors (smoking, diabetes, cardiovascular disease), risk for incident MI was not associated with the cumulative duration of prescribed treatment with erythromycin, tetracycline, doxycycline, or the three agents combined (Table 2). In addition, risk for incident MI was not associated with increasing cumulative duration of therapy across these categories for any of the agents individually or for the three agents combined. Further, no association was detected when assessment of the use of antibiotics was restricted to 1 year before the index date (data not shown).

Table 1. Characteristics of case-patients with myocardial infarction and controls

Variable	Case-patients n=1,796	Controls n=4,882
Mean age (yr)	67.0	66.7
Male	38%	41%
Mean duration of enrollment in GH[a] (yr)	16.8	17.4
Angina	26%	10%
Hypertension	75%	70%
Diabetes mellitus	27%	12%
Current smoker	28%	15%

[a]Group Health Cooperative of Puget Sound, Seattle, WA.

There are several possible explanations for these findings. Treatment with antibiotics active against *C. pneumoniae* may not affect the risk for heart disease, either because *C. pneumoniae* does not play a causal role in the atherosclerotic process or because its effect on that process cannot be modified by antibiotics. Although two published clinical trials have suggested a protective effect of antibiotics on the secondary prevention of coronary outcomes, these findings are not conclusive. The study of azithromycin (5), which enrolled 80 men with a history of MI who had serologic evidence of *C. pneumoniae*, was not a randomized controlled trial and so was subject to bias. The results reported from the roxithromycin study (6), which randomized patients hospitalized for unstable angina or non-Q wave infarctions to 1 month of treatment with roxithromycin or placebo, were preliminary findings from the first 31 days of the 6-month follow-up. Even if the protective effect indicated by the preliminary analysis persists in the final analysis, further studies will be needed to replicate and confirm those findings. Increasing evidence supports a causal association of *C. pneumoniae* and atherosclerotic disease; however, additional data are needed to validate this hypothesis.

Alternatively, treatment with antichlamydial antibiotics may be associated with a protective effect, but this effect may vary depending on the specific agent; the dose, duration, or timing of treatment; or the patient's clinical status. Azithromycin and roxithromycin (both highly active against *C. pneumoniae* in vitro) achieve much higher intracellular levels, and in particular much higher levels in macrophages, than do erythromycin, doxycycline, or tetracycline; they also have longer half-lives than those agents (10,11). The beneficial effect of roxithromycin in the published clinical trial may have been due to a nonspecific antiinflammatory effect (12,13) rather than to a direct antimicrobial effect. A true cardiovascular protective effect associated with azithromycin or roxithromycin treatment may not, therefore, be seen after treatment with erythromycin, tetracycline, or

Table 2. Cumulative duration of prescribed treatment with erythromycin, tetracycline, doxycycline, and the three agents combined, and the risk for incident myocardial infarction

Drug	Cumulative duration (day)[a]	Case-patients (n=1,796) (%)	Controls (n=4,882) (%)	OR[b] (95% CI)	OR[c] (95% CI)
Erythromycin	0	1,266 (70)	3,493 (72)	1.0 reference	1.0 reference
	1-14	401 (22)	1,124 (23)	0.99 (0.87-1.13)	0.91 (0.79-1.05)
	15-28	92 (5)	182 (4)	1.41 (1.08-1.82)	1.18 (0.89-1.54)
	29+	37 (2)	83 (2)	1.23 (0.83-1.83)	1.05 (0.69-1.59)
Tetracycline	0	1,507 (84)	4,149 (85)	1.0 reference	1.0 reference
	1-14	223 (12)	564 (12)	1.11 (0.94-1.31)	1.02 (0.86-1.22)
	15-28	39 (2)	88 (2)	1.24 (0.84-1.81)	1.04 (0.69-1.55)
	29+	27 (2)	81 (2)	0.95 (0.61-1.47)	0.98 (0.62-1.54)
Doxycycline	0	1,597 (89)	4,365 (89)	1.0 reference	1.0 reference
	1-14	37 (2)	86 (2)	1.18 (0.79-1.74)	1.06 (0.71-1.59)
	15-28	85 (5)	244 (5)	0.94 (0.73-1.22)	0.90 (0.69-1.18)
	29+	77 (4)	187 (4)	1.10 (0.84-1.45)	1.17 (0.88-1.56)
Erythromycin,	0	1,021 (57)	2,821 (58)	1.0 reference	1.0 reference
tetracycline,	1-14	422 (24)	1,178 (24)	0.99 (0.87-1.14)	0.93 (0.81-1.07)
or doxycycline	15-28	185 (10)	454 (9)	1.13 (0.94-1.35)	0.99 (0.81-1.20)
	29+	168 (9)	421 (9)	1.11 (0.91-1.34)	1.03 (0.84-1.26)

[a]For duration of each agent, 1 day is equivalent to 2 g erythromycin, 2 g tetracycline, or 100 mg doxycycline.
[b]Adjusted for sex, age, hypertension status, menopausal status, and index year.
[c]Adjusted for sex, age, hypertension status, menopausal status, index year, smoking status, diabetes, and cardiovascular disease.
OR = odds ratio; CI = confidence interval.

doxycycline because of differences in pharmacodynamics or in the mechanisms of action of those agents. Additionally, in our study population, the cumulative duration of treatment with the antibiotics assessed was relatively limited; only 9% of all participants had been prescribed more than a total of 28 days of treatment with the three antibiotics combined during the 5-year study period. Thus, the exposure to antibiotics in routine clinical care may be insufficient to reduce risk. A protective effect of antibiotic treatment may also be limited to the secondary, but not the primary, prevention setting; to patients in the high-risk period after an acute event; or to subsets of patients defined by factors that we could not evaluate, such as seropositivity to *C. pneumoniae*. Further, if the organism plays a role during the initiation or early progression of atherosclerotic lesions, but not in later stages, treatment of older adults may not be effective.

Lastly, while it is possible that our study may have failed to detect a true beneficial effect of past antibiotic treatment, our sample size was relatively large. Assuming a prevalence of exposure among the control group of 42%, this sample size had 90% power (at a 95% confidence level) to detect a 20% reduction in risk associated with antibiotic use.

In summary, even though the results of two small clinical trials have suggested that newer macrolidelike antibiotics active against *C. pneumoniae* may provide effective secondary prevention of coronary artery disease, their effectiveness in the primary prevention setting has not been evaluated prospectively. Our results suggest that treatment with erythromycin, tetracycline, and doxycycline in doses commonly prescribed in routine clinical practice is not associated with a reduction in the risk for incident MI among our study population. Further clinical trials of the newer agents for secondary prevention and further observational studies of these agents for the primary prevention of heart disease are indicated.

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