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# Population pharmacokinetics of hydroxyurea in cancer patients

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**Abstract.** The pharmacokinetics of hydroxyurea (HU) were investigated in cancer patients after intravenous infusion or oral administration. On the basis of the minimal value of the objective function (MVOF) and prior knowledge of the disposition of HU in animals and man, the data were best described by a one-compartment pharmacokinetic model with parallel Michaelis-Menten metabolism and first-order renal excretion. The computer program NONMEM (*non*linear *m*ixed *e*ffects *m*odel) was used to perform the nonlinear regression and provide estimates of the population parameters. For the combined intravenous and oral data set, these parameters were estimated to be: maximal elimination rate ($V_{max}$), 0.097 mmol $h^{-1}$ $l^{-1}$; Michaelis constant for HU elimination ($K_M$), 0.323 mmol/l; renal clearance ($Cl_R$), 90.8 ml/min; volume of distribution ($V_d$), 0.186 × (body weight) + 25.4 l; absorption rate constant ($K_a$), 2.92 $h^{-1}$; and availability to the systemic circulation ($F$), 0.792. The principal findings of the investigation are that HU undergoes nonlinear elimination in cancer patients and that HU is reasonably well absorbed following oral administration.

**Key words** Hydroxyurea · Pharmacokinetics · NONMEM

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## Introduction

Hydroxyurea (HU), a structural analogue of urea, inhibits ribonucleotide reductase activity [10] and has been used clinically as a cytotoxic agent for more than 20 years. Its principal use has involved the treatment of chronic myeloid leukemia, although it has also been shown to be effective against other malignancies. No formal evaluation of the pharmacokinetics of this drug in humans has appeared in the literature, although several reports concerning aspects of the absorption and disposition of HU are available. These studies indicate that HU is fairly well absorbed following oral administration in humans, since plasma HU concentrations are similar following intravenous and oral administration [5, 22]. Also, a significant, but highly variable, fraction of the dose is recovered in the urine [5]. In rodents the drug is rapidly and widely distributed throughout the body [1]. Finally, studies in mice demonstrate hepatic biotransformation of HU to urea [8].

On the basis of empirical evidence of sequence-dependent synergy between HU and other antineoplastic drugs in a rat myelocytic leukemia model [19], we have begun a series of clinical trials of high-dose intravenous and oral HU in combination chemotherapy [18, 20]. In addition, due to the paucity of toxicity data on HU, a phase I trial involving escalating, prolonged HU infusions was simultaneously conducted. Because of the lack of pharmacokinetic data on this drug, especially at high doses, HU blood concentration-time data from all of these studies were combined and evaluated to determine the population pharmacokinetics of this drug.

## Patients and methods

### Patients

The data used in this study were obtained from 54 patients treated with HU at Duke University Medical Center (DUMC) and the University of Nebraska Medical Center (UNMC). In all, 28 patients were treated at DUMC and 26, at UNMC. There were 28 men and 26 women. The average weight and age ( ± SD) of these patients was 71.8 ± 15.6 kg and 53 ± 13.5 years, respectively. The respective ranges for weight and age were 43.2–118 kg and 23–76 years.

In 46 individuals, HU was given by intravenous infusion. Of these, 18 were patients at UNMC. Eight patients were diagnosed with lymphoma; five, with brain tumors; two, with acute myelocytic leukemia; and one each, with lung cancer, melanoma, and renal-cell carcinoma. These patients were receiving 48- to 72-h HU infusions at rates varying from 1.9 to 8.7 mmol/h (84–315 $mg\,m^{-2}\,h^{-1}$). The lymphoma patients were being treated concurrently with carmustine (BCNU), cyclophosphamide, and etoposide (VP-16).

Of the remaining 28 patients, all of whom were treated at DUMC, 12 were diagnosed with head and neck cancer; 8, with colon cancer; 3, with lung cancer; 2, with ovarian cancer; 1, with gallbladder cancer; 1, with prostate cancer; and 1, with leiomyosarcoma. These patients received a 30-min loading infusion immediately prior to initiation of the maintenance infusion. The duration of the maintenance infusion was either 24 or 48 h and the infusion rate varied from 3.1 to 24.3 mmol/h (165–950 $mg\,m^{-2}\,h^{-1}$). Of the 46 patients who received intravenous infusions, 10 received 2 separate treatments and 4 received 3 treatments. Treatments were given 3–4 weeks apart.

In eight patients, all from UNMC, HU was given orally at doses of 20 $mmol/m^2$ every 6 h in a high-sequential-drug-dose regimen for metastatic breast cancer. HU was given as a single agent for 3 days immediately following the administration of high-dose cyclophosphamide and thiotepa. The number of oral doses taken prior to the study dose ranged from one to eight. One patient received one dose of HU, four received five doses, two received six doses, and one received eight doses prior to the study.

From each of the 18 patients at UNMC who received intravenous infusions, only 1 blood sample was taken at the end of the infusion. From the eight UNMC patients who received HU orally, blood samples were drawn every 30 min for 5 h, then every hour until 8 h after the dose. From the DUMC patients, blood samples were drawn at 15 and 30 min and at 4, 8, 16, 20, and 24 h after the beginning of the maintenance infusion. Additional samples were drawn at 32, 40, and 48 h from those patients who received 48-h infusions.

Creatinine clearance measurements were reported in 24 patients. The mean value ( ± SD) was 71.5 ± 25.4 ml/min (range, 24–117 ml/min).

### HU assay

HU was assayed by the method of Fabricius and Rajewsky [11]. Briefly, blood was drawn into a heparinized tube. After centrifugation, plasma was removed and frozen until analysis. After thawing, the plasma was deproteinated with perchloric acid, centrifuged, and filtered. The filtrate was treated with iodine to oxidize the HU. The nitrite thus formed diazotizes sulfanilic acid. The diazotised sulfanilic acid was coupled with *N*-(1-naphthyl)-ethylenediamine dihydrochloride. The coupled product absorbs UV light at 540 nm. All samples were assayed at UNMC. The within-day, inter-run coefficient of variation (CV) was 13% for 1 μg/ml and 4.8% for 5 μg/ml. The assay was always performed with standards to minimize inter-run variability. The assay was sensitive to 1 μg/ml.

### Pharmacokinetic analysis

The plasma HU concentration-time data were analyzed using the computer software package NONMEM (*non*linear *m*ixed *e*ffects *m*odel, version III) and the PREDPP package (version II) [2, 3]. The data were fit to two different models. The first was a one-compartment model with Michaelis-Menten elimination. Model 1 can be described by Eq. 1 after intravenous administration and by Eq. 2 after oral administration.

$$\frac{dX_C}{dt} = K_0 - \frac{V_{max}X_C}{K_M + X_C} \tag{1}$$

$$\frac{dX_C}{dt} = K_a F X_D - \frac{V_{max}X_C}{K_M + X_C} \tag{2}$$

The rate of change in the amount of drug in the central compartment is denoted by $dX_C/dt$, $X_C$ is the amount of drug in the central compartment, $K_0$ is the infusion rate of drug, $V_{max}$ is the maximal elimination rate, $K_M$ is the Michaelis constant for HU elimination, $F$ is the fraction of the oral dose of HU that is available to the systemic circulation, $K_a$ is the apparent first-order absorption rate constant, and $X_D$ is the amount of drug in the depot compartment remaining to be absorbed.

Model 2 includes a pathway for first-order renal excretion in addition to saturable metabolism. Equations 3 and 4 describe the disposition of drug in the central compartment following intravenous and oral administration, respectively:

$$\frac{dX_C}{dt} = K_0 - \frac{V_{max}X_C}{K_M + X_C} - K_e X_C \tag{3}$$

$$\frac{dX_C}{dt} = K_a F X_D - \frac{V_{max}X_C}{K_M + X_C} - K_e X_C \tag{4}$$

The first-order excretion rate constant is denoted by $K_e$, and all other symbols are as defined above. Not shown in any of the equations is the apparent volume of distribution of the drug, $V_d$. This parameter is estimated by NONMEM as a scaling factor, adjusting for input in terms of amount and observations in concentration.

As mentioned above, the data were analyzed using the software package NONMEM. For both models, a general nonlinear model, ADVAN6, was chosen from the PREDPP library. The differential equations describing the desired model were included in a user-supplied subroutine. Estimates were sought for the population pharmacokinetic parameters, including intersubject and residual variability. First, only those patients who received infusions were included in the NONMEM data set. The data were initially fit to a one-compartment model with either linear or Michaelis-Menten elimination to ascertain the linearity or nonlinearity of the data. The data were then fit to both models (Eqs. 1, 3) to determine the better pharmacokinetic model and to obtain estimates of the disposition parameters. The oral data were then added to the NONMEM data set and the combined set was fit to model 2. Why model 2 was ultimately chosen to fit this combined data set is discussed below.

Several models were examined to describe interpatient variance. Superior results were achieved when interpatient variance was modeled as being proportional to the magnitude of the parameters. For example, the error model for volume of distribution was

$$V_d = V_d^*(1 + \eta_{Vd}) \tag{5}$$

where $V_d$ is the volume of distribution for an individual, $V_d^*$ is the mean volume of distribution for the population, and $\eta_{Vd}$ represents patient-specific deviations from $V_d^*$. Values for $\eta_{Vd}$ were assumed to have a mean of zero and variance (equal to the square of the interpatient CV) $\omega^2_{Vd}$. The effect of various covariates on the pharmacokinetic parameters, specifically age, gender, weight, body surface area, creatinine clearance, weight, and dose rate, was also

examined using both the proportional error and the exponential error models.

The residual error model includes error due to intrasubject variability, model misspecification, and assay variability as described by

$$C_{ij} = C_{Mij}(1 + \varepsilon_{ij}) \quad (6)$$

in which $C_{ij}$ is the *ith* observed concentration for the *jth* individual, $C_{Mij}$ is the corresponding concentration predicted by the model, and $\varepsilon_{ij}$ represents independent, identically distributed statistical errors with a mean of zero and variance $\sigma^2$. Use of this type of error model allows the size of the statistical error to be proportional to the magnitude of the fitted concentration. All off-diagonals of the population covariance matrix were set to zero.

## Results

After an unsuccessful attempt to analyze all of the infusion data with a one-compartment model with either linear or Michaelis-Menten disposition, it was determined that the steady-state concentrations in patients who received HU at very high infusion rates exhibited extremely large variability. Therefore, patients with infusion rates of greater than 14 mmol/h ($600\ mg\ m^{-2}\ h^{-1}$) were not included in the pharmacokinetic analysis. Thus, 11 patients given a total of 16 treatments were excluded from analysis. For the remaining data (35 patients and 48 treatments) a significantly better fit was obtained with the Michaelis-Menten model than with linear elimination. Pharmacokinetic analysis was further refined by comparing two nonlinear models: one with saturable elimination (model 1) and one with saturable elimination plus a first-order pathway (model 2). Model 2 provided a slightly better fit [MVOF, −424.562 (model 1) versus −426.443 (model 2)], although the two models were not statistically different with respect to the objective function values of the two analyses. However, we feel that there is enough evidence from other sources to support the use of model 2 over that of model 1. Drug concentration-time data obtained in other studies indicate that HU undergoes nonlinear elimination in animals [13, 15, 17] and humans [4, 5]. Furthermore, it has been demonstrated that HU is excreted in the urine in significant amounts [15], even at plasma concentrations lower than those achieved in this study [5]. Because it is very unlikely that glomerular filtration is saturated, the linear pathway of model 2 is consistent with renal excretion and the saturable pathway is consistent with liver metabolism.

Figure 1 shows HU steady-state concentrations as a function of infusion rate. A curve representing model-predicted values is included. The solid line is the predicted curve based on the parameter values determined by NONMEM, and the dashed line is a continuation of this curve at infusion rates of greater than 14 mmol/h. Steady-state concentrations were obtained from plots of HU concentration-time data from individual patients. HU demonstrates nonlinearity between 0.06 and 2.8 mmol/l or between 5 and 213 mg/l. Below this concentration the saturable pathway is linear. Above this range the linear pathway predominates, with the saturable pathway contributing little to the overall elimination of the drug. This graph also demonstrates the extreme variability in steady-state concentrations at infusion rates of greater than 14 mmol/h.

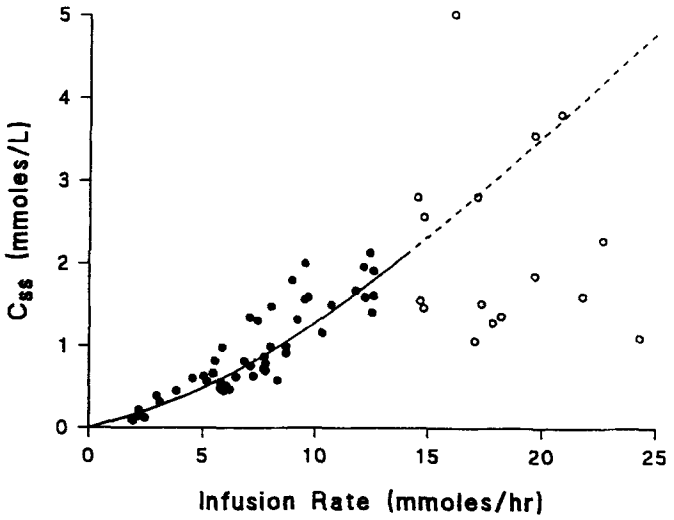


**Fig. 1** Steady-state serum HU concentrations as a function of infusion rate for cancer patients receiving intravenous infusions of HU. (*Filled circles* measured concentrations, *open circles* data not included in the pharmacokinetic analysis, *solid line* simulated curve based on the population mean parameter values determined by NONMEM using Eq. 3, *dashed line* extrapolation of this curve for infusion rates greater than 14 mmol/h)

Table 1 shows the estimates of the population parameters and the corresponding standard errors from the analysis of the infusion data using model 2. There was no significant difference between patients from DUMC and those from UNMC in terms of both the regression parameters and the estimates of inter- and intrapatient variability. $V_{max}$ and $K_M$ may be converted to units of concentration by dividing their values by the estimate for $V_d$. Estimates of interindividual variability for $K_M$ and $K_e$ are not reported because they were estimated by NONMEM to be nearly zero. This does not mean that there is no interindividual variability in the population with respect to $K_M$ and $K_e$. However, it may be interpreted to mean that the variability associated with $V_{max}$ is sufficient to explain all of the interindividual variability observed in the elimination of HU [6]. It was also determined for intravenously delivered HU that the volume of distribution for HU was not significantly correlated with either total body weight or body surface area ($P > 0.05$). The variance of the residual error, $\sigma^2$, was estimated to be 0.0599, which corresponds to a CV of 24.5%.

The final parameter estimates for the combined data set (intravenous and oral) are shown in Table 2. The

**Table 1** Estimates of population parameters for the disposition of HU after intravenous infusion

| Parameter | NONMEM estimate | SE |
|---|---|---|
| $V_{max}$ (mmol/h) | 3.40 | 0.912 |
| $K_M$ (mmol) | 8.10 | 4.73 |
| $K_e$ ($h^{-1}$) | 0.142 | 0.0130 |
| $V_d$ (l) | 38.1 | 2.50 |
| $\omega^2_{V_{max}}$ | 0.262 | 0.151 |
| $\omega^2_{Vd}$ | 0.0266 | 0.0143 |
| $\sigma^2$ | 0.0581 | 0.0138 |

**Table 2** Estimates of population pharmacokinetic parameters for HU after intravenous infusion and oral administration

| Parameter | NONMEM estimate | SE |
|---|---|---|
| $V_{max}$ (mmol/h) | 3.71 | 1.44 |
| $K_M$ (mmol) | 12.3 | 10.6 |
| $K_a$ ($h^{-1}$) | 2.92 | 1.13 |
| $K_e$ ($h^{-1}$) | 0.143 | 0.0161 |
| $V_d$, intercept (l) | 25.4 | 8.01 |
| $V_d$, slope (l/kg) | 0.186 | 0.125 |
| $F$ | 0.792 | 0.0622 |
| $\omega^2_{V_{max}}$ | 0.330 | 0.219 |
| $\omega^2_{Ka}$ | 2.48 | 1.72 |
| $\omega^2_{Vd}$ | 0.0181 | 0.0145 |
| $\omega^2_F$ | 0.0282 | 0.0451 |
| $\sigma^2$ | 0.0571 | 0.0132 |

values calculated for the disposition parameters do not differ greatly from those determined for the infusion data alone. For the combined data set it was determined that $V_d$ was significantly correlated with total body weight ($P < 0.05$). The values reported in Table 2 for $V_d$ are the slope and intercept terms for a plot of $V_d$ versus total body weight. It was also determined that HU is highly available to the systemic circulation following oral administration. Bioavailability (F) was determined to be 0.792.

## Discussion

The HU concentration-time data were initially fit to a one-compartment model with either linear disposition or Michaelis-Menten elimination. A significantly better fit was obtained with the nonlinear model. Nonlinear elimination of HU is also evident in other studies conducted in humans. Beckloff and co-workers [4] reported plasma HU concentrations following 20- and 80-mg/kg oral doses. The area under the HU plasma concentration-time curves and the peak concentrations differed by a factor of more than 6 rather than by a factor of 4, which would be predicted by linear kinetics. In the study by Belt et al. [5], HU was infused to steady state at rates varying from 2.0 to 3.5 $mg\,min^{-1}\,m^{-2}$. A plot of the resulting steady-state HU plasma concentrations versus infusion rates is curvilinear (concave up), whereas linear elimination kinetics would result in a straight-line relationship. More recently Charache et al. [7] reported plasma HU concentrations in sickle-cell anemia patients receiving doses ranging from 10 to 35 mg/kg. The plot of plasma concentrations as a function of dose was markedly curvilinear (concave up).

Nonlinear elimination of HU has also been demonstrated in rats. In the study by Navarra et al. [13], rats were given HU orally once a day for 6 days, with doses ranging from 10 to 800 mg/kg. There was a disproportionate increase in HU plasma concentrations as compared with the increase in the amount of the dose.

It is also evident from previous reports that HU is in part eliminated by renal excretion. The data of Philips et al. [15] is particularly useful in describing the disposition of HU. These authors gave intravenous bolus doses of 46, 184, and 1840 mg/kg HU to rats. HU blood concentration-time curves and urine values were obtained. The concentration-time curves are linear at the lowest and highest doses but curvilinear, concave down, at the intermediate dose. Renal clearance as calculated from the authors' data is 75% of glomerular filtration in the rat and dose-independent. These data suggest that HU is eliminated by Michaelis-Menten and parallel first-order pathways.

This model was therefore used to fit the data in our study; however, convergence was not attained, regardless of the choice of initial parameter estimates. Examination of the data shown in Fig. 1 suggests two possible reasons for the lack of convergence:

1. Model misspecification—it is possible to envision an apparent clustering of data points in the lower right quadrant of the graph, which could arise from increased clearance at higher infusion rates. One possible mechanism for this would be saturable plasma protein binding. The binding of HU in serum has not been reported. Indirect evidence of the extent of binding may be inferred from the data of Beckloff et al. [4]. Concentrations of HU were simultaneously measured in serum and either ascites fluid or cerebro-spinal fluid following oral administration of 20- to 80-mg/kg doses of HU. The resulting serum concentrations ranged from 12.4 to 156.8 mg/l. The ratio of ascites or cerebrospinal fluid to serum was approximately 0.2 and showed no dependence on the serum concentration. This suggests significant but concentration-independent HU serum binding in humans.
2. The lack of convergence could be due to the high variability in steady-state HU concentrations at the higher infusion rates (see Fig. 1). Difficulty in fitting data to Michaelis-Menten models has been noted by other investigators. At least three papers describe the problem of poor convergence of various algorithms using data with noise or scatter [12, 14, 16]. Recognition of this increased variability and its effects on model fitting led us to refit the data to the model, excluding those concentrations obtained from infusions of 14

mmol/h or more. Under these conditions, convergence was readily attained with reliable parameter estimates (Tables 1, 2).

When the model-fitted line obtained was extended to the higher concentrations it took on the appearance of a straight line. Based on the model, elimination at higher infusion rates occurs primarily by renal excretion, with non-renal elimination contributing relatively little to the overall removal of the drug from the body. The variability in steady-state concentrations at high infusion rates would therefore be due to variability in renal clearance. In support of this, patients' creatine clearance values associated with steady-state concentrations above the model-fitted line tended to be lower than those found below the line. Including creatine clearance in the model just failed to achieve a statistically significant improvement in the fit ($P < 0.042$). Dover et al. [9] have reported a significant correlation between serum creatinine and HU plasma levels in patients with sickle-cell anemia.

In this study, we conclude that the elimination of HU in humans is a nonlinear process. HU undergoes elimination through two parallel pathways. One is a saturable pathway, presumably liver metabolism, and the other is a first-order pathway, presumably renal excretion. Renal clearance can be calculated by multiplying the estimates of $K_e$ and $V_d$. Using the values shown in Table 2, renal clearance is 90.8 ml/min, or approximately 75% of the normal glomerular filtration rate. The data of Philips et al. [15] also indicate a renal clearance for HU of 75% of glomerular filtration in the rat.

HU was found to be 79% available to the systemic circulation following oral administration. Previous studies in the literature present a similar view since plasma HU concentrations are comparable following chronic intravenous and oral administration [5, 22]. We have previously reported a similar value ($F = 0.728$) for HU availability in the rat [17]. Lack of complete bioavailability of the oral dose may be due to one or more of the following: incomplete absorption, gut-wall metabolism, and first-pass liver metabolism. Consideration of the estimates of $V_{max}$ and $K_M$ from the intravenous data suggest that even at low doses, only 10% of an oral HU dose is removed by the liver on first pass.

For the combined intravenous and oral data set, $V_d$ was found to be significantly correlated with total body weight ($P < 0.05$) according to the equation $V_d = 0.186 \times WT + 25.4$ l, where $WT$ is body weight. On the basis of the estimates given in Table 2, a 71.8-kg individual (the mean for this study) would have a $V_d$ of 38.8 l, or approximately that of total body water. Philips et al. [15] also report the $V_d$ of HU to be equivalent to total body water in the rat.

Finally, the large variability observed in steady-state concentrations suggests that treatment of patients with doses higher than 14 mmol/h (600 mg $m^{-2}$ $hr^{-1}$) may result in unpredictable HU plasma concentrations. If, as the model suggests, this variability is due to HU renal clearance, it might be prudent to monitor renal function in patients receiving high-dose HU therapy.

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