Absorption and Elimination of Ethosuximide in Children


ETHOSUXIMIDE* was first described for control of petit mal epilepsy by Zimmermann and Burgemeister in 1958.1 Many authorities now consider it the drug of choice for petit mal.2,3,4 Hansen and Feldberg5 indicated that blood levels in adults following a single dose reach a peak two to four hours after ingestion. Elimination then occurs slowly although the half-life was not determined. The blood levels reached a plateau after four days of constant administration, then remained level with very little diurnal variation. Dill and Glazko6 studied the metabolism of ethosuximide in animals and man. Following a single 1.0 gram oral dose in adults, a half-life of nearly 60 hours was observed.

Petit mal epilepsy is a disease of young children usually having an onset between age 4 and 8 years.7 Children in the age range most affected by petit mal may have difficulty swallowing capsules so a syrup form of ethosuximide has been developed. A cross-over study in children was initiated to compare the absorption, distribution, and excretion of the syrup and capsule forms. The results of this study are reported here and provide further information about the pharmacology of ethosuximide in children.

Method

Five institutionalized children who did not routinely require any medication were selected for this study. Informed consent was obtained by one of the authors (L.F.). They ranged in age from 6 years 11 months to 8 years 7 months. History, physical examination, and clinical laboratory determinations (hemoglobin, white blood count, differential, urinalysis, blood urea nitrogen, bilirubin, and serum glutamic oxalacetic transaminase) were normal, indicating each was free of any metabolic defect which might interfere with ethosuximide metabolism. Each patient then received a single 500-mg dose of ethosuximide syrup following a clear liquid breakfast. This dose was considered appropriate for this age.

Venous blood specimens were obtained prior to medication, then at 1, 3, 7, 24, 48, and 72 hours following medication. One month later the same group of patients received a single 500-mg dose of ethosuximide capsules. Venous blood specimens were obtained according to the same schedule, except that the 72-hour specimen was eliminated.

Chemical Analysis: The ethosuximide

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plasma samples were assayed by gas chromatography using the method of Dill et al.\(^6\) The analyses were carried out on an F & M 402 using a 6 ft. glass column with 5% XE-60 Chromosorb W (AW-DMCS) support 80-100 mesh at 155°C using a flame ionization detector. Twenty micrograms of internal standard (\(\alpha,\alpha\)-dimethyl-\(\beta\)-methylsuccinimidine) in 0.1 ml water were added to a 1 ml plasma sample; then 0.5 ml 2 M phosphate buffer pH 6.5 and 1 ml water were added to the sample in a conical glass stoppered centrifuge tube. The sample was extracted with 9 ml chloroform (Bakers Analyzed Reagent grade). The chloroform phase was then filtered through paper (Schechter & Schuell No. 497), 1 drop of iso-amylacetate (Fishers Certified A719) was added, and the chloroform solution was evaporated to a volume of approximately 24 microliters on a 70°C water bath. The concentration of unknown was determined from a standard curve of ethosuximide concentration versus the ratio of peak areas of the ethosuximide to the internal standard.

The individual plasma levels were analyzed using a simple two-compartment pharmacokinetic model. The utility of pharmacokinetic models in evaluating the quantitative aspects of drug absorption, distribution and elimination from various dose forms has been described.\(^8\),\(^9\),\(^\text{10}\) The two-compartment model assumes that the drug in the gastrointestinal tract is absorbed by a first order process into the blood which is in equilibrium with the tissues. The elimination of drug from the body by excretion or metabolism is also a first order process.

The model can be expressed as a differential equation and integrated to the following equation which describes the concentration of drug in the plasma \((C)\) as a function of time \((t)\) where:

\[
C = \frac{FD}{V} \frac{k_1}{k_2 - k_1} \left[ e^{-k_2(t-t_0)} - e^{-k_1(t-t_0)} \right]
\]

\(k_2 = \) First order elimination rate constant
\(k_1 = \) First order absorption rate constant
\(t_0 = \) Lag time or time following oral ingestion of the drug before the absorption process begins
\(F = \) Fraction of administered dose which is absorbed
\(D = \) Dose
\(V = \) Apparent volume of distribution

Results

The plasma levels following a single dose of ethosuximide syrup or capsules are illustrated in Tables I and II, respectively. The mean levels are graphically displayed in Fig. 1. Both forms of the drug show good absorption one hour after administration; the mean level after syrup dosage is higher than the mean level after capsules. Peak levels occur at approximately three to seven hours after administration with no difference between the two forms. A slow decline occurs with a mean half-life of 33.4 hours for the syrup and 29.7 hours for the capsule material.

The unknown constants \(\left(\frac{FD}{V}, k_1, k_2, to\right)\) were determined by a least squares best fit procedure, which when put into the above equation will describe accurately the individual plasma levels as a function of time. The values of these constants from the above equation are tabulated in Table III. The results indicate that there are no significant differences in average
TABLE I

Plasma Levels (µg/ml) Following a Single 500-mg Dose of Ethosuximide Syrup

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pre Rx</th>
<th>1 Hr.</th>
<th>3 Hrs.</th>
<th>7 Hrs.</th>
<th>24 Hrs.</th>
<th>48 Hrs.</th>
<th>72 Hrs.</th>
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<tbody>
<tr>
<td>#1</td>
<td>0</td>
<td>43.0</td>
<td>41.0</td>
<td>40.0</td>
<td>26.0</td>
<td>11.8</td>
<td>6.0</td>
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<tr>
<td>#2</td>
<td>0</td>
<td>27.2</td>
<td>34.2</td>
<td>39.3</td>
<td>27.6</td>
<td>14.7</td>
<td>7.8</td>
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<td>30.0</td>
<td>27.8</td>
<td>26.5</td>
<td>21.2</td>
<td>13.9</td>
<td>5.4</td>
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<tr>
<td>#4</td>
<td>0</td>
<td>34.8</td>
<td>51.2</td>
<td>54.0</td>
<td>38.2</td>
<td>21.1</td>
<td>12.3</td>
</tr>
<tr>
<td>#5</td>
<td>0</td>
<td>27.1</td>
<td>27.4</td>
<td>24.3</td>
<td>20.0</td>
<td>12.6</td>
<td>8.4</td>
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<tr>
<td>Mean</td>
<td>0</td>
<td>32.4</td>
<td>36.3</td>
<td>36.8</td>
<td>26.6</td>
<td>14.8</td>
<td>8.0</td>
</tr>
<tr>
<td>C. V.</td>
<td>0</td>
<td>.21</td>
<td>.28</td>
<td>.33</td>
<td>.27</td>
<td>.25</td>
<td>.34</td>
</tr>
</tbody>
</table>

TABLE II

Plasma Levels (µg/ml) Following a Single 500-mg Dose of Ethosuximide Capsules

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pre Rx</th>
<th>1 Hr.</th>
<th>3 Hrs.</th>
<th>7 Hrs.</th>
<th>24 Hrs.</th>
<th>48 Hrs.</th>
</tr>
</thead>
<tbody>
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<td>36.8</td>
<td>47.0</td>
<td>46.4</td>
<td>29.6</td>
<td>13.8</td>
</tr>
<tr>
<td>#2</td>
<td>0</td>
<td>25.0</td>
<td>27.6</td>
<td>33.2</td>
<td>23.0</td>
<td>12.3</td>
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<tr>
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<td>0</td>
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<td>34.6</td>
<td>34.6</td>
<td>23.0</td>
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<td>28.2</td>
<td>26.1</td>
<td>20.3</td>
<td>11.6</td>
</tr>
<tr>
<td>Mean</td>
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<td>26.4</td>
<td>37.7</td>
<td>38.1</td>
<td>26.2</td>
<td>13.3</td>
</tr>
<tr>
<td>C. V.</td>
<td>0</td>
<td>.31</td>
<td>.39</td>
<td>.26</td>
<td>.23</td>
<td>.26</td>
</tr>
</tbody>
</table>

values of the lag time, biologic half-life (t½ = 0.693/ \( k_2 \)), and amount of drug absorbed per apparent volume of distribution (\( \frac{FD}{V} \)) between the syrup and capsule forms (\( P<0.05 \)). The mean absorption rate constant (\( k_1 \)) for patients receiving the syrup form is significantly greater than for patients receiving the capsule form (\( P<0.01 \)).

A correlation of dose in mg/kg body weight versus amount of drug absorbed per apparent volume of distribution is shown in Fig. 2. The slope of the straight line equals 0.69 l/kg body weight with the intercept being forced through the origin. Assuming that the fraction of the dose absorbed is constant and approaches 1, or complete absorption, as suggested by the linear relationship, the slope equals the ratio of the apparent volume of distribution of the drug to the body weight in kilograms. The value of 0.69 l/kg (69%) is in good agreement with published values for the ratio of body water per kilogram of body weight in lean subjects. This indicates that the concentration of ethosuximide is uniformly distributed in the various tissues of the body. It also agrees with the data of Dill et al. which indicates that the tissue distribution of ethosuximide in the rat is extremely uniform, including the brain but excepting body fat, which is slightly lower.

The individual biologic half-lives for the same patient receiving either the capsule or syrup forms show good duplication as expected. The mean biologic half-lives for children (33.4 and 29.7 hours) are shorter than the 60 hour half-life reported in adults. Upon comparing the individual patient weights to drug half-lives (t ½) in Table III, there appears
to be a correlation of half-life and body weight, the half-life increasing with weight (correlation coefficient = 0.72).

Discussion

This study provides further information about the metabolism of ethosuximide which should be useful in the clinical management of children with petit mal epilepsy. The syrup form was found to be absorbed faster than the capsule form as would be expected. The mean absorption rate constant for the syrup ($k_1 = 2.52$) from Table III is statistically

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**Fig. 1.** Mean Ethosuximide Plasma Levels Following a Single 500-mg Dose.

**Fig. 2.** Correlation of dose versus fraction of dose absorbed per volume of distribution ($FD/V$ from equation 1). Syrup formulation (○); capsule formulation (×). Slope equals 0.692 liters per kilogram.
significantly greater than for the capsule ($k_1=1.22$). A syrup is readily absorbable whereas a capsule would require somewhat longer to dissolve in the gastrointestinal tract. No difference in the fraction of the dose absorbed, time lag from ingestion to absorption, or biologic half-life is observed, indicating equal total absorption. Therefore, the same dosage schedule could be used for both forms. A patient could be moved from one form to the other without concern about either loss of seizure control or increased toxicity.

The levels do not start to decline until after hour seven with a mean half-life of 33.4 hours for the syrup and 29.7 hours for the capsule form. Therefore, an evening dose should provide adequate seizure control through the early morning hours. Ethosuximide could also be prescribed to children on a flexible schedule compatible with other activities rather than a rigid schedule (e.g., morning, after school, and bedtime). Missing an occasional dose should not precipitate petit mal status. Finally, the half-lives suggest that a single daily dose may provide anticonvulsant activity for a 24-hour period. Further clinical information is necessary to support this.

The slow elimination of ethosuximide should also be considered in the management of a massive overdosage (accidental or intentional). A four- to five-day observation period may be necessary before one could be certain that blood levels have fallen to an insignificant level.

Conclusion

Ethosuximide is widely used for petit mal epilepsy, a disease of onset in childhood. A syrup form was developed for the child unable to swallow capsules. This report compares the two forms by means of a single-dose, cross-over study in children. The results, analyzed by a pharmacokinetic model, indicate the syrup is
absorbed more rapidly than the capsule but both forms demonstrate equivalent total absorption. Peak levels occur at 3 to 7 hours for both forms. The half-life is 33.4 hours for the syrup and 29.7 hours for the capsule as compared to 60 hours in adults. The half-life in children correlates with body weight and the drug is uniformly distributed in the body tissue.

References