Pharmacokinetics of Erythromycin Ethylsuccinate and Estolate in Infants Under 4 Months of Age

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We studied the pharmacokinetics of erythromycin estolate and ethylsuccinate suspensions in infants under 4 months of age who were being treated for chlamydial infections or pertussis. We conducted our studies after the initial dose of 10 mg/kg and subsequently during steady-state treatment. The estolate preparation resulted in higher peak concentrations in sera, and its absorption and elimination half-lives were longer. Peak concentrations occurred 3 h after a dose with the estolate preparation and 1 h after a dose with the ethylsuccinate preparation. The area under the curve for the estolate preparation was about three times greater than that for the ethylsuccinate preparation. Based on these findings, we recommend that erythromycin estolate suspensions be given to young infants at 8- or 12-h intervals (30 mg/kg per day in three divided doses or 20 mg/kg per day in two divided doses) and that erythromycin ethylsuccinate is best given at 6-h intervals (40 mg/kg per day in four divided doses).

Erythromycin is recommended and used for treatment of chlamydial infections and pertussis in young infants. To our knowledge, the only previously reported pharmacokinetic data concerning this age group were from a study in which the estolate salt of erythromycin was given to preterm infants (1). Our study involved a pharmacokinetic evaluation in infants under 4 months of age of the two forms of erythromycin available in suspension, namely, the ethylsuccinate salt and the estolate salt.

MATERIALS AND METHODS

The parents of patients under 4 months of age who were being treated for chlamydial conjunctivitis or pneumonia or for pertussis were asked to participate. The study patients were outpatients and inpatients at the Children's Medical Center and Parkland Memorial Hospital, Dallas, Texas. Signed, informed consent was obtained from the parents.

Initial dose studies. A dose of erythromycin estolate or ethylsuccinate equivalent to 10 mg of erythromycin per kg of body weight was given after blood was drawn at zero time. Additional blood samples were collected through a heparin lock or by heel sticks at 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 h. Immediately after blood samples were drawn, the serum was separated and kept in the freezer at -20°C until the time of analysis (within 48 h).

Steady-state studies. After patients had been receiving erythromycin ethylsuccinate or estolate for 5 to 7 days, blood samples were collected at the intervals described above. The following two groups were studied. One group of patients received the ethylsuccinate or estolate preparation on a schedule of 10 mg/kg every 6 h (40 mg/kg per day); in this group serum specimens were collected for only 6 h. The other group of patients received the estolate preparation on a schedule of 10 mg/kg every 12 h (20 mg/kg per day).

Tears. When possible, specimens of tears were collected 1 h after a dose for an assay of erythromycin content.

Bioassay. The concentrations of erythromycin in sera and tears were assayed by a microbioassay method, using Sarcina lutea N1886 (FDA 1001; ATCC 9341) as the test organism. Agar plates were prepared from antibiotic medium 11 (Difco Laboratories). Erythromycin glucosinate standards (Eli Lilly & Co.) were used for standard concentration-zone diameter curve construction. This technique permitted determination of erythromycin concentrations within a 5% range of error (8).

Analysis of data. The pharmacokinetics of erythromycin were calculated from curves of serum concentration versus time fit to a one-compartment model with first-order absorption (4) by using the NONLIN program and the following formula:

\[ C_p = A e^{-K_a t} - t_{lw} - e^{-K_d t} \]

where \( C_p \) is the serum concentration at time \( t \), \( A \) is a constant coefficient or intercept, \( K_a \) and \( K_d \) are absorption and elimination rate constants, respectively, and \( t_{lw} \) is the lag time for absorption. Rate constants were determined after computer fitting of curves by an iterative least-squares method. The smaller and larger rate constants were assumed to represent elimination and absorption, respectively. The pharmacokinetic data were obtained using the UTHSCD DEC 10 computer program, including statistical anal-
ysis. We tested statistical analyses of differences between means ± standard errors of the means by the nonpaired, two-tailed Student's t test, and statistical significance was defined as a P value of <0.05.

RESULTS

Between February 1980 and August 1980, we studied 30 patients. Two patients were excluded from our analysis because one had received an unknown drug which interfered with the erythromycin assay and the other was given penicillin during the study period. Thus, 28 patients were analyzed for the pharmacokinetics of erythromycin. Each study group contained six patients, except for the estolate preparation steady-state study with the drug given every 6 or 12 h, in which each group contained five patients. The mean body weight in the study groups varied from 3.5 to 4.6 kg, and the mean age varied from 29 to 49 days; these differences were not significant.

Initial dose study. In the initial dose study (Fig. 1 and Table 1), the mean peak serum concentration of erythromycin in infants taking the estolate preparation was not significantly greater than the mean peak serum concentration in infants taking the ethylsuccinate preparation (P < 0.536), nor was the time at which the peak occurred after the estolate treatment significantly later (P < 0.189). The absorption half-lives were not significantly different (P < 0.126), but the elimination half-lives were longer (P < 0.042) in infants who received the estolate preparation. The larger area under the curve (AUC) for the estolate group was not significantly larger than the AUC for the ethylsuccinate group (P < 0.083).

Steady-state study. In the steady-state study (Fig. 2 and Table 1), the trend to differences found after the initial dose persisted and were magnified when the drugs were given every 6 h. There were significant differences between the times until peak serum concentrations were attained (P < 0.001), the absorption half-lives (P < 0.004), the elimination half-lives (P < 0.054), and the AUC (P < 0.046). In all cases, the values in patients taking the estolate preparation were greater. The greater peak serum concentration found in infants taking the estolate preparation was not significant (P < 0.142).

When the estolate preparation was given every 12 h, the pharmacokinetic values obtained were similar to the values observed in infants taking the drug every 6 h (Fig. 2 and Table 1).

![Fig. 1. Erythromycin serum concentration time curves after the initial dose. The horizontal dashed line represents the highest MIC of erythromycin for most strains of C. trachomatis.](image-url)

![Fig. 2. Erythromycin serum concentration time curves from patients during steady-state treatment. The ethylsuccinate preparation was given every 6 h. The horizontal dashed line represents the highest MIC of erythromycin for most strains of C. trachomatis.](image-url)

<table>
<thead>
<tr>
<th>Study</th>
<th>Erythromycin salt</th>
<th>No. of patients</th>
<th>Peak conc (μg/ml)</th>
<th>Time to peak (h)</th>
<th>Absorption half-life (h)</th>
<th>Elimination half-life (h)</th>
<th>AUC (μg·h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose</td>
<td>Estolate</td>
<td>6</td>
<td>1.6 ± 0.60</td>
<td>2.7 ± 0.42</td>
<td>1.04 ± 0.18</td>
<td>4.06 ± 0.69</td>
<td>17.15 ± 4.98</td>
</tr>
<tr>
<td></td>
<td>Ethylsuccinate</td>
<td>6</td>
<td>1.1 ± 0.5</td>
<td>1.8 ± 0.48</td>
<td>0.62 ± 0.17</td>
<td>2.26 ± 0.41</td>
<td>6.32 ± 0.63</td>
</tr>
<tr>
<td>Steady state, every 6 h</td>
<td>Estolate</td>
<td>5</td>
<td>1.76 ± 0.2</td>
<td>3.2 ± 0.38</td>
<td>0.72 ± 0.11</td>
<td>6.58 ± 2.04</td>
<td>16.2 ± 4.99</td>
</tr>
<tr>
<td></td>
<td>Ethylsuccinate</td>
<td>6</td>
<td>1.3 ± 0.2</td>
<td>0.8 ± 0.11</td>
<td>0.3 ± 0.04</td>
<td>2.42 ± 0.31</td>
<td>5.41 ± 1.09</td>
</tr>
<tr>
<td>Steady state, every 12 h</td>
<td>Estolate</td>
<td>5</td>
<td>1.4 ± 0.4</td>
<td>3.0 ± 0.3</td>
<td>1.1 ± 0.12</td>
<td>3.98 ± 1.2</td>
<td>9.9 ± 1.92</td>
</tr>
</tbody>
</table>

* Mean ± standard error of the mean.
We measured erythromycin concentrations in tears 1 h after a dose for 16 patients. In the ethylsuccinate preparation steady-state study, the antibiotic concentration ranged from 2.0 to 5.4 μg/ml (mean ± standard error of the mean, 2.78 ± 0.083 μg/ml). This concentration was greater than the mean serum concentration measured at the same time (1.29 ± 0.14 μg/ml), but it was not significantly different (P < 0.084). The erythromycin contents of tears collected from infants in the estolate preparation steady-state study ranged from 0.6 to 5.0 μg/ml (mean ± standard error of the mean, 2.35 ± 0.88 μg/ml), which also was not significantly greater than the serum concentration at the same time (1.26 ± 0.22 μg/ml; P < 0.257). The mean erythromycin concentrations in the tears of patients taking the ethylsuccinate and the estolate preparations were not different (P < 0.732). Of the 16 specimens of tears, 11 (69%) had higher erythromycin concentrations than the highest serum concentration measured in the patients.

**DISCUSSION**

In infants under 4 months of age there are substantial differences in the pharmacokinetics of the estolate and ethylsuccinate suspensions of erythromycin. In children taking the estolate preparation, serum concentrations of erythromycin peak later and are greater than the corresponding values in children taking the ethylsuccinate preparation. Absorption and elimination half-lives are longer with the estolate preparation than with the ethylsuccinate preparation. The AUC measures bioavailability, and it is greater with the estolate preparation.

The peak serum concentrations of erythromycin achieved with the two suspensions used are two to three times greater than the highest minimal inhibitory concentrations (MICs) reported for *Chlamydia trachomatis* (0.5 μg/ml) (6) and six to eight times greater than MICs reported for *Bordetella pertussis* (0.2 μg/ml) (3). Trough serum levels 8 h after the estolate treatment were still greater than the MICs for *C. trachomatis* and *B. pertussis*. After erythromycin ethylsuccinate administration, the trough serum levels of erythromycin were lower than the MICs for the majority of *C. trachomatis* strains and only slightly higher than the MICs for *B. pertussis*.

The amount of time that erythromycin serum concentrations were maintained over 0.5 μg/ml was estimated by using the computer to be 10.5 h with the estolate preparation and 4.8 h with the ethylsuccinate suspension. Therefore, if maintenance of suprainhibitory antibiotic concentrations in serum is desirable for treating chlamydial infections, the estolate preparation could be given at 8- or 12-h intervals, and the ethylsuccinate preparation could be given at 6-h intervals. However, serum concentrations may be less important than antibiotic contents in tissues and other body fluids. It is characteristic of erythromycin that tissue and other body fluid levels are greater than levels in the serum (5). This was supported by the observation in our study that erythromycin concentrations in tears were greater than the highest serum concentration in the majority of patients. Therefore, the relevance of serum concentrations to clinical efficacy can be misleading, and concentrations in the body fluids or tissues of the patient being treated may be a more reliable criterion.

There have been only two previous studies of erythromycin pharmacokinetics in infants; one was with preterm neonates (1), and one was with older infants (7). From the data in these reports we calculated pharmacokinetic values by using the same methods that we applied to our data (Table 2). The data are similar in the studies, with the notable exceptions of the far greater peak serum concentrations and AUC in the older infants taking erythromycin estolate. The most obvious explanation for this is the smaller volume of distribution in the older infants, but other factors may be operative. With both forms of erythromycin, the absorption half-lives were shorter in the older infants, but elimination half-lives were similar.

**Table 2. Comparative erythromycin pharmacokinetics in pediatric studies after a single oral dose**

<table>
<thead>
<tr>
<th>Erythromycin salt</th>
<th>Mean age of patients</th>
<th>Reference</th>
<th>Peak serum conc (μg/ml)</th>
<th>Time to peak (h)</th>
<th>Absorption half-life (h)</th>
<th>Elimination half-life (h)</th>
<th>AUC (μg·h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estolate</td>
<td>1.5 days</td>
<td>(1)</td>
<td>1.5</td>
<td>1</td>
<td>0.75</td>
<td>4.2</td>
<td>15.1</td>
</tr>
<tr>
<td></td>
<td>15 days</td>
<td>(1)</td>
<td>2.0</td>
<td>3</td>
<td>0.76</td>
<td>4.5</td>
<td>18.3</td>
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<tr>
<td></td>
<td>29 days</td>
<td>This study</td>
<td>1.6</td>
<td>2.7</td>
<td>1.04</td>
<td>4.1</td>
<td>17.2</td>
</tr>
<tr>
<td></td>
<td>19 mo</td>
<td>(7)</td>
<td>4.8</td>
<td>2</td>
<td>0.36</td>
<td>5.1</td>
<td>40</td>
</tr>
<tr>
<td>Ethylsuccinate</td>
<td>48 days</td>
<td>This study</td>
<td>1.1</td>
<td>1.8</td>
<td>0.6</td>
<td>2.3</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>19 mo*</td>
<td>(7)</td>
<td>1.4</td>
<td>1</td>
<td>0.27</td>
<td>1.6</td>
<td>4.8</td>
</tr>
</tbody>
</table>

* Dose, 15 mg/kg. The doses for all other groups were 10 mg/kg.
In our study erythromycin concentrations were determined by a microbioassay which measured total erythromycin content. A large portion of the erythromycin in the sera of patients receiving the estolate preparation was in the form of erythromycin propionate, which is biologically inactive (2, 9). During the bioassay procedure, the propionate salt is hydrolyzed to yield erythromycin base. It is not known whether similar hydrolysis occurs in body fluids or tissues, and the clinical significance of this hydrolysis is disputed. From a practical standpoint, we have shown that infants with chlamydial conjunctivitis treated with 10 mg of the estolate preparation per kg every 12 h responded as well as those given the same dosage of the ethylsuccinate preparation every 6 h (P. Pata.masucon, P. J. Rettig, K. Faust, and J. D. Nelson, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 20th, New Orleans, La., abstr. no. 528, 1980).

Based upon these pharmacokinetic studies, we recommend that infants under 4 months of age being treated for chlamydial infections or pertussis be given the estolate suspension at 8- or 12-h intervals (30 mg/kg per day in three divided doses or 20 mg/kg per day in two divided doses) or the ethylsuccinate suspension at 6-h intervals (40 mg/kg per day in four divided doses).

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LITERATURE CITED