Pharmacokinetics of the Diastereoisomers of Leucovorin after Intravenous and Oral Administration to Normal Subjects

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ABSTRACT

After i.v. administration of d,l-, 5-formyltetrahydrofolate (d,l-CHO-THF) CHO-THF was rapidly cleared from the plasma by conversion to 5-methyltetrahydrofolate (5-CH₃-THF) and urinary excretion, whereas d-CHO-THF, which was not metabolized and was slowly excreted in the urine, persisted in plasma at concentrations greatly exceeding those of /-CHO-THF and 5-CH₃-THF. The plasma half-life (ß) of the unnatural (d) isomer was 451 ± 24 (S.E.) min compared to 31.6 ± 1.1 min for the natural (/) isomer, indicating that mechanisms for distribution, metabolism, and excretion are not saturable over the dose range tested.

The urinary clearance of i-CHO-THF or 5-CH₃-THF differed only slightly from creatinine clearance, whereas urinary clearance of d-CHO-THF was only one-fifth creatinine clearance, indicating that d-CHO-THF was extensively reabsorbed. Absorption of d,l-CHO-THF after p.o. administration was stereoselective in that absorption of the /isomer was approximately 5 times that of the d isomer. Thus, p.o. administration resulted in a more favorable ratio of active to inactive folates in plasma. At a dose of 25 mg, absorption approached 100% for l-CHO-THF compared to 20% for d-CHO-THF. However, absorption was saturable, and lower percentages of both compounds were absorbed at doses of 50 and 100 mg.

INTRODUCTION

Leucovorin calcium is the soluble calcium salt of CHO-THF, a chemically stable form of reduced folate which is used to treat or prevent host toxicity due to MTX. It is produced by chemical rather than enzymatic reduction and therefore consists of equal amounts of the diastereoisomers (d,l-CHO-THF). It is generally accepted that only the natural (/) isomer is active as a cofactor (1). Previous studies of the human pharmacokinetics of leucovorin have only considered the disposition of the active isomer. Nixon and Bertino (8) reported that, at 90 min after i.v. infusion of radiolabeled l-CHO-THF, greater than 60% of the radiolabel was present as its active metabolite (5-CH₃-THF), whereas, after p.o. administration, almost all of the serum radioactivity was in the form of 5-CH₃-THF. Mehta et al. (5) administered d,l-CHO-THF and studied the disposition of l-CHO-THF and its metabo-

1 This work was supported by a grant from American Cyanamid Co., Lederle Laboratories, Pearl River, NY.
2 To whom requests for reprints should be addressed.
3 The abbreviations used are: CHO-THF, 5-formyltetrahydrofolate; MTX, methotrexate; 5-CH₃-THF, 5-methyltetrahydrofolate; HPLC, high-pressure liquid chromatography; AUC, area under the concentration curve versus the time curve.

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HPLC separation and quantitation of 5-CH$_3$-THF and d,J-CHO-THF were performed using a modification of the technique described by Montgomery et al. (7). The HPLC system consisted of Waters Associates (Milford, MA) Models 6000 A and M45 solvent delivery system in conjunction with a Model 330 solvent programmer. The column was C$_18$ 5μm spherical (Waters No. 86180 5μg mounted in a Waters Z-module in series with a Whatman precolumn filled with CO:PeII octadecyl silane (Whatman, Inc. Clifton, NJ). Samples were injected using a Waters WISP automatic injector. The column eluate was passed through a variable wavelength UV detector (Laboratory Data Control Corp., Riviera Beach, FL) set for 300 nm. Quantitation was by the external standard method and peak integration using a Waters Data Module.

The primary mobile phase was 30% methanol and 4 mm tetrabutyl ammonium hydroxide in water adjusted to pH 5.5 with acetic acid. The secondary phase was 60% methanol and 4 mm tetrabutyl ammonium hydroxide in water adjusted to pH 5.5. A linear gradient (0 to 100% secondary phase) for 20 min was followed by 5 min of equilibrations with the primary phase. Retention times were approximately 13 min for CHO-THF and 14.5 min for 5-CH$_3$-THF. Recovery of standards added to plasma samples was in excess of 90% for both CHO-THF and 5-CH$_3$-THF. The lower limit of the assay was about 50 ng/ml for 200-μl injection volumes.

Sample Preparation

Acetonitrile (1.5 ml) was added to 1 ml of plasma to precipitate plasma proteins. Following centrifugation, the supernatant was removed and added to a mixture of 5.5 ml of ethyl ether and 1 ml of n-butyl alcohol, the mixture was shaken and centrifuged, and the nonaqueous layer was aspirated and discarded. The ether removed the acetonitrile, and the n-butyl alcohol reduced the sample volume by extracting a portion of the water.

 Urine samples were injected directly or diluted appropriately to give peaks within the linear range of detection.

Assay for l-CHO-THF. The biologically active form of CHO-THF was measured in plasma and urine samples by the disc assay method of Mehta and Hutchinson (6). The test organism was a MTX-resistant strain of Pediococcus cerevisiae obtained from Dr. Bipin M. Mehta, Sloan-Kettering Institute for Cancer Research, Rye, NY.

Assay for d-CHO-THF. Concentrations of d-CHO-THF in plasma and urine were calculated as the differences between the concentration of d,J-CHO-THF measured by HPLC and l-CHO-THF measured by the microbiological assay.

Data Analysis

1. The plasma concentration versus time data for the elimination phases of l-CHO-THF, d-CHO-THF, and 5-CH$_3$-THF were fit to the equation $C = Be^{-\beta t}$ by the method of least-squares to calculate the elimination rate constants ($\beta$s) and $V_s$ for each subject.

2. The AUCs were calculated using observed values at each time point and the trapezoid method. For i.v. infusions, the zero time concentrations of l-CHO-THF and d-CHO-THF were estimated by extrapolating a plot of the concentration versus time data, and the zero time concentration of 5-CH$_3$-THF was taken as zero. For both i.v. and p.o. administration, the area from the final data point to infinity was estimated as $C/\beta$, where $C$ is the concentration at the last data point.

3. Plasma clearance ($C_l$) was calculated using:

$$C_l = \frac{Dose}{AUC}$$

For calculation of $C_{l_p}$ of 5-CH$_3$-THF, the dose used was the dose of l-CHO-THF minus the amount of l-CHO-THF excreted unchanged in the urine.

4. The apparent volume of distribution ($V_d$) was calculated using:

$$V_d = \frac{C_l}{\beta}$$

5. Urinary clearance ($C_i$) was calculated using:

$$C_i = \frac{Amount \ in \ urine \ (0 \ to \ time \ t)}{AUC \ (0 \ to \ time \ t)}$$

6. Apparent availability ($F$) of d-CHO-THF was calculated as:

$$F = \frac{(AUC) \ p.o. \times \beta \ p.o.}{(AUC) \ i.v. \times \beta \ i.v.}$$

Only small amounts of l-CHO-THF were measurable in plasma after p.o. administration of leucovorin. Therefore, the availability of l-CHO-THF was estimated from the AUCs of its active metabolite, 5-CH$_3$-THF, measured after i.v. and p.o. administration of leucovorin. After i.v. administration of d-CHO-THF, approximately 20% (22 ± 1.7) of administered l-CHO-THF was excreted unchanged in the urine, whereas after p.o. administration, only 0.6 ± 0.12% of administered l-CHO-THF was excreted unchanged in the urine. Because that portion of a dose of l-CHO-THF excreted unchanged does not contribute to the 5-CH$_3$-THF AUC, the following formula was used to calculate the availability of l-CHO-THF. Dose equals the amount of l-CHO-THF administered, i.e., 50% of the dose of leucovorin.

$$F = \frac{(AUC) \ p.o. \times \beta \ p.o.}{(AUC) \ i.v. \times \beta \ i.v.} \times \frac{Dose \ p.o. - l-CHO-THF \ in \ urine}{(Dose \ i.v. - l-CHO-THF \ in \ urine)}$$

7. Statistical analysis was by analysis of variance and the Neuman-Keuls test for determinations of significance when more than 2 treatments were being tested (14). For comparison of 2 treatments in the same group, the paired t test was used.

8. For the studies described here, it was necessary to make certain assumptions in order to estimate the pharmacokinetic parameters of 5-CH$_3$-THF and to calculate the availability of l-CHO-THF after p.o. administration of leucovorin. These assumptions were as follows. (a) For calculation of $C_{l_p}$ and $V_d$ of 5-CH$_3$-THF, the dose of 5-CH$_3$-THF was assumed to be the i.v. dose of l-CHO-THF minus the amount of l-CHO-THF excreted unchanged in the urine. (b) For calculations of the availability of l-CHO-THF, it was assumed that presystemic (after p.o. administration) and systemic (after i.v. administration) metabolism of l-CHO-THF follow the same pathways.

Results of studies by Nixon and Bertino (8) who administered radio-labeled l-CHO-THF to human subjects indicate that relatively small errors are likely to occur because of these assumptions. The major metabolite identified in serum after either i.v. or p.o. administration was 5-CH$_3$-THF. Furthermore, products attributable to pathways that did not necessarily involve metabolism to 5-CH$_3$-THF constituted only 6 and 9% of the radioactivity after i.v. and p.o. administration, respectively.

RESULTS

Administration i.v. As shown in Chart 1 and Table 1, the plasma half-life of l-CHO-THF after i.v. administration of leuco-
Table 1

<table>
<thead>
<tr>
<th>Plasma half-lives of l-CHO-THF, d-CHO-THF, and 5-CH3-THF after i.v. leucovorin</th>
<th>Dose of leucovorin (mg)</th>
<th>No. of subjects</th>
<th>Mean plasma half-life (min)</th>
<th>Mean plasma half-life (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>l-CHO-THF</td>
<td>25</td>
<td>6</td>
<td>29.9 ± 1.0b</td>
<td>31.6 ± 1.1</td>
</tr>
<tr>
<td>d-CHO-THF</td>
<td>25</td>
<td>6</td>
<td>32.7 ± 1.9</td>
<td>NSc</td>
</tr>
<tr>
<td>5-CH3-THF</td>
<td>25</td>
<td>6</td>
<td>418 ± 33</td>
<td>451 ± 24</td>
</tr>
</tbody>
</table>

The plasma half-lives and volumes of distribution of l-CHO-THF, d-CHO-THF, or 5-CH3-THF were the same at all i.v. doses from 25 to 100 mg (Tables 1 and 2). The consistency of these pharmacokinetic parameters indicates that the factors responsible for the distribution, excretion, and/or metabolism of these compounds are not saturable over the dose range examined.

In Table 3, the plasma clearance (Clp) and renal clearances (Clr) of the 3 compounds are compared. Clp of l-CHO-THF was about 4-fold more than the Clr, indicating that elimination occurs extensively by nonrenal mechanisms, presumably by metabolism to 5-CH3-THF. Clr of 5-CH3-THF also exceeded its Clr, indicating that metabolism (catabolism and/or anabolism) plays a major role in its disposition. In contrast, the Clr of d-CHO-THF was the same as its Clr, indicating that d-CHO-THF was not metabolized or excreted by nonrenal mechanisms. This indicates that the source of 5-CH3-THF is l-CHO-THF and that d-CHO-THF is not converted to 5-CH3-THF. This is in agreement with our finding in dogs that 5-CH3-THF excreted after administration of d,l-5-CH3-THF had twice the biological activity of d,l-5-CH3-THF, indicating that the 5-CH3-THF is derived only from the biologically active isomer (12).

Examination of Table 4 reveals that Clr of unbound l-CHO-THF was slightly greater than creatinine clearance. This difference is of borderline significance but indicates that the net effect of excretion and reabsorption in the kidney favors excretion. In contrast, d-CHO-THF was cleared at a rate of only one-fifth that of creatinine, and this difference was highly significant. Clr of unbound 5-CH3-THF was not significantly different from creatinine clearance. Thus, the unnatural isomer (d-CHO-THF) was extensively reabsorbed, while the natural isomer (l-CHO-THF) and its active metabolite were cleared at rates approximating creatinine clearance.

Administration p.o. As shown in Table 5, the half-life of d-CHO-THF was the same for all doses. In contrast, the half-life of 5-CH3-THF was significantly increased at the 25-mg dose of
Plasma concentrations were determined after single p.o. doses of 50 and 100 mg or after the final dose of 9 doses of 25 mg every 8 hr.

Table 4
Comparison of renal clearance of unbound drug to creatinine clearance

<table>
<thead>
<tr>
<th>% of unbound drug</th>
<th>CI of unbound drug (ml/min)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-CHO-THF</td>
<td>54</td>
<td>159 ± 12^a</td>
<td>2.32</td>
</tr>
<tr>
<td>d-CHO-THF</td>
<td>54</td>
<td>24 ± 2.5</td>
<td>8.91</td>
</tr>
<tr>
<td>5-CH₃-THF</td>
<td>31</td>
<td>104 ± 9.3</td>
<td>0.99</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td>123 ± 10</td>
<td></td>
</tr>
</tbody>
</table>

^a Protein binding of d-CHO-THF and d-CHO-THF as determined in vitro by ultracentrifugation was 46 ± 6%. Protein binding of 5-CH₃-THF was reported by Spector et al. (11) to be 69% as measured by ultracentrifugation.

^b Clearance of unbound drug was calculated as:

\[ \text{Cl}_\text{u} = \frac{C_l \times 100}{\% \text{ of unbound}} \]

^c Probability that Cl, of unbound drug is not different when compared to creatinine clearance.

^d Mean ± S.E.

^e NS, not significant.

Table 5
Plasma half-lives of d-CHO-THF and 5-CH₃-THF after p.o. administration of leucovorin

<table>
<thead>
<tr>
<th>Dose of leucovorin (mg)</th>
<th>No. of subjects</th>
<th>Mean plasma half-life (min)</th>
<th>Analysis of variance, dose effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-CHO-THF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>6</td>
<td>481 ± 51^a</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>11</td>
<td>480 ± 37</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>10</td>
<td>369 ± 37</td>
<td></td>
</tr>
<tr>
<td>5-CH₃-THF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>6</td>
<td>310 ± 25</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>11</td>
<td>190 ± 22</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>10</td>
<td>178 ± 14</td>
<td></td>
</tr>
</tbody>
</table>

^a Mean ± S.E.

^b NS, not significant.

Only the half-life of 25-mg dose was significantly different from the half-life obtained after i.v. administration.

leucovorin. The increase in the half-life of 5-CH₃-THF apparently occurred during repeated administration of leucovorin. As shown in Chart 2, 5-CH₃-THF had not achieved steady state at 48 hr (9–12 half-lives). However, the plasma levels at 64 and 72 hr were the same, thus indicating that steady state was achieved by 64 hr.

Plasma clearance of 5-CH₃-THF was estimated using the \( V_d \) obtained from the i.v. experiments for each subject and \( \beta \) from the 25-mg p.o. experiment. The assumption was made that \( V_d \) did not change during repeated administration of leucovorin. Clₚ was calculated from the AUCs during the final dosing interval and the cumulative amount of 5-CH₃-THF excreted during the 8-hr period. The values obtained for Clₚ and Cl, were 61.8 ± 8.6 and 42 ± 5.4 ml/min, respectively. After i.v. administration of leucovorin, Clₚ and Cl, of 5-CH₃ were 77.5 ± 9.0 and 32.2 ± 2.0, respectively, as shown in Table 3. Thus, after single i.v. doses of leucovorin, nonrenal mechanisms accounted for 58% of the plasma clearance of 5-CH₃-THF, whereas, after repeated p.o. administration of leucovorin, nonrenal mechanisms accounted for only 32% of the plasma clearance. This comparison suggests that the increase in the plasma half-life of 5-CH₃-THF during repeated p.o. administration occurred due to a decrease in nonrenal disposition of the compound.

Table 6 shows the AUCs for d-CHO-THF, d-CHO-THF, and 5-CH₃-THF after i.v. and p.o. administration of leucovorin. After i.v. administration, the AUCs for all 3 compounds increased in proportion to increasing dose, whereas after p.o. administration there was considerable deviation from linearity. The failure of p.o. AUCs to increase in proportion to dose is indicative of saturation of the absorption mechanisms for d-CHO-THF and l-CHO-THF. Because the plasma half-life of 5-CH₃-THF was different following p.o. administration of leucovorin (Table 5), it was not possible to estimate p.o. availability from the ratios of the p.o. to i.v. AUCs. Therefore, the AUCs for both p.o. and i.v. administration were corrected for the change in half-life as described in "Materials and Methods." This calculation not only corrects for changes in half-life associated with different experimental conditions, but also reduces intrasubject variability associated with change in biological half-life (2). In one subject at the 50-mg dose and 2 subjects at the 100-mg dose, absorption appeared to be biphasic so that terminal half-lives could not be reliably estimated from the p.o. experiments. Although the AUCs for d-CHO-THF and 5-CH₃-THF were within the range of those observed for the other subjects, these data were not included in calculating the p.o. availability of leucovorin.

The AUCs of 5-CH₃-THF reported by Lasseter et al. (4) for p.o. administration of 20 mg of leucovorin (107 ± 4) are comparable to the AUCs reported here for the single p.o. dose of 50 mg (240 ± 29) when adjusted for dose and apparent availability. This is of particular significance because the above group used a microbiological assay for 5-CH₃-THF, whereas we used HPLC assay.

The AUCs for l-CHO-THF after p.o. administration of leucovorin indicate that only small amounts of l-CHO-THF escape...
J. A. Straw et al.

Table 7

<table>
<thead>
<tr>
<th>Dose of leucovorin (mg)</th>
<th>No. of subjects</th>
<th>Mean apparent availability</th>
<th>Analysis of variance (mg per p.p. x ß p.p.)</th>
<th>ns*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-CHO-THF*</td>
<td>25</td>
<td>6</td>
<td>0.97 ± 0.16</td>
<td>25:50</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>11</td>
<td>0.75 ± 0.10</td>
<td>25:100</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>10</td>
<td>0.37 ± 0.04</td>
<td>50:100</td>
</tr>
<tr>
<td>d-CHO-THF*</td>
<td>25</td>
<td>6</td>
<td>0.19 ± 0.01</td>
<td>25:50</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>11</td>
<td>0.20 ± 0.03</td>
<td>25:100</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>10</td>
<td>0.067 ± 0.006</td>
<td>50:100</td>
</tr>
</tbody>
</table>

* Availability of I-CHO-THF was calculated from the AUC of 5-CH3-THF as described in "Materials and Methods."

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<td>10</td>
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<td></td>
<td>100</td>
<td>10</td>
<td>0.067 ± 0.006</td>
<td>50:100</td>
</tr>
</tbody>
</table>

**Table 7**

Apparent availability of I-CHO-THF and d-CHO-THF after p.o. administration of leucovorin

Discussion

The data presented for the i.v. administration of leucovorin substantiate previous reports that I-CHO-THF is rapidly cleared from the plasma and that its disappearance is accompanied by the appearance of 5-CH3-THF (8). We further show that this behavior is constant over a dose range of 25 to 100 mg. The much longer half-life observed for d-CHO-THF is similar to what we reported previously for dogs (12) and is in agreement with the observation of Rothenberg et al. (9).

The apparent volumes of distribution of I-CHO-THF, d-CHO-THF, and 5-CH3-THF were 17.5, 7.9, and 22.9 liters, respectively (Table 2). These data suggest that the unnatural isomer (d-CHO-THF) may not distribute as extensively as the natural isomer. This conclusion is consistent with the reports that I-CHO-THF is selectively transported in preference to d-CHO-THF in murine tumor cells (10). However, one must use caution in interpreting Vd data. These values are dynamic pharmacokinetic VdS and not steady-state VdS which are more representative of physiological volumes of distribution. The volumes of distribution of d- and I-CHO-THF were not different when measured in dogs during constant i.v. infusion (12). However, we observed a species difference in the renal transport of d-CH1-OHF (see below), and other differences may exist in transport in other cells.

Studies of the renal handling of the compounds revealed some surprising results. After i.v. administration of leucovorin, unbound 5-CH3-THF was excreted at a rate approximating creatinine clearance, and unbound I-CHO-THF was excreted at a rate slightly greater than creatinine clearance. In contrast, d-CHO-THF was excreted at a rate only one-fifth of creatinine clearance, which indicates that the unnatural isomer is extensively reabsorbed. The finding that plasma clearance of d-CHO-THF was the same as renal clearance showed that d-CHO-THF was not metabolized. Therefore, the prolonged half-life of d-CHO-THF may be attributed to lack of metabolism in conjunction with limited renal excretion due to reabsorption. In consideration of the size and hydrophilicity of the CH1-OHF molecule, it is highly unlikely that d-CHO-THF is passively reabsorbed. Furthermore, folates are presumed to cross biological membrane only by active transport (1), and folic acid is reabsorbed in the kidney by a saturable, carrier-mediated system (3). Therefore, we conclude that d-CH1-OHF is actively reabsorbed in the human kidney. This is in contrast to our finding in dogs that the renal elimination of both d-CHO-THF and I-CHO-THF approximated inulin clearance (12). Furthermore, the fact that CI of d-CHO-THF was the same at all dose levels suggests that the transport system of d-CHO-THF has a relatively high capacity which was not saturated even after an i.v. dose of 100 mg of leucovorin.

The p.o. absorption studies indicate that both d-CHO-THF and I-CHO-THF are absorbed by a saturable process and that the system is stereoselective. Absorption of I-CHO-THF was 4- to 5-fold greater than absorption of d-CHO-THF at all doses tested. Furthermore, repeated p.o. administration of leucovorin resulted in approximately equal plasma levels of 5-CH3-THF and d-CHO-THF (Chart 2), whereas, after i.v. administration of leucovorin, the concentration of the unnatural isomer greatly exceeded the concentration of the biologically active isomer (Fig. 1). The consequences of the presence of large amounts of the inactive isomer are unknown. However, d-CHO-THF is approximately one-20th as effective as I-CHO-THF in competing for uptake of MTX in murine tumor cells and only one-100th as effective as the l-isomer in preventing inhibition of growth of L1210 by MTX (10). Repeated parenteral administration would result in selective accumulation of the inactive isomer which may compete with the active isomer. It is thus possible that repeated parenteral administration of leucovorin may be less effective than p.o. administration in rescuing from MTX toxicity. These findings argue that p.o. administration of leucovorin may be preferred to parenteral administration in the treatment and/or prevention of toxicity associated with MTX treatment.

Absorption p.o. of both isomers was saturated at a dose of leucovorin of 50 mg. The fact that absorption was essentially
complete at 2 hr after ingestion suggests that higher plasma levels of 5-CH$_3$-THF could best be achieved by frequent administration of relatively small doses rather than increasing the size of individual doses.

The observation that the plasma half-life of 5-CH$_3$-THF increased during repeated administration of leucovorin should be interpreted with caution. These studies were conducted in normal subjects, and it is likely that the increase in half-life occurred due to less active anabolic pathways for 5-CH$_3$-THF as body stores of reduced folates were saturated. In patients treated with MTX, the anabolic pathway would be expected to be maximally active due to inhibition of dihydrofolate reductase and depletion of stores of reduced folates. Consequently, the half-life of 5-CH$_3$-THF would be expected to be equal to or perhaps even shorter than observed after single doses in normal subjects. Studies in MTX-treated patients are indicated to answer this question.

REFERENCES

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