DRUG DISPOSITION

Clin. Pharmacokinet. 1997 Feb; 32 (2): 120-131
0312-5963/97/0002-0120/$06.00/0

The Clinical Pharmacokinetics of Cladribine

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Summary

Cladribine is a new purine nucleoside analogue with promising activity in low-grade lymphoproliferative disorders, childhood acute myelogenous leukaemia and multiple sclerosis. Reversed phase high performance liquid chromatography and radioimmunoassay have been used for the analysis of the plasma pharmacokinetics of cladribine. The major (inactive) metabolite in plasma, chloroadenine, can only be detected by liquid chromatography.

The oral bioavailability of cladribine is 37 to 51%, and that of subcutaneous administration is 100%. The terminal half-life varies from 5.7 to 19.7 hours and the apparent volume of distribution from 54 to 357 L/m^2. The concentration in the cerebrospinal fluid is 25% of that in plasma in patients without central nervous system disease; in patients with meningeal disease, the cladribine concentration in the cerebrospinal fluid exceeds that in plasma.

Cladribine is a prodrug and needs intracellular phosphorylation to active nucelotides. The intracellular concentration of these metabolites is several hundred-fold higher than that of cladribine in plasma and they are retained in leukaemia cells with half-lives between 9 and >30 hours depending on diagnosis and

sampling schedule. There is no correlation between the plasma concentration of cladribine and that of the intracellular metabolites.

The renal clearance of cladribine is 51% of total clearance and 21 to 35% of an intravenously administered dose is excreted unchanged in the urine. Pretreatment with cladribine increases the intracellular accumulation of the active metabolite of cytarabine, cytosine arabinoside 5′-triphosphate, by 36 to 40%.

The first report on the synthesis and antileukaemic effect of cladribine (2-chloro-2′-deoxycytidine, CdA) was published in 1972.[1] Later it was discovered that severe immunodeficiency in children was, in a fraction of patients, caused by deficient adenosine deaminase (ADA).[2] Deoxyadenosine accumulates in plasma and dATP in cells with high deoxycytidine kinase (dCK) activity. Such perturbations of the deoxyribonucleotide pools leads to DNA-strand breaks, poly(ADP)ribosyl transferase activation, consumption of NAD, ATP depletion and loss of viability.[3] Cladribine and other C-2 halogenated purines (e.g. fludarabine) are resistant to ADA due to protonation at N-7 instead of N-6[4] which prevents hydroxylation and deamination at N-6. Cladribine 5′-triphosphate, with similar toxic effects to those of dATP, accumulates in dCK-rich tissues; treatment with cladribine can, therefore, mimic ADA-deficiency.

Due to the lack of a solid patent, the development of the drug for clinical use was severely slowed. Thanks to the efforts of Dennis Carson and Ernest Beutler at Scripps Clinic, La Jolla, cladribine was eventually taken through preclinical and early clinical testing.[5-7] Under the Orphan Drug Act, cladribine was licensed as Leustatin® in 1994 and has emerged as one of the more important drugs in the therapeutic armament against lymphoproliferative disorders.[8] The use of cladribine in children was investigated independently at St Jude Children's Hospital, Memphis, USA.[9] While the metabolism and mechanism of action of cladribine was elucidated early, the clinical pharmacokinetics have not been delineated until recently. The pharmacokinetic data has, however, grown steadily during recent years.

Cladribine is the drug of choice for the treatment of hairy cell leukaemia.[10,11] It has definite activity in chronic lymphocytic leukaemia[12-15] and low-grade non-Hodgkin's lymphoma[15-18] although the exact role of cladribine in the treatment of these diseases is still a matter of some controversy. The use of purine analogues in the treatment of low-grade lyphoproliferative disorders was recently reviewed.[19] Responses are also seen in acute myelogenous leukaemia in children[20] and in psoriatic arthritis.[21] A randomised, double-blind, cross-over trial showed impressive activity in patients with chronic progressive multiple sclerosis.[22,23] In experimental systems, cladribine potentiates the immunosuppressive effect of cyclosporin and has potential in the treatment of transplant rejection.[24]

1. Bioanalysis

The plasma pharmacokinetics of cladribine have been studied during continuous infusion and after intravenous short infusion, subcutaneous injection, oral, and rectal administration. The concentration of cladribine has been determined with liquid chromatography[25,26] and radioimmunoassay.[20,27] Liquid chromatography has the advantage of identifying the catabolite 2-chloroadenine (CAde) while radioimmunoassay can be somewhat more

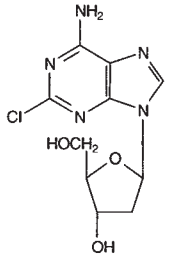

Fig. 1. The chemical structure of cladribine (2-chloro-2′-deoxyadenosine).

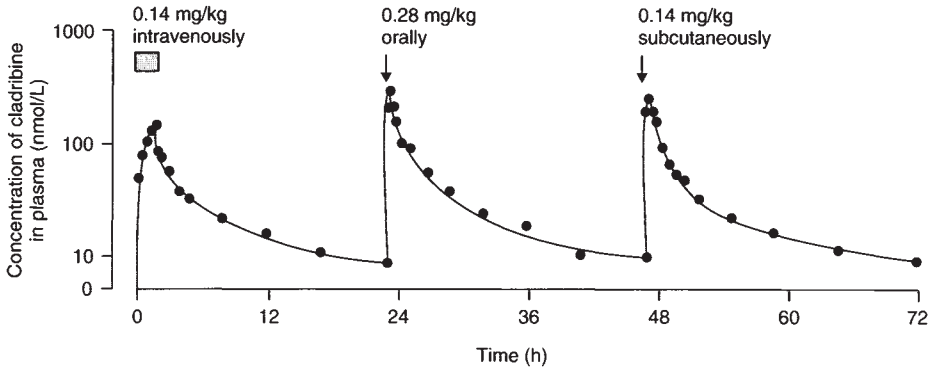

Fig. 2. The plasma concentration of cladribine after intravenous [area under the concentration-time curve (AUC) = 791 nmol/L • h], oral (AUC = 878 nmol/L • h), and subcutaneous (AUC = 709 nmol/L • h) administration of cladribine (from Liliemark et al.,[30] with permission).

sensitive (detection limit 1 *vs* 0.2 nmol/L). The comparison of pharmacokinetic data for cladribine between investigators is obscured by differences in the absorption coefficient ($\varepsilon = 15.0 \times 10^3$ L/mol)[1,28] used for determination of the cladribine concentration in standards.[5] In the early clinical and pharmacokinetic studies (before 1993) the absorption coefficient for chloroadenine ($\varepsilon = 12.6 \times 10^3$ L/mol) was used. Therefore, the dose and plasma concentration in these studies were overestimated by 15%.

2. Bioavailability

2.1 Oral Administration

There are 4 reports on the oral bioavailability of cladribine.[29-32] The oral bioavailability in these trials varies from 37 to 51% when the saline solution for intravenous administration is given to patients to drink.[29,30,32] Thus, when administered orally at about twice the intravenous dose, the areas under the concentration-time curve (AUC) are similar (fig. 2).

When compared with 2-hour intravenous infusion (0.12 mg/kg ≈ 5 mg/m^2) the maximum concentration was slightly higher but the peak briefer after oral (0.24 mg/kg ≈ 10 mg/m^2) or subcutaneous administration (0.12 mg/kg) [142 nmol/L after intravenous infusion *vs* 165 nmol/L after oral and and 268 nmol/L after subcutaneous administration].[30] In some other antimetabolites (i.e. cytarabine and 6-mercaptopurine),[33,34] bioactivation is impaired when the drug concentrations achieved are above the Michaelis-Menten constant (Km) of the bioactivating enzymes. The plasma concentration of cladribine achieved by subcutaneous or oral administration is, however, at least one log lower than the Km of dCK, the intracellular CdA phosphorylation enzyme.[35] Thus, the drug concentrations achieved with a standard dose are far from saturating the bioactivation.

The interindividual variability of the bioavailability is considerable [coefficient of variation (CV) = 28%] but the variability of the AUC after oral administration is not any greater than that after intravenous administration (CV = 38 *vs* 36%).[30]

Cladribine is not stable at low pH (pH < 2). However, attempts to increase the pH in the stomach with omeprazole before the oral administration of cladribine have not improved the bioavailability significantly.[29] Neither was the use of enteric coated capsules of any benefit.[30] Concomitant food intake slowed and lowered the uptake of cladribine.[29] However, despite a limited bioavailability, oral administration of cladribine has been used successfully in the treatment of previously untreated chronic lymphocytic leukaemia[36,37] and psoriatic arthritis.[21]

2.2 Subcutaneous Administration

Cladribine has no local tissue toxicity and when given subcutaneously, the bioavailability is 100%.[30] Subcutaneously administered cladribine was used in 1 large trial on hairy cell leukaemia. The therapeutic results seems to be equivalent with those after continuous intravenous infusion.[10]

2.3 Rectal Administration

Based on the impressive improvement of the bioavailability of 6-mercaptopurine with rectal administration as compared with oral administration,[38] an attempt has been made to improve the bioavailability of cladribine with rectal administration. However, cladribine is degraded by bacterial enzymes and the bioavailability by the rectal route is poor, only 20%.[39]

3. Distribution

During continuous infusion (5 to 10 mg/m^2 per 24 hours which corresponds to a dose of 0.12 to 0.24 mg/kg per 24 hours)[40] the concentration of cladribine in plasma is 10 to 50 nmol/L,[6,20,41] while during a 2-hour infusion of 5 mg/m^2 it is 100 to 400 nmol/L[27,41,42] (fig. 3). There appears to be a linear dose/concentration relationship for cladribine in this dose range (0.2 mg/m^2 per hour to 2.5 mg/m^2 per hour) although Marks et al.[42] reported a dose-dependent clearance decreasing from 52.7 to 26.5 L/h/m^2 with increasing dosages from 3.5 to 10.5 mg/m^2.

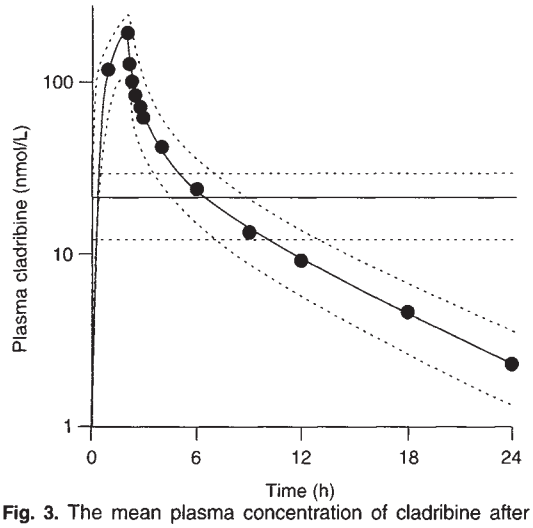

Fig. 3. The mean plasma concentration of cladribine after 2 hours intravenous infusion in 12 patients. The data are fitted to a 3-compartment open model. The horizontal line shows the steady-state concentration of cladribine in the same patients after continuous intravenous infusion of the same dose during 24 hours. The broken lines represent 1 SD in the population (from Liliemark and Juliusson,[41] with permission).

The plasma elimination follows a 2- or 3-compartment open model depending on sampling procedure. The terminal half-life ($t_{1/2}$) is relatively long, 7 to 19 hours. The pharmacokinetics of cladribine after intravenous administration are summarised in table I.

3.1 Penetration of the Blood-Brain Barrier

The concentration of cladribine in the cerebrospinal fluid is approximately 25% of the plasma concentration at dose rates between 0.17 mg/m^2/h and 2.5 mg/m^2/h intravenously in patients without known meningeal disease.[43,44,46] The kinetics of the cerebrospinal fluid concentration roughly follows those of the plasma.[43] The cerebrospinal fluid concentration increases linearly with dose.[43,46] No data are available on the penetration of cladribine into cerebral tissues. However, several responses have been noted in patients with astrocytomas, indicating that the drug is distributed to the brain, at least when the blood-brain barrier is damaged. Furthermore, cerebral toxicity was noted in patients treated with higher doses of cladribine (0.4 to 0.5 mg/kg daily for 7 to 14 days) than commonly used.[27]

In 2 papers it has been reported that cladribine can indeed have an effect on meningeal disease when administered intravenously.[47,48] In 1 patient, with a meningeal involvement of Waldenström's macroglobulinaemia, the cerebrospinal fluid concentration of cladribine exceeded that in plasma, which suggests that meningeal involvement increases the penetration of cladribine into the cerebrospinal fluid.[47]

Table I. Plasma pharmacokinetics of cladribine

Diagnosis	n	Dose/day (mg/m^2)	Duration (h)	Mean AUC (μmol/L • h)	$t_{½\alpha}$ mean (min)	$t_{½\beta}$ (h)	$t_{½\gamma}$ (h)	Vd_{SS} mean (SD) [L/m^2]	Cl mean (SD) [$L/h/m^2$]	Reference
CLL, HCL, and NHL	12	5.5	2	0.59	8	1.1	6.3	368 (216)[a]		41
CLL and NHL	13	5.0	2	0.76		0.7	9.9	53.6 (23.7)	25.9 (7.8)	43
CLL	4	5.0	2	0.70			13.4		39.1 (6.8)	29
Paediatric AML and ALL	5	8.9	24		3.1		14.2	305.1	36.1	20
Paediatric AML	25	8.9	24				19.7	356.6 (225.2)	39.4 (12.4)	44
Solid tumour	25	3.5-10.5	2	0.26-1.47			5.7	121	26.5-52.7[b]	45
CML	11	6-12	2	0.53-1.14	11.9	1.5	6.0	174	45.1	42

a Vd of the peripheral compartment.

b Dose dependent.

Abbreviations and symbols: ALL = acute lymphocytic leukaemia; AML = acute myelogenous leukaemia; AUC = area under the concentration-time curve; Cl = clearance; CLL = chronic lymphocytic leukaemia; CML = chronic myelogenous leukaemia; h = hour(s); HCL = hairy cell leukaemia; NHL = non-Hodgkin's lymphoma; n = number of patients; $t_{½\alpha}$ = distribution half-life; $t_{½\beta}$ = elimination half-life; $t_{½\gamma}$ = terminal half-life; Vd = volume of distribution.

4. Metabolism

4.1 Catabolism

CAde is the major metabolite in plasma.[25] The higher concentration of this catabolite in plasma after the oral administration of cladribine (fig. 4) is probably due to the degradation of cladribine by gastric acid and the subsequent absorption of the metabolite or by hepatic or intestinal first-pass effect. CAde has no cytotoxic or antitumour effect at the concentrations achieved.

4.2 Bioactivation

Cladribine is phosphorylated to its 5′-monophosphate by dCK[7] and deoxyguanosine kinase.[49] This latter enzyme is found in mitochondria and a high activity is present in samples from brain tumours and melanomas[49] and may be of importance for the therapeutic effect in these tumours.[46] However, deoxyguanosine kinase is a mitochondrial enzyme and it is unclear whether the phosphorylation of cladribine in mitochondria induces the same cytotoxic effects as phosphorylation in the cytoplasm by dCK. dCK phosphorylates a number of nucleoside analogues and is the rate limiting enzyme in the bioactivation of cytarabine (ara-C) and fludarabine, another adenosine deaminase resistant purine analogue (fig. 5). Cladribine, however, seems to be phosphorylated readily to the monophosphate but, at least *in vitro*, the concentrations of the di- and triphosphate nucleotides are approximately 7 and 3 times lower than those of the monophosphate.[9,50]

Cytoplasmatic 5′-nucleotidase[51] dephosphorylates and deactivates cladribine 5′-monophosphate. The level of this enzyme in tumour cells seems to be important for sensitivity to cladribine treatment[51,52] and probably determines the retention of cladribine nucleotides in tumour cells.

4.3 Intracellular Pharmacokinetics

The intracellular pharmacokinetics of the total cladribine nucleotide pool have been described in hairy cell, chronic lymphocytic, and acute myelogenous leukaemias after intravenous, oral, and subcutaneous administration.[31] The intracellular concentration of the cladribine nucleotides is several hundred-fold higher than the plasma concentration of the parent drug (fig. 6). Furthermore, the cladribine nucleotides are well retained in leukaemia cells in patients with chronic lymphocytic leukaemia with a terminal $t_{½}$ of around 30 hours when the cellular concentration is monitored during 3 to 7 days (fig. 6). These data support the use of intermittent administration, which has been gaining widespread use lately.[53-55]

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