Regional Differences in Metronidazole Resistance and Increasing Clarithromycin Resistance among *Helicobacter pylori* Isolates from Japan

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Received 20 January 2000/Returned for modification 10 May 2000/Accepted 18 May 2000

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**H. pylori** infection is now established as a major cause of peptic ulcer disease (5, 10), and it has been shown that successful treatment of *H. pylori* infection results in the cure of peptic ulcer diseases (6, 17). Although the standard treatment for *H. pylori*-related disease is a combination of two or more antimicrobial agents and acid suppression, no therapy is universally successful. Poor patient compliance with treatment and the presence of resistant organisms are thought to be the most important variables predicting a low cure rate. Antibiotic resistance in *H. pylori* is a growing problem. The reported frequencies of resistance to the antibiotics have varied widely between geographic regions and among subgroups within a study population (1, 3, 4, 7, 14–16, 18). For example, metronidazole resistance varies from 10 to 80% among geographic regions (3, 4, 7, 15, 18). Knowledge of the prevalence of antibiotic resistance of *H. pylori* in any area is important because treatment for *H. pylori* infection is often started on an empirical basis. If the infecting strain is resistant, therapy is likely to be unsuccessful. Macrolide use is widespread in Japan, suggesting that resistance to clarithromycin may be prevalent. The aim of this study was to assess the frequencies of primary resistance to metronidazole, clarithromycin, and amoxicillin among *H. pylori* isolates from two different metropolitan hospitals in Japan.

The patterns of antibiotic resistance in *Helicobacter pylori* were assessed in two different regions in Japan. Overall, prevalences of resistance to metronidazole and clarithromycin were 12.4 and 12.9%, respectively. While there was no difference in clarithromycin resistance, the prevalence of metronidazole resistance was significantly higher in Kyoto (23.8%) than in Sapporo (8.1%). From 1996 to 1999, the prevalence of metronidazole resistance did not change but the prevalence of clarithromycin resistance doubled (from 9.1 to 18.7%).

**TABLE 1.** Comparison of antibiotic resistance of *H. pylori* isolates between Sapporo and Kyoto

<table>
<thead>
<tr>
<th></th>
<th>Sapporo (%)</th>
<th>Kyoto (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>8.1 (23/283)</td>
<td>23.8 (25/105)*</td>
<td>12.4 (48/388)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>12.0 (34/283)</td>
<td>15.2 (16/105)</td>
<td>12.9 (50/388)</td>
</tr>
</tbody>
</table>

* MICs were >8 µg/ml for metronidazole and >1 µg/ml for clarithromycin.

* P < 0.05 compared to results for Sapporo.
TABLE 2. Annual prevalences of metronidazole- and clarithromycin-resistant *H. pylori* isolates in Japan

<table>
<thead>
<tr>
<th>Year</th>
<th>Metronidazole % Prevalence of resistance (no. resistant/total) to:</th>
<th>Clarithromycin % Prevalence of resistance (no. resistant/total) to:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sapporo</td>
<td>Kyoto</td>
</tr>
<tr>
<td>1996</td>
<td>5.7 (2/35)</td>
<td>17.0 (9/53)</td>
</tr>
<tr>
<td>1997</td>
<td>5.9 (8/136)</td>
<td>40.0 (1230)</td>
</tr>
<tr>
<td>1998–1999</td>
<td>11.6 (13/112)</td>
<td>18.2 (4/22)</td>
</tr>
</tbody>
</table>

* MICs were >8 μg/ml for metronidazole and >1 μg/ml for clarithromycin.

In Japan, the government (The Ministry of Health and Welfare) has not allowed the use of the antibiotics for *H. pylori* therapies in the study period. For this reason, Japan should be the ideal country for examining primary resistance rates of *H. pylori* to various antibiotics. The primary resistances to clarithromycin and metronidazole observed in this study are probably due to the previous use of these antimicrobial agents for other infections. The reported prevalence of primary resistance of *H. pylori* to clarithromycin varies between 1 and 17% in other countries (1, 14, 16, 18). The prevalence of clarithromycin resistance in *H. pylori* was high and increasing despite the fact that *H. pylori* therapy is not used in Japan. Clarithromycin was developed in Japan and is very popular for the treatment of respiratory tract infections. Reducing the use of clarithromycin might reduce the prevalence of clarithromycin resistance. For example, a 50% decrease in macrolide consumption between 1988 and 1992 in Finland led to a decrease in resistance of group A streptococci from 19 to 9%, but after a 5-year lag phase (13).

The overall prevalence of metronidazole resistance in *H. pylori* (12.4%) was within the range reported from other countries (less than 10% to greater than to 80% between geographic regions) (2, 3, 4, 7, 14). Metronidazole-resistant *H. pylori* isolates were significantly more prevalent in Kyoto than in Sapporo (23.8 versus 8.1%; *P* < 0.05). Our preliminary observation for multicenter analysis indicates that there is a north-to-south gradient in metronidazole resistance in Japan. There was a similar tendency for macrolide resistance rates in Europe, high in the south and low in the north, possibly due to a difference in consumption of the antibiotic (8). Debets-Ossenkopp et al. examined metronidazole resistance in three different parts of The Netherlands and found that resistance rates were different (south, 11.6%; west, 24.3%) although the rates of consumption of metronidazole were similar (2). There was no significant difference in clarithromycin and metronidazole resistance in relation to age, sex, or disease presentation in this study. Other studies have shown a higher frequency of metronidazole-resistant isolates from women, possibly due to the use of this agent for the treatment of genitourinary tract infections.

In summary, we found regional differences in metronidazole resistance and increasing clarithromycin resistance among *H. pylori* isolates from Japan. These results suggest that differential factors may be involved in the development of metronidazole resistance in the two areas. In addition, the high rate of clarithromycin resistance suggests that the effectiveness of clarithromycin-based anti-*H. pylori* therapies may soon be compromised in Japan.

REFERENCES


