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ORIGINAL ARTICLE

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Pharmacokinetics of 2-chloro-2′-deoxyadenosine administered subcutaneously or by continuous intravenous infusion

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Abstract *Purpose*: Cladribine (2-chlorodeoxyadenosine, 2-CDA) is effective in the treatment of various lymphoproliferative disorders. In the standard protocol the compound is administered by continuous intravenous (i.v.) infusion. In order to allow outpatient therapy alternative modes of administration such as subcutaneous (s.c.) injection would be desirable. The aim of the present study was to compare the pharmacokinetics of 2-CDA after i.v. and s.c. administration. *Patients and methods*: Nine patients received 0.1 mg/kg 2-CDA per 24 h on one occasion by continuous i.v. infusion and on another occasion as a bolus subcutaneously. The concentrations of 2-CDA in the plasma and urine were determined by HPLC. *Results*: During i.v. infusion the concentration of 2-CDA in the plasma reached a plateau after 4–8 h, whereas with s.c. administration almost ten times higher peak concentrations were reached within 20 to 60 min. A two-compartment model was fitted to the data points whereby the goodness-of-fit statistics showed R^2 values of >0.98. The calculated rate of elimination, k_{elim}, averaged 0.336 h^{-1} with s.c. and 0.397 h^{-1} with i.v. administration. The estimated volumes of distribution were 1.67 and 1.58 l/kg. The areas under the concentration time curves (608 ± 65 pmol·h/ml after s.c. administration vs 571 ± 50 pmol·h/ml during i.v. infusion) and the urinary excretion of 2-CDA in 24 h (4.75 ± 0.95 vs 3.55 ± 0.53 μmol/24 h) were similar in both groups, indicating identical bioavailability. *Conclusions*: Although the pharmacokinetic profile of 2-CDA administered s.c. differs substantially from the profile of a continuous i.v. infusion the areas under the plasma concentration time curves, the urinary excretion of unchanged drug and the estimated pharmacokinetic variables were similar with both modes of administration, indicating that the different time-courses of the plasma concentration did not influence the fraction metabolized or eliminated.

Key words Cladribine · 2-Chlorodeoxyadenosine · Pharmacokinetics · Bioavailability · Intravenous · Subcutaneous

Introduction

Cladribine (2-chlorodeoxyadenosine, 2-CDA) is a purine nucleoside analogue resistant to deamination by adenosine deaminase and is effective in the treatment of hairy-cell leukemia and other lymphoproliferative disorders [6]. In the initial studies the drug was administered by continuous intravenous infusion which requires hospitalization of the patient. Alternative modes of administration would be desirable in order to simplify the treatment and to reduce costs. The bioavailability of 2-CDA administered orally or rectally is limited [1, 10, 11]. Administered subcutaneously, however, the bioavailability of 2-CDA is 100% when compared to a 2-h infusion of 2-CDA [9]. The profiles of the plasma concentrations with these two modes of application are similar but may differ substantially from the profile obtained with continuous intravenous infusion over 24 and more hours. Since concentration-dependent alterations in the disposition of 2-CDA cannot be ruled out, the goal of the present investigation was to compare the pharmacokinetics of 2-CDA following subcutaneous administration and during a continuous 24-h infusion.

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Material and methods

Patients

Nine patients (seven males and two females, 46–70 years of age, weight 58–86 kg) were studied on two occasions. On one occasion, 0.1 mg/kg of 2-CDA was administered as a bolus subcutaneously. On the other occasion, a continuous intravenous infusion of 2-CDA was infused over 48 h at a dose of 0.1 mg/kg per 24 h. Heparinized 5-ml blood samples were obtained at 0.5, 1, 1.5, 2, 4, 8, 24, 36, 48, 49, 51 and 56 h during and after the infusion of 2-CDA and at 5, 10, 20, 30, 60, 90, 120, 240, 480, and 1440 min after subcutaneous injection. Urine was collected at intervals.

The study was approved by the local ethics committee and all patients gave informed consent to participation in the study.

Analysis

For the analysis of 2-CDA in plasma and urine the procedure of Albertioni et al. [2] was used with the following modifications. For sample preparation a C8 cartridge with 500 mg adsorbent was used (Isolute, ICT AG Basel, Switzerland). The column was rinsed with 4×1 ml water and 4×1 ml 1:1 toluol/ether. 2-CDA was then eluted with 3×0.75 ml 5% methanol in ethyl acetate. The mobile phase for the isocratic analysis by reversed-phase high-performance liquid chromatography consisted of 10 m*M* KH_2PO_4, 15.9 m*M* triethylamine, 18.2 m*M* phosphoric acid, pH 4.0, and 7.8% acetonitrile at a flow rate of 0.8 ml/min. Separation was accomplished using a C_{18}-column (3 μm, 125×4 mm; Macherey Nagel, Egerkingen, Switzerland). 6-Nitroimidazole-6-thioguanine served as internal standard. After each run the column was washed with the same buffer containing 30% acetonitrile for 15 min.

Standard curves were obtained by spiking human plasma with 12.5 to 200 pmol/ml of 2-CDA. The recovery assessed by comparing peak area ratios of drug to internal standard after extraction with the ratio obtained from direct injection of equivalent quantities of standards exceeded 95% at 25 and 100 pmol/ml. To determine interassay and intraday variability, plasma samples spiked with 2-CDA were assayed repeatedly. The interassay and intraday coefficients of variation amounted to less than 10% ($n = 6$) at concentrations of 12.5 and 100 pmol/ml, similar to those that have been reported for the method [2].

Calculations and statistics

The areas under the plasma concentration time curves (AUC) were calculated using the trapezoidal rule. Clearance was calculated as dose/AUC. A two-compartment model with first-order input for the subcutaneous mode of administration and with timed constant input for the intravenous mode of administration was fitted to the pooled data using the program PKAnalyst (MicroMath Scientific Software). All data are reported as means ± SE unless mentioned otherwise.

Results and discussion

The time-course of the concentration of 2-CDA in plasma during the continuous intravenous infusion and following a bolus subcutaneous administration is shown in Fig. 1. During the intravenous infusion the concentration of 2-CDA in plasma reached a plateau after approximately 12 h. After stopping the infusion the plasma concentration decreased with a half-life averaging 6.1 h. With subcutaneous administration peak concentrations of almost ten times the concentrations obtained with continuous intravenous infusion were reached within 20 to 60 min (Table 1). The concentration then gradually decreased in a biexponential fashion. By 8 h after subcutaneous administration the concen-

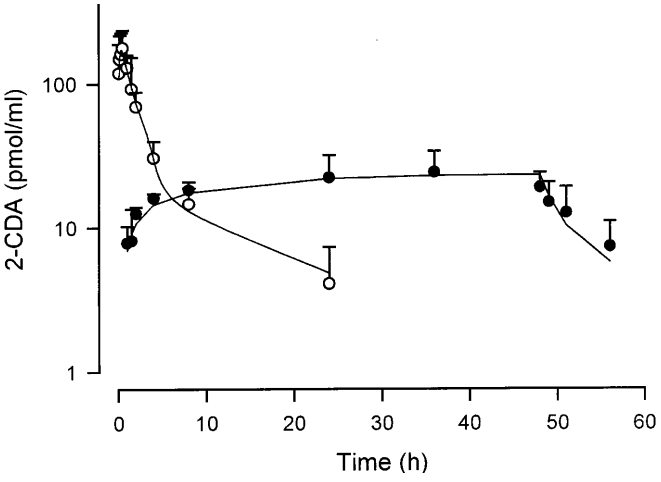

Fig. 1 Plasma concentration of 2-CDA during intravenous infusion of 2-CDA for 48 h at a rate of 0.1 mg/kg per 24 h (*closed circles*) and following a subcutaneous bolus injection of 0.1 mg/kg (*open circles*). The values are means ± 95% confidence intervals ($n = 9$). The lines represent the curves fitted to the data based on a two-compartment model with first-order and constant-rate input for subcutaneous and intravenous administration, respectively

Table 1 Peak plasma concentration of 2-CDA after subcutaneous administration, plateau plasma concentration during intravenous infusion and areas under the plasma concentration-time curve for the two modes of administration in individual patients

Patient	Weight (kg)	Age (years)	C_{max} s.c. (pmol/ml)	$C_{plateau}$ i.v. (pmol/ml)[a]	AUC_{0-24h} s.c. (pmol·h/ml)	AUC_{0-24h} i.v. (pmol·h/ml)
1	73	70	168	21	659	619
2	64	68	137	21	713	600
3	75	55	148	19	601	545
4	70	46	359	15	226	449
5	82	52	128	12	500	402
6	86	62	134	20	605	927
7	58	70	225	17	492	490
8	70	59	156	16	757	575
9	77	61	160	17	915	535
Mean ± 95% CI			179 ± 56	18 ± 2	608 ± 149	571 ± 116

[a] Average concentration between 8 and 24 h

tration averaged 14.6 ± 1.9 pmol/ml compared to 16.1 ± 0.6 pmol/ml at the same time-point during intravenous infusion.

A two-compartment model was fitted to the data points and the goodness-of-fit statistics showed R^2 values of 0.996 and 0.983 for subcutaneous and intravenous administration, respectively. The calculated rate of elimination, k_{elim}, averaged 0.336 h^{-1} with subcutaneous and 0.397 h^{-1} with intravenous administration. The estimated volumes of distribution were 1.67 and 1.58 l/kg body weight.

The areas under the concentration time curves (608 ± 65 pmol·h/ml after subcutaneous administration vs 571 ± 50 pmol·h/ml during intravenous infusion) and the urinary excretion of 2-CDA in 24 h (4.75 ± 0.95 vs 3.55 ± 0.53 μmol/24 h) were similar in both groups. The urinary excretion amounted to 17.7 ± 3.4% and 13.6 ± 2.2% of the administered dose for subcutaneous and intravenous administration, respectively. The calculated plasma clearance was 814 ± 121 ml/min after subcutaneous administration and 794 ± 62 ml/min during intravenous infusion.

Subcutaneously administered 2-CDA was rapidly absorbed from the site of injection and peak concentrations in plasma were reached within 30 min in most instances. The pharmacokinetic profile of 2-CDA administered subcutaneously thus differed substantially from the profile of a continuous intravenous infusion. Initially, much higher concentrations of the drug were reached in plasma, whereas the concentrations were lower than during intravenous infusion from approximately 8 h onwards. The areas under the plasma concentration time curves, the urinary excretion of unchanged drug and the estimated pharmacokinetic variables such as volume of distribution and rate of elimination were similar with both modes of administration, indicating that the different time-course of the plasma concentration does not influence the fraction metabolized or eliminated via the kidneys.

2-CDA must be metabolically activated to the triphosphate by intracellular deoxycytosine and deoxyguanosine kinases. Since the rate of phosphorylation depends on the concentration of the phosphate acceptor, i.e 2-CDA, it is conceivable that the much higher concentrations of 2-CDA reached after subcutaneous administration will result in higher intracellular concentrations of the active nucleotide. However, there is a poor correlation between the plasma concentration of 2-CDA and intracellular 2-CDA nucleotides [8]. Moreover, in several comparative, albeit not randomized, clinical studies, the efficacy of 2-CDA administered subcutaneously has been found to be similar to that of intravenous infusion in the treatment of hairy-cell leukemia [7, 12] and chronic lymphocytic leukemia [4, 5], and 2-CDA has also been found to be effective in the treatment of patients with Waldenstrom's macroglobulinemia [3].

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