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Hypoxanthine-Arabinoside Pharmacokinetics After Adenine Arabinoside Administration to a Patient with Renal Failure

GEORGE R. ARONOFF,[1]* JAMES J. SZWED,[1] ROBERT L. NELSON,[1] EDWIN L. MARCUS,[2] AND STUART A. KLEIT[1]

Renal Section, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana 46223,[1] and Warner-Lambert Pharmaceutical Research Division, Ann Arbor, Michigan 48106[2]

Hypoxanthine arabinoside pharmacokinetics were measured during an adenine arabinoside continuous intravenous infusion and during hemodialysis in a patient with renal failure. Therapeutic guidelines for adenine arabinoside in renal failure are provided based on an elimination half-life of 4.7 h and a plasma clearance of 87.9 ml/min for the hypoxanthine metabolite.

Adenine arabinoside (Ara-A) is an antiviral purine nucleoside which is effective in the treatment of herpes simplex encephalitis (6). After intravenous infusion, Ara-A is rapidly deaminated to its hypoxanthine metabolite, Ara-Hx. In patients with normal renal function, peak Ara-Hx plasma concentrations range from 3 to 6 mg/liter during 12-h infusions of 10 mg/kg. The parent compound is barely detectable in plasma. An elimination half-life ($t_{1/2}$) of approximately 3.5 h has been determined for Ara-Hx, with about 40% of the administered dose appearing in the urine as Ara-Hx and 2% as Ara-A (2).

Although Ara-Hx accumulation is thought to occur in patients with renal insufficiency, precise pharmacokinetic information is limited. Recently, we had the opportunity to study the infusion kinetics and hemodialysis clearance of Ara-Hx in a patient with renal failure.

A 17-year-old girl with aplastic anemia and acute oliguric renal failure developed hepatomegaly, pulmonary infiltrates, and oro-facial vesicles. Pharyngeal culture grew herpes simplex virus. On hospital day 18, the patient became disoriented and lethargic. Ara-A (12.5 mg/kg) was administered intravenously over 10 h by a manually calibrated IVAC (Eli Lilly and Co., Indianapolis, Ind.) infusion pump for presumed disseminated herpes virus infection. The patient remained anuric during the drug infusion, after which hemodialysis was performed. Biopsies of lung and liver did not contain herpes simplex virus, and Ara-A infusion was not repeated. Gradual improvement of sensorium was followed by return of normal hematopoietic and renal functions. Although the etiology of her illness remains unknown, she has remained well since discharge from the hospital.

Blood samples were obtained through a Butterfly intermittent infusion set placed in a forearm vein opposite to the arm of drug infusion. Samples were drawn before the start of Ara-A administration at 0.0833, 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, and 9.0 h during infusion and at the end of the drug administration. After the 10-h infusion, hemodialysis was performed. Simultaneous arterial and venous blood samples were drawn during hemodialysis at blood flows of 50, 100, 150, 200, and 300 ml/min. Plasma was immediately removed from blood cells by refrigerated centrifugation and frozen at −20°C until assayed.

Hemodialysis was performed with a recirculating single-pass delivery system (Travenol Laboratories, Deerfield, Il.) and the Ultraflow II Dialyzer Standard Ultrafiltration model Ml7-51 (Travenol Laboratories, Deerfield, Il.). Dialysis flow rate was maintained at 800 ml/min and dialysate temperature was held at 37°C. Blood flow was measured by an ultrasound Clinical Flowmeter model 1505 (Ward Associates, San Diego, Calif.).

Ara-A and Ara-Hx assays were performed at Warner-Lambert Pharmaceutical Research Division, Ann Arbor, Mich. with high-pressure liquid chromatography. Analysis of the data was performed using the on-line computer modeling program, MLAB (3).

During constant-rate drug infusion, plasma concentration is described by the equation

$$C_P = D \sum_{i=1}^{n} \frac{C_i}{\lambda_i} (1 - e^{-\lambda_i t}) \quad (1)$$

where C_P (milligrams per liter) is the plasma concentration at time t (hours) during infusion rate D (milligrams per kilogram per hour). C_i (kilograms per liter) is the dose invariant hybrid coefficient of each term in the polyexponential equation describing the plasma concentration after bolus intravenous injection, and λ_i

(hours^{-1}) is the hybrid exponent in each term of the equation (5). After graphical analysis to obtain initial best estimates of C_i and λ_i, pharmacokinetic parameters were estimated by computer fitting equation 1 to the data.

Dialysis clearance was calculated from the relationship

$$Cl_D = [(A_X - V_X)/A_X]Q_P \quad (2)$$

where Cl_D (milliliters per minute) is the dialysis clearance of substance X; A_X, and V_X are arterial (inflow) and venous (outflow) concentrations of X, respectively; and Q_P (milliliters per minute) is the plasma flow. Plasma flow was determined from blood flow (Q_b) by the relationship

$$Q_P = Q_b \cdot (1 - \text{hematocrit}) \quad (3)$$

Plasma flow was related to Cl_D by means of a least squares linear regression.

The plasma concentrations of Ara-Hx are shown in Fig. 1. The peak plasma concentration was 10 mg/liter. The parent compound, Ara-A, was not measurable in plasma. Computer fitting equation 1 to the data for Ara-Hx yields an equation of one exponential term in the form

$$C_P = D \cdot \frac{C}{\lambda}(1 - e^{-\lambda t}) \quad (4)$$

where $C = 1.55$ kg/liter and $\lambda = 0.147$. Thus, for Ara-Hx in our anuric patient

$$C_P = 10.54D\ (1 - e^{-0.147t}) \quad (5)$$

This relationship is seen as the solid line in Fig. 1. The elimination half-life ($t_{1/2}$) is 4.7 h as determined from the relationship $t_{1/2} = (1n2)/\lambda$. The plasma clearance (Cl_p) calculated from the equation $Cl_p = 1/(C/\lambda)$ is 0.095 liters per kg per h, or for this 55.5-kg patient, 87.9 ml/min. The volume of distribution at steady state (V_dSS) for Ara-Hx from the relationship $V_dSS = (C/\lambda^2)/(C/\lambda)^2$ is 0.645 liters per kg. The dialysis clearance of Ara-Hx, Cl_D, is correlated with plasma flow (Q_p), as shown in Fig. 2. By least squares linear regression, the relationship between the variables is as follows:

$Cl_D = 0.24\ Q_p + 26.79$, $r = 0.94$.

Ara-A is a useful antiviral agent. Although serious dose-related toxicity has not yet been reported, side effects including nausea, vomiting, tremor, and the syndrome of inappropriate antidiuretic hormone secretion resolve when the drug is discontinued (4). Since Ara-Hx is known to accumulate in renal failure patients treated with Ara-A, the dose should be reduced in such patients. If a linear relationship between the terminal elimination rate constant for Ara-Hx and renal function is assumed, the dose (D_A) of

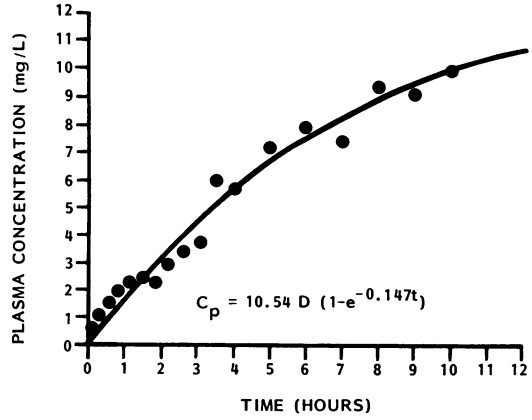

FIG. 1. *Ara-Hx plasma concentration during 10-h constant infusion.*

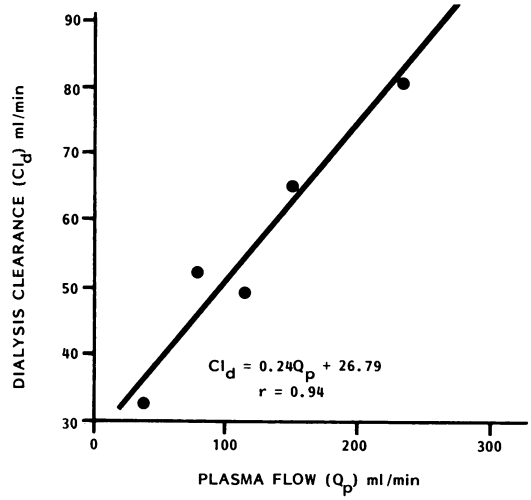

FIG. 2. *Dialysis clearance (Cl_D) was correlated with plasma flow (Q_P).*

Ara-A appropriate for an anuric patient is given by the expression

$$D_A = \frac{t_{1/2}(N)}{t_{1/2}(A)} D_N \quad (6)$$

where $t_{1/2}(N)$ and $t_{1/2}(A)$ are the elimination half-lives of Ara-Hx for normal and anuric patients, respectively, and D_N is the dose appropriate for a patient with normal renal function (1). From the data obtained in our single patient, and from equation 6, we recommend that the dose of Ara-A in patients with severe renal insufficiency be reduced by 25%.

Dialysis clearance of Ara-Hx varies in a linear fashion with plasma flow rate over the range used clinically. From this relationship, we esti-

mate that as much as 50% of the Ara-Hx in the body may be removed during a 6-h hemodialysis at a plasma flow rate of 200 ml/min. Since Ara-A is given by 12-h daily infusion, the dose should be given after dialysis.

Pharmacokinetic assumptions based on data from one patient require cautious interpretation. Until more extensive studies of Ara-A in renal failure are performed, however, the parameters calculated here may serve as a guideline for dosing such patients.

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