Regional Pharmacokinetics of 5-Fluorouracil in Dogs: Role of the Liver, Gastrointestinal Tract, and Lungs

Han-Yi Kuan, David E. Smith, William D. Ensminger, James A. Knol, Susan J. DeRemer, Zhaomin Yang, and Philip L. Stetson


ABSTRACT

The purpose of this study was to determine the presence and extent of pulmonary elimination for 5-fluorouracil (FUra). A secondary aim was to characterize the relative importance of the liver, gastrointestinal tract, splanchnic region, and lungs toward the overall elimination of FUra. A total of 10 mixed-breed male and female dogs were used in these acute studies in which FUra was administered through a cephalic vein. Six dogs were studied at sequentially escalated dose rates of 0.125, 0.250, 0.500, 0.750, and 1.00 μmol/min/kg (8-fold range); four dogs were studied at sequentially escalated dose rates of 0.0625, 0.250, 0.750, 1.50, and 2.00 μmol/min/kg (32-fold range). Each infusion lasted 2 h, at which time steady-state plasma concentrations were obtained (i.e., portal vein, carotid artery, hepatic vein, and pulmonary artery), perfusion rates were measured (hepatic artery, portal vein, and cardiac output), and pharmacokinetic parameters were directly assessed. Pulmonary elimination of FUra was conclusively demonstrated. Although only 17% of the drug was extracted by the lungs at the lowest dose rate, pulmonary clearance (16.0 ml/min/kg) was on the order of splanchnic clearance (13.5 ml/min/kg), or larger. As the dose rate increased, pulmonary clearance was more easily saturated than splanchnic clearance. Thus, it appears that at increasing dose rates, the splanchnic region becomes a more significant pathway, whereas the lungs have a reduced role in the overall elimination of FUra.

INTRODUCTION

FUra has been widely used in the treatment of solid tumors and remains the most effective drug for colorectal cancer. Following parenteral administration, FUra is mainly eliminated from the body by metabolism, predominantly through catabolic processes (1, 2). Due to its structural similarity, FUra is handled by the enzymes responsible for degradation of uracil and thymine. In this regard, catabolism of pyrimidine bases is rate limited by DPD, and the resultant nonlinear kinetics (1–7) have been noted as a precaution in FUra chemotherapy. Although not biologically active, FUra exerts its antitumor activity and toxicity after being converted to nucleotide anabolites. However, the dominance of catabolism in the elimination of FUra precludes anabolism from being distinguished in the overall kinetic profile (4). As a consequence, current therapeutic adjustment may best be made on the basis of FUra kinetics and its systemic exposure.

The liver is generally acknowledged as the major organ for degradation of FUra. Yet, DPD is present in many normal and neoplastic human tissues, including the liver, pancreas, lung, intestinal mucosa, and lymphocytes (8). In an attempt to explain clearance values in excess of liver blood flow and approaching or exceeding that of cardiac output, it has been suggested that FUra must be cleared by the lung, by the blood, or by both (4, 5, 9). However, blood does not appreciably contribute to the observed total body clearance of FUra (9), and pulmonary extraction has yet to be verified experimentally.

The determination of pulmonary metabolism is important, because, although smaller in weight than the liver, the lungs process all of the cardiac output (as opposed to 25% by the liver). A combined effect by the liver and lungs following hepatic regional administration of FUra (i.e., hepatic artery or portal vein) would also be noteworthy. Given their anatomical relationship, these two organs could act, in concert, as a powerful filter after hepatic regional FUra administration by protecting tissues from excessive systemic drug or by preventing the attainment of therapeutic drug levels. In our study, the dog was used as an animal model to determine the presence and extent of pulmonary elimination for FUra. A secondary aim of our study was to characterize the relative importance of the liver, gastrointestinal tract (including the pancreas and spleen), splanchnic region, and lungs toward the overall elimination of FUra.

MATERIALS AND METHODS

Chemicals. FUra (lot 81F-0093; Sigma Chemical Co., St. Louis, MO) was obtained as powder. Aqueous solutions were prepared immediately prior to use by dissolving the powder in 0.1 m sodium carbonate-sodium bicarbonate buffer at pH 9.8. All other chemicals and solvents were reagent grade or better.

Experimental Methods. A total of 10 mixed-breed male and female dogs (body weight, 36.2 ±6.3 kg) were used in these acute pharmacokinetic studies. The surgical design was adapted from that of a previous procedure (10), with minor modifications. Briefly, after an overnight fast, each dog was administered a preanesthetic mixture consisting of acepromazine maleate (1.1 mg/kg i.m.) and atropine sulfate (0.04 mg/kg i.m.). Anesthesia was then induced with sodium pentobarbital (35 mg/kg i.v.). Supplemental doses of the anesthetic agent were provided on an as-needed basis, and respiration was maintained on a volume-controlled ventilator (Harvard Apparatus, South Natick, MA). Catheters were placed by laparotomy into the portal vein and hepatic vein, by thoracotomy into the pulmonary artery, and by cutdown into the carotid artery. These catheters served as sites for serial blood sampling. Perivascular ultrasonic transit time flow probes (Transonic Systems, Inc., Ithaca, NY) were placed for blood flow measurements around the following vessels: common hepatic artery, portal vein, and ascending aorta. The gastroduodenal artery was ligated. Catheters and flow probe wires were tunnelled s.c. to exit the skin, and the abdomen and chest were closed (Fig. 1).

Immediately following surgery, FUra was administered through a cephalic vein via a syringe infusion pump (Harvard Apparatus, South Natick, MA) set at 0.167 ml/min. Six dogs were studied at five sequentially escalated dose rates of 0.125, 0.250, 0.500, 0.750, and 1.00 μmol/min/kg (8-fold range); four dogs were studied at five sequentially escalated dose rates of 0.0625, 0.250, 0.750, 1.50, and 2.00 μmol/min/kg (32-fold range). Each infusion lasted 2 h, and steady-state blood samples (3 ml) were obtained from all four catheters at 105 min, 140 min, and 180 min. Pulmonary elimination for FUra was determined by sequential analysis. The experimental design (i.e., dose rates and infusion times) in this study was based on our previous experience with similar studies in dogs (11, 12) and cancer patients (3, 6). The resultant steady-state plasma concentrations of FUra were consistent with those reported in the clinical setting (1, 2).

Analytical Methods. The plasma concentrations of FUra were analyzed by a gas chromatography-mass spectrometry method with selected-ion monitoring, modified from that developed for determination of 5-bromouracil in DNA.
Regional Pharmacokinetics of Fluorouracil (FuRa)  

Hepatic (CLH), gastrointestinal (CLGI), splanchic (CLSp), and pulmonary (CLLa) blood clearances were then determined as:

\[ CL_H = \frac{Q_H \cdot E_H}{1 - E_H} \]
\[ CL_{GI} = \frac{Q_{PV} \cdot E_{GI}}{1 - E_{GI}} \]
\[ CL_{Sp} = \frac{Q_H \cdot E_{Sp}}{1 - E_{Sp}} \]
\[ CL_{La} = \frac{Q_{CO} \cdot E_{La}}{1 - E_{La}} \]

in which \( Q_{CO} \) was the cardiac output. The total body plasma clearance of drug \( (CL_{TB}) \) was calculated as:

\[ CL_{TB} = \frac{R_o}{C_{CA}} \]

in which \( R_o \) is the i.v. infusion rate. Using a venous equilibration model and steady-state conditions, the following quadratic equation was adopted to estimate the Michaelis-Menten parameters \( (i.e., V_m \text{ and } K_m) \) of drug in specific organs \( (12) \):

\[ C_{out} = 0.5 \cdot \left( \frac{C_{in} - V_m}{Q} - K_m + \sqrt{\left( \frac{C_{in} - V_m}{Q} - K_m \right)^2 + 4 \cdot K_m \cdot C_{in}} \right) \]

For the liver, \( C_{out} = C_{HIV}, C_{in} = C_{ave} \), and \( Q = Q_{HIV} \); for the gastrointestinal tract, \( C_{out} = C_{PV}, C_{in} = C_{CA} \), and \( Q = Q_{PV} \); for the splanchic region, \( C_{out} = C_{HIV}, C_{in} = C_{CA} \), and \( Q = Q_{HIV} \); and for the lungs, \( C_{out} = C_{CA}, C_{in} = C_{PA} \), and \( Q = Q_{CO} \). In applying this equation, plasma and blood concentrations were assumed to be equal, because FuRa has been shown to be evenly distributed between these two compartments \( (9, 16) \). On the basis of the estimates of \( V_m \) and \( K_m \) (and respective blood flows), the intrinsic extraction (\( E \)) and clearance (\( CL \)) of specific organs were calculated according to the following \( (6, 12, 15) \):

\[ V_m/Q \]
\[ E_i = \frac{K_m}{1 + \frac{V_m/Q}{K_m}} \]
\[ CL_i = V_m/K_m \]

Statistics. Data are reported as means ± SD, unless otherwise indicated. To test parameter differences for statistical significance among treatment groups, an ANOVA was performed with repeated measures. When the F ratio showed that there were significant differences among groups, a Tukey’s test was used to determine which groups differed \( (a = 0.05) \). Means that were significantly different appear with the same capital letters in Tables 1–7. All statistical computations were performed using SYSTAT \( (version \ 5.03; \ \text{SYSSTAT, Inc., Evanston, IL}) \). Michaelis-Menten parameters \( (V_m \text{ and } K_m) \) were obtained using the nonlinear least-squares regression program SCIENTIST \( (version \ 2.01; \ \text{MicroMath Scientific Software, Salt Lake City, UT}) \) and a weighting factor of unity. \( C_{out} \) was the dependent variable, and \( C_{in} \) and \( Q \) were the independent variables. The quality of the fit was determined by evaluating the coefficient of determination \( (r^2) \), the standard error of parameter estimates, and by visual inspection of the residuals.

RESULTS

Initial Dose-Rate Studies: 0.125–1.00 \( \mu \text{mol/min/kg} \). The extraction ratios of FuRa across specific organs are shown in Table 1. As observed, hepatic extraction of FuRa remained unchanged at about 0.74, whereas gastrointestinal extraction decreased significantly from about 0.60 to 0.44 as the dose rate increased. Taken as a whole region, the splanchic area had a rather constant extraction ratio for FuRa of...
about 0.83. Pulmonary extraction of FUra was evident in this dose range, with the mean value decreasing from 0.11 to 0.03 as the dose rate increased. Although the extremes of dosing showed concentration-dependent pulmonary extraction, ANOVA was inconclusive when all of the treatments were considered ($P = 0.059$).

Table 2 shows the fraction of FUra that escaped regional extraction by each organ. In agreement with the extraction data, hepatic and splanchnic availabilities were low but constant, averaging about 0.26 and 0.17, respectively. In contrast, the fraction of FUra surviving elimination by the gastrointestinal tract increased from 0.40 to 0.56 as the dose rate increased. The fraction of drug surviving pulmonary elimination remained high at ≥89% ($P = 0.061$).

Blood clearances by the liver, gastrointestinal tract, splanchnic region, and lungs, as well as the total body plasma clearance of FUra, are summarized in Table 3. As the dose rate increased, hepatic and splanchnic clearances did not change significantly, maintaining values on the order of 12.3 and 14.0 ml/min/kg, respectively. Clearance by the gastrointestinal tract, on the other hand, showed a significant decrease from mean values between 6.22 and 6.88 ml/min/kg to 4.65 ml/min/kg when the dose rate approached 1.00 µmol/min/kg. Similarly, mean values for the pulmonary clearance decreased noticeably by about 70–75%. Finally, the total body plasma clearance of FUra decreased, from about 40 to 25 ml/min/kg, as the doses increased.

Regional estimates of $V_m$ and $K_m$ could not be obtained with satisfactory measures of fit in the initial dose-rate studies. Apparently, a wider range of infusion doses was needed to address this issue. Thus, our dose range was extended from an 8-fold to a 32-fold difference between the highest and lowest infusion rates. This extended range consisted of two previously selected dose rates (0.250 and 0.750 µmol/min/kg) and two dose rates producing higher saturating drug concentrations (1.50 and 2.00 µmol/min/kg). In addition, a dose rate of 0.0625 µmol/min/kg was chosen to further explore the pulmonary elimination of FUra.

**Extended Dose-Rate Studies: 0.0625–2.00 µmol/min/kg.** Extraction ratios and fractions of drug escaping regional extraction for the extended dose range are shown in Tables 4 and 5, respectively. As dose rate increased from 0.0625 to 2.00 µmol/min/kg, significant changes were observed in the extraction ratios across all regions.
Hepatic extraction decreased from about 0.78 to 0.60, with the fraction rates, from about 0.89 to 0.69 on average. This led to an almost 3-fold increase in the fraction of drug that survived hepatic elimination increasing by 1.8-fold. Moreover, pulmonary extraction of FUra was 17% at the lowest infusion rate but decreased with increasing dose rate. This change was statistically significant in spite of some of the variability that occurred at the dose rates of 1.50 and 2.00 μmol/min/kg. In this regard, variable estimates of pulmonary extraction may be the result of experimental errors that are magnified when input and output concentrations are very close to one another (i.e., for drugs of low extraction). Finally, pulmonary availability was 0.83 at low perfusing concentrations and approached unity as the dose rate was increased.

As observed in Table 6, hepatic clearance was reduced by about 15–20% at the higher dose rates, but the change was not statistically significant. In contrast, gastrointestinal clearance was reduced by more than 50% within this dose range. Under the influence of both organs, splanchnic clearance decreased from 13.5 to 11.2 ml/min/kg, with the difference approaching significance ($P = 0.055$). For pulmonary clearance, the significant dose dependency was attributed to differences between the low and high ends of the dose range in accordance with the observed extraction ratios. With respect to total body plasma clearance, the change was more significant in the extended as opposed to the initial dose range.

Michaelis-Menten parameters of FUra in the liver, gastrointestinal tract, and splanchnic region were obtained with good measures of fit ($r^2 \geq 0.963$ for all analyses). The metabolic capacity of the liver and

Table 4 Extraction ratios by the liver ($E_{hl}$), gastrointestinal tract ($E_{glt}$), splanchnic region ($E_{spl}$), and lungs ($E_{lu}$) following five sequentially escalated iv. infusions of FUra (extended dose-rate studies)$^a$

<table>
<thead>
<tr>
<th>Dose rate (μmol/min/kg)</th>
<th>$E_{hl}$</th>
<th>$E_{glt}$</th>
<th>$E_{spl}$</th>
<th>$E_{lu}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0625</td>
<td>0.775 ± 0.079</td>
<td>0.713 ± 0.046</td>
<td>0.890 ± 0.041</td>
<td>0.169 ± 0.085</td>
</tr>
<tr>
<td>0.250</td>
<td>0.711 ± 0.041</td>
<td>0.640 ± 0.040</td>
<td>0.880 ± 0.023</td>
<td>0.0768 ± 0.053</td>
</tr>
<tr>
<td>0.750</td>
<td>0.703 ± 0.024</td>
<td>0.460 ± 0.074</td>
<td>0.825 ± 0.023</td>
<td>0.0702 ± 0.038</td>
</tr>
<tr>
<td>1.50</td>
<td>0.680 ± 0.052</td>
<td>0.423 ± 0.084</td>
<td>0.783 ± 0.030</td>
<td>0.0052 ± 0.0104</td>
</tr>
<tr>
<td>2.00</td>
<td>0.602 ± 0.097</td>
<td>0.291 ± 0.042</td>
<td>0.686 ± 0.075</td>
<td>0.0539 ± 0.0578</td>
</tr>
<tr>
<td>Significance$^b$</td>
<td>0.020</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.008</td>
</tr>
</tbody>
</table>

$^a$ Data are reported as mean ± SD of four dogs. Dose-rate conversion: μmol/min/kg × 32.5 = μmol/min/m$^2$.

$^b$ P were determined by ANOVA with repeated measures. For a given parameter, mean values with the same capital letter are significantly different (Tukey’s test; $\alpha = 0.05$).

Table 5 Fraction escaping extraction by the liver ($F_{hl}$), gastrointestinal tract ($F_{glt}$), splanchnic region ($F_{spl}$), and lungs ($F_{lu}$) following five sequentially escalated iv. infusions of FUra (extended dose-rate studies)$^a$

<table>
<thead>
<tr>
<th>Dose rate (μmol/min/kg)</th>
<th>$F_{hl}$</th>
<th>$F_{glt}$</th>
<th>$F_{spl}$</th>
<th>$F_{lu}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0625</td>
<td>0.225 ± 0.079</td>
<td>0.288 ± 0.046</td>
<td>0.110 ± 0.041</td>
<td>0.831 ± 0.085</td>
</tr>
<tr>
<td>0.250</td>
<td>0.229 ± 0.041</td>
<td>0.361 ± 0.040</td>
<td>0.120 ± 0.023</td>
<td>0.923 ± 0.053</td>
</tr>
<tr>
<td>0.750</td>
<td>0.298 ± 0.024</td>
<td>0.540 ± 0.074</td>
<td>0.195 ± 0.023</td>
<td>0.930 ± 0.038</td>
</tr>
<tr>
<td>1.50</td>
<td>0.320 ± 0.052</td>
<td>0.577 ± 0.084</td>
<td>0.218 ± 0.030</td>
<td>0.995 ± 0.010</td>
</tr>
<tr>
<td>2.00</td>
<td>0.398 ± 0.097</td>
<td>0.709 ± 0.042</td>
<td>0.314 ± 0.075</td>
<td>0.946 ± 0.058</td>
</tr>
<tr>
<td>Significance$^b$</td>
<td>0.020</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.008</td>
</tr>
</tbody>
</table>

$^a$ Data are reported as mean ± SD of four dogs. Dose-rate conversion: μmol/min/kg × 32.5 = μmol/min/m$^2$.

$^b$ P were determined by ANOVA with repeated measures. For a given parameter, mean values with the same capital letter are significantly different (Tukey’s test; $\alpha = 0.05$).

Table 6 Blood clearances by the liver ($Cl_{hl}$), gastrointestinal tract ($Cl_{glt}$), splanchnic region ($Cl_{spl}$), and lungs ($Cl_{lu}$), and the total body plasma clearance ($Cl_{p, TB}$) following five sequentially escalated iv. infusions of FUra (extended dose-rate studies)$^a$

<table>
<thead>
<tr>
<th>Dose rate (μmol/min/kg)</th>
<th>$Cl_{hl}$ (ml/min/kg)</th>
<th>$Cl_{glt}$ (ml/min/kg)</th>
<th>$Cl_{spl}$ (ml/min/kg)</th>
<th>$Cl_{lu}$ (ml/min/kg)</th>
<th>$Cl_{p, TB}$ (ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0625</td>
<td>11.7 ± 1.9</td>
<td>7.90 ± 1.12</td>
<td>13.5 ± 2.2</td>
<td>16.0 ± 8.3</td>
<td>30.7 ± 7.0</td>
</tr>
<tr>
<td>0.250</td>
<td>11.8 ± 2.2</td>
<td>7.26 ± 1.44</td>
<td>13.5 ± 2.7</td>
<td>6.89 ± 5.45</td>
<td>27.5 ± 5.2</td>
</tr>
<tr>
<td>0.750</td>
<td>11.2 ± 3.0</td>
<td>5.42 ± 1.47</td>
<td>12.8 ± 3.2</td>
<td>6.21 ± 3.90</td>
<td>27.7 ± 5.5</td>
</tr>
<tr>
<td>1.50</td>
<td>11.0 ± 3.6</td>
<td>4.98 ± 1.56</td>
<td>12.6 ± 3.8</td>
<td>0.288 ± 0.575</td>
<td>18.1 ± 3.3</td>
</tr>
<tr>
<td>2.00</td>
<td>9.88 ± 3.04</td>
<td>3.42 ± 0.74</td>
<td>11.2 ± 3.0</td>
<td>4.68 ± 5.42</td>
<td>14.9 ± 3.1</td>
</tr>
<tr>
<td>Significance$^b$</td>
<td>0.219</td>
<td>&lt;0.001</td>
<td>0.055</td>
<td>0.007</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

$^a$ Data are reported as mean ± SD of four dogs. Dose-rate conversion: μmol/min/kg × 32.5 = μmol/min/m$^2$; clearance conversion: ml/min/kg × 32.5 = ml/min/m$^2$.

$^b$ P were determined by ANOVA with repeated measures. For a given parameter, mean values with the same capital letter are significantly different (Tukey’s test; $\alpha = 0.05$).

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splanchnic region were found to be substantially larger than that of the gastrointestinal tract (i.e., they had larger Vm values). However, no statistical differences in Km were observed (Table 7). As a result, the intrinsic clearance of the splanchnic region was about 2-fold greater than that of the liver, which was about 2–2.5-fold greater than the gastrointestinal tract. The intrinsic extraction ratios, which are blood flow dependent, were ordered according to the following regions: splanchnic > liver > gastrointestinal. Unfortunately, estimates of Vm and Km in the lungs were not possible using this kinetic model. As a result, information on the intrinsic clearance and extraction of FUra in the lungs is lacking.

Blood Flow Measurements. Hepatic arterial, portal venous, and total hepatic blood flows, as well as cardiac output, are depicted following the initial and extended dose-rate studies. In the initial dose-rate studies, blood flow was 5.63 ± 2.97 ml/min/kg in the hepatic artery, 11.5 ± 3.4 ml/min/kg in the portal vein, 17.2 ± 5.3 ml/min/kg in the total liver, and 70.5 ± 18.1 ml/min/kg for cardiac output. In the extended dose-rate studies, blood flow was 4.16 ± 1.59 ml/min/kg in the hepatic artery, 11.6 ± 1.7 ml/min/kg in the portal vein, 15.7 ± 3.2 ml/min/kg in the total liver, and 75.4 ± 13.2 ml/min/kg for cardiac output. As noted, the measurements from both dose ranges were similar. They were also consistent with data reported in the literature (11, 17, 18). More importantly, there were no time-dependent changes (i.e., from 0 to 2, 2 to 4, 4 to 6, 6 to 8, and 8 to 10 h) in flow for hepatic artery (P = 0.298 or 0.903), portal vein (P = 0.156 or 0.909), total liver (P = 0.335 or 0.767), or cardiac output (P = 0.797 or 0.525) in either the initial or the extended dose ranges, respectively (Fig. 2; data only shown for extended dose-rate studies).

In the present study, pulmonary extraction of FUra was conclusively demonstrated in the dog. Compared to estimates in the liver and gastrointestinal tract, pulmonary extraction ratios were relatively low (≤17%), whereas clearance values were relatively high. This indicates that pulmonary clearance, particularly at low dose rates, may be substantial due to large perfusion rates to the lungs. In fact, at the 0.0625 μmol/min/kg dose rate, the pulmonary clearance of FUra exceeded its splanchnic clearance and approximated liver blood flow. In addition, metabolism of FUra in the lungs appeared to be saturable. Despite the large interanimal variability, pulmonary extraction and clearance approached 0 as the dose rate was increased to ≥1.00 μmol/min/kg. This tendency toward rapid saturation (i.e., dose dependency) could prevent the detection of pulmonary elimination for FUra if the experimental dose was not low enough.

The individual components that make up the splanchnic elimination of FUra were evaluated in the present study. In this regard, the liver and gastrointestinal tract were both found to be organs of high extraction (i.e., >0.70). However, the gastrointestinal tract appeared to be more susceptible to saturation, and, as a result, this tissue was still able to extract 60% of perfusing drug concentrations. This finding suggests that liver and gastrointestinal enzymes have a different affinity for FUra. Whereas the Km for FUra in the gastrointestinal tract was about 30% lower than that in the liver, the difference was not statistically significant. However, it should also be appreciated that

**DISCUSSION**

Despite its widespread use as an anticancer drug over the past 30 years, the disposition kinetics of FUra remain unclear. In particular, total plasma clearances of FUra have been reported to approximate or even exceed cardiac output (1, 2), and, as a result, extrathoracic pathways would be needed to explain such a phenomenon. In this regard, Collins and coworkers (4, 5) have speculated that FUra was being cleared by the lungs and/or blood. However, these investigators (4), as well as others (9), have found degradation of FUra in the blood to be minimal at best. Other investigators have studied the potential for pulmonary metabolism of FUra in the rat (19) and pig (20), but with little success. In a theoretical analysis, Collins (5) reported on the upper limits of pulmonary extraction in different animal species by assuming that all clearance was by the lungs. The dog was found to be most similar to human, as opposed to the rat and monkey, with respect to total body plasma clearance and cardiac output (both surface area corrected) and maximal extraction by the lungs (36% in dog versus 52% in humans). Nevertheless, the author was cautious in his conclusions, because he recognized the need for hepatic/splanchnic clearance determinations as well as experimental verification.
and lungs, are there other organs or tissues that contribute to drug elimination? Assuming that plasma clearance is a reasonable approximation of blood clearance (9, 16), this question may be approached by taking the difference between the total body clearance and the sum of splanchnic and pulmonary clearances \( [i.e., CL_{\text{other}} = CL_{\text{TB}} - (CL_{\text{SPA}} + CL_{\text{PA}})] \). Thus, the contribution (\%) of drug elimination represented by \( CL_{\text{other}} \) in the initial dose-rate studies was estimated at 46\% (0.125 \( \mu \text{mol/min/kg} \)), 42\% (0.250 \( \mu \text{mol/min/kg} \)), 38\% (0.500 \( \mu \text{mol/min/kg} \)), and 36\% (1.00 \( \mu \text{mol/min/kg} \)); the contribution (\%) of drug elimination represented by \( CL_{\text{other}} \) in the extended dose-rate studies was estimated at 4\% (0.0625 \( \mu \text{mol/min/kg} \)), 26\% (0.250 \( \mu \text{mol/min/kg} \)), 31\% (0.750 \( \mu \text{mol/min/kg} \)), 29\% (1.50 \( \mu \text{mol/min/kg} \)), and 0% (2.00 \( \mu \text{mol/min/kg} \)). Taken as a whole, it appears that about 30–35\% (median values) of FUra may be eliminated by other clearance mechanisms. Although speculative, remaining clearance pathways may reflect renal excretion, which accounted for up to 32\% of drug elimination in the dog (21), as well as catabolism by other tissues containing DPD, which may be ubiquitous within the body (22, 23).

In conclusion, we demonstrate for the first time that the lungs are involved in the elimination of FUra and that pulmonary clearance is substantial at low dose rates. At the lowest dose rate studied (0.0625 \( \mu \text{mol/min/kg} \)), pulmonary clearance was at least as important as splanchnic clearance, although extraction by the lungs was only 17\%. This finding highlights the uniqueness of the lungs in that efficient removal of drug is possible from this low extraction organ, because it receives the entire blood supply (i.e., cardiac output). In addition, metabolism of FUra by the lungs was rapidly saturated as the dose rate increased. In contrast, splanchnic clearance of FUra did not change very much as the dose rate was increased in both the initial and extended dose-rate studies. Therefore, it appears that the splanchnic region becomes a more significant pathway, whereas the lungs have a reduced role in the overall elimination of FUra at increasing dose rates. It is possible that the myelosuppression observed in humans after i.v. bolus doses may be due, in part, to metabolic saturation of the lungs so that systemic arterial and venous concentrations of FUra are essentially the same. Following low i.v. infusions, pulmonary extraction of FUra may be substantial enough so that systemic arterial concentrations are mitigated and myelosuppression is minimized. Still, caution is warranted, because this premise assumes that the data in dogs can be translated to that in cancer patients.

**ACKNOWLEDGMENTS**

We thank Martin Bocks for his help with the data collection and experimental aspects of the study.

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