Br. J. clin. Pharmac. (1981), **12**, 507–510

THE PHARMACOKINETICS OF SUBCUTANEOUS CYTOSINE ARABINOSIDE IN PATIENTS WITH ACUTE MYELOGENOUS LEUKAEMIA

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1 The pharmacokinetics of subcutaneous cytosine arabinoside were compared with bolus intravenous injection and intravenous infusion in five patients with acute myelogenous leukaemia.

2 Subcutaneous cytosine arabinoside was rapidly absorbed and then declined biexponentially with initial and terminal half-lives similar to intravenous bolus injection.

3 Cytosine arabinoside levels declined rapidly after intravenous bolus and subcutaneous bolus injection, and fell below steady state infusion levels after a mean time of 40 min (intravenous bolus) and 100 min (subcutaneous injection).

Introduction

Cytosine arabinoside (ara.C) is a pyrimidine antagonist which remains the most effective drug in the treatment of acute myelogenous leukaemia. Its short half-life and S phase specificity have led most workers to administer it by continuous i.v infusion over a period of several days. When administered by i.v. bolus injection, it is rapidly deaminated, and consequently single i.v. doses have little effect on the bone marrow, and doses of 4 g/m^2 by i.v. bolus injection have been administered without haematological toxicity (Frei *et al.*, 1969). The subcutaneous route provides an alternative method of administration once the patient's platelet count has returned to normal. The rationale for this method of administration was based on the convenience to the patient, and the assumption that absorption from the subcutaneous tissue would be slow and would thus approximate a continuous infusion. Little is known of the pharmacokinetics of subcutaneous ara. C in man, and to our knowledge only one such study has been reported (Finklestein, Scher & Karon, 1970). Their data suggested that subcutaneous ara.C was slowly absorbed and plasma levels reached a peak at 1 h and then declined with a half-life of 5–8 h. However, the data is difficult to assess as the majority of the radioactivity is probably due to the inactive metabolite uracil arabinoside (ara.U) and the low activity of the tritiated ara.C did not permit its separation. This study was undertaken to determine the kinetics of ara.C when administered by subcutaneous injection to patients with acute myelogenous leukaemia.

Methods

Patients

Five adult patients with untreated acute myelogenous leukaemia were studied. All patients received ara.C 200 mg m^{-2} day^{-1} for 7 days. In addition they received adriamycin 25 mg/m^2 on Days 1, 2 and 3, and 6-thioguanine 200 mg/m^2 for 7 days. The patients were studied during the first 3 days of treatment. On the first day they received ara.C 100 mg/m^2 12-hourly by i.v. bolus injection. On the second day, ara.C was given at a dose of 100 mg/m^2 12-hourly by subcutaneous bolus, and on the third day it was administered by continuous intravenous infusion at a dose of 100 mg/m^2 12-hourly. In order to achieve a steady state rapidly in the infusion studies, a loading dose of ara.C was administered at the start of the infusion. This was given at a dose of 3 times the hourly rate of infusion according to the method described by Wan, Huffman & Azarnoff in 1974.

Blood sampling

Samples were taken following Ara.C injection for 12 h on each of the 3 successive days of the study. Blood (4 ml) was taken at the following intervals during the first hour: 3, 6, 10, 15, 21, 30, 45 and 60 min, and then at 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h. Each sample was taken into a pre-cooled tube containing tetrahydrouridine (THU) (1×10^{-5} M) and 50 units of heparin. The tubes were chilled immediately and centrifuged at 1,000 rev/min for 5

0306–5251/81/100507–05 $01.00

min. The plasma was then separated and stored frozen at −20°C.

Assay

The radioimmunosassay used for measuring ara.C levels was developed by Piall, Aherne & Marks (1979).

Antibody was raised in a sheep to an ara.C-mono-phosphate-ovalbumin conjugate. The antiserum did not cross-react with ara.U, THU, adriamycin, 6-thioguanine and other drugs commonly co-administered with ara.C, but cross-reaction of over 100% occurred with ara.C-mono-phosphate and ara.C-triphosphate. The radiolabel used was 5-[^{3}H]-cytosine-β-arabinoside from the Radiochemical Centre, Amersham. The assay had a sensitivity of 1 ng/ml (4.1 nmol l^{-1}) in unextracted plasma, and recovery of ara.C added to a plasma pool was complete over a 100-fold range from 10 ng/ml to 1 μg/ml (41 nmol l^{-1}–4.1 μmol l^{-1}). Quality controls, pooled plasma from patients who had received ara.C, were set up with each assay, and the between batch variation observed was as follows:

mean = 4.6 ng/ml, s.d. = 0.36, s.e. mean = 0.11, c.v. = 7.8%, n = 10
mean = 375 ng/ml, s.d. = 28.9, s.e. mean = 9.2, c.v. = 7.7%, n = 10

The assay buffer used for all dilutions was 0.05 M phosphate buffer, pH 7.4, containing 0.1% (w/v) gelatin 0.6% (w/v) sodium chloride. The assay incubation time was 1 h. Antibody bound and free antigen were separated with dextran-coated charcoal. The bound antigen was quantitated by liquid scintillation counting the amount bound in unknowns being compared with the standard curve set up in the same batch.

Pharmacokinetics

Pharmacokinetic parameters were determined from the semilog plot of plasma ara.C levels against time, using the interactive computer program (STRIPACT, Leferink & Maes, 1979). The plasma ara.C levels after 6 h were excluded from the half-life calculations, since the assay cross-reacts with intracellular phosphorylated ara.C and at these low levels even minimal cell lysis may artificially elevate the results.

Results

The mean plasma levels of ara.C *v* time for the i.v. bolus, subcutaneous bolus and continuous intravenous infusion are displayed in Figure 1. After an i.v. bolus injection, plasma ara.C levels declined tri-exponentially. The mean half-life for the initial phase was 1.9 ± 0.28 min, for the intermediate phase 14.2 ± 1.3 min, and for the terminal phase 8.4 ± 3.8 h. Following subcutaneous administration, there was a rapid absorption phase (mean half-life of absorption, Ka, 3.4 ± 1.0 min), and then the decline in ara.C was bi-exponential with a mean initial half-life of 15.7 ± 4.8 min, and a mean terminal half-life of 1.4 ± 0.1 h.

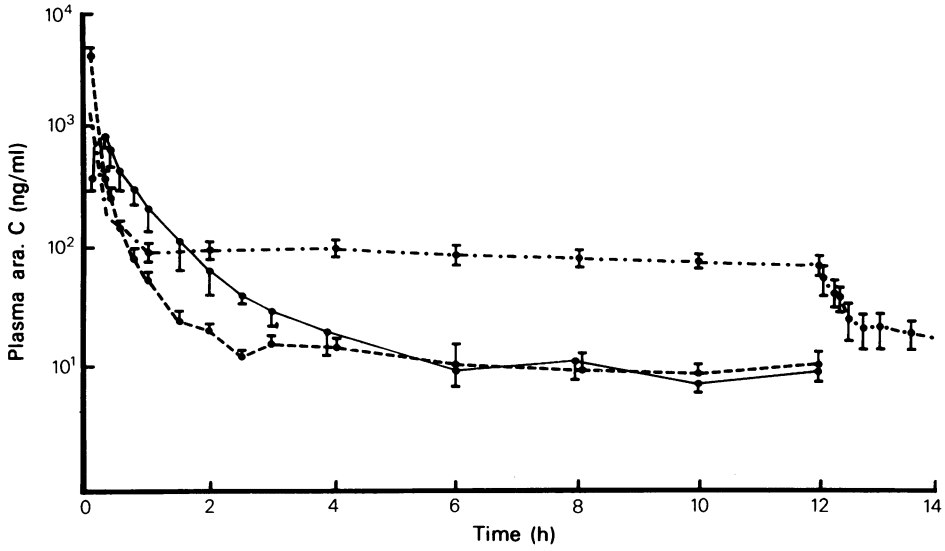

Figure 1 Mean plasma concentrations (± s.e. mean) after i.v. (- - -), s.c.(——) and i.v. infusion (— · — · —) of ara.C in five patients.

The individual patients' pharmacokinetic parameters are shown in Table 1. In patients 2 and 5 erratic values were obtained during the elimination phase of the i.v. bolus and these gave rise to the extended terminal half-lives. Levels were above steady-state infusion levels for only 40 min following the i.v. bolus and for 100 min following subcutaneous administration. The decline in plasma ara.C concentrations continued rapidly following both these routes of administration and after 5 h were approximately 10% of the steady state infusion level.

Discussion

The pharmacokinetics of i.v. bolus injections of ara.C reported here are similar to those described by others using different methods of ara.C assay including tritiated ara.C (Ho & Frei, 1971), high pressure liquid chromatography (Kreis *et al.*, 1977), and gas chromatography-mass spectrometry (Harris *et al.*, 1979). The majority of published reports describe a biphasic distribution; however, van Prooijen, van der Kleijn & Haanen (1977) found that the initial phase could be divided into two exponentials, and this has been confirmed by our results. The terminal half-lives of the i.v. bolus, subcutaneous injection, and following discontinuation of the continuous infusion are all similar with the exception of the erratic values following i.v. bolus in patients 2 and 5. The results of this study suggest that continuous infusions of this S phase specific drug are likely to be superior to subcutaneous injections in the remission induction of acute myelogenous leukaemia. It was hoped that ara.C would be released slowly from the subcutaneous tissues, and might thus approximate a continuous infusion. However, the pharmacokinetics of subcutaneous ara.C bolus more closely approximate of those of an i.v. bolus. Whether the delayed absorption and higher ara.C plasma concentration in the first few hours after this route of administration have any clinical benefit is yet to be established (Figure 1).

The results of this study demonstrate that it is not possible to achieve comparable steady state levels of ara.C with the same total dose given by subcutaneous bolus as by continuous i.v. infusion.

If, therefore, it is considered necessary to obtain such steady state levels, and it is overwhelmingly more convenient to use the subcutaneous route, continuous subcutaneous infusion as described by Weinstein *et al.* (1978) must be employed.

The authors are grateful to the Drug Synthesis and Chemistry Branch, Division of Cancer Treatment, National Cancer Institute, U.S.A., for the supply of tetrahydrouridine. E. Piall and G.W. Aherne thank the Leukaemia Research Fund for generous financial support.

We would like to thank Mrs J. Barton for helping with the preparation of this manuscript.

Table 1 Individual patients' pharmacokinetic data after i.v., s.c. and i.v. infusion of ara.C.

Patient	*i.v. half-lives*			*s.c. half-lives*			*Post-infusion half-life*	*AUC* ($ng\,ml^{-1}\,h$)		*VC* ($l kg^{-1}$)
	α_1 (*min*)	α_2 (*min*)	β (*h*)	*Ka* (*min*)	α (*min*)	β (*h*)	β (*h*)	*i.v.*	*s.c.*	
1	2.8	18.4	3.1	1.4	11.4	1.3	1.6	533	562	0.37
2	1.1	12.3	(16.1)	1.9	7.3	1.2	1.2	574	473	0.41
3	2.0	12.3	2.2	5.3	8.7	1.4	1.2	463	483	0.19
4	1.6	16.0	1.5	6.0	33.4	1.6	1.6	472	1085	0.23
5	2.1	11.8	(19.0)	2.2	17.5	1.3	2.4	1011	833	0.53
Mean	1.9	14.2	8.4	3.4	15.7	1.4	1.6	611	637	0.35
± s.e. mean	±0.3	±1.3	±3.8	±1.0	±4.8	±0.1	±0.2	±102	±119	±0.06

Ka, absorption half-life; AUC, area under the curve 0–∞; VC, volume of central compartment

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(Received December 24, 1980)