Pharmacokinetics of Intraarterial Mitomycin C in Humans

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ABSTRACT

The pharmacological advantage of mitomycin C (MMC) given by intraarterial infusion as compared to i.v. infusion was studied in seven patients with cancer metastatic to the liver. Hepatic artery, hepatic vein, and peripheral vein catheters were placed, and each patient received constant infusions of MMC via the intraarterial and peripheral i.v. routes at 0.4, 1.2, and 4.0 mg/sq m/hr. MMC concentrations were measured in the hepatic artery, hepatic vein, and a peripheral vein by high-pressure liquid chromatography after steady state had been reached at 2 hr. Mean plasma clearance increased significantly with infusion rate from 0.6 liter/min at 0.4 mg/sq m/hr to 1.1 liters/min at 4.0 mg/sq m/hr. The calculated relative advantage of treating hepatic tumors via the intraarterial route (Ri) was found to be 2.5- to 3.6-fold at a plasma flow rate of 0.4 liter/sq m and MMC infusion rates of 0.4 to 4.0 mg/sq m/hr. The hepatic vein MMC concentration averaged 30% higher during intraarterial than during i.v. infusion. Hepatic extraction of MMC averaged only 23%, so that the intraarterial route offered little advantage with respect to reduced systemic toxicity. These data suggest a limited pharmacological rationale for the selection of the intraarterial route for the treatment of hepatic tumors with MMC.

INTRODUCTION

There are 2 basic rationales for the selection of the i.a. route rather than the i.v. route for administration of chemotherapeutic agents (1). The first is the possibility that the i.a. route can produce a greater total tumor exposure to drug, and thus result in a higher response rate. The second is that if the drug is extensively extracted and metabolized in the tumor or tumor-bearing organ, then the amount of drug reaching the systemic circulation may be less following i.a. than i.v. infusion. The relative advantage of the i.a. route from the point of view of total drug exposure for the tumor (Ri) is a function of the total body clearance and tumor blood flow as indicated by Equation A (1). Ri is greatest when tumor blood flow is low and when the systemic clearance of the drug is high. Ri is not influenced by the amount of drug extracted and metabolized in the tumor (extraction ratio) (4). The relative advantage of the i.a. route over the i.v. route from the point of view of reducing systemic toxicity (Rt) is, however, highly dependent on the extraction ratio, as indicated by Equation B.

\[
R_i = \frac{1}{1 - \text{extraction ratio}} \quad (A)
\]

\[
R_t = \frac{\text{apparent total body clearance}}{\text{tumor blood flow}} \quad (B)
\]

5-Fluoro-2'-deoxyuridine has a hepatic extraction of 94 to 99% (6), and thus from the point of view of the systemic circulation (Rt) there is a strong pharmacological rationale for its infusion into the hepatic artery for the treatment of tumor masses in the liver. On the other hand, the Ri values for 5-fluorouracil (6), doxorubicin, bleomycin, and methotrexate are much lower (1), and from the point of view of reducing overall toxicity, the rationale for i.a. use of these agents is less well established.

Several investigators have used i.a. MMC for the treatment of hepatic tumors, and encouraging responses have been reported (7, 13–15). However, no pharmacokinetic data were obtained in these studies, and thus there is no way of estimating the magnitude of Ri and Rt for the i.a. use of MMC. We have used a recently developed high-pressure liquid chromatographic technique for the quantitation of MMC in plasma to measure the systemic clearance and hepatic extraction ratio for MMC at various infusion rates in 7 patients.

MATERIALS AND METHODS

Study Design. This study was designed to compare MMC pharmacokinetics during i.a. infusions into the hepatic artery, and during i.v. infusions into a peripheral vein in the same patient at various dose rates. In each instance, MMC was infused at a constant rate until steady state was achieved, and blood samples were obtained from the hepatic artery and vein, and from a peripheral vein (the hepatic artery was sampled only during i.v. infusions). All infusions were carried out using constant-infusion pumps. Following achievement of steady state at the starting dose rate, the MMC infusion rate was escalated in steps from 0.4 to 1.2 to 4.0 mg/sq m/hr; i.v. and i.a. studies were carried out sequentially over a 24- to 48-hr period.

Patients. Seven patients with histologically proven metastatic carcinoma in the liver gave their informed consent to enter this study. There were 5 males and 2 females, and the median age was 61 years (range, 51 to 86 years). Six patients had colon carcinoma and one had metastatic melanoma. The entrance criteria for the study included a predicted lifespan of >1 month; leukocyte count, >3,000/cu mm; platelet count, >100,000/cu mm; blood urea nitrogen, <40 mg/dl; creatinine, <2 mg/dl; the presence of a tumor mass massive that could be infused via a single artery; and recovery from the toxicity associated with prior therapies.

Treatment Plan. All patients were hospitalized in the Clinical Research Center at the University of California, San Diego Medical Center. Hepatic artery and vein catheters were introduced through the femoral artery and vein by the Seldinger technique (18) and guided into position using angiographic monitoring. Both dynamic and static liver scans were obtained using 4 mCi 99mTc-labeled macroaggregated albumin at a flow rate of 30 ml/hr (9). Each patient was fully heparinized by continuous infusion of 500 to 1000 units of heparin per hr. The requisite dose of MMC was mixed in 0.9% NaCl solution, and infusions were performed at 0.4, 1.2, and 4.0 mg/sq m/hr at flow rates of 10, 30, and 100 ml/hr, respectively.

MMC Assay. MMC was assayed in heparinized plasma samples using a modification of the technique reported by den Hartigh et al. (3). Crystalline sodium chloride was added to saturation (0.2 to 0.3 g), and
the plasma sample was mixed thoroughly for 1 min with 9 volumes of chloroform/isopropyl alcohol (1:1) before being centrifuged at 990 × g for 10 min. The upper organic phase was transferred to a conical test tube and evaporated to dryness under nitrogen. The residue was reconstituted in 100 µl of 100% methanol, and 20-µl aliquots were chromatographed using a Waters Associates (Milford, Mass.) instrument consisting of a Model 6000 A pump, Model 710B sample processor, Model 730 data module, a Model 450 variable-wavelength detector, and an RCM radial compression column (10 cm x 8.0 mm C18 Radial-PAK cartridge, 10-µm particle size). The mobile phase was 70% 20 µM potassium phosphate buffer (pH 6.0) and 30% methanol. Analysis was carried out isocratically at a flow rate of 1.5 ml/min, and the column effluent was monitored at 365 nm. The retention time of the MMC was 5.3 min, and there was base-line separation of the MMC peak from all other peaks in the chromatogram. MMC concentration was calculated from integration of the area under the MMC peaks, and by comparison to external standards run on the pretreatment plasma from each patient. The limit of sensitivity of this assay was 1 ng/ml, and recovery was 78.7 ± 5.7% (S.D.), with a coefficient of variation of 2.5%.

RESULTS

Relative Advantage for the Tumor. Steady-state MMC peripheral and hepatic vein concentrations were reached within 2 hr of starting either an i.a. or an i.v. MMC infusion, and the rate of approach to steady state was not influenced by the MMC infusion rate over the range of 0.4 to 4.0 mg/sq m/hr. Chart 1 shows the mean steady-state peripheral vein concentrations as a function of infusion rate. The plasma concentration increased linearly with infusion rate, and was nearly the same for i.a. and i.v. infusions performed at the same dose rate. The peripheral vein plasma concentration was approximately 6 times higher at an infusion rate of 4 mg/sq m/hr than at 0.4 mg/sq m/hr. From the data depicted in Chart 1, the plasma clearance of MMC can be calculated as indicated by Equation C.

\[
\text{Clearance} = \frac{\text{infusion rate}}{\text{steady-state plasma concentration}} \quad (C)
\]

Chart 2 shows plasma clearance as a function of infusion rate for both the i.a. and i.v. routes of administration. At an i.v. infusion rate of 0.4 mg/sq m/min, the plasma clearance was 0.59 ± 0.15 (S.D.) liter/min; the clearance of 0.59 ± 0.34 liter/min during i.a. infusion was not significantly different. Interestingly, for both routes, plasma clearance rose as the infusion rate was increased from 0.4 to 4.0 mg/sq m/hr. The increase was statistically significant \((p < 0.05, t\text{ test})\) for both i.a. and i.v. infusions; the differences between the clearances associated with i.a. and i.v. infusions were not significant.

Using the mean of the clearance values for both the i.a. and i.v. route at each infusion rate, it was possible to calculate \(R_i\) as a function of tumor plasma flow rate from Equation A, and the resulting family of curves for MMC infusion rates of 0.4 to 4.0 mg/sq m/min are presented in Chart 3. It can be seen that in the case of MMC, \(R_i\) values of greater than 3 could only be obtained with plasma flow rates of less than approximately 0.4 liter/min. However, with each incremental reduction in plasma flow rate below this value, the value of \(R_i\) increases more and more rapidly, and at a flow rate of 0.2 liter/min there is potentially a 6-fold advantage to the i.a. over the i.v. route from the point of view of total drug exposure for the tumor.

If one assumes that the tumor hepatic vein concentration is a minimal estimate of actual MMC concentration in the tumor bed, then it is possible to independently estimate the relative advantage of an i.a. over an i.v. infusion by comparing the steady-state hepatic vein MMC concentration during infusion via the 2 routes. Chart 4 shows the mean MMC concentrations in the hepatic vein during i.a. and i.v. infusions as a function of MMC dose rate. As was the case for the peripheral vein measurements, the hepatic vein MMC concentrations were linearly related to the infusion rate. The ratio of the slope of the i.a. curve to that of the i.v. curve was 1.3, indicating an advantage of approximately 30% for the i.a. route at each of the 3 infusion rates. Thus, for

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the tumors included in this study, the i.a. route of administration afforded only a relatively small advantage over the i.v. route, when estimated by this technique.

Relative Advantage for the Systemic Circulation. The relative advantage of an i.a. infusion from the point of view of reduction in systemic toxicity ($R_s$) is related to the amount of drug removed by the perfused organ before the blood reaches the venous circulation (Equation B). Hepatic artery and hepatic vein MMC concentrations were measured at steady state during i.v. MMC infusion, and the hepatic extraction ratio (ER) was calculated according to Equation D.

$$ER = \frac{\text{hepatic artery} - \text{hepatic vein}}{\text{hepatic artery}} \quad (D)$$

The extraction ratios were $0.30 \pm 0.12$ (S.E.), $0.16 \pm 0.01$, and $0.21 \pm 0.08$ for MMC infusion rates of 0.4, 1.2, and 4.0 mg/sq m/min, respectively. The variation with dose rate was not statistically significant; however, the extraction ratio for all dose rates was $0.22 \pm 0.05$, and this was significantly different from zero ($p > 0.05$, Student’s $t$ test). The value of $R_s$ for the 7 patients included in this study was $1.39 \pm 0.11$ (S.E.). Thus, the i.a. route of administration afforded an independent estimate of $R_s$, and an estimate of $R_s$ for the 7 patients was $1.3$. This represents a minimal estimate, since during passage from the tumor bed to the hepatic vein there is dilution due to the admixing of portal blood during i.a. infusion. As a check on this estimate of $R_s$, Equation A can be solved for blood flow to the liver; $R_s$ of 1.3 would yield a hepatic blood flow of approximately 2 liters/sq m/min which is somewhat high, but an $R_s$ of 1.6 would yield a blood flow of 1 liter/sq m/min, which is within the range previously reported (6).

Both the calculated and measured estimates of $R_s$ for intrahepatic arterial MMC infusions suggest that there is not a strong pharmacological rationale for selection of the i.a. over the i.v.
route for the treatment of resistant tumors in this or other organs with high plasma flow rates. The $R_i$ curves suggest that the high dose rate of MMC infusion was slightly more favorable than the low dose rate, and that i.a. treatment with MMC should be very much more effective for tumors resident in organs with plasma flows of less than 0.3 liter/min. The relationship between plasma flow rate and $R_i$ suggests that the i.a. route for the delivery of MMC may be most useful when combined with a technique to simultaneously diminish plasma flow.

The relative advantage of the i.a. over the i.v. route from the point of view of reducing systemic toxicity ($R_s$) is a function of how much of the drug administered into the tumor-bearing organ fails to reach the vein draining the tumor and enters the systemic circulation. As indicated in Equation B, $R_s$ is directly related to the extraction ratio; the greater the extraction ratio, the greater the value of $R_s$. In this study, the extraction ratio for MMC was found to average only 22%, resulting in an $R_s$ value of only 1.39. Although, since the liver plays an important part in the metabolism of MMC, one might expect a variation in extraction ratio with changes in infusion rate due to saturation of enzymatic processes, this was not observed over the range of dose rates used in this study. We conclude from these data that i.a. therapy via the hepatic artery cannot be counted on to significantly reduce systemic toxicity due to MMC.

Although the data from this study indicate that there is only a limited pharmacokinetic rationale for the selection of the i.a. over the i.v. route for the treatment of intrahepatic tumors, MMC remains one of the most interesting candidates for future studies of i.a. therapy. MMC is activated in areas of low oxidation-reduction potential, and the presence of oxygen significantly slows its activation to a cytotoxic form (11). Recently, the i.a. injection of starch microspheres (Spheres; Pharmacia, Inc.) that can be degraded by serum amylase has been used to markedly reduce tumor plasma flow rates for periods of up to approximately 30 min (5). Since interruption of blood flow simultaneously enhances $R_i$ and creates a microenvironment favoring the activation of MMC, the combined injection of both agents via the i.a. route may be very much more effective than the use of i.a. MCC alone. A cooperative study of such a program is currently under way.

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REFERENCES

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