Evaluation of Pertussis Treatment with Erythromycin Ethylsuccinate and Stearate According to Age

Hirokazu KAWAI, Tatsuo AOYAMA, Akira GOTO, Hidehito IWAI and Yuji MURASE
Department of Pediatrics, School of Medicine, Keio University, Tokyo, and Department of Pediatrics, Kawasaki Municipal Hospital, Kawasaki Japan
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Summary

Although erythromycin estolate has been fully assessed for pertussis treatment, the evaluation of erythromycin ethylsuccinate and stearate, the main erythromycin preparations used in Japan and the US, is inadequate. We evaluated these preparations to establish an appropriate treatment for pertussis according to age. Sixty-six patients with culture-confirmed pertussis were treated with erythromycin administered at a dosage of 40–50 mg/kg/day (maximum, 1.2 g/day). Negative culture was obtained in 39% (15/38) of patients aged 0–2 years within one week and in 71% (27/38) within two weeks, in 78% (7/9) of those aged 3–15 years within one week and in 100% (9/9) within two weeks. All 12 adult patients had a negative culture within one week.

The efficacy of erythromycin for the eradication of B. pertussis was significantly lower in children aged 0–2 years than in older children. In conclusion, it is desirable to administer erythromycin for three weeks to children aged 0–2 years, two weeks to those aged 3–15 years and one week to adults.

Introduction

Pertussis is a contagious disease caused by Bordetella pertussis, a short, gram-negative bacillus. Its major symptom is prolonged refractory coughing, which sometimes results in sudden death. Currently, the disease is treated with erythromycin, a macrolide antibiotic with a low minimum inhibitory concentration (MIC) against B. pertussis and favorable secretion into the airway. Furthermore, no strains of B. pertussis resistant to erythromycin have been found. However, once the disease has reached the paroxysmal stage, the drug does little to improve clinical symptoms, but if used during the catarrhal stage, it is effective in relieving clinical symptoms and preventing secondary infection by eradicating the causative organism.

Based on the results of Bass and others, erythromycin estolate (50 mg/kg/day, maximum, 1 to 2 g/day) for 14 days was recommended for pertussis treatment. However, erythromycin estolate is now rarely used in Japan and the United States because of its potential liver toxicity. Erythromycin ethylsuccinate (dry syrup) and stearate (tablet) are used instead because they have fewer side effects, although their absorption is not as good as that of the estolate.
As the efficacy of erythromycin ethylsuccinate (dry syrup) and stearate (tablet) have not been evaluated fully for pertussis treatment, and the eradication rate of *B. pertussis* with these erythromycins appeared to vary depending on the patient’s age, we assessed their efficacy in different age groups to establish appropriate treatment schedules.

**Materials and Methods**

The study was conducted in 66 patients (29 males and 37 females) treated with erythromycin ethylsuccinate or stearate from among 77 with culture-confirmed pertussis seen at Keio University Hospital, Tokyo, and its affiliated hospitals located in the Tokyo metropolitan area, between 1983 and 1990. Of these 66 patients, 38 (all unvaccinated) were 2 years of age or under, 16 (9 unvaccinated and 7 vaccinated with 3 or more doses of diphtheria-tetanus-pertussis (DTP) vaccine) were 3-15 years old and 12 were adults (their vaccination status was unknown).

Children aged 8 years or under were given erythromycin ethylsuccinate (dry syrup) and patients aged 9 years or over were given erythromycin stearate (tablet). Both preparations were administered orally at a dosage of 40 to 50 mg/kg/day (maximum 1.2 g/day) in three divided doses. Nasopharyngeal cultures for *B. pertussis* were carried out as follows: nasopharyngeal mucus was collected from each patient using a nasal swab (Medical Wire and Equipment, MW173C) before and 1, 2 and 3 weeks after starting treatment. The mucus was inoculated directly onto Bordet-Gengou medium (Difco) containing 5 μg/ml cephalexin (CEX) and Cyclodextrin Solid Medium (CSM) containing 5 μg/ml CEX, then incubated at 35°C for seven days. Charcoal agar medium (Oxoid) containing 40 μg/ml CEX was also used for some specimens. A standardized three-fold streak method was used to quantify the amount of *B. pertussis* isolated.

On each patient’s visit to the hospital, information about his/her symptoms and compliance in taking medication were ascertained from the child’s parents.

The chi-square and Fisher’s exact probability tests were used to compare the eradication rates in each age group.

**Results**

The mean duration of pertussis before starting erythromycin therapy was 10.9 ± 5.6 days in the patients who were 2 years old or under, 11.6 ± 6.3 days in those 3-15 years old and 11.5 ± 4.5 days in the adults. As the parents were informed of the importance of erythromycin for treatment, drug compliance was very good. One week after administration of erythromycin (week 1), the nasopharyngeal cultures were negative for *B. pertussis* in 39% (15/38) of the patients 2 years old or under and 88% (14/16) of those 3-15 years old (p<0.01. Table 1). At the end of week 2, the cultures were negative in 71% (27/38) of the patients 2 years old or under and 100% (9/9) of those 3-15 years old.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Eradication rates of <em>B. pertussis</em> with erythromycin according to age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eradication</td>
<td>0-2 years*1</td>
</tr>
<tr>
<td>VC(+)</td>
<td>VC(-)</td>
</tr>
<tr>
<td>Week 1</td>
<td>15/38 (39%)</td>
</tr>
<tr>
<td>Week 2</td>
<td>27/38 (71%)</td>
</tr>
</tbody>
</table>

*1 All were unvaccinated.

*2 Seven of 16 children aged 3-15 years were vaccinated with 3 or more doses of DTP vaccine (vc(+)), and the remaining 9 children were unvaccinated (vc(-)).

*3 Vaccination status was unknown.

**a : p<0.05 b : p<0.01 c : p=0.069**
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Table 2 Changes in quantity of isolated *B. pertussis* after administration of erythromycin in 38 children 0-2 years of age

<table>
<thead>
<tr>
<th>Treatment period</th>
<th>Quantity of isolates*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(+++)</td>
</tr>
<tr>
<td>Pretreatment</td>
<td>20</td>
</tr>
<tr>
<td>Week 1</td>
<td>0</td>
</tr>
<tr>
<td>Week 2</td>
<td>0</td>
</tr>
<tr>
<td>Week 3</td>
<td>0</td>
</tr>
</tbody>
</table>

*Quantities of isolated *B. pertussis* were assessed semi-quantitatively using a standardized three-fold streak method and rated using four grades, ++, +, +, −.

in 71% (27/38) and 100% (16/16), respectively (p<0.05). The eradication rates at week 1 and week 2 were significantly lower in those 2 years old or under than in those 3-15 years old. The remaining 11 patients aged 2 years or younger who were culture-positive after week 2 became negative at the end of week 3. All 12 adult patients with pertussis were culture-negative at the end of week 1. Of the 16 3-15-year-old patients, 9 had not been vaccinated at all and 7 had received 3 or more doses of DTP. When the eradication rates in unvaccinated and vaccinated patients were compared, they were 78% (7/9) and 100% (7/7), respectively, at the end of week 1 and 100% at the end of week 2 in both groups. The eradication rates in the vaccinated and unvaccinated groups did not differ significantly. As all children aged 0-2 years were unvaccinated, their eradication rates were compared with 9 unvaccinated children aged 3-15 years. The rates were 39% (15/38) in children aged 0-2 years and 78% (7/9) in those aged 3-15 years at the end of week 1 (p<0.05), and 71% (27/38) and 100% (9/9) at the end of week 2 (p=0.069).

Eleven of the 16 3-15-year-old children were given erythromycin ethylsuccinate (dry syrup) and the remaining 5 children were given erythromycin stearate (tablet). When the eradication rates of *B. pertussis* in the erythromycin ethylsuccinate group and stearate group were compared, they were 82% (9/11) and 100% (5/5), respectively, at the end of week 1 and 100% at the end of week 2 in both groups. Our study showed no significant differences between the eradication rates of *B. pertussis* in the erythromycin ethylsuccinate group and stearate group.

In order to assess changes in the quantity of *B. pertussis* isolated after erythromycin therapy, we used a standardized three-fold streak method. Although *B. pertussis* was still isolated at the end of week 2 in patients aged 2 years or under, the proportion of those from whom a large quantity of *B. pertussis* (+++) was recovered decreased dramatically from 52.6% (20/38) before treatment to 0% (0/38) after week 1 (Table 2).

Although it was difficult to quantify the patients’ symptoms, improvement in symptoms was evaluated on the basis of information given by their parents. No differences in improvement seemed to be present between the culture-positive group and the culture-negative group after week 1 and at the end of week 2.

Discussion

In 1969, Bass reported that *B. pertussis* was eradicated several days after administration of erythromycin estolate and that the organism reemerged in 10% of the patients to whom erythromycin had been administered for 7-10 days. According to these results, Bass recommended continuing erythromycin estolate therapy for 14 days. Islur published a similar report on pertussis treatment.
Pertussis Treatment with Erythromycin According to Age

Administration of erythromycin for 14 days is now recommended to eradicate the causative organism\(^8\). Because of its potential to cause liver damage, the estolate preparation is rarely used in Japan and the US. Instead, erythromycin ethylsuccinate and stearate are used currently because they have fewer side effects, although their absorption is not as good as that of the estolate. Henry reported that one of six patients (6 young children aged 1 to 14 months) treated with erythromycin stearate (50 mg/kg/day) for seven days was culture-positive 10 days after treatment and that the administration of erythromycin stearate for 7 days was inadequate to eradicate \textit{B. pertussis}\(^9\).

Bergquist\(^{10}\) and Hoppe\(^{11}\) assessed erythromycin ethylsuccinate for pertussis treatment. The former reported that all 17 patients treated with the ethylsuccinate (50 mg/kg/day) for 10 days had a negative culture 5 days after treatment, but one tested positive 15 days after treatment. Hoppe observed no statistically significant difference between the eradication rates of the estolate (40 mg/kg/day) and ethylsuccinate (60 mg/kg/day) administered for 14 days, with eradication rates of 97.8\% (91/93 cases) vs. 99.0\% (96/97). However, in the later report, the dosage of erythromycin ethylsuccinate (60 mg/kg/day) was much higher than that recommended for oral administration\(^9\). Although they both reported unresponsive cases after 10 or 14 days of erythromycin therapy, their eradication rates were higher than the overall rate in our study after treatment for 14 days. We postulate the following reasons for this difference: [1] more young children were included in our study than theirs, and [2] we used a more ideal isolation technique that made it possible to isolate small quantities of organisms. We used two kinds of medium, including CSM, with which better isolation rates are obtained compared with Bordet-Gengou medium or charcoal agar medium, which these other authors used for \textit{B. pertussis} isolation. [3] A high dosage of erythromycin ethylsuccinate (60 mg/kg/day) was used, although high dosages of erythromycin for pertussis treatment are not widely accepted. [4] Another possibility could be the lower degree of absorption of erythromycin from the gastrointestinal tract in infants compared with older children\(^12\).

Our study showed no significant differences between the eradication rates in 3-15-year-old vaccinated and unvaccinated children. As reported by Hallander\(^{16}\) and us\(^{17}\), the vaccine has a definite effect on the eradication of \textit{B. pertussis} for 1-2 years after vaccination. The long interval after the last dose of DTP may have decreased its protective effect considerably in some of the patients.

As it was difficult for young children to take erythromycin in tablet form, children in this study aged 8 years or under were given erythromycin ethylsuccinate (dry syrup), whereas children aged 9 years or over were given erythromycin stearate (tablet). No differences in the eradication rates of \textit{B. pertussis} seemed to be present between the erythromycin ethylsuccinate group and stearate group.

In our study, 11 of the 38 patients aged 2 years or under still carried the organisms after 2 weeks.
of erythromycin therapy. Nevertheless, the number of patients carrying a large quantity (+ + +) of B. pertussis decreased dramatically from 20 before treatment to 0 at the end of week 1. As the load of organisms carried was reduced substantially after 1 week of erythromycin therapy, it is likely that the organism's infectious ability had been diminished considerably.

Patients with pertussis should be isolated for 5 days after erythromycin, as recommended on the basis of administration of erythromycin estolate\(^{18}\). However, in the administration of erythromycin ethylsuccinate or stearate, we suggest that an appropriate isolation period would appear to be 1 week after erythromycin therapy.

For young children with pertussis, 3 weeks of erythromycin therapy is extremely long. New acid-stable macrolide antibiotics, such as azithromycin and clarithromycin, have better absorption and longer half-lives than erythromycin. In our preliminary study, these macrolide antibiotics eradicated the organisms within 1 week in children 0-2 years. It would be desirable for these macrolides to replace erythromycin in the treatment of pertussis.

As the efficacy of erythromycin ethylsuccinate and stearate for the treatment of pertussis varies according to the patient's age, appropriate treatment period adjustments are needed. Therefore, for pertussis treatment, it is desirable to administer erythromycin for three weeks to children aged 2 years or under, two weeks to children aged 3 years or over, and one week to adults.

Acknowledgement

We would like to thank Prof. N. Matsuo for advice.

References

エチルコハク酸エリスロマイシン、ステアリン酸エリスロマイシンの
年齢別百日咳菌除菌効果

慶應義塾大学医学部小児科学教室
川合 宏和 後藤 亮 岩井 英人 村瀬 雄二
川崎市立川崎病院小児科
青山 辰夫

（平成6年5月16日受付）
（平成6年7月28日受理）

要 目
百日咳菌除菌効果の検討はエリスロマイシン・エストレートでは数多くなされているが、我が国および米国で頻用されているエチルコハク酸エリスロマイシン（ドライシロップ、顆粒）及びステアリン酸エリスロマイシン（錠剤）においては十分とはいえない。そこでエリスロマイシン（エチルコハク酸エリスロマイシン及びステアリン酸エリスロマイシン）の年齢別百日咳菌除菌効果を比較し、適切なエリスロマイシンの投与法について検討を行った。対象は、百日咳菌培養陽性例77例中エリスロマイシンを投与した66例とした。エリスロマイシンは、40〜50mg/kg/日（最大1.2g/日）経口投与した。0〜2歳児では39％（15例/38例）が1週以内に、71％（27例/38例）は2週以内に菌陰性化した。3〜15歳児では78％（7例/9例）が1週以内に、全例2週以内に菌陰性化した。成人は12例全例1週以内に菌陰性化した。エリスロマイシンの百日咳菌除菌効果について0〜2歳児は、年長児、成人に比べ有意に劣っていた。そのため0〜2歳時には3週、3歳以上の児は2週、成人は1週間エリスロマイシン投与が必要と考えられた。

平成6年11月20日