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Pharmacokinetics of Carminomycin in Man: Biweekly Schedule vs Single Dose every Three Weeks

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Abstract—*Carminomycin was administered to five patients at a dose of* 7.5 mg/m² *twice weekly. Plasma and urine samples were obtained during two subsequent* 72-*hr periods following drug administration, and assayed for carminomycin (C) and carminomycinol (Col) by HPLC with fluorescence detection. Distribution of carminomycin was rapid and drug levels decreased below the detection limit* (5×10^{-9} M) *within* 24 hr. *Carminomycinol appeared very quickly and surpassed carminomycin levels in* 10 min–4 hr, *disappearing very slowly, with a half-life of* 40–98 hr. *No major differences in pharmacokinetic behavior were found when comparing the five patients in this study with patients who received* 18 mg/m², *as described in a previous report. After the second dose of carminomycin in the* 7.5 mg/m² *twice weekly schedule, however, carminomycin pharmacokinetics were found to be altered in comparison with the first dose, the most pronounced difference being an increase in the* $t_{\frac{1}{2}}$ *for Col from* 65 ± 28 *to* 173 ± 81 hr.

INTRODUCTION

CARMINOMYCIN was reported to have a spectrum of antitumor activity comparable to that of doxorubicin [1, 2] but with less cardiac toxicity in animal models [3, 4]. In previous studies the pharmacokinetics of carminomycin in patients receiving 15 [5, 6], 18 [7] and 20 mg/m² [8] were reported. Since in these dose schedules carminomycin showed little or no therapeutic activity, and since in most reports indicating clinical activity of this drug a different schedule was used, a new phase II clinical trial was introduced based on the original drug administration schedule used in the Soviet Union, i.e. 7.5 mg/m² twice weekly for 3 weeks repeated every 4 weeks [2]. To investigate the presumed differences in the activity of this drug depending on the dose schedule employed, a pharmacokinetic study was performed.

MATERIALS AND METHODS

Drugs

Carminomycin was kindly provided by Bristol Laboratories (Syracuse, NY, U.S.A.) in vials containing 10 mg carminomycin hydrochloride and 20 mg mannitol. Each vial was reconstituted with distilled water for i.v. injection immediately prior to drug administration. 4'-Epidoxorubicin was provided by Farmitalia Carlo Erba (Milan, Italy).

Blood and urine samples

Samples of blood (5 ml) were taken through an indwelling venous catheter prior to and at timed intervals after carminomycin administration. Blood was collected in heparinized tubes and centrifuged within 10 min. Aliquots of urine were collected at 6-hr intervals for 72 hr. Plasma and urine samples were stored at −20°C until analysis.

Patients

Plasma and urine samples were collected from five female patients with progressive advanced breast cancer (age range 40–74 yr) during the first course of treatment consisting of a dose of 7.5 mg/m² twice weekly. Prior chemotherapy consisted of cyclophosphamide, methotrexate and 5-fluorouracil (3–34 courses) in 4/5 patients. One patient had received three courses of mitomycin C. None had received radiotherapy, hormonal

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therapy or chemotherapy for 4 weeks (6 weeks for mitomycin C) prior to carminomycin administration. Carminomycin was administered by rapid i.v. injection.

Sample clean-up and chromatographic conditions [7]

4'-Epidoxorubicin was added to the plasma samples as an internal standard for the assay (100 ng/ml). Plasma samples (1 ml) were kept on ice prior to extraction and carefully vortexed with 5 ml of a mixture of isopropanol/chloroform (1:4, v/v), the organic layer was removed and the aqueous residue re-extracted with another 5 ml of organic solvent. The combined organic layers were evaporated to dryness within 40 min with air at 35°C. The residue was dissolved in 150 μl methanol, 100 μl of which were then injected into the column. A C18 reverse-phase column was used (Whatman Partisil ODS, 25 cm × 4.6 mm) with a phosphate buffer (0.05 M, pH 4.0)–acetonitrile mixture (70:30, v/v) as the mobile phase. For detection, a fluorometric monitor (Perkin Elmer, model 3000) was used (excitation and emission wavelengths being 490 and 550 nm respectively). The detection limit was 5×10^{-9} M. In order to decrease adsorption, all glassware was treated with dichlorodimethylsilane (5% in chloroform). All chemicals were of analytical grade.

RESULTS AND DISCUSSION

An example of a plasma vs time curve is represented in Fig. 1. The mean area under the plasma concentration vs time curve (AUC) for these five patients could have been predicted from the results of the pharmacokinetic study of the single dose every 3 weeks schedule of 18 mg/m^2 (Table 1) [7], indicating linear dose-dependent pharmacokinetics. No correlation was found between white blood cell nadir and the AUC of C or Col (Table 2). When comparing carminomycin pharmacokinetics after the first and second doses,

Table 1. Mean AUC (10^{-8} mol.hr/l) *for C and Col* (t = 0–48 hr) *for patients receiving their first dose of* 7.5 mg/m^2 *compared with patients who received* 18 mg/m^2 [7]

Dose (ng/m^2)	n	AUC (C)	AUC (Col)
7.5	5	14 ± 4	54 ± 9
18	9	29 ± 16	95 ± 46

Table 2. Area under the curve (AUC, units, 10^{-8} mol.hr/l) *for carminomycin* (0–24 hr) *and carminomycinol* (0–48 hr) *of five patients who received* 2 × 7.5 mg/m^2 *i.v.*

Patients	1° dosage AUC$_C$	1° dosage AUC$_{Col}$	2° dosage* AUC$_C$	2° dosage* AUC$_{Col}$	WBC nadir†
G	17	62	10	77	2.2
H	10	59	15	66	0.9
N	17	57	8	78	1.1
L	10	53	11	87	0.5
R	16	40	7	47	0.7

*2° dose was given 72 hr after the 1° dose.
†Units, 10^5/ml.

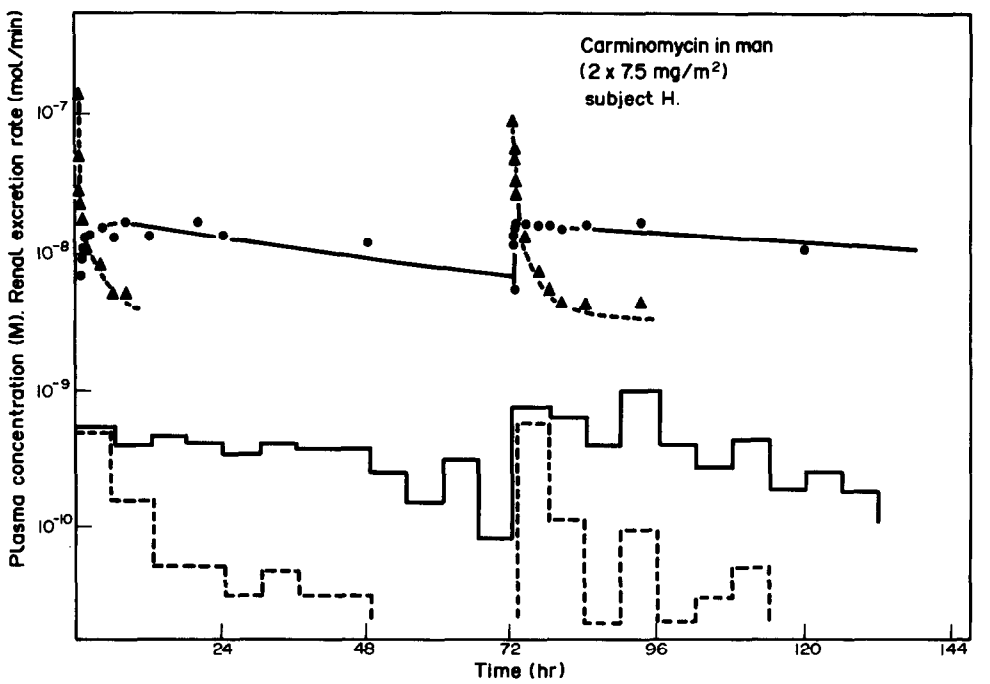

Fig. 1. Carminomycin ■ ■ ■ ■ and carminomycinol ■■■■ plasma concentrations and urine excretion rates vs time of patient H.

the only statistically significant difference ($P < 0.05$) observed was that the $t_{½}$ for Col after the second dose was longer than after the first dose (Table 3). The half-lives for Col were calculated based on linear regression of log C vs t, with t = 12–72 hr. If one extrapolates these results, it can be expected that in multiple dosage regimens the $t_{½}$ for Col will increase further and high plasma concentrations may be observed for a long period of time. Given the known cytotoxic activity of Col [9], this might well have clinical implications. An increase in the $t_{½}$ following multiple doses has also been reported for doxorubicin in rats [10].

Table 3. Mean pharmacokinetic parameters (± S.D.) for the five patients in this study

Parameter	Unit	1° dose	2° dose
AUC (C)*	10^{-8} mol.hr/l	14 ± 4	10 ± 3
AUC (Col)	10^{-8} mol.hr/l	54 ± 9	71 ± 15
CUE (C)†	%	1.9 ± 0.3	1.1 ± 0.2
CUE (Col)	%	7.8 ± 1.6	6.6 ± 1.3
k_{Cren} (Col)‡	l/hr	2.4 ± 0.5	1.7 ± 0.5
$t_{½}$ (Col)	hr	65 ± 28	173 ± 81
k_{Cel} (C)§	l/hr/m²	103 ± 27	143 ± 36

*AUC = area under the curve, t = 0–72 hr.

†CUE = cumulative urine excretion, as a percentage of dose administered (t = 0–72 hr).

‡k_{Cren} = renal clearance = urine excretion rate/plasma concentration.

§k_{Cel} = total body clearance = D/AUC (t = 0–48 hr).

After 9 daily doses of 1.0 mg/kg doxorubicin i.p. (with 2 days of rest between days 5 and 6), the $t_{½}$ calculated from plasma concentrations at 3 and 24 hr increased from 8.3 to 14.6 hr. Similarly, $t_{½}$ for doxorubicinol increased from 8.9 to 53.8 hr under these conditions. In addition, the doxorubicin plasma concentration 24 hr after the last dose given increased almost two-fold after 5 weeks of treatment (5 daily doses of 1 mg/kg i.p., 2 days of rest × 5) when compared with the plasma concentration after 2 weeks [10]. This cannot be explained by linear multiple dose pharmacokinetics, but is in agreement with the observed increase in the $t_{½}$ with multiple doses in our study.

The antitumour effects of doxorubicin [11, 12] and carminomycin [13] appeared to be independent of the dose schedule employed, but may be related to total drug exposure. Cardiotoxicity and drug-induced vomiting have been reduced by long-term infusions and weekly schedules, suggesting a relationship between peak plasma levels and these toxicities. In view of this, the kinetics of multiple dosage regimens will be investigated in more detail, with special emphasis on the concentration profiles after several drug administrations.

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