Short communication

The difference in pharmacokinetics of mitomycin C, given either as a single agent or as a part of combination chemotherapy

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Summary. In a previous report it was suggested that the total body clearance of mitomycin C (MMC) was different after single agent treatment compared to combination chemotherapy. This suggestion was based on recalculations to one dose level. In the present study a fixed dose of 10 mg/m² was used. Seven patients on single agent MMC and eight on combination chemotherapy were studied. Terminal half-life varied from 25 to 78 min, volume of distribution from 7 to 73 l/m², total body clearance from 11 to 56 l/h per m², and area under the plasma concentration-time curve (AUC) from 177 to 933 µg/h per l. Total body clearance was significantly higher and AUC significantly lower in patients on combination chemotherapy. The cause of this difference was not investigated.

Key words: Pharmacokinetics – Mitomycin C – Combination chemotherapy.

Introduction

Mitomycin C (MMC) was isolated from *Streptomyces caespitosus* by Wakaki et al. in 1958 [11]. Because of the severe myelosuppressive side effects occurring after the previously used continuous low dose regimen, the drug initially gained limited interest. MMC has a broad spectrum of antitumor activity [2] and was therefore used much more frequently when it became clear some 15 years ago, that myelosuppressive side effects could be diminished to a great extent by using an intermittent high dose schedule. Only recently, after the introduction of a sensitive HPLC assay [3] have detailed pharmacokinetic data on MMC in humans become available [1, 4, 6, 7, 9]. MMC pharmacokinetics are compatible with a two-compartment open model, with

dose-independent linear pharmacokinetics at doses up to 60 mg/m² [4, 6, 9]. Interestingly, based on recalculations of results to one dose level, den Hartigh et al. suggested that the total clearance in patients on combination chemotherapy exceeded the clearance in patients receiving single agent treatment [4]. The present study was initiated to investigate MMC clearance in patients receiving 10 mg/m² either as a single agent or as a part of combination chemotherapy.

Materials and methods

A total of 15 patients, 10 males and 5 females, aged 34–79 years, were studied. Of these patients, 7 received MMC 10 mg/m² as a single agent for prostatic or breast cancer, 8 received MMC 10 mg/m² combined with doxorubicin (DX) 30 mg/m² and 5-fluorouracil (5-FU) 600 mg/m² for gastric cancer.

MMC was always given as a 1–3 min infusion. In the combination regimen 5-FU was administered first, DX second, and MMC last. The total amount of fluid in which the drugs was dissolved was 60 ml in all patients. The total number of treatment courses during which pharmacokinetic data were obtained, was 14 in the single agent group and 10 in the combination chemotherapy group, with 4 patients having pharmacokinetic studies performed more than once. All patients had normal liver function tests and normal renal function at the start of the study.

Blood samples were collected in heparinized tubes from the arm opposite to the infusion site prior to MMC administration and after 0, 1, 2, 3, 4, 5, 10, 20, 30, 60, 90, 120, 180, 240, 300, and 360 min. The samples were cooled on ice prior to centrifugation. Chromatographic analysis and pharmacokinetic data analysis were performed according to the methods published by den Hartigh et al. [4]. Terminal half-life ($T_{1/2\beta}$), volume of distribution (V_D), total body clearance (Cl_{tot}) and area under the plasma concentration-time curve (AUC) were all calculated by standard methods.

Results

The pharmacokinetic data obtained are presented in Table 1. $T_{1/2\beta}$ varied from 25 to 78 min, V_D from 7 to 73 l/m², Cl_{tot} from 11 to 56 l/h per m², and AUC from 177 to 933 µg/h per l. However, AUC was significantly lower and Cl_{tot} significantly higher in patients on

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Table 1. Pharmacokinetic data of mitomycin C given as a short-term i.v. infusion (median $\pm$ 2 SEM)

	Single agent therapy	Combination chemotherapy
No. of studies	14	10
No. of patients	7	8
$T_{1/2\beta}$ (min)	54 $\pm$ 7	55 $\pm$ 8
Dvdd V_D (l/m ²)	19 $\pm$ 3	27 $\pm$ 10
Cl _{tot} (l/h per m ²)	13 $\pm$ 2 ^a	21 $\pm$ 3 ^a
AUC (μ g/h per l)	773 $\pm$ 87 ^a	476 $\pm$ 108 ^a

^a $P < 0.05$ (Students *t*-test)

combination chemotherapy, while $T_{1/2\beta}$ and V_D did not differ significantly.

In one of the patients renal function deteriorated before the third pharmacokinetic study. However, the results remained the same compared to those obtained during the first two treatment courses.

Discussion

In the present study in man we found that if 10 mg/m² of MMC was administered by short-term i.v. infusion, as a single agent or as a part of combination chemotherapy, Cl_{tot} was significantly lower in the former group of patients than in the latter ($P < 0.05$), while the AUC was significantly higher ($P < 0.05$). Such a difference was not observed in Wistar rats [8].

The previous data on AUC suggesting the presently confirmed differences were obtained from recalculations to one dose level [4]. Because our data were obtained with a fixed dose of MMC of 10 mg/m², they provide stronger evidence for the existence of such a difference. Although van Hazel et al. did not discuss this subject [6], their data suggested that a similar conclusion concerning AUC might have been drawn.

As stated by den Hartigh et al. [4], the difference may possibly be explained by a difference in binding to plasma proteins or other blood constituents. Indeed preliminary data [5] have shown 22% protein binding, and 58% uptake in and partial binding of MMC to red blood cells (RBC) in vitro.

In those in vitro experiments, neither 5-FU nor DX influenced the binding of MMC to proteins or RBCs.

As for the in vitro situation, one may wonder if in vitro binding can explain the observed differences, but for MMC such data are not yet available. Binding to proteins and/or RBC may be different in animals and man. If binding really plays a role in the observed

difference between single agent and combination treatment in man, than a difference in binding between animal and man might explain the observation in Wistar rats where single agent and combination treatment result in comparable pharmacokinetics [8]. However, our present data on $T_{1/2\beta}$ and V_D do not support the influence of binding to proteins or RBC in man.

Nevertheless, the fact that in man single agent MMC leads to a different clearance than MMC in a combination regimen may be important with regard to the serious renal toxicity of MMC, which is more frequently seen in combination chemotherapy than in single agent treatment [10]. In conclusion we were able to confirm a difference in Cl_{tot} of MMC after single agent treatment as compared to combination chemotherapy. The cause of this difference remains to be elucidated.

References

1. Buice RG, Niell HB, Sidhu P, Gurley BJ (1984) Pharmacokinetics of mitomycin C in non-oat cell carcinoma of the lung. *Cancer Chemother Pharmacol* 13:1-4
2. Doll DC, Weiss RB, Issell BF (1985) Mitomycin: ten years after approval for marketing. *J Clin Oncol* 3:276-286
3. den Hartigh J, van Oort WJ, Bocken MCYM, Pinedo HM (1981) High performance liquid chromatography determination of the antitumor agent mitomycin C in human blood plasma. *Anal Chim Acta* 127:47-53
4. den Hartigh J, McVie JG, van Oort WJ, Pinedo HM (1983) Pharmacokinetics of mitomycin C in humans. *Cancer Res* 43:5017-5021
5. den Hartigh J, Voortman G, van Oort WJ, Pinedo HM, Weenen H (1983) Binding of mitomycin C to red blood cells and plasma proteins. *Proc ECCO* 2:15
6. van Hazel GA, Scott M, Rubin J (1983) Pharmacokinetics of mitomycin C in patients receiving the drug alone or in combination. *Cancer Treat Rep* 67:805-810
7. Hu E, Howell SB (1983) Pharmacokinetics of intraarterial mitomycin C in humans. *Cancer Res* 43:4474-4477
8. Kerpel Fronius S, Verweij J, Stuurman M, Lelieveld P, Pinedo HM (1986) Pharmacokinetics of mitomycin C given to Wistar rats alone, in combination or after induction of microsomal drug metabolism (in press)
9. Schilcher RB, Young JD, Ratanatharathorn V, Karanes C, Baker LH (1984) Clinical pharmacokinetics of high dose mitomycin C. *Cancer Chemother Pharmacol* 13:186-198
10. Verweij J, Boven E, van der Meulen J, Pinedo HM (1984) Recovery from mitomycin C induced haemolytic uraemic syndrome. A case report. *Cancer* 54:2878-2881
11. Wakaki S, Marumo H, Tomioka K (1958) Isolation of new fractions of antitumor mitomycins. *Antibiot Chemother* 8:228-240

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