Antibiotic Prophylaxis for Lyme Disease: How the Way of Reporting a Clinical Trial Can Alter the Perception of Effectiveness

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Commentary on: Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite

*N Engl J Med*. 2001;345:79-84

**Question:** Is a single 200-mg dose of doxycycline effective for preventing Lyme disease after an *Ixodes scapularis* tick bite?

**Design:** Nadelman et al conducted a randomized, double-blind (patients and study personnel), placebo-controlled clinical trial over a period of 9.5 years (May 1987 to December 1996) to determine the effect of a single dose of doxycycline on prevention of Lyme disease after a tick bite. Some patients were included twice during this time. At baseline and at 3 weeks’ and 6 weeks’ follow-up, patients were interviewed and examined, and serum antibody tests were performed and blood cultures done for *Borrelia burgdorferi*. A randomization list was used to maintain a 1:1 ratio. Patients swallowed the pills under direct observation of study personnel. Sample size calculations were clearly defined. The trial included 506 patients with 482 evaluations occurring at a different site from that of the identified tick bite and laboratory evidence of *B burgdorferi* infection (positive skin culture or seroconversion) in the absence of erythema migrans.

**Interventions:** A single 200-mg dose of doxycycline (2 capsules, 100 mg each) or matched placebo (lactose).

**Main Outcome Measures:** The primary outcome was the development of erythema migrans at the site of the tick bite. Secondary outcomes were erythema migrans occurring at a different site from that of the identified tick bite and laboratory evidence of *B burgdorferi* infection (positive skin culture or seroconversion) in the absence of erythema migrans.

**Results:** End points and follow-up data were available for 431 subjects (89.4%), 235 in the doxycycline group and 247 in the placebo group. One patient (1/235, 0.4%) in the doxycycline group and 8 patients (8/247, 3.2%) in the placebo group developed erythema migrans at the site of the tick bite. The authors reported the efficacy of prophylaxis as the relative risk reduction (using an indirect formula: 1–relative risk, where relative risk is the ratio of the risk in the experimental group in relation to the risk in the control group) that for the primary outcome was 87% (95% confidence interval [CI], 14%-160%). The risk difference was 2.8% (95% CI, 0.5%-5.2%) and the number needed to treat was 36 (95% CI, 19-220). One patient in the doxycycline group and one in the placebo group developed erythema migrans at a different site from that of the identified tick bite. One patient in the doxycycline group and 2 patients in the placebo group had laboratory evidence of *B burgdorferi* infection. The rela-
Calculation and Comparison of Different Efficacy Measures

Tabulation of Results

<table>
<thead>
<tr>
<th>Development of Erythema</th>
<th>Placebo Group</th>
<th>Doxycycline Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migrans at the Site of the Tick Bite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (a)</td>
<td>1 (b)</td>
<td>9</td>
</tr>
<tr>
<td>No</td>
<td>239 (c)</td>
<td>234 (d)</td>
<td>473</td>
</tr>
<tr>
<td>Total</td>
<td>247</td>
<td>235</td>
<td>482</td>
</tr>
</tbody>
</table>

Quantifying the Risk of Developing the Outcome in Each Group

Risk in control group (Rc) = a/(a + c) = 0.032 (3.2%)
Risk in experimental group (Re) = b/(b + d) = 0.004 (0.4%)

Relative risk reduction = (Rc−Re)/Rc = 0.869 (86.9%) 14.0%-159.7%
Relative risk = Re/Rc = 0.13
OR = (b × c)/(a × d) = 0.13

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The absolute risk reduction (ARR) is 3.2% (95% CI, 0.2%-6.1%), and the number needed to treat was 31 (95% CI, 16-433). Information for the adverse events was provided for 309 of the 506 original subjects. Adverse events occurred more in the doxycycline group (30.1%) than in the placebo group (11.1%). The complaints were primarily nausea (15.4% vs 2.6%, respectively) and vomiting (5.8% vs 1.3%, respectively). It was not stated if any patient had to leave the study due to adverse effects, only that no serious adverse events occurred.

Authors’ Conclusion: A single 200-mg dose of doxycycline given within 72 hours after an *I scapularis* tick bite is highly effective in preventing the development of Lyme disease.

Comment

I recommend the complementary reading of other commentaries about the applicability of this study. Shapiro, in an accompanying editorial, pointed out the difficulty in clinical practice to know the species, stage, degree of engorgement of the tick, and even the difficulty to determine if the “tick” is actually a tick; the side effects of therapy; and the importance of other effective strategies for prevention such as educating the population in endemic areas to check carefully for ticks and to remove them promptly and correctly. In another commentary by Meyerhoff, attention was drawn to the fact that an adequate follow-up period is needed to allow for the development of Lyme disease.

This randomized trial appears to be valid and well designed. However, the authors provided no description of how the randomization sequence was generated or about concealment of allocation. Patients and investigators were blinded for interventions, there was an evaluation of compliance and only 51 (10.6%) of 482 people were lost to follow-up. The outcome measures and endpoints were clearly defined and explained and the analysis of results was by intention to treat.

The results of this trial contrasted with those of previous studies, which showed no clear protection attributable to antibiotic prophylaxis given after a tick bite. These earlier studies failed to establish definitive treatment efficacy because of small sample size and the very low risk of infection even in endemic areas. Although, in the study of Nadelman et al the authors concluded that “doxycycline is highly effective in preventing Lyme disease,” they were equally clear that the relative risk reduction (87%) should be interpreted cautiously because of the small number of patients who developed the outcome and the wide 95% CI.

Besides relative risk reduction (RRR), there are other measures for quantifying the benefit of an intervention in a clinical trial. Although they are derived from the same data, they may lead to different inferences with regard to the efficacy level. The other commonly used measures of the benefits of an intervention are absolute risk reduction or risk difference (ARR), its inverse (1/AAR), the number needed to treat (NNT), the relative risk (RR), and the odds ratio (OR). The *Table* shows how these measures can be calculated from tabulated results of controlled clinical trials comparing 2 interventions and with binary (yes or no) outcomes. In the Nadelman et al study, the efficacy of prophylaxis was expressed as RRR. But this measure is not the best way of expressing the overall efficacy of doxycycline in this trial. As with the RR, the RRR does not tell anything about the absolute baseline risk and therefore the real benefit to be gained. In addition, with these relative measures the impact of an intervention can be overestimated or underestimated if the risk in the control group is very low or very high, respectively. In the calculation of RRR for the primary outcome in this study, a small absolute difference in risk (2.8%) can seem rather high (87%) when compared with a fairly low (3.2%) baseline (control group) risk of developing erythema migrans. In this case, the absolute difference between the risk in the control and the experimental group (AAR) and the NNT are more clinically relevant and useful measures of benefit to use than RRR. The NNT tells us the number of patients who need to be treated to prevent one bad outcome. In this trial, the NNT was 36; in other words, 36 patients need to be treated to prevent 1 case of erythema migrans. Once the effect has been quantified, the CI measures the precision of the estimate of the treatment effect. A wide CI indicates that the estimate of the treatment effect is imprecise. In the trial by Nadelman et al the 95% CIs are wide and con-
sequently the efficacy measures should be interpreted cautiously.

**Bottom Line:** It is important that clinicians be familiar with all these measures, as they are often used indistinctly in analysis of clinical trials. Furthermore, there is some empirical evidence that the perception of effectiveness by the readers of clinical trials depends on the outcome metric used.\(^4\)\(^5\) Clearly, the study of Nadelman et al is more impressive expressed with an efficacy (RRR) of 87% than an ARR of 2.8%. It is known that most patients consulting physicians for tick bites in endemic areas receive prophylactic antibiotic therapy.\(^6\) The type of reporting used in this trial can predispose more to the routine use of antibiotic therapy for prophylaxis of Lyme disease, even when the value of this intervention is still controversial.

Accepted for publication September 12, 2002.

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**News and Notes**

The 24th Arcachon Annual Course of Pediatric Dermatology will be held from April 22 to April 25, 2003, at the Palais des Congres, Boulevard Veyrier Montagnères, F-33120 Arcachon, France. Topics will include cutaneous tumors in children; the eye in pediatric dermatology; immunomodulation in pediatric dermatology; and the umbilicus/clinical cases from Bordeaux Children’s Hospital. For more information and registration, contact Gisèle Latournerie, Unité Dermatologie Pédiatrique, Hôpital Pellegrin Enfants, 33076 Bordeaux Cedex, France (phone: 335567956542; fax: 33557821450; e-mail: gisèle.latournerie@chu-bordeaux.fr).