Cancer Chemother Pharmacol (1996) 38: 110–112

SHORT COMMUNICATION

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Bioavailability of subcutaneous 5-fluorouracil: a case report

Received: 27 August 1995 / Accepted: 16 November 1995

Abstract The optimal schedule for the administration of 5-fluorouracil (5-FU) in the management of advanced colorectal cancer remains to be determined. It has been suggested that this drug may be given by the subcutaneous route and that following a short infusion the bioavailability is similar to that observed after intravenous administration. We report the results we obtained in a patient treated with an intravenous bolus of 5-FU followed by a 22-h subcutaneous infusion. In this patient the bioavailability of 5-FU given by subcutaneous infusion was 0.94. The steady-state plasma levels of 5-FU reached during subcutaneous infusion were comparable with those achieved during intravenous infusion. Following four cycles of subcutaneous therapy, painless blistering was noted at the infusion sites, which healed following the cessation of subcutaneous therapy. Further studies are required to evaluate this route of therapy as an alternative to protracted intravenous therapy. The main dose-limiting side effect appears to be local skin toxicity.

Key words Bioavailability · 5-Fluorouracil · Subcutaneous administration · Colorectal cancer

Introduction

Since its discovery in 1957 by Heidelberger et al. [5], 5-fluorouracil (5-FU) has been the mainstay of medical treatment for metastatic colorectal cancer. Despite more than 30 years of experience with this drug, the optimal treatment schedule remains to be determined. The activity of 5-FU is cell-cycle-specific and this, in conjunction with a short plasma half-life of 20 min, favours its prolonged administration or the concomitant administration of agents that modulate its activity in vivo, such as folinic acid.

It has been suggested that the bioavailability of 5-FU given s.c. is comparable with that observed after i.v. administration [2] and that it may be possible to use this route of administration over a prolonged period. We present our findings in a patient who received a s.c. infusion of 5-FU as treatment for an advanced colorectal cancer.

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Case report

Case history

A 51-year-old man who had previously been in good health presented with a 4-month history of weight loss and altered bowel habit. Investigation showed a rectal carcinoma with hepatic metastases, and laparotomy with the formation of a defunctioning colostomy was subsequently performed. At laparotomy, extensive intra-abdominal tumour was found involving the entire greater omentum, with multiple peritoneal metastases being detected in the abdomen and pelvis. A pre-treatment computed tomography (CT) scan showed multiple hepatic metastases, a soft-tissue mass in the pelvis and a mass located anteriorly in the abdomen at the level of the kidneys. The pre-treatment carcino-embrionic antigen (CEA) level was elevated at 480 U/l.

The patient was treated with 5-FU and folinic acid in the following regimen based on that initially described by De-Gramont et al. [4]. On the 1st day of each treatment cycle, 200 mg/m^2 folinic acid was given by i.v. infusion over 2 h; 500 mg/m^2 5-FU was then given by i.v. bolus injection, followed by s.c. infusion of 500 mg/m^2 5-FU over 22 h. This treatment was repeated on the 2nd day of treatment. Treatment cycles were given at 14-day intervals. The 5-FU infusion for the second course of treatment was given i.v.; plasma 5-FU levels were measured and compared with those obtained during s.c. infusion of this drug. Seven cycles of treatment were given whereby the 5-FU infusion was carried out using the s.c. route, and one cycle was conducted whereby the 5-FU infusion was given by the i.v. route.

A partial response on CT scan was noted after four pulses of treatment, involving resolution of the pelvic mass, partial resolution of the abdominal mass and hepatic metastases but persistence of pelvic lymphadenopathy. This was associated with a fall in the CEA value to 160 U/l. A total of eight pulses of treatment were delivered and the patient's disease remained stable radiologically during the remaining four treatments. The s.c. administration of 5-FU was terminated after eight pulses of therapy due to observed local skin toxicity manifesting

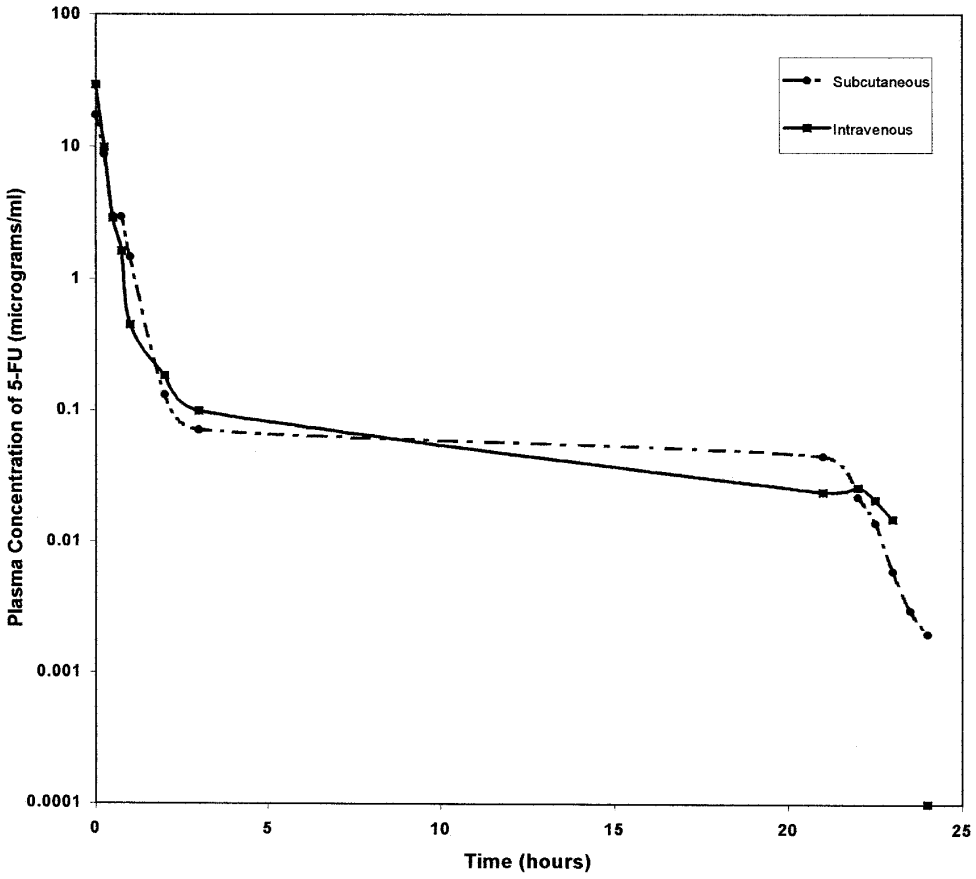

Fig. 1 Plasma concentration versus time curves generated for subcutaneous and intravenous infusion of 5-FU following bolus injection

Table 1 5-FU concentrations measured following i.v. and s.c. administration. Values are expressed in μg/ml ±SE for several analyses of each sample

Sample	Plasma 5-FU (μg/ml) for i.v. administration	Plasma 5-FU (μg/ml) for s.c. administration
0	29.135±2.731	17.234 ±0.453
15 min	9.857±1.167	8.789 ±0.815
30 min	2.878±0.111	2.969 ±0.870
45 min	1.629±0.011	2.952 ±0.506
60 min	0.449±0.009	1.47 ±0.03
120 min	0.184±0.021	0.131 ±0.007
180 min	0.099±0.018	0.071 ±0.01
21 h		0.045 ±0.002
22 h	0.024±0	0.022 ±0.002
22.5 h	0.026±0.0007	0.014
23 h	0.021±0	0.006 ±0.001
23.5 h		0.003 ±0.0002
24 h	0.0001	0.002 ±0.0001
AUC	9.063 μg h ml^{-1}	8.4765 μg h ml^{-1}

as recurrent painless bullae and skin discolouration at the site of infusion. This toxicity was not seen until the fourth course of treatment; however, it became more prominent with each pulse of therapy.

On the cessation of s.c. 5-FU administration a Hickman line was inserted and a continuous i.v. infusion of 5-FU at 250 mg/m^2 per day was commenced. The patient has now received 9 months of continuous treatment with little toxicity, continues to have stable disease and remains well.

Methods

The s.c. 5-FU infusion was delivered using a portable syringe driver (Graseby MS16A) via a butterfly cannula and was commenced immediately following the i.v. bolus dose of 5-FU as described above. The site of the infusion was covered with a sterile transparent adhesive dressing to allow observation of any skin change during the infusion of 5-FU. Seven cycles of s.c. 5-FU were given, and one cycle of treatment was given i.v.

Venous blood samples were collected in vials containing ethylenediaminetetraacetic acid (EDTA) at time zero (immediately following the bolus injection of 5-FU) and at 15, 30, 45, 60, 120 and 180 min. As the terminal half-life of 5-FU is around 20 min, a steady state was assumed to exist 3 h following the commencement of the infusion of 5-FU. Further samples were again taken at 21, 22, 22.5, 23, 23.5, and 24 h. Samples were centrifuged for 10 min and the plasma was separated and frozen at –70 °C until analysed.

The 5-FU concentration in plasma was analysed using a gas chromatography–negative-ion chemical ionisation mass spectrometry method described by Bates et al. [1]. The area under the plasma concentration-time curve (AUC) from 0 to 24 h was calculated using the trapezoidal rule, and the bioavailability was calculated by dividing the AUC recorded following s.c. administration by the AUC noted following i.v. administration.

Results

The results of analysis of plasma 5-FU concentrations obtained following i.v. and s.c. methods of administration are shown in Table 1. The AUC recorded for i.v. administration was 9.063 μg h ml^{-1} and that noted for s.c. administration was 8.477 μg h ml^{-1}. The bioavailability of s.c. 5-FU as calculated from the above values was 0.93.

The plasma concentration/time curves are shown in Fig. 1. A close correlation can be seen between the two sets of values, and the calculated correlation coefficient is 0.98. It would appear that in the individual studied, no significant difference in the bioavailability or AUC exists between the two methods of administration. In addition, the steady-state plasma drug concentrations were similar at 0.099 μg/ml for the i.v. route and 0.071 μg/ml for the s.c. route.

The major toxicity encountered was the formation of painless bullae at the site of administration: however, this did not occur until the fourth cycle of treatment had been completed. These bullae healed completely following the cessation of the s.c. 5-FU administration.

Discussion

The results obtained in this patient support the suggestion that 5-FU may be safely given by the s.c. route as a 24-h infusion. 5-FU is an integral component of many commonly used regimens in the treatment of solid tumours. In the case of colorectal cancer it has been shown that prolonged administration is superior to bolus administration both in terms of tolerability and in terms of response rates [8]. The Southwest Oncology Group has recently reported the results of a randomised phase II study of a number of 5-FU regimens in the treatment of metastatic colorectal cancer and has suggested that infusional 5-FU is associated with lower toxicity and improved survival as compared with other methods of administration [6].

A number of infusion regimens have been suggested for 5-FU, ranging from a few days to a number of weeks in duration. Magnetic resonance fluoroscopy can be employed to assess the intratumoural half-life of 5-FU. Using this technique it is possible to show that a clinical response is more likely to be associated with an intratumoural half-life of greater than 20 min than with one of less than 20 min following bolus administration [7]. This lends further support to the use of treatment schedules favouring the prolonged administration of 5-FU.

The more protracted continuous infusion regimens require the insertion of a permanent central venous catheter. This catheter is associated with significant complications such as infection, thrombus formation and catheter dislodgement. In attempts to avoid these complications, other routes of administration are being assessed, including the s.c. route.

Our results and those of Borner et al. [2] suggest that the s.c. route is an acceptable one for the administration of 5-FU, with the bioavailability approaching that observed after i.v. administration. The s.c. route of administration over long periods requires evaluation in a greater number of patients and may be limited by cutaneous toxicity at the site of the infusion. If the toxicity is tolerable and the bioavailability is similar to that obtained following i.v. administration, as suggested by our results, then the use of a s.c. infusion may be an acceptable route for protracted administration of 5-FU without the drawbacks of an indwelling central venous catheter.

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