Relationship between clinical parameters and pharmacokinetics of mitomycin C

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Summary. Although the number of reports on mitomycin C (MMC) pharmacokinetics is increasing, data on possible relations between clinical parameters and pharmacokinetics are usually lacking. The present report concerns the results of a detailed study on this subject in 35 patients receiving MMC, either as a single agent or as a part of combination chemotherapy. MMC concentrations were determined by HPLC. $T_{1/2\beta}$ varied from 23 to 78 min, V_D from 11 to 48 l/m², Cl_{tot} from 12 to 42 l/h per m², and AUC from 138 to 1221 µg/h per l, confirming previously reported data. Infusion time, cholestasis, and urinary pH did not influence the pharmacokinetic data. There were no relations between other clinical data and pharmacokinetics, nor between AUC and bone marrow toxicity. An interaction between MMC and furosemide could not be excluded, but there was no interaction with other comedication. Consecutive pharmacokinetics in 6 patients showed consistent results. Because renal impairment does not alter MMC pharmacokinetics and renal excretion is not a major route of elimination, it is suggested that renal impairment does not call for dose adjustment.

Key words: Pharmacokinetics – Mitomycin C

Introduction

Although mitomycin C (MMC) was isolated in 1958 [14], extensive pharmacokinetic data have been reported only in the past few years because of earlier problems with insensitive microbiologic assays [3]. Detailed pharmacokinetic data on MMC in man only recently became available [1, 5, 8, 9, 12] using different modifications of an HPLC assay, with detection limits

as low as 1 ng/ml per sample [4]. It appeared that the pharmacokinetic behavior of MMC is compatible with an open two-compartment model with linear pharmacokinetics up to doses as high as 60 mg/m² [5, 8, 12]. Possible relationships between clinical parameters and pharmacokinetics were suggested to be present but were only briefly discussed in the reported pharmacokinetic studies. For this reason we have performed a detailed investigation of such data.

Materials and methods

A total of 35 patients, 21 males and 14 females, aged 34–79 years, were studied, 22 of whom had been pretreated. Of the patients, 10 had breast cancer, 8 prostatic cancer, 7 gastric cancer, 3 cervical cancer, and 7 miscellaneous types of cancer. Single agent MMC treatment with doses of 10–20 mg/m² was received by 21 patients, and 14 received combination chemotherapy with MMC doses of 5–10 mg/m² (Table 1). MMC was always administered as a short-term i.v. infusion, lasting 1–10 min. A total of 46 pharmacokinetic studies were performed.

Blood samples from the arm opposite to the infusion site were collected in heparinized tubes prior to MMC administration and directly after, as well as 1, 2, 3, 4, 5, 10, 20, 30, 60, 90, 120, 180, 240, 300, 360, and 420 min afterwards. They were cooled on ice, centrifuged and plasma was stored at –25 °C. For analysis according to the method of den Hartigh et al. [4] the drug was extracted from plasma with chloroform: propan-2-ol (1:1, v/v), the organic layer

Table 1. Patient characteristics

Type of treatment	Dose of MMC (mg/m ²)	No. of studies	No. of patients
Single agent	10	13	6
	15	13	10
	20	5	5
Combination*	5	5	5
	10	10	9

* MMC combined with one or more of the following drugs: doxorubicin, vincristine, bleomycin, cisplatin, 5-fluorouracil and hydroxyurea

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evaporated to dryness under a nitrogen stream, and the residue dissolved in 100 μ l methanol. Aliquots of 10 μ l were injected into the chromatograph, using a Bondapack C₁₈ reversed phase column and UV detection at 365 nm. The detection limit was 1 ng/ml sample. The internal standard used was porfiromycin, structurally related to MMC. Methods for pharmacokinetic data analysis have been published by den Hartigh et al. [5]. The investigated clinical data included a complete physical examination, body temperature, heart rate, blood pressure, urine output, values of hemoglobin, white blood cell and platelet count, serum sodium, potassium, creatinin, alkaline phosphatase, γ -glutamyl transferase (γ -GT), serum lactate dehydrogenase, albumin, and urinalysis including pH, protein and glucose excretion, and the time and nature of administration of any comedication.

The mean and median values, standard deviation, and standard errors of the pharmacokinetic parameters were calculated for separate dose levels in single agent treatment and combination chemotherapy. Relationships between the obtained pharmacokinetic parameters, the duration of infusion, and the administered dose were analyzed. For individual patients with one or more pharmacokinetic parameters falling beyond the limits of mean ± 2 SD, we searched for possible relationships with the available clinical data.

This was also done in case of a deviation of the pharmacokinetic curve. The relationship between the pharmacokinetic data and the clinical data was plotted graphically.

Our next approach was to relate pharmacokinetic parameters with the occurrence and degree of clinical toxicity (WHO criteria), which was limited to myelosuppression.

Finally, in patients in whom we performed two or more pharmacokinetic studies, we related the consecutive curves obtained in each patient to the clinical data.

Results

Pharmacokinetic data

The pharmacokinetic data obtained were as follows: half-life ($T_{1/2\beta}$) varied from 23 to 78 min, volume distribution (V_D) from 11 to 48 l/m², total body clearance (Cl_{tot}) from 12 to 42 l/h per m², and area under the curve (AUC) from 138 to 1221 μ g/h per l. The data confirm the previously reported linear pharmacokinetics of MMC (Fig. 1). No relationship was found between the pharmacokinetic data obtained and infusion time.

Relation with clinical parameters

Values outside the range mean ± 2 SD for one or more of the pharmacokinetic parameters were found on 6 occasions in 6 patients. Physical and laboratory data as investigated did not indicate a reason for the observed abnormal pharmacokinetic values. In cholestatic patients pharmacokinetics appeared not to be different (Fig. 2) from noncholestatic patients. In 16 patients urinary pH was measured. No influence of urinary pH on pharmacokinetic values was encountered. In 26 patients adequate follow-up data on bone marrow toxicity were available. Bone marrow toxicity occurred much more frequently after combination chemotherapy. We did not find any relation between AUC and bone marrow toxicity.

Fig. 1. Correlation between dose and pharmacokinetic parameters of MMC. Correlation coefficient (r) was -0.22 for $T_{1/2\beta}$, 0.27 for V_D , -0.16 for Cl_{tot} , and 0.95 for AUC in single agent treatment ($\bullet$), and 0.20 for $T_{1/2\beta}$, 0.0 for V_D , -0.38 for Cl_{tot} , and 0.99 for AUC in combination chemotherapy ($\circ$)

Interaction with comedication

The deviations that were present in 6 pharmacokinetic curves in 6 different patients could not be explained by data on comedication in 5 of them. In the 6th patient we performed 7 consecutive pharmacokinetic studies. In the 1st course he received 10 mg/m² MMC because of prostatic cancer; during the other courses the dose was 12 mg/m². During all cycles comedication consisted of furosemide, isosorbide dinitrate, and digitalis, all given orally. The pharmacokinetics obtained are depicted in Fig. 3. They show uniform results in 6 out of the 7 studies. The only deviating pharmacokinetic data were obtained from the 2nd cycle (b), while the only difference appearing from the clinical charts for this cycle when compared to the others, was the ad-

Fig. 2. Relation between pharmacokinetics of MMC and cholestasis. Cholestasis is defined as grade 0 (normal), grade 1 (alkaline phosphatase 120–350 units/l and/or γ -GT 35–100 units/l) or grade 2 (alkaline phosphatase > 350 units/l and/or γ -GT > 100 units/l)

ministration of 40 mg of furosemide i.v., 90 min following MMC. The observed change was a decrease in $T_{1/2\beta}$, consistent with a more rapid elimination. The V_D decreased simultaneously. The values at 2.5 and 4 h after MMC in this curve differed when compared to the same time points on other curves. After 4 h the slope of the curve changed to normal, possibly coinciding with the end of action of furosemide. During 2 other studies the patient had temporary obstructive impairment of renal function. This did not alter the pharmacokinetics.

Consecutive pharmacokinetics

Apart from the patient reported above, 2 pharmacokinetic studies per patient were performed in 5 other patients; 4 of these patients received single agent MMC,

Fig. 3. Pharmacokinetic curves in a patient studied 7 times. The arrow indicates the time of administration of furosemide during cycle b

Fig. 4. Consecutive pharmacokinetics of MMC. Patients A–C were treated with single agent MMC, 15 mg/m², for prostatic cancer; patient D with similar treatment, for breast cancer. Patient E was treated with MMC 10 mg/m², combined with 5-fluorouracil and doxorubicin for gastric cancer

1 received combination chemotherapy. The intraindividual findings in these 5 patients were consistent (Fig. 4). No effect of any clinical condition was observed on the pharmacokinetics in these patients.

Discussion

In this study on 35 patients, we did not find correlations between pharmacokinetics of MMC and clinical parameters. We did confirm the previously reported linear pharmacokinetics of the drug.

We also found that cholestasis did not influence the pharmacokinetic behavior of MMC, which confirms previous observations of van Hazel et al. [8]. Although the concentration of MMC in the bile is much higher than in plasma, in rats as well as in man [5, 10],

biliary excretion appears not to be an important pathway of elimination in animals [10]. The present and van Hazel's previous observations in man indicate that metabolism of MMC, occurring at the microsomal level, is not inhibited by cholestasis. It has been suggested that MMC pharmacokinetics are influenced by enterohepatic recycling of the drug [11,13]. Whether both biliary flow and enterohepatic recycling of MMC play a role in its elimination is not known.

We confirmed previous data [8] that pharmacokinetics of MMC are independent of renal function. In one patient we could not exclude an effect of furosemide on MMC pharmacokinetics. For this reason we initiated a study to investigate this potential effect, the results of which will be reported separately. Another observation was that urinary pH did not influence the elimination of MMC, at least within pH ranges of 5–7. This indicates that the in vitro changes of detectability of MMC at different pHs [7] are not reflected in normal pH fluctuations in the in vivo situation.

In previous studies using the HPLC assay it has been reported that the pharmacokinetic data on MMC showed wide variations [5,8]. However, the results obtained in the patient in whom we performed 7 pharmacokinetic studies, as well as the results in 5 patients studied twice, indicated that if clinical data remain stable during treatment, and even if renal function changes, the pharmacokinetics of MMC do not change. If these findings are confirmed in a larger number of patients, they support the advantage of the HPLC assay for MMC pharmacokinetic studies. But still the mechanisms of interindividual variations in those pharmacokinetics have to be elucidated, as they appear not to be dependent on the assay used, or on the clinical variables studied. Preliminary data indicated a protein binding of MMC of $22\% \pm 3\%$ in plasma from 6 healthy volunteers [6]. It seems unlikely that this small range in protein binding can account for the observed interindividual differences in pharmacokinetics. Myelosuppression was infrequent in our patient group and mainly occurred in patients receiving combination chemotherapy. The often delayed bone marrow toxicity of MMC is known to be directly related to cumulative dose and to be rare below a cumulative dose of 50 mg in patients who have not been pretreated [2], while the mean cumulative

dose in the patients we studied was only 20 mg/m². The majority of them had not been pretreated with other cytotoxic drugs. This probably explains the absence of any relationship between pharmacokinetics and the occurrence and degree of bone marrow toxicity, while the observed toxicity may have been caused by concomitantly administered cytostatics.

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