Short Communication

Application of a First-Pass Effect Model to Characterize the Pharmacokinetic Disposition of Venlafaxine after Oral Administration to Human Subjects

ABSTRACT:

Venlafaxine (VEN), a drug used in the treatment of depression, undergoes significant first-pass metabolism after oral dosing to O-desmethylenvenlafaxine (ODV), a metabolite with comparable therapeutic activity to that of parent drug. The pharmacokinetic disposition of VEN was characterized using a "first-pass" model that incorporates a presystemic compartment (liver) to account for the first-pass metabolism of VEN to ODV. A series of differential equations were simultaneously fitted to plasma concentrations of parent and metabolite. A good fit of the model to observed data was demonstrated, generating estimates for the following parameters: \( k_e \) (1.31 ± 0.009 hr\(^{-1}\)), \( V_{VEN} \) (252 ± 87.6 liters), \( CL_{int} \) (65.8 ± 39.7 liters/hr), \( R_L \) (liver:plasma partition coefficient, 29.6 ± 18.3), \( V_{ODV} \) (181 ± 84.1 liters), and \( CL_{ODV} \) (23.5 ± 12.5 liters/hr). Parameter estimates correlated closely with those obtained through noncompartmental methods. These results indicate that the time-course disposition of a compound undergoing first-pass hepatic metabolism after oral dosing can be successfully modeled.

The consequences of presystemic metabolism on the bioavailability of orally administered compounds are well-established. In this regard, there are several pharmacokinetic models of presystemic metabolism reported in the literature. Gibaldi and Feldman introduced a three-compartment model to describe the first-pass effect (1). Colburn and Gibaldi (2) later proposed a pharmacokinetic perfusion model to describe the disposition of drugs that are susceptible to both first-pass hepatic and gut wall metabolism. Combined with subsequent papers—including those by Rowland (3, 4), Wilkinson and Shand (5), and Pang and Rowland (6)—these investigators have provided the theoretical basis on which oral bioavailability is mathematically described. However, pharmacokinetic models that incorporate the effect of presystemic hepatic metabolism have seldom been tested experimentally in terms of describing the time-course disposition of drugs after oral dosing.

VEN is a phenylethylamine derivative used clinically in the management of depression (7, 8). After oral administration, VEN undergoes extensive first-pass metabolism by the liver to two minor, less active metabolites (N-desmethylenvenlafaxine and N,N-didesmethylenvenlafaxine) and a major metabolite (ODV). ODV is a compound with antidepressant activity comparable with the parent drug (9).

In this communication, we demonstrate that first-pass metabolism after oral dosing can be successfully modeled. Plasma concentration-time data for both VEN and ODV were simultaneously fitted using a pharmacokinetic model that accounts for first-pass hepatic metabolism of VEN to ODV.

Materials and Methods. VEN, ODV, and IS (WY-45,818; IS) were supplied by Wyeth-Ayerst Research (Philadelphia, PA). Aceto-nitrile was obtained from Mallinckrodt Chemicals (Orlando, FL). Diethyl ether and sodium borate were purchased from Sigma Chemical Company (St. Louis, MO).

Study Design. The study was conducted in accordance with the provisions of the Declaration of Helsinki and its amendments. Approval from both the Long Island University Research Approvals Committee and Brookdale University Hospital and Medical Center’s Research and Clinical Projects Committee was obtained. Subjects gave written informed consent to participate in the study. Five healthy male volunteers (ages 23–38) provided a medical history and were given a physical examination, including blood chemistry and hemato logical tests before initiation of the study.

After a 7-hr overnight fast, subjects were given a 1.5 mg/kg dose of VEN tablets, rounded to the nearest 18.75 mg, with 6 oz of water. Plasma samples were collected at time 0 (before drug administration) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, and 36 hr post dose. Samples were stored at −20°C before analysis.

Drug Analysis. VEN and ODV were quantitated in plasma samples by HPLC through slight modification of a previously reported assay (10). To 1 ml of plasma sample, 50 μl of IS (0.15 mg/ml), 300 μl of saturated sodium borate solution (pH 9), and 5 ml of diethyl ether were added. The mixture was vortexed and centrifuged at 2,500 rpm for 10 min. Three hundred microliters of 0.01 N HCl was added to the organic phase, and the mixture was vortexed and centrifuged at 2,500 rpm for 10 min. The organic phase was then discarded, and the resultant solution was aerated under mild heat to remove any dissolved ether. One hundred microliters of the extract was injected into the HPLC system. The HPLC consisted of a Thermo Separation P1000 Solvent Delivery Pump, a UV1000 Ultraviolet Detector, and a personal computer with PC1000 Integration Software (Thermo Separation Products, Riviera Beach, FL). Separation was accomplished with a Supelcosil LC8-DB deactivated base column (Supelco, Bellefonte, PA) using a mobile phase consisting of 0.1 M ammonium phosphate buffer (pH 4.4) and acetonitrile (25.5%). Mobile phase was introduced at a flow rate of 1 ml/min. The detection wavelength was 229 nm. VEN and ODV concentrations were calculated using a peak
A schematic illustration of the proposed model is provided in fig. 1.

Data Analysis. A pharmacokinetic model was simultaneously fitted to both VEN and ODV plasma concentrations using the least squares regression program PCNONLIN (Statistical Consultants, Apex, NC). A schematic illustration of the proposed model is provided in fig. 1.

There are several underlying assumptions to the model:

1. VEN is 100% metabolized by the liver. Although previous investigations found that ~5% of VEN is excreted unchanged by the kidney (11), introduction of a renal clearance parameter into the proposed model did not significantly reduce the weighted sums of squares.

2. VEN is 55% metabolized to ODV (11, 12).

3. Hepatic blood flow is 90 liters/hr, and liver volume is 1.5 liters (13).

4. The blood-plasma partition coefficient for VEN and ODV is 1. After administration of 14C-venlafaxine, the ratio of total radioactivity (venlafaxine plus metabolites) ranged from 0.9 to 1.1. Consequently, it was assumed that plasma and blood concentrations were similar for both VEN and ODV.

5. One hundred percent of the administered dose is absorbed across the gastrointestinal tract. A previous study found that 92% of an oral VEN dose is absorbed (11). Therefore, it seems that this assumption should not significantly affect the modeling results.

6. All clearance processes are first order. Whereas earlier studies found that, after administration of multiple doses, the metabolic pathway for VEN is saturable (14, 15), VEN and ODV have exhibited linear pharmacokinetics over a daily dosage range of 75–450 mg of parent drug (data on file, Wyeth-Ayerst Research). Because subjects in the investigation received a single 1.5 mg/kg dose of drug (range: 93.75–150 mg), linear pharmacokinetics was assumed.

The model consisted of four differential equations that were simulta-
metabolize drug in the absence of flow restrictions, was 65.8 ± 39.7 liters/hr. Extraction ratio was estimated to be 0.40 ± 0.12. Although this value is not indicative of a high extraction ratio compound \((E > 0.70)\), there is evidence of extensive hepatic uptake of VEN. Specifically, the liver:plasma partition coefficient \((R_L)\) was 29.6 ± 18.3, suggesting that this compound is efficiently sequestered and ultimately cleared by the liver.

Plasma concentration-time profiles of VEN and ODV are shown in figs. 2 and 3, respectively. Presented in these profiles are the mean observed plasma concentrations of the individual subjects, along with concentrations predicted by the proposed first-pass effect model. These predicted concentrations were obtained by model simulation, using the mean model parameter estimates listed in table 1. The model yield a good fit to experimental data. Although a good correlation between observed and predicted concentrations was achieved with for both compounds, observed ODV concentrations after 12 hr declined much slower than those predicted by the first-pass model. Inclusion of a "tissue" compartment for ODV was able to describe better the terminal phase of the concentration-time curve, but this more complex model (eight parameters) neither improved the fit nor resulted in a significant reduction in weighted sums of squares over the present model (unpublished data).

Table 2 contains mean values of parameters determined by noncompartmental analysis. \(CL_{\text{int}}\) was 59.6 ± 26.5 liters/hr, which is similar to the model estimate of 65.8 ± 39.7 liters/hr. Although a disparity exists between estimates of \(V_{\text{ven}}\), correction of the noncompartmental estimate (459 ± 192 liters) for a apparent bioavailability of 60% \((F = 1 - E)\) makes this estimate comparable with the model generated value of 252 ± 87.6 liters. Likewise, noncompartmental estimates of \(CL_{\text{ODV}}\) and \(V_{\text{ODV}}\) must be corrected for \(f_m\) before a useful comparison can be made between the two methods (assuming that 100% of the administered dose is absorbed, a correction for \(F\) is not necessary). Assuming \(f_m\) to be 0.55, adjustment of the noncompartmental estimate of 309 ± 60 liters correlates closely with the value obtained with the first-pass model (181 ± 84.1). The corrected estimate of \(CL_{\text{int}}\), however, is lower than the model estimate of 23.5 ± 12.5 liters/hr. This divergence may possibly be attributed to the previously discussed assignment of "one-compartment pharmacokinetics" to describe ODV disposition. Despite this limitation, a good correlation was observed between both methods of analysis.

In addition to the previously stated assumptions of the model was that the liver was solely responsible for the presystemic metabolism of VEN. In vitro studies have identified two CYP isozymes involved in VEN metabolism: CYP2D6 and CYP3A4 (12). The majority of VEN degradation proceeds via CYP2D6, including the O-demethylation of VEN to form ODV. N-demethylation of VEN involves the CYP3A4 enzyme, a minor pathway for this compound. Although intestinal metabolism has been attributed to the CYP3A enzyme system (19), it was considered of little significance in the present study. Thus, a presystemic intestinal compartment was not incorporated into the model, thereby attributing all first-pass loss of drug to hepatic degradation.

In summary, the disposition of VEN and its active metabolite ODV

TABLE 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
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</thead>
<tbody>
<tr>
<td>(CL_{\text{int}}) (liters/hr)(^a)</td>
<td>65.8 ± 39.7</td>
</tr>
<tr>
<td>(R_L)</td>
<td>29.6 ± 18.3</td>
</tr>
<tr>
<td>(V_{\text{ven}}) (liters)</td>
<td>252 ± 87.6</td>
</tr>
<tr>
<td>(CL_{\text{ODV}}) (liters/hr)</td>
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</tr>
<tr>
<td>(V_{\text{ODV}}) (liters)</td>
<td>181 ± 84.1</td>
</tr>
<tr>
<td>(k_P) (hr(^{-1}))</td>
<td>1.31 ± 0.009</td>
</tr>
<tr>
<td>(E)</td>
<td>0.40 ± 0.13</td>
</tr>
</tbody>
</table>

See text for abbreviations.

\(^a\) \(CL_{\text{int}}\): Intrinsic hepatic clearance of VEN.

\(^b\) \(R_L\): Liver:plasma partition coefficient for VEN.

\(^c\) \(E\): Hepatic extraction ratio = \(CL_{\text{int}}/(Q + CL_{\text{int}})\).
acknowledgments. We thank Wyeth-Ayerst Research for supplying the compounds used in this study. In addition, we acknowledge Dr. Steven Troy and Dr. Soong Chiang for providing helpful insight regarding VEN disposition, which was useful in the preparation of this manuscript.

TABLE 2

Mean (SD) pharmacokinetic parameters for VEN and ODV using noncompartmental analysis after oral administration of a single dose (1.5 mg/kg) of VEN to human subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VEN</th>
<th>ODV</th>
</tr>
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<tbody>
<tr>
<td>AUC (ng-hr/ml)</td>
<td>2370 ± 734</td>
<td>3753 ± 700</td>
</tr>
<tr>
<td>k (hr⁻¹)</td>
<td>0.127 ± 0.033</td>
<td>0.064 ± 0.013</td>
</tr>
<tr>
<td>CL (liters/hr)</td>
<td>59.6 ± 26.5</td>
<td>19.2 ± 2.7</td>
</tr>
<tr>
<td>V (liters)</td>
<td>459 ± 92</td>
<td>309 ± 60</td>
</tr>
</tbody>
</table>

See text for abbreviations.

a AUC(0 – ∞) calculated using the trapezoidal rule.

b CLint = D/AUCven.

c CLfint = D/AUCobs.
d VIF = CLvial/kven.
e VIF = CLobs/kobs.

after oral administration was successfully characterized using a pharmacokinetic model that accounts for the presystemic hepatic metabolism of drug. Parameter estimates correlated closely with those obtained through noncompartmental methods. The results demonstrate that first-pass metabolism can be successfully modeled after oral drug administration. In consideration of the model assumptions, however, it should be noted that the ability to apply this model depends on the particular characteristics of a specific drug. Although the model may not be applied universally to all compounds that undergo first-pass metabolism, it can potentially be adapted for other compounds whose metabolites can be accurately measured. This communication validates the use of a first-pass effect model as a pharmacokinetic tool for exploring changes in presystemic metabolism and drug disposition secondary to disease or drug–drug or drug–food interactions in human subjects.

References


