Bioavailability and Related Pharmacokinetics in Man of Orally Administered L-5-Hydroxytryptophan in Steady State

By
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Abstract: The bioavailability of orally administered L-5-hydroxytryptophan in steady state was investigated at four increasing multiple dose levels in five patients suffering from various myoclonic disorders. An L-aromatic amino acid decarboxylase inhibitor was co-administered in all the experiments. The disposition pharmacokinetics of the amino acid had been established in the same patients in preceding intravenous single dose experiments. The finding of a direct proportionality between the size of the oral dose level of L-5-hydroxytryptophan and the corresponding areas under the plasma concentration curves within a dosage interval at steady state strongly indicates dose independent, linear pharmacokinetics of the compound. The systemic availability of L-5-hydroxytryptophan exhibited an interindividual range of 47-84%, with a mean value of 69.2% ± 4.7 S.E.M. The absorption took place at a rather slow rate as judged from times of 1.8 to 3.3 hours elapsing from administration of the compound until occurrence of the maximum measured plasma concentrations. Transitory nausea and vomiting were only recognized in few instances during the gradual building up of increasing steady state levels of L-5-hydroxytryptophan in the patients, and the importance of a slow initiation of therapeutical treatment with the amino acid is emphasized.


The aromatic amino acid L-5-hydroxytryptophan (5-HTP) is used orally for treatment of different kinds of involuntary movement disorders (Van Woert & Chung Hwang 1978). Animal experiments indicate an active transport mechanism involved in the intestinal absorption of 5-HTP (Shindo et al. 1977). L-aromatic amino acid decarboxylase degradates 5-HTP to serotonin. The enzyme is widely distributed in the organism. It appears with high activity in the gut wall and liver and affects the plasma levels of 5-HTP obtained after oral administration of the amino acid. Magnussen & Engbæk (1978) observed in patients that the presence of an extracerebral decarboxylase inhibitor caused about 10 times increase in the plasma concentration levels of 5-HTP obtained after a single oral dose, probably by reducing the enzymatic barrier for the uptake of 5-HTP into the circulating blood. An occasional poor accumulation of 5-HTP, as visualized by the blood concentration level in relation to long-term co-administration of 5-HTP and a decarboxylase inhibitor, has, however, been observed (Magnussen & Olivarius 1978).

Gastrointestinal adverse reactions limit the use of intravenously administered 5-HTP for prediction of the therapeutic response to the amino acid (Magnussen & Nielsen-Kudsk 1979). During initiation of oral 5-HTP treatment the frequency of nausea (58%) and vomiting (30%) has been found rather high (Van Woert & Chung Hwang 1978).

The aim of the present study has been to investigate the systemic availability and related pharmacokinetics of 5-HTP co-administered orally with an extracerebral decarboxylase inhibitor in a
drug regimen including slowly increased 5-HTP dosage levels. The relationship between dose level and gastrointestinal adverse reactions has been observed without any concomitant administration of antiemetic drugs.

Materials and Methods

The investigation was carried out in five patients (cfr. table 1) suffering from various types of myoclonic disorders, in three cases of hypoxic and in the others of unclassified origin. Informed consent was obtained from all patients. Laboratory tests for blood, liver, and kidney function were within normal ranges.

Intravenous administration of 5-HTP. The patients were pretreated for one week with the extracerebral amino acid decarboxylase inhibitor, carbidopa (MSD), 150 mg per day in three divided oral doses. On the last day a single dose of 0.908 pmol (0.2 mg) per kg body weight of 5-HTP (from Ajinomoto Co., Inc., Tokyo) dissolved in saline (91 pmol per 50 ml) was administered at 9 a.m. as a 20 min. lasting intravenous infusion. At the same time 50 mg carbidopa was ingested orally. At various times afterwards blood was drawn from a forearm vein into tubes containing EDTA. Plasma was separated within 30 min. and stored at −70° until analyzed. The concentration of 5-HTP in plasma was determined by high performance liquid chromatography with fluorometric detection after phthalaldehye reaction as described previously (Engbæk & Magnussen 1978). The pharmacokinetic analyses of the plasma concentration curves obtained after the single dose intravenous infusions have been described in details in a previous report (Magnussen & Nielsen-Kudsk 1979).

Oral administration of 5-HTP. To all patients were orally co-administered 50 mg carbidopa and 50 mg 5-HTP at 8 a.m., 4 p.m., and 12 p.m. for one week. On the last day venous blood samples were obtained as described above from 2 p.m. to 10 p.m. The experiments were repeated with increasing doses of 100, 150, and 200 mg 5-HTP, and in patients no. 1, 2, and 4 the dosage level of 200 mg 5-HTP was combined with the double dose of carbidopa (300 mg per day) in a succeeding study. The areas under the plasma concentration curves, AUC_t, corresponding to the steady state dosage intervals related to the different dosage level regimens were determined by numerical integration using the trapezoidal rule.

Results

The mean plasma concentration values of 5-HTP obtained from all subjects after individual administration of a short-lasting intravenous infusion of a single dose are shown in fig. 1 together with a computer generated function of best fit based upon a pharmacokinetic analysis of the biexponential plasma concentration profile constituted by the composite mean concentration/time data. The function is representative of the pharmacokinetics of an open two compartment system with elimination from the central compartment. The deter-

Table 1.

Steady state bioavailability parameters for L-5-hydroxytryptophan determined in 5 patients receiving the compound orally at four increasing dose levels (50, 100, 150 or 200 mg every 8 hour). The systemic availability was calculated as A (%) = 100 (A_u, AUC_t,)/A_o, AUC_t, where A_U is the area under the plasma concentration curve obtained during and after a short-lasting intravenous infusion of 0.908 pmol (0.2 mg) of L-5-hydroxytryptophan per kg of body weight (BW). AUC_t, is the area under the plasma concentration curve corresponding to a dosage interval at steady state. T_max, mean is the mean time elapsing within a steady state dosage interval until occurrence of the maximum measured plasma concentration of the compound.

<table>
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<tr>
<th>Pharmacokinetic parameter</th>
<th>Sex</th>
<th>Subject no.</th>
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<th>Sex</th>
<th>Subject no.</th>
<th>Sex</th>
<th>Subject no.</th>
<th>Mean ± S.E.M.</th>
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<tbody>
<tr>
<td>Sex</td>
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<tr>
<td>Age (years)</td>
<td>52</td>
<td>42</td>
<td>45</td>
<td>19</td>
<td>23</td>
<td>66.6 ± 6.7</td>
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<td>BW (kg)</td>
<td>56</td>
<td>79</td>
<td>86</td>
<td>60</td>
<td>52</td>
<td>8.765 ± 0.609</td>
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<tr>
<td>AUC_t, (μmol l⁻¹ hr)</td>
<td>8.472</td>
<td>7.211</td>
<td>10.965</td>
<td>8.546</td>
<td>8.632</td>
<td>8.765 ± 0.609</td>
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<tr>
<td>A, 50 mg (%)</td>
<td>121.5</td>
<td>74.6</td>
<td>79.2</td>
<td>44.6</td>
<td>67.3</td>
<td>77.4 ± 12.5</td>
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<td>A, 100 mg (%)</td>
<td>48.9</td>
<td>89.0</td>
<td>84.7</td>
<td>54.3</td>
<td>64.8</td>
<td>68.3 ± 8.0</td>
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<td>A, 150 mg (%)</td>
<td>61.7</td>
<td>75.9</td>
<td>60.6</td>
<td>51.2</td>
<td>62.9</td>
<td>62.5 ± 4.0</td>
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<td>A, 200 mg (%)</td>
<td>64.4</td>
<td>98.0</td>
<td>96.6</td>
<td>36.8</td>
<td>47.1</td>
<td>68.6 ± 12.5</td>
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<tr>
<td>A, mean (%)</td>
<td>74.1</td>
<td>84.4</td>
<td>80.3</td>
<td>46.7</td>
<td>60.5</td>
<td>69.2 ± 4.7</td>
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<tr>
<td>± S.E.M.</td>
<td>16.2</td>
<td>5.6</td>
<td>7.5</td>
<td>3.9</td>
<td>4.6</td>
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<td>t_max, mean (hr)</td>
<td>3.25</td>
<td>1.80</td>
<td>2.00</td>
<td>2.25</td>
<td>1.80</td>
<td>2.17 ± 0.20 (n=23)</td>
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<td>± S.E.M.</td>
<td>0.48</td>
<td>0.37</td>
<td>0.45</td>
<td>0.48</td>
<td>0.20</td>
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</table>
Fig. 1. The mean plasma concentrations of L-5-hydroxytryptophan obtained after administration of short-lasting (20 min.) intravenous infusions of single doses (a) of 0.908 μmol (0.2 mg) per kg of body weight in 5 patients are shown as black dots as a function of time in a semilogarithmic plot. The heavy drawn curve is the computer generated function of best fit. The residual concentration values defining the distributory α-phase are shown as black triangles. The coefficients of variation of the mean plasma concentrations are all less than 25%. Determined pharmacokinetic parameters are $V_c$: 0.325 l kg⁻¹, $V_p$: 0.432 l kg⁻¹, $k_{10}$: 0.321 hr⁻¹, $k_{12}$: 0.719 hr⁻¹ and $k_{21}$: 0.541 hr⁻¹.

The 5-HTP plasma concentrations obtained in patient no. 2 following oral administration at the four different 5-HTP dosage regimens and the two carbidopa levels are shown in fig. 2. The 50 mg dose produced obviously only a very small increase in the plasma concentration of 5-HTP with regard to the mean of the dose interval limit concentrations. The mean $AUC_{Tpo}$ values obtained are plotted in fig. 3, which further shows the linear correlation between the increasing doses and the corresponding $AUC_{Tpo}$-values. The regression line is described by the equation $y = 5.995 x + 1.920$, where y and x equals $AUC_{Tpo}$ and the dose, respectively. The correlation coefficient was $r = 0.9972$ ($P<0.01$). The standard error of the y-axis intercept ($s_a$) was calculated to 2.249, while the 95% confidence interval at the intercept determined as $y_o \pm s_a (t_{0.05, n-2})$ figured $1.92 \pm 9.68$. This interval includes zero, which implies, according to Wagner (1975), that the regression line may be forced through the (0,0) point. The slope of this new line is calculated as $\frac{\Sigma xy}{\Sigma x^2}$ with a standard error of $(s_y^2/\Sigma x^2)^{1/2}$, and is in the actual case $6.175 \pm 0.150$ S.E.M.

The finding of direct proportionality between the size of the administered dose and the corresponding area under the concentration curve strongly indicates dose independent, linear pharmacokinetics of 5-HTP. The systemic availability (A) of the drug, defined as the fraction or percentage of the dose reaching the systemic circulation, may thus be determined on basis of the ratio between the areas under the concentration curves obtained in the intravenous single dose experiments and those
Fig. 2. The steady-state time courses of L-5-hydroxytryptophan concentrations in plasma in patient no. 2 after oral administration of the following single doses of the compound: 50 mg (■—■), 100 mg (□—□), 150 mg (○—○) and 200 mg (●—●), in these cases together with 50 mg carbidopa, and 200 mg (△—△) combined with 100 mg carbidopa. The increasing dose levels were sustained for one week before the plasma concentration determinations corresponding to a single dose interval were carried out.

determined in the peroral multiple dose, steady state experiments according to the equation 
\[
\text{Area Ratio (A) = } \frac{100 \times (\text{oral AUC}_{\text{per}})}{(\text{intravenous dose})}
\]
where \( \text{oral AUC}_{\text{per}} \) is the oral and \( \text{intravenous dose} \), the mean area of 8.765 

\( \mu \text{mol} \cdot \text{hr} \) corresponding to an intravenous dose of 0.908 \( \mu \text{mol kg}^{-1} \), the calculated systemic availability of 5-HTP in the preparation used amounts to 64.0% ± 1.6 S.E.M. Calculations based upon the individual availabilities determined in each of the peroral experiments yields a slightly higher mean value of 69.2% ± 4.7 S.E.M. The systemic availabilities determined in each patient are given in table 1.

Fig. 3. Mean values ± S.E.M. of measured areas under L-5-hydroxytryptophan plasma concentration curves plotted as a function of increasing mean doses ± S.E.M. of the orally administered compound in four experiments in each of five patients. The equation of the determined regression line is: \( y = 5.995x + 1.920 \) and the related correlation coefficient \( r \) equals 0.9972 (\( P < 0.01 \)).

Fig. 4. Scatter diagram showing the dose interval areas under the plasma concentration curves (AUC_{Tirth}-values) at increasing dosage levels at steady state correlated to the means of the minimum plasma concentrations determined at the beginning and at the end of the dose interval. The regression line equation is: \( y = 10.813x + 9.886 \) \( (r = 0.9249, \ P < 0.01) \). The plotted AUC_{Tirth}-values are marked corresponding to the five patients: no. 1 (▲), no. 2 (○), no. 3 (●), no. 4 (□) and no. 5 (■).
BIOAVAILABILITY OF L-5-HYDROXYTRYPTOPHAN IN MAN

four dose levels varied from about 1.8-3.3 hours as shown in table 1.

Doubling of the carbidopa dose did not significantly increase the systemic availability of 5-HTP. Only three of the patients participated in this part of the study.

Nausea was experienced after 16 out of totally 188 administered doses (8.5%) and vomiting was produced in patient no. 2 at three occasions (1.5%), when doses of 150 mg of 5-HTP was administered. The plasma concentrations obtained following doses of 100-200 mg 5-HTP were 1.5-4 times the critical concentration of about 6 \mu mol L^{-1} at which four out of the same five patients became severely nauseated and vomited during the previous intravenous infusion study (Magnussen & Nielsen-Kudsk 1979).

Discussion

L-5-hydroxytryptophan is the immediate precursor of serotonin, which has been identified as a neurotransmitter in the brain (Aghajanian & Wang 1978). The clinical implications of increasing the serotonin level in the central nervous system by 5-HTP in various neuro-psychiatric disorders is under investigation. The amino acid has with success been administered therapeutically in different kinds of neurological diseases characterized by involuntary jerking movements (Van Woert & Chung Hwang 1978). However, investigations of the therapeutic indications based on clinical double blind trials remain to be done. Two characteristics of 5-HTP could impede the evaluation of orally administered 5-HTP, when compared to inert substances, namely, episodic gastrointestinal absorption deficiency (Magnussen & Olivarius 1978) and the high frequency of adverse reactions observed, especially those refering to the gastrointestinal system (Van Woert & Chung Hwang 1978).

We have consequently during the initiation of 5-HTP treatment investigated the steady state pharmacokinetics and bioavailability of 5-HTP administered orally at increasing dose levels together with carbidopa, an extracerebral decarboxylase inhibitor, and we have especially focused on the relationship between the dose level and the frequency of gastrointestinal side effects.

In the dose range of 150-600 mg 5-HTP per day, combined with 150 mg carbidopa in three divided doses, the concentration level of the amino acid in plasma increased according to linear kinetics. A considerable interindividual variability seems to exist with regard to the relative amount of drug which appears in the blood stream. A reduced systemic availability (A) caused exclusively by the influence of a possible hepatic first pass effect may, according to Gibaldi et al. (1971), be roughly estimated as A = 1 - (a_u/ (AUC_u F)), where F is the hepatic blood flow, about 1.5 l min^{-1}. Substituting the actual experimental figures into this formula yields an A-value of 0.92. The hereby predicted systemic availability of 92% of orally administered 5-HTP deviates substantially from the 64% found experimentally, which indicates that incomplete absorption and/or presystemic degradation of the compound other than hepatic may also be factors responsible for the reduced availability of 5-HTP. The fact that a two fold increase in the dose of carbidopa given with 600 mg 5-HTP for one week did not influence the systemic availability, suggests that maximum decarboxylase inhibitory effect of carbidopa was obtained with 150 mg per day. However, a 10-fold increase in the serotonin content of platelets obtained from long-term treated patients indicates, when compared to normal subjects, an incomplete blocking of the extracerebral enzymatic degradation of 5-HTP (Magnussen & Van Woert, unpublished results).

Very low or completely lacking bioavailability after orally administered 5-HTP seems to be rather infrequent, as only one (fig. 2) out of the 23 steady state plasma concentration curves obtained in the present study apparently discloses this phenomenon.

The gastrointestinal absorption of 5-HTP, as judged by the measured t_{max}-values, seems to be a rather slow process exhibiting a moderate interindividual and a somewhat more pronounced intra-individual variation. The t_{max}-values were without any correlation to the size of dose, which is consistent with the assumption, that the absorption process obeys first order kinetics.

The finding of only few incidences of nausea and vomiting despite plasma levels 1.4-5.0 times the critical concentration (6 \mu mol L^{-1}) at which four of the five patients became severely nauseated and
vomited during the previous intravenous infusion study (Magnussen & Nielsen-Kudsk 1979) emphasizes the importance of a slow initiation of treatment with 5-HTP in order to induce tolerance against these unwanted effects of the amino acid.

Acknowledgements
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References