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Subcutaneous Infusion of Cytosine Arabinoside

A Practical Alternative to Intravenous Infusion

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Summary. *The administration of cytosine arabinoside (araC) by continuous IV infusion requires the patient to be in hospital and have prolonged IV cannulation. In this study the pharmacokinetics of araC during continuous IV infusion were compared with those of continuous SC infusion in six patients with acute myelogenous leukaemia. Each patient acted as his own control. The mean plasma levels of araC reached a plateau within 2 h and the plasma concentrations and the area under the curve were similar for both methods of administration. The mean area under the curve (AUC) was 1147 ± 230 ng/ml for the IV infusion and 1017 ± 238 ng/ml for the SC infusion. The plasma araC concentrations showed wide interpatient variation, and there was also considerable variability in the plasma concentrations of araC within the individual patients after a plateau had apparently been reached.*

Subcutaneous infusion was well tolerated by the patients without any local discomfort or excoriation and SC infusion of araC is thus a feasible alternative to IV infusion. It allows the patients the benefits of being at home, while avoiding unnecessary thrombophlebitis.

Introduction

The therapeutic advantages of continuous IV infusions of araC have to be balanced against the disadvantages of hospitalisation and the medical and nursing supervision required to establish and maintain continuous IV therapy. Furthermore, prolonged IV cannulation frequently results thrombophlebitis, which compromises the patients' future venous access.

The rapid absorption of araC from the SC tissues [8], its high aqueous solubility, and the lack of local excoriation make SC infusion a rational alternative to IV infusion. Subcutaneous infusion has been used for continuous infusions of insulin [7] and desferioxamine [4]. Furthermore, Weinstein et al. [10] recently compared steady-state levels of araC in three patients who received both IV and SC infusions for longer than 24 h and demonstrated similar plasma concentrations of araC. The time taken to achieve these steady-state levels by the two methods of administration was not, however, examined.

This study was undertaken to determine whether continuous SC infusion of araC would be tolerated by the patients, and whether the time to reach a plateau and the plasma levels achieved would be comparable to those recorded with continuous IV infusion.

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Materials and Methods

Patients. Six patients with acute myelogenous leukaemia who were receiving remission induction or consolidation therapy with araC (200 mg/m^2 per day × 7), adriamycin (40 mg/m^2 on day 1 and 35 mg/m^2 on day 2) and 6-thioguanine (200 mg/m^2 per day for 7 days) were studied. All patients had a platelet count of $> 100 \times 10^9$/l at the time of the study. The study was undertaken during the first 2 days of treatment. On 1 day araC 100 mg/m^2 was administered by continuous IV infusion and on the other day by continuous SC infusion, each over 12 h. The patients were randomised as to the order in which they received the infusions. Three patients received the IV infusion first and the other three the SC infusion. The patients thus received an almost identical dose of adriamycin on the 2 days and the same dose of 6-thioguanine. If was felt that studying patients during different cycles might have led to greater variability, especially in patients with acute leukaemia, whose general condition can improve dramatically after they achieve complete remission.

At least 3 h were allowed between the end of one infusion and the next, to allow araC plasma levels to decline. Infusions were administered via a Handley Intravenous Injector. AraC was delivered over 12 h in 22 ml saline for IV infusions, and 1.1 ml saline for SC infusions.

Blood Sampling. Blood samples were taken during the infusions for 12 h on each study day. Blood (4 ml) was withdrawn at 0, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 h. The samples were taken into precooled tubes containing tetrahydrouradine (1×10^{-5} *M*) and 50 U of heparin. The tubes were chilled immediately and centrifuged at 1,000 rev/min for 5 min. The plasma was then separated and stored at −20° C.

Assay. The plasma araC concentrations were measured by radioimmunoassay as previously described [6]. Antibody was raised in a sheep to an araC monophosphate ovalbumin conjugate. The radiolabel used was 5 [^{3}H] cytosine-*B*-arabinoside, from the Radiochemical Centre, Amersham. Using this radiolabel and antiserum, cross reactivity with araC was 100%, and with ara-CMP and ara-CTP it was > 100%. Cross reaction with endogenous nucleosides and nucleotides and with the major metabolite of araC, uracil arabinoside (ara U), THU, and a wide range of drugs commonly co-administered with araC, such as adriamycin and 6-thioguanine, was < 0.02%.

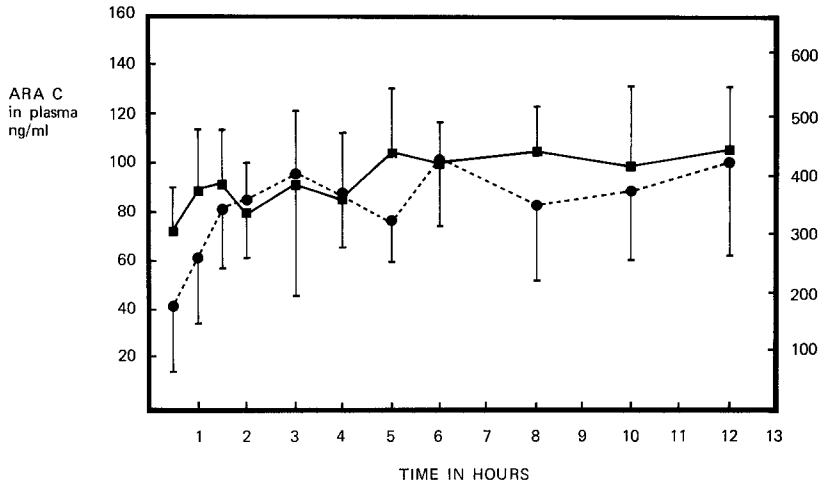

Fig. 1. The mean plasma concentrations (± SD) of AraC (100 mg/m^2) during IV and SC infusions in six patients with acute myelogenous leukaemia. (■———■) IV infusion; (●· · · ·●) SC infusion

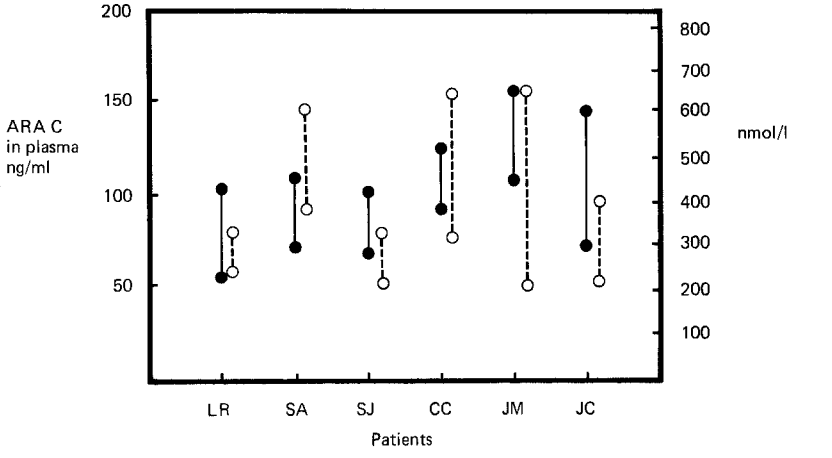

Fig. 2. The range of AraC concentrations in individual patients during the 'plateau' phase of IV and SC infusions. (●———●) IV infusion; (○– – –○) SC infusion

Table 1. Comparison of AUC during IV and SC infusions of AraC 100 mg/m^2

Patient	Area under the curve	
	IV infusion	SC infusion
L. R.	898	806
S. A.	1016	1215
S. J.	976	799
C. C.	1252	1370
J. M.	1521	1033
J. C.	1221	872
Mean	1147	1017
SD	230	238

The assay sensitivity was 1 ng/ml (4.1 nmol/l) in unextracted plasma and recovery of araC added to a plasma pool was complete over a 100-fold range from 10 ng/ml to 1 μg/ml (41 nmol/l) to 4.1 μmol/l). Quality controls made up of pooled plasma from patients who had received araC were set up with each assay. Between-batch variation for two quality controls gave < 8% as the coefficient of variance, the mean values for the controls being 4.6 ng/ml and 375 ng/ml.

Results

The SC infusions were well tolerated by the patients, without local excoriation or discomfort. The mean plasma levels of araC ± standard deviation versus time for the six patients are shown in Fig. 1. The mean plasma concentrations of araC reached a plateau within 2 h, and the plasma concentrations and the area under the curve (AUC) were similar for both methods of administration. The mean AUC was 1,147 ± 230 for the IV infusions and 1,017 ± 238 for the SC infusions. A comparison of the AUC during the IV and SC infusions for the individual patients is shown in Table 1. The standard deviations shown in Fig. 1 demonstrate the wide interpatient variation. There was also a wide variability in the plasma concentrations of araC in individual patients after a plateau had apparently been reached. In some patients a greater than twofold within-patient difference between the minimum and maximum plasma araC concentrations during the 'plateau' phase of the infusion was demonstrated. The accuracy of the pumps was checked and they were not at fault. The range of araC concentrations in individual patients during IV and SC infusions is shown in Fig. 2.

Discussion

AraC is one of the most important drugs used in the treatment of acute myelogenous leukaemia. Despite the confusion about the best schedule of administration the S phase specificity of araC has led most workers to administer it by continuous IV infusion [5, 11]. The majority of phase II studies support this [1, 9]. However, for many patients the discomfort associated with repeated re-siting of IV cannulae is one of the most unpleasant aspects of treatment for acute leukaemia. This has

prompted the search for alternative methods of maintaining continuous concentrations of araC in the plasma. To date these have proved unsatisfactory. The data presented here show that SC infusion of araC is equivalent to IV infusion. The time to achieve a plateau, the steady-state plasma concentrations, and the area under the curve, were similar for both methods of administration (Fig. 1 and Table 1). Furthermore the SC infusions were associated with minimal discomfort and allowed the patients full mobility.

There were, however, large interpatient differences in plasma levels during both types of infusion, and a wide variation in the plasma concentrations in the same patients after the plateau had been achieved. Similar observations have been made by Harris et al. [3], who showed up to twofold within-patient variation in the plasma araC concentrations during IV infusions continued for at least 48 h. These authors suggest that this wide interpatient variation during infusions may be explained by variations in patient posture resulting in alterations of hepatic blood flow. Wilkinson and Shand [12] demonstrated that hepatic clearance of drugs with high hepatic extraction ratios was related to hepatic blood flow, which may be markedly dependent on posture [2]. The patients reported here were receiving their second or subsequent courses of chemotherapy and were all active and mobile, which may explain the failure to achieve a true steady state with either type of infusion. The variable plasma concentrations during the so-called steady state must be taken into account in any attempt to correlate steady-state araC levels during continuous infusion with therapeutic outcome.

This study demonstrates that SC infusion of araC is a feasible alternative to and comparable with IV infusion. It allows the patient the physical, psychological, and financial benefits of being at home during therapy, and avoids unnecessary thrombophlebitis.

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