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Short communication

Absence of interaction between furosemide and mitomycin C

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Summary. The possible interaction between furosemide and mitomycin C (MMC) was studied in five patients. The pharmacokinetics of MMC were studied using an HPLC assay. Furosemide was administered prior to, or 120 min after MMC. Furosemide did not change the pharmacokinetics of MMC, nor did it change the amount of MMC excreted in the urine. There appears to be no interaction between the two drugs.

Introduction

We have recently performed a detailed study to determine any relationships between clinical data and pharmacokinetics of MMC. We did not find hard evidence for a distinct correlation [9].

These results confirm the data of previous, less extensive studies [4, 8]. Our only remarkable observation was that concomitant administration of furosemide might have influenced MMC pharmacokinetics in one patient. In view of the fact that MMC is being given increasingly often to elderly patients, who often take furosemide, we considered it of great importance to exclude any interaction between the two drugs. Therefore, a study was initiated to evaluate the effect of furosemide on MMC elimination.

Materials and methods

Five patients (4 women and 1 man; age range 27–69 years) with advanced solid tumors entered on this study. Renal function and liver function tests were normal. All patients received MMC 10 mg/m^2 i.v. (patient A, cycle 2:12 mg/m^2) over 1–2 min. The only drug co-administered was furosemide. Furosemide was administered as a 40-mg i.v. bolus, either 120 min after MMC (courses indicated as A_1, B_1, C_1, and D) or after 200 min (course E). Patients A–C were also studied during a second course of MMC treatment (courses indicated as A_2, B_2 and C_2), with furosemide 40 mg given immediately before MMC administration. Adequate urine output during the study was assured by an oral fluid intake of 250–500 ml/h.

Blood samples were collected in heparinized tubes from the opposite arm to the infusion site, before MMC infusion and then immediately after and 20, 40, 60, 75, 90, 105, 120, 135, 150, 165, 180, 200, 220, 240, 260, 280, 300, 330 and 360 min after the infusion.

Urine samples were collected prior to MMC administration, and every hour thereafter for 4–6 h. Chromatographic analysis of urine and plasma and pharmacokinetic data analysis were performed as published by den Hartigh et al. [3–5].

Results

The pharmacokinetic parameters are reported in Table 1. In patient E it appeared that furosemide had been given only 20 min before the detection limit of MMC was reached. Only 0.5% of the MMC was excreted in the urine (pH 6.5). In patients A–D all pharmacokinetic data obtained were within normal limits for patients receiving the drug as a single agent [4, 8]. The patients' pharmacokinetic curves showed no abnormalities. Moreover, for the second treatment course in patients A–C, the pharmacokinetic data and curves were similar to the first (Fig. 1).

The proportion of the administered dose of MMC ultimately excreted in the urine varied from 0.5% to 22%. Of the total excreted amount, 68%–93% was excreted within the first hour after MMC administration. There was no significant difference ($P = 0.1$) in the intraindividual pattern of MMC excretion in patients A–C when furosemide was given immediately before MMC administration or after 120 min.

Discussion

In the present study no interaction between furosemide administration and MMC pharmacokinetics could be demonstrated. The background for this study was the observation that in a previous retrospective study [9] it was indicated that furosemide administration might have influenced MMC pharmacokinetics in one patient. Considering the fact that MMC is being given increasingly often to elderly patients, who often take furosemide, we considered it of great importance to exclude any interaction between the two drugs.

Furosemide acts in the thick segment of the medullary ascending limb of Henle and exerts its effect within minutes after i.v. administration. Its effect lasts 30–120 min. Furosemide produces renal vasodilatation [6], resulting in

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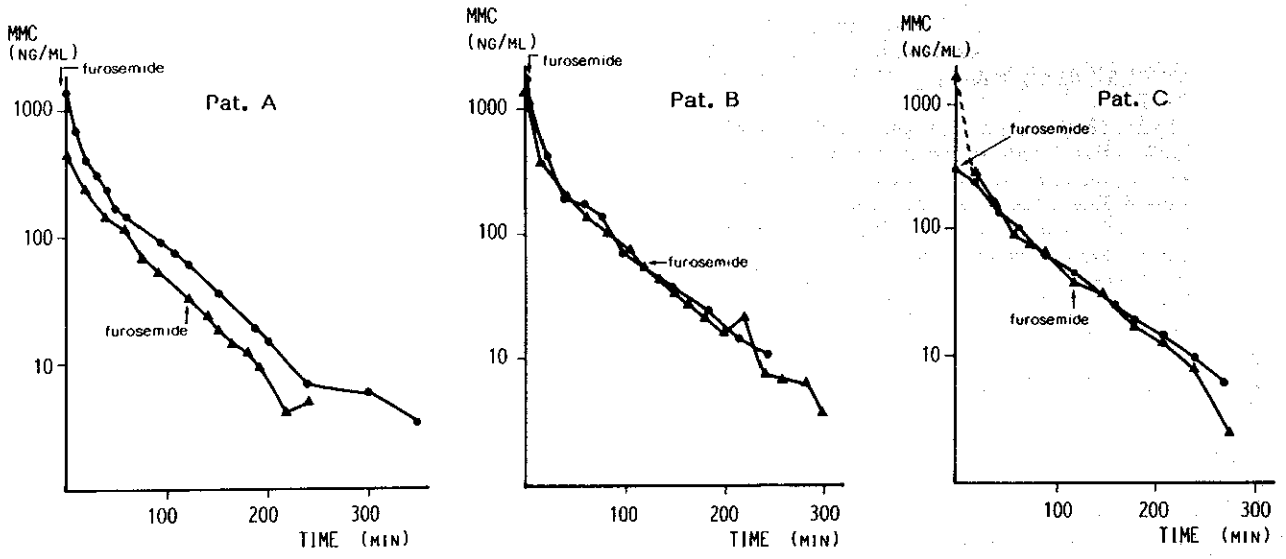

Fig. 1. Plasma concentration-time curves of MMC in patients A–C. Furosemide was administered just before (●) or 120 min after (▲) MMC administration. The time points of furosemide administration are also indicated by *arrows*. In patient A the small difference observed between the two curves is caused by a difference in dose

Table 1. Pharmacokinetic data on mitomycin C with concomitantly administered furosemide

Case	Pharmacokinetic parameter				Urinary MMC
	T1/2β (min)	V_D (l/m^2)	Cl_{tot} ($l\ h^{-1}\ m^{-2}$)	AUC ($\mu g\ h^{-1}\ l^{-1}$)	Excretion (% of dose)
A_1	37.9	23.1	24.9	401	11
A_2	51.9	23.3	18.2	653	16
B_1	47.1	18.2	16.4	609	21
B_2	47.0	18.8	16.3	612	14
C_1	51.3	21.7	17.3	577	12
C_2[a]	42.9	–	–	–	9
D	44.4	16.4	15.8	633	22
E	40.1	25.9	26.4	379	0.5

[a] Accurate values could not be determined because of the absence of a peak value

an increase in renal blood flow, particularly in the outer cortex [1]. The drug blocks tubular reabsorption, and since reabsorption in the affected segment is essential for both concentration and dilution, furosemide causes the production of large volumes of relatively isotonic urine [2, 7]. The pattern of renal MMC excretion we found was similar to the pattern previously observed by others, without concomitant use of diuretics [4, 8]. Normally, most of the renal MMC excretion occurs within the first hour after administration [3]. Even the administration of furosemide prior to the i.v. administration of MMC did not change its urinary excretion rate. In one patient there was very limited renal excretion of MMC. The other parameters in this patient suggest a very rapid and extensive metabolism of the drug. This patient did not receive any other drug, nor were there reasons to expect problems in detecting MMC in the urine, as the acidity of the urine was normal.

If furosemide had increased MMC excretion in the patients studied we would have expected a change in the slope of the pharmcokinetic curve, or a steeper slope of the curve, both dependent on the time of administration of furosemide. These changes did not occur (Fig. 1). For this reason we believe that furosemide does not influence the renal excretion of MMC. The fact that furosemide exerts its effect on the limb of Henle, and does not appear to influence renal MMC excretion, suggests that renal MMC excretion will probably be mainly glomerular.

In conclusion, these data show that furosemide does not influence MMC pharmacokinetics.

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