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Pentostatin pharmacokinetics and dosing recommendations in patients with mild renal impairment

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Abstract *Purpose*: The purpose of this study was to determine the pharmacokinetic parameters of pentostatin in renally impaired patients in order to establish dosing guidelines for this population. *Methods*: Pentostatin doses were administered as 15-min intravenous infusions to patients based on their measured creatinine clearance (CLcr) as follows. Patients with normal renal function (NRF), defined as CLcr >60 ml/min, received 4 mg/m^2 repeated every14 days. Patients with impaired renal function (IRF) included those with CLcr 41–60 ml/min who received 3 mg/m^2 and those with CLcr 21–40 ml/min who received 2 mg/m^2, also repeated every 14 days. Heparinized plasma samples were collected during drug infusion and out through 96 h after dosing, except in two patients in whom sampling was extended to 144 h after dosing. Urine sampling extended to 96 h after dosing, and all samples were analyzed by a validated enzyme immunoassay for pentostatin concentrations. *Results*: Enrolled in the study were 13 patients (7 IRF and 6 NRF), of whom 12 contributed samples for pharmacokinetic analysis. Median baseline CLcr values were 71.5 ml/min for NRF patients and 44 ml/min for IRF patients. Following the end of intravenous infusion, pentostatin plasma concentrations declined biexponentially with time. In some patients there was a transient increase in pentostatin equivalents 2 to 4 h after dosing. There was a good correlation between measured CLcr and pentostatin total plasma clearance. The AUC(0-∞) values seen in IRF patients, at lower doses, were within the range of the AUC(0-∞) values seen in patients with normal CLcr. Toxicities observed in the two groups of patients were similar. *Conclusions*: The pentostatin doses used in the study appear to be appropriate for administration to cancer patients with varying degrees of renal impairment.

Keywords Pentostatin · Renal impairment · Pharmacokinetics · Toxicity · Dosing recommendations

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Introduction

Pentostatin (2′-deoxycoformycin) is a potent tight-binding inhibitor of adenosine deaminase (ADA), a key enzyme in the purine salvage pathway [1]. It is the oldest of the nucleoside analogs in clinical practice [2], and is currently approved for the treatment of adult patients with hairy cell leukemia at a dose of 4 mg/m^2 every other week. Toxicities associated with this dose are tolerable and include mild to moderate nausea and vomiting, rash, occasional diarrhea, transient reversible elevations in liver enzymes, malaise, flu-like syndrome, and mild to moderate thrombocytopenia and leukopenia [3, 4]. Pentostatin has also been associated with

infections with opportunistic organisms, sepsis and death. Cardiac arrhythmias and abnormal electrocardiograms have been observed following administration with pentostatin. Reversible liver function test abnormalities and serum creatinine elevations have also been observed.

Pentostatin has also demonstrated activity in a variety of indolent lymphoid malignancies including chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma, and cutaneous T-cell lymphoma [3, 4, 5, 6]. It is worth noting that the pentostatin package insert states that two patients with mild renal impairment (50–60 ml/min) achieved a complete response without unusual adverse events when treated at a dose of 2 mg/m^2.

Among patients with normal renal function (NRF), the pharmacokinetic profile of pentostatin has been relatively well characterized [7, 8]. The terminal elimination half-life is approximately 6 h following doses ranging from 2 to 30 mg/m^2 administered either as single doses or multiple daily doses over 3 to 5 days [7, 8, 9]. Mean clearance estimates following doses ranging from 2 to 10 mg/m^2 are also similar with values of 52.4 and 67.9 ml/min per m^2 [2, 7]. Finally, the clearance of pentostatin and creatinine are positively correlated (Pearson correlation coefficient 0.65, $P = 0.003$) with over 90% of drug recovered in the urine [7, 8, 10]. However, because patients with renal dysfunction have not been adequately studied, pharmacokinetic parameters and dosing guidelines for these patient do not currently exist.

The objectives of this study were to determine the effect of renal dysfunction on the pharmacokinetics of a single dose of pentostatin, to assess the toxicity of pentostatin in cancer patients with varying degrees of renal dysfunction and to document the antitumor effects observed.

Patients and methods

Patients

Eligible patients included those with histopathologically confirmed hairy cell leukemia or a malignancy that was either refractory to conventional therapy or without effective therapeutic alternatives. Patients were at least 18 years of age, had a WHO performance status of 2 or less, and had adequate hepatic function as demonstrated by SGOT and SGPT not more than four times the upper limit of normal. Patients were to be without other severe medical or psychiatric illness, and all signed written informed consent in accordance with federal and institutional guidelines. This single-center study was planned to enroll 24 patients; 6 patients with NRF and 18 patients with impaired renal function (IRF) of varying degrees. The dose of pentostatin was determined for each patient based on their measured baseline creatinine clearance (CLcr) (Table 1). CLcr was measured prior to the start of the study by obtaining a 24-h urine collection to determine the creatinine excretion rate over 24 h. Serum creatinine was also measured by colorimetric methods and CLcr was calculated as the ratio of the urinary excretion rate to serum creatinine concentration. Based on anecdotal data from IRF patients treated previously with pentostatin, the following dose levels were selected: 4 mg/m^2 for CLcr ≥60 ml/min, 3 mg/m^2 for CLcr 40–59 ml/min, 2 mg/m^2 for CLcr 20–39 ml/min, and 1 mg/m^2 for CLcr <20 ml/min.

Table 1. Patient characteristics by baseline renal function: impaired (*IRF*) versus normal (*NRF*)

	IRF patients (CLcr <60 ml/min)	NRF patients (CLcr ≥ 60 ml/min)
No. of patients	7	6
Gender (*n*)		
Women	5	3
Men	2	3
Age (years)		
Median	67	65
Range	46–80	55–73
WHO performance status, *n* (%)		
0	2 (29)	3 (50)
1	3 (43)	3 (50)
2	2 (29)	0
Primary tumors, *n* (%)		
Colon	3 (43)	2 (33)
Lymphoma	1 (14)	1 (17)
Lung	1 (14)	0
Cervical	1 (14)	0
CLL	1 (14)	0
Kidney	0	1 (17)
Mesothelioma	0	1 (17)
Bladder	0	1 (17)
Prior treatment, *n* (%)		
Chemotherapy		
1 or 2 regimens	5 (71)	3 (50)
3 or 4 regimens	2 (29)	3 (50)
Immunotherapy	1 (14)	1 (17)
Radiotherapy	5 (71)	2 (33)

Drug administration

Drug was supplied by Parke-Davis Pharmaceutical Research as a lyophilized powder in 5-ml vials, each containing 10 mg pentostatin. Reconstitution with 5 ml sterile water resulted in a concentration of 2 mg/ml and the prescribed drug dose was further diluted in normal saline or dextrose 5% in water for infusion over 15 min. Infusion start and end times were noted for pharmacokinetic analysis. Courses of treatment were repeated every 14 days with dosage adjustments based on tolerance. Pentostatin doses for second and subsequent courses could be increased by 33% if previous toxicities were grade 1 or less, were to remain unchanged if toxicities were grade 2 and were to be reduced by 50% if toxicities reached grade 3. Treatment was discontinued if toxicities reached grade 4. Safety monitoring consisted of clinical laboratory and hematology assessments twice weekly during the initial course of treatment and weekly thereafter. Adverse events were monitored throughout the study based both on solicited patient reports and on physical examinations every 2 weeks. Patients were assessed for response every 28 days. Radiologic studies for disease reassessment were to be conducted every 56 days, and patients with possible evidence of response were permitted to continue on the study.

Pharmacokinetic sampling

Heparinized blood samples were obtained after the first dose from the arm opposite that used for drug administration. Samples were collected predose, and 0.133, 0.25 (end of infusion), 0.333, 0.416, 0.65, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 h after the start of infusion. Samples were also drawn at 120 and 144 h for patients with a CLcr of less than 30 ml/min. Following collection, all blood samples were centrifuged, and the plasma was transferred to polypropylene tubes, and stored at –20°C within 30 min.

Urine samples were collected after the first dose during the following time intervals after the start of infusion: before dosing, and 0–6, 6–12, 12–24, 24–48, 48–72, and 72–96 h after dosing. Following measurement of volume and pH, a 20-ml aliquot was stored at –20°C.

Analytical procedures

Plasma and urine samples were measured by an enzyme assay. Pentostatin concentrations were measured by spectrophotometrically monitoring the inhibition of the conversion of adenosine to inosine by ADA. Briefly, standards, samples, and quality controls (QCs) were incubated with ADA. Samples were first heated in a bath of boiling water for 5 min to inactivate endogenous ADA. Following centrifugation, ADA was added to the sample. The mixture was incubated in a water bath for 5 min, then placed back on ice. The adenosine solution was then added to the sample, and the decrease in UV absorbance of the sample was monitored. A calibration curve was developed with pentostatin in samples to evaluate the decrease in sample absorbance ($\subset$A) after the addition of adenosine. Linear regression analysis of calibration curve data were determined by a plot of log[$\subset$A/(1–$\subset$A)] versus pentostatin concentration where $\subset$A is the change in absorbance over 1.5 min. The equivalent concentrations of pentostatin in plasma/urine were determined from the calibration curves by interpolation.

Plasma pharmacokinetic parameters were obtained by noncompartmental analysis of the plasma concentration-time data using WinNONLIN PRO v1.5 using the methods described here. Cmax was the observed maximum concentration. Tmax was the time to reach Cmax. Area under the concentration-time curve from time zero to the last detectable concentration (ldc), AUC(0-tldc), was estimated used the linear trapezoidal rule. Half-life (t1/2) was calculated from the slope of the terminal elimination phase (λ_z) of the natural log of the plasma concentration-time profile. AUC(0-inf) was calculated as the sum of AUC(0-ldc) and the Cn/λ_z where Cn is the last observed plasma pentostatin equivalent concentration. Total plasma clearance was calculated by dividing the dose by AUC(0-inf). AUMC(0-tldc) was calculated using the trapezoidal rule and AUMC(tn-inf) was calculated as $Cn \times tn/\lambda_z + Cn/\lambda_z^2$. AUMC(0-inf) was calculated as AUMC(0-tldc) + AUMC(0-inf). Mean residence time (MRT) was calculated by dividing the area under the first moment curve (AUMC(0-inf) by AUC(0-inf). Volume of distribution at steady state was by calculated by multiplying the MRT by total plasma clearance. The total amount of drug excreted in urine was obtained by summing the amounts excreted during individual collection intervals. The percent of dose excreted in urine was obtained by dividing the total amount excreted in urine for each individual by the administered dose. Renal clearance (CLr) was calculated by dividing the amount excreted in urine by AUC(0-inf).

Results

A total of 13 patients (7 with IRF and 6 with NRF) with confirmed malignancies not amenable to curative treatments were enrolled between May 1993 and August 1996. Baseline characteristics are shown in Table 1. The study closed before reaching the planned number of patients because of difficulty recruiting patients with IRF. A total of 30 doses were administered, a median of 1 per patient (range 1–9). Nine courses were administered to patients with IRF and 21 courses to patients with NRF (Table 2). One patient enrolled at the 2 mg/m^2 dose level was not sampled for pentostatin levels due to inadequate venous access.

Table 2. Treatment exposure by renal function group: impaired (*IRF*) versus normal (*NRF*)

	IRF patients ($n=7$)	NRF patients ($n=6$)
No. of courses		
1	5	2
2	2	1
3 or 4	0	2
>4	0	1 (9 courses)
Starting dose (mg/m^2)		
2	2	0
3	5	0
4	0	6

Analytical

Plasma

The pentostatin plasma calibration curve ranged from 25 to 200 ng/ml. QCs were used to evaluate the stability of pentostatin in plasma frozen at –20°C and to assess the acceptability of the assay. Plasma samples frozen at –20°C from this study were analyzed between 92 and 290 days after sample collection. The integrity of pentostatin in frozen plasma was demonstrated by its stability in plasma QCs frozen at –20°C for 290 days.

Urine

The pentostatin urine calibration curve ranged from 25 to 500 ng/ml. QCs were used to evaluate the stability of pentostatin in urine frozen at –20°C and to assess the acceptability of the assay. Urine samples were analyzed between 93 and 373 days after collection. Pentostatin was stable in human urine up to 93 days at –20°C. Samples from patient 7 were analyzed 88 days after collection assuring the integrity of pentostatin in those samples. All other patient samples were analyzed after between 114 and 364 days of storage at –20°C. Pentostatin equivalents in these samples stored at –20°C are likely to be 4.72% to 27.1% lower than their initial concentrations based on evaluation of QCs stored at –20°C for 373 days. Because urine concentrations may be underestimated due to pentostatin instability, the calculated values of percent of dose excreted in urine presented in Table 3 may be slight underestimates of the true values.

Pentostatin pharmacokinetics

Pentostatin equivalent pharmacokinetic parameters are presented in Table 3. A significant portion of the plasma AUC(0-inf) was obtained by extrapolation for patients 1 and 4. Pentostatin clearance estimates in these patients may be less accurate than those in other patients. Following completion of the intravenous infusion,

Table 3. Pentostatin plasma and urinary pharmacokinetic parameters following a 15 min intravenous infusion of pentostatin to patients with varying degrees of renal impairment (protocol 825-01-1) (*CLcr* creatinine clearance obtained by dividing urine creatinine excretion rate by serum creatinine concentration, *Cmax* maximum dosed plasma concentration, *AUC(0-tldc)* area under the plasma concentration-time curve from time zero to last detectable concentration, *t1/2* terminal elimination half-life, *AUC (0-inf)* area under the plasma concentration curve from time zero to infinity, *CL* total plasma clearance, *CLr* renal clearance, *Vss* plasma volume of distribution at steady state, *% Dose in urine* percent of dose excreted in the urine as pentostatin equivalents)

Patient no.	Dose (mg/m^2)	CLcr (ml/min)	Cmax (ng eq/ml)	AUC(0-tldc) (ng eq·h/ml)	t1/2 (h)	AUC(0-inf) (ng eq·h/ml)	CL (ml/min)	CLr (ml/min)	Vss (l)	% Dose in urine
1	3	44.0	448	866	8.62	1325	53.6	11.1	36.0	20.6
2	3	49.0	412	656	3.67	861	94.4	31.0	26.2	32.8
3	4	103	556	997	6.63	1291	99.4	29.4	45.6	29.6
4	2	35.0	188	429	9.01	833	56.0	21.2	38.9	37.9
5	4	176	468	543	2.85	663	206.1	44.1	39.5	21.4
6	3	55.0	354	597	4.52	792	92.6	49.7	30.2	53.6
7	3	53.0	348	1210	10.3	1644	62.8	20.3	49.8	32.2
8	4	75.0	330	982	6.32	1297	95.1	53.4	46.5	56.2
9	4	61.0	318	645	4.55	860	128	84.0	44.9	65.6
10	3	42.0	319	956	6.84	1342	72.7	32.1	40.8	44.2
11	4	61.0	780	1801	5.65	2011	72.1	40.0	32.1	55.4
12	4	68.0	481	998	6.08	1272	84.9	38.1	37.5	44.9

pentostatin plasma equivalents appeared to decline biexponentially with time. In some patients there was a transient increase in pentostatin equivalents between 2 and 4 h after dosing. Pentostatin total clearance is plotted as a function of measured CLcr in Fig. 1. As seen previously [4], there was a linear correlation between these two variables. CLcr appeared to be predictive of total plasma clearance with a coefficient of determination of 0.790 ($P = 0.00012$). Pentostatin renal clearance was evaluated as a function of measured CLcr. Pentostatin renal clearance was not correlated with CLcr. While the precise reason for this lack of correlation is unknown, it may have been due to inconsistent and incomplete urinary collections in several patients and potentially to binding of pentostatin to collection and measurement containers.

Figure 2 is a plot of the area under the plasma concentration-time curve versus dose. Doses in this study were adjusted based on the measured CLcr at screening. The AUC(0-inf) values seen in the IRF patients at lower doses were within the range of AUC(0-inf) values seen in patients with normal CLcr receiving doses of 4 mg/m^2 or higher. Similarly, Cmax values in IRF patients were in the same range as the Cmax values in patients with CLcr >60 ml/min. This suggests that the doses used in this study administered to the IRF patients gave exposures similar to the doses administered to the NRF patients (CLcr >60 ml/min).

The mean plasma clearance in the NRF patients was 114 ml/min compared to 72 ml/min in the IRF patients. The mean terminal half-life in the NRF patients was 5.35 h compared to 7.16 h in the IRF patients. Pentostatin renal clearance was 48.2 ml/min in the NRF patients versus 27.5 ml/min in the IRF patients.

Toxicities

Treatment-related toxicities were generally mild, and consisted primarily of nausea, vomiting, anorexia, and fatigue (Table 4). One patient with heavily pretreated non-Hodgkin's lymphoma and normal renal function developed a cutaneous herpes zoster infection after 11 doses. This resolved uneventfully. Her CD4 count was noted at the time to be 28.

Three deaths occurred on study. Patient 4 who had advanced CLL and received a dose of 2 mg/m^2 was admitted on study day 7 with weakness, fatigue, and

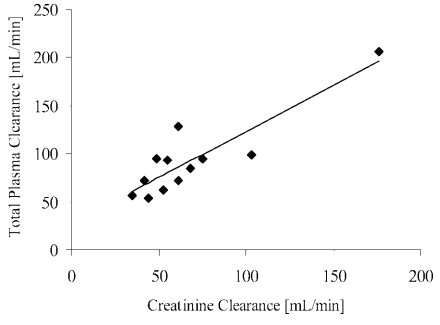

Fig. 1. Pentostatin total plasma clearance versus creatinine clearance in cancer patients with varying degrees of renal function. *Solid line* is the linear regression line ($r^2 = 0.79$, $P = 0.00012$)

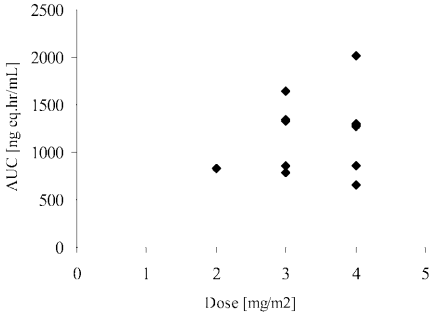

Fig. 2. Pentostatin plasma AUC(0-inf) versus dose following a 15-min intravenous infusion of pentostatin (CI-825) administered to patients with varying degrees of renal function

Table 4. Adverse events expressed as NCI common toxicity grade by renal function group: impaired (*IRF*) versus normal (*NRF*) (values indicate the numbers of patients with each toxicity grade)

Toxicity	IRF ($n=7$)				NRF ($n=6$)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Nausea/vomiting	1	3	–	–	3	1	–	–
Anorexia/weight loss	1	1	1	–	–	–	–	–
Diarrhea/constipation	–	1	–	–	1	–	–	–
Stomatitis	–	–	–	–	1	–	–	–
Fever	–	1	–	–	–	–	–	–
Malaise/fatigue	–	1	–	–	2	1	–	–
CNS (depression/confusion)	1	–	–	–	–	1	–	–
Cardiovascular[a]	–	1	–	1	–	–	–	–
Abdominal pain	–	1	–	–	–	–	–	–
Respiratory infection	–	–	–	–	–	1	–	–
Intermittent numbness	–	–	–	–	–	1	–	–
Herpes zoster	–	–	–	–	–	–	1	–
Clinical laboratory toxicities								
Transaminase/bilirubin	2	–	–	1	1	1	1	–
Urea/creatinine	2	–	2	–	–	–	–	–
Uric acid	–	1	–	–	–	–	–	–
Neutropenia	–	–	–	–	–	–	1	–
Decreased CD4[b]	–	–	–	–	–	–	1	–

[a]One patient each with chest pain and venous occlusion
[b]Decrease in CD4 cell count noted in one patient only but levels not assessed routinely in all patients

dehydration. However, she did not become neutropenic. Her clinical picture was initially felt to be consistent with sepsis, but no organism was isolated. She died on day 13. Autopsy revealed complete occlusion of the inferior vena cava. It was felt that this was unlikely to have been related to pentostatin. Patient 7 was an 80-year-old male with colon cancer metastatic to the liver treated with 3 mg/m^2. He developed fever, hyperbilirubinemia, neutrophilia, and abdominal pain. No infectious source was isolated. He was treated with antibiotics, including tobramycin. His creatinine rose to 4.3 mg/dl. Even though the fever resolved, he died on day 10. This event was considered possibly related to pentostatin. Patient 10 had advanced non-small-cell lung cancer, a history of coronary artery disease and IRF. He developed worsening chest pain after the first dose of pentostatin at 3 mg/m^2. The patient's cardiologist authorized further pentostatin treatment, and the dose was increased to 4 mg/m^2, as there had not been significant toxicity. On day 4 following the second dose the patient was admitted with dehydration and increasing hypoxemia. Symptoms were attributed to progression of underlying pulmonary and cardiac disease, and he died on day 11 of his second course.

No complete or partial responses were observed in this study following pentostatin administration.

Discussion

In patients with NRF, pentostatin pharmacokinetics have been evaluated at doses ranging from 2 to 30 mg/m^2 administered both as single and multiple daily doses for 3 to 5 days. The mean half-life is approximately 6 h and pentostatin total plasma clearance is reported to range from 52.4 to 67.9 ml/min per m^2. Clearance of pentostatin has been reported to be correlated with CLcr with recovery of greater than 90% of drug in urine [4]. However, other investigators have reported a smaller percent of dose excreted unchanged in urine. Major et al. have reported excretion of between 50% and 73% of the administered dose [8] while Smyth et al. have reported 32–48% recovery in urine [9]. Pentostatin is not highly bound to plasma proteins (3.8%) and binding is reported to be independent of plasma drug concentrations. The mean apparent volume of distribution at steady-state is 20 l/m^2 whereas the mean volume of distribution of the central compartment is 5.94 l/m^2.

An anecdotal report of two patients with IRF (CLcr < 50 ml/min) [10] describes pentostatin doses of 0.4, 1.0, 2.0, and 3.0 mg/m^2 administered to one patient and 3 mg/m^2 administered to the other patient. The terminal elimination half-life of pentostatin was prolonged by approximately two- to fourfold (range 11–23 h) with a comparable decrease in total plasma clearance to 16.6 ml/min per m^2. Pentostatin pharmacokinetics were subsequently evaluated in 28 patients with NRF and 8 patients with IRF (CLcr < 60 ml/min) [11]. Pentostatin plasma clearance in patients with NRF was 64.12 ± 23.89 ml/min per m^2 compared to 26.7 ± 13.16 ml/min per m^2 in patients with IRF. Similarly, the harmonic mean terminal elimination half-life was 6.05 h in patients with NRF and 11.26 h in patients with IRF. This study recommended a dose reduction for patients with a CLcr of 30–50 ml/min and adequate performance status to one-quarter the recommended starting dose in patients with NRF.

The results of this study reveal that CLcr predicts total pentostatin plasma clearance but not pentostatin renal clearance. Pentostatin total plasma clearance and

renal clearance were lower in patients with IRF. Patients with IRF eliminated pentostatin more slowly, as indicated by a longer half-life. Pentostatin AUC(0-∞) values were similar across the various renal clearance groups, suggesting that initial pentostatin doses used in this study are appropriate: specifically 3 mg/m^2 for patients with a CLcr in the range 41–60 ml/min. Two patients with a baseline CLcr in the range 35–40 ml/min were treated with a dose of 2 mg/m^2 pentostatin. Pharmacokinetic data were obtained from only one of these two patients. One patient with CLcr in the range 35–40 ml/min tolerated 2 mg/m^2 without clinical problems.

Toxicities experienced by both NRF and IRF patients were comparable and generally mild in this study. Pentostatin doses can be adjusted in patients with IRF based on their CLcr. No patients were enrolled in this study with a CLcr of less than 35 ml/min. Therefore, caution should be exercised in administering pentostatin to patients with a CLcr of less than 35 ml/min. Patients with IRF should be dosed cautiously and monitored frequently as very few patients with IRF have been dosed and evaluated for safety.

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