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Pharmacokinetics of BW12C and mitomycin C, given in combination in a phase 1 study in patients with advanced gastrointestinal cancer

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Abstract. The effect of combining the oxygen-transport-modifying drug BW12C with mitomycin C was investigated in a phase 1 study of 26 patients with advanced gastrointestinal cancer. The dose of BW12C was increased from 20 mg/kg to 60 mg/kg. Dose-limiting toxicity of vomiting was experienced at doses greater than 50 mg/kg. This corresponded to whole blood levels ≥ 700 μg/ml and to >50% haemoglobin modification. Whole blood concentrations of BW12C and modification of the haemoglobin oxygen saturation curve were linearly dependent on dose. BW12C whole blood pharmacokinetics were best described by a one-compartment model and were clearly dose-dependent. The half-life increased from 2.1 h at a dose of 20 mg/kg to 7.2 h at a dose of 60 mg/kg. The AUC increased in a similar non-linear fashion with increasing dose. Mitomycin C was given at a fixed dose of 20 mg/m^2 at the end of the BW12C infusion. Mitomycin C plasma pharmacokinetics fitted a two-compartment model, giving a mean beta half-life of 50 ± 7 min and AUC of 1.1 ± 0.08 μg/ml h, and were unaffected by the combined treatment. There was no evidence of increased mitomycin C toxicity.

Introduction

BW12C (5-[2-formyl-3-hydroxyphenoxy] pentanoic acid) (Fig. 1) is a substituted benzaldehyde that has been specifically designed to bind preferentially to the oxy conformation of human haemoglobin, therefore stabilizing the molecule in a form that has a high affinity for oxygen [2]. This process leads to a left shift in the haemoglobin-oxygen saturation curve (OSC), thus reducing the release of oxygen to the tissues [5]. In murine studies this has been shown to increase in vivo tumour hypoxia [1, 7]. Moreover, in human tumour xenografts BW12C has been shown to potentiate the effects of bioreductive drugs [3], which are activated preferentially under hypoxic conditions.

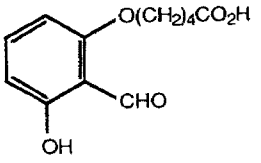

Fig 1. Chemical structure of BW12C

Mitomycin C (MMC) is a clinically well-established cytotoxic agent used in gastrointestinal cancer treatment [14]. It is metabolized under reducing conditions to form a bifunctional alkylating agent which crosslinks and inhibits the synthesis of DNA [6]. As such, it is considered to be the prototype of bioreductive drugs [12]. In studies with a variety of tumour cells the drug was found to be on average about twice as cytotoxic to hypoxic than aerobic cells [6, 8, 11, 13]. Thus, an increase in tumour hypoxia should potentiate the antitumour activity of MMC. It was therefore proposed to combine BW12C with MMC, with the aim of increasing the efficacy of MMC against human tumours.

We investigated the pharmacokinetics of BW12C and MMC as part of a phase 1 study, in which patients with advanced gastrointestinal cancer were treated with a combination of the two drugs.

Methods

Patient selection. Patients up to and including the age of 70 years with progressive metastatic gastrointestinal cancer who had failed previous therapy were entered into the study. All patients had reasonable renal function with serum creatinine less than 150 mmol/l. Eleven patients had liver metastases with mild abnormalities in liver enzymes; serum bilirubin, however, was within normal levels. Patients not showing progressive disease or clinical deterioration proceeded to a second course of

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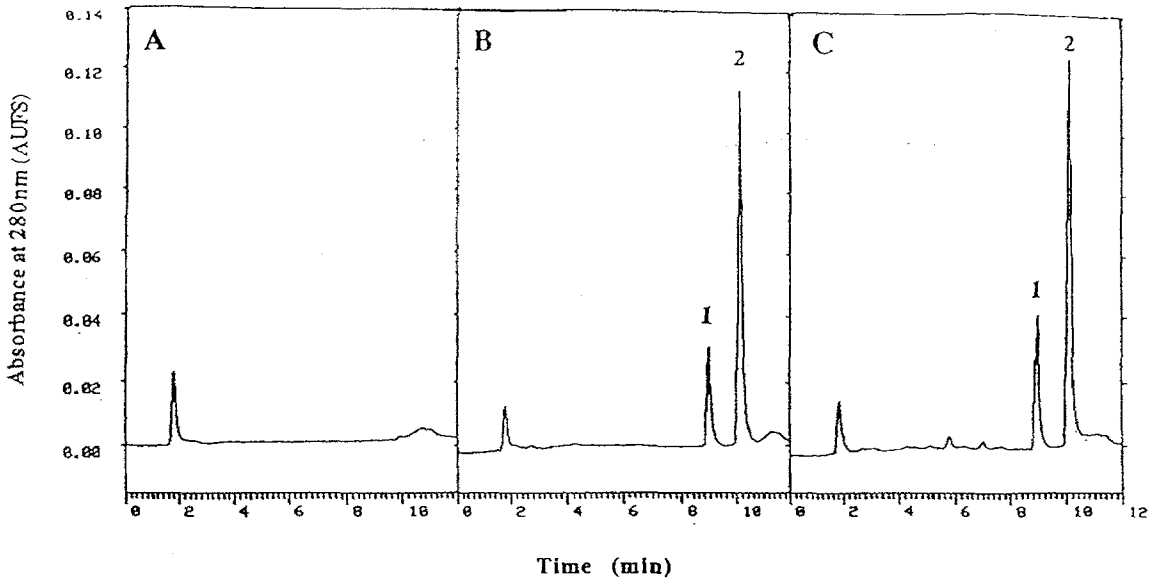

Fig 2. Representative HPLC chromatograms of patient whole blood haemolysate: **A** before treatment; **B** control haemolysate spiked with BW80C (185 μg/ml peak 1) and BW12C (750 μg/ml peak 2); **C** 1 hour after the end of an infusion of BW12C (60 mg/kg loading infusion for 1 h followed by a maintenance infusion of 4 mg·kg^{-1}·h^{-1} for 3 h). Chromatographic conditions: column, Waters Nova-Pak C18 Rad-Pak; mobile phase linear gradient of 45–70% methanol in 10 mmol·l^{-1} sodium phosphate buffer pH 3 over 8 min and held at final conditions for a further 2 min; flow rate, 2 ml/min; detection, absorbance at 280 nm; injection volume 10 μl

treatment after 6 weeks. Consent was obtained from the hospital ethical committee and from the individual patients before commencement of the study.

Drug administration. Cohorts of 2 patients received 1-h i. v. infusions of BW12C (Wellcome, UK), commencing at a dose of 20 mg/kg based on previous experience with the drug in human volunteers (Wellcome, unpublished data). The dose was escalated in the first four cohorts through 30 mg/kg and 35 mg/kg up to 40 mg/kg. The next three cohorts received a loading infusion of 40 mg/kg followed by a maintenance infusion of 6 mg·kg^{-1}·h^{-1} increased at hourly intervals from 1 to 3 h. The final four cohorts were treated with a loading infusion escalating in 5 mg/kg intervals from 45 to 60 mg/kg followed by a 3-h maintenance infusion of 4 mg·kg^{-1}·h^{-1}. These doses were selected to provide approximately spaced incremental steps in oxyhaemoglobin modification by the BW12C. MMC was administered as an i. v. bolus injection at a dose of 20 mg/m^2 immediately on completion of the total BW12C infusion.

Blood samples were taken into heparinized tubes at 0, 30 and 60 min during the loading infusion, hourly during the maintenance infusion, and at 5, 15, 30, 60, 120, 180 min and, for patients not receiving a loading infusion, 240 and 300 min after the end of infusion. An equal volume of distilled water was added to a 1-ml aliquot of blood to form a haemolysate. Plasma was recovered by centrifugation (1000 g for 5 min) of the remainder of the sample. Urine was collected when possible for 24 h after the start of infusion. Haemolysate, plasma and urine were stored frozen at –20° C prior to analysis.

Drug extraction. BW12C was extracted from 200-μl aliquots of haemolysate by acidification with hydrochloric acid (50 μl, 1 mol·l^{-1}), followed by protein precipitation with 400 μl acetonitrile (HPLC grade, Rathburn) containing 300 μg/ml BW80C (5-[4-formyl-3-hydroxyphenoxy] pentanoic acid) (Wellcome, UK) as internal standard. After centrifugation (10 000 *g*, 5 min) an aliquot of the supernatant was removed for analysis by HPLC.

MMC was extracted from 0.5-ml aliquots of plasma using a Waters C18 Sep-pak which had been prewashed with 10 ml methanol (HPLC grade Rathburn) and 5 ml sodium phosphate buffer (0.1 mol·l^{-1}, pH 7.4). Plasma was loaded onto the cartridge with an equal volume of buffer to which 100 μl porfiromycin (100 μg/ml) was added as internal standard. The cartridge was washed with 5 ml of buffer and 5 ml of *n*-hexane (Analar, BDH), air-dried, and eluted with 1.5 ml 95% methanol/5% sodium maleate buffer (0.1 mol·l^{-1}, pH 6.8). The eluate was evaporated to dryness in vacuo using a Savant Speed Vac concentrator, and the residue was redissolved in mobile phase prior to analysis by HPLC.

High-performance liquid chromatography

The HPLC equipment used (Waters Millipore) typically included a Model 710B automated sample injector (WISP), Model 6000A HPLC pumps, a Model 440 fixed wavelength detector, a radial compression Z-module and a Model 845 data station.

Separations for BW12C were carried out on a Waters Nova-Pak C18 (10 cm × 8 mm, 4 μm particle size) radial compression cartridge. This was eluted at a constant flow rate of 2 ml/min with a linear gradient run over 8 min of 45–70% methanol (HPLC grade Rathburn) in a 10 mmol·l^{-1} sodium dihydrogen orthophosphate buffer adjusted to pH 3.0 with hydrochloric acid and held at the final conditions for a further 2 min before reequilibration at the initial conditions. BW12C and BW80C were detected by UV absorbance at 280 nm. Quantitation was by peak area with reference to linear standard curves.

Separations for MMC were also carried out on a Waters Nova-Pak C18 (10 cm × 8 mm, 4 μm particle size) radial compression cartridge, in this case eluting at a constant flow rate of 2 ml/min with a linear gradient run over 15 min of 12.5–50% methanol in a 10 mmol·l^{-1} sodium phosphate buffer at pH 7.4 and held at the final conditions for a further 3 min before reequilibration at the initial conditions. MMC and porfiromycin were detected by UV absorbance at 365 nm. MMC concentrations were determined by peak height, rather than peak area, because it was more suitable for quantitating the very low levels of MMC as it disappeared from detection at the later time points.

Pharmacokinetic parameters. Pharmacokinetic parameters for both drugs were calculated by non-linear regression analysis using the

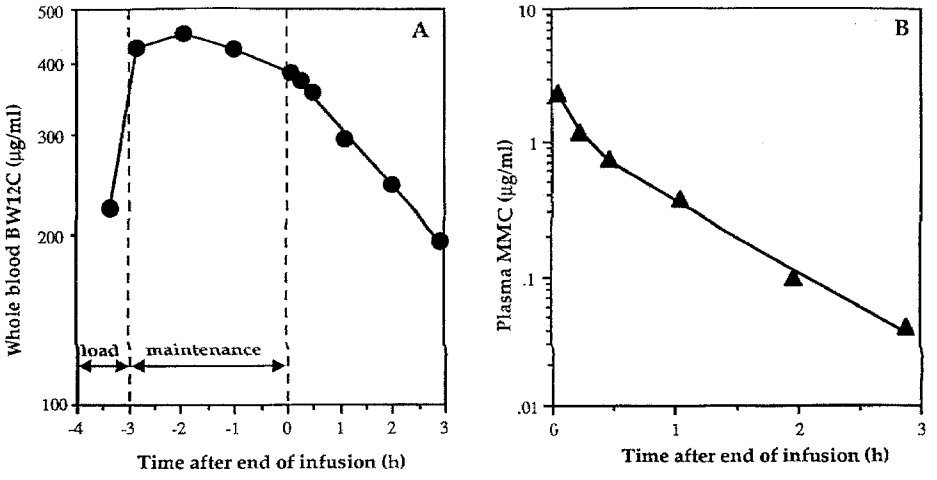

Fig 3. Example of pharmacokinetic profiles: **A** BW12C in whole blood (40 mg/kg loading infusion followed by maintenance infusion of 6 mg·kg^{-1}·h^{-1} for 3 h; **B** MMC in plasma (20 mg/m^2) given as a single bolus injection i. v. at the end of the BW12C infusion. Each *point* is the mean of duplicate assays of samples for the same patient

UltraFit (Biosoft) curve fitting package. Area under the curve for time 0 to t ($AUC_{0->t}$) was calculated using the trapezoidal rule, and the remaining AUC from t to ∞ was given by C_t/k_{el}, where C_t is concentration at time t and k_{el} is the elimination rate constant. The $AUC_{0->\infty}$ was then obtained by the sum of $AUC_{0->t}$ and $AUC_{t->\infty}$.

Modification of haemoglobin-oxygen saturation curve. Blood samples taken during and after the infusion were stored on ice and transported within 24 h to Wellcome Research Laboratories for analysis. The OSC was measured spectrophotometrically using a commercially available semiautomated apparatus (Hem-O-Scan, Aminco) as previously described [2]. BW12C reacts stoichiometrically with haemoglobin and the resulting OSC has a biphasic appearance; the degree of left shifting can be measured by comparing the OSC with theoretical curves calculated for the proportional summation of a normal curve and the fully left-shifted curve (i.e. where 100% of the haemoglobin is bound to the BW12C). The degree of left shift is expressed in erms of percentage modification of haemoglobin.

Results

Clinical observations

Preliminary results on BW12C toxicity in 18 patients given doses of up to 40 mg/kg have already been published [10]. The present study involved a total of 26 patients, 6 of whom reported mild pain or erythema around the injection site. This was seen at doses of greater than 40 mg/kg and related to the overall concentration of the loading infusion. Drowsiness was seen with 2 patients receiving 55 mg/kg and 60 mg/kg, and mild headache in 2 patients receiving 40 mg/kg and 60 mg/kg. One patient receiving 35 mg/kg had an episode of syncope with full recovery after 2–3 min; this occurred at the end of the infusion and was associated with a high whole blood level of BW12C.

Table 1. Summary of the whole blood pharmacokinetics of BW12C in humans

Cohort no.	Loading dose (mg/kg)	No. of treatments	K_{el} (/h)	Co (µg/ml)	$t_{1/2}$ (h)	AUC (µg/ml h)	Cl (l/h)	V_d (l)
1	20	3	0.338 0.30–0.37	162 110–200	2.07 1.9–2.3	571 360–760	1.95 1.19–3.15	6.57 4.5–10.0
2	30	3	0.219 0.14–0.27	283 240–320	3.42 2.6–4.9	1480 1300–1800	1.24 0.97–1.38	6.42 5.7–7.3
3	35	4	0.214 0.19–0.25	352 290–420	3.27 2.8–3.6	1840 1600–2300	1.08 0.84–1.24	5.62 4.6–6.7
4	40	10	0.207 0.13–0.29	305 240–390	3.63 2.4–5.5	2160 1300–3100	1.54 0.98–2.76	10.04 7.7–16.3
8	45	5	0.199 0.14–0.27	354 210–460	3.72 2.6–4.8	3650 1600–4900	1.17 0.74–1.94	10.41 7.8–15.2
9	50	6	0.157 0.14–0.18	432 270–620	4.47 3.8–5.1	3709 2600–5500	1.11 0.64–1.46	9.73 5.7–14.3
10	55	3	0.126 0.12–0.13	637 620–650	5.49 5.2–5.8	7298 7100–7500	0.66 0.63–0.68	7.55 7.4–7.7
11	60	3	0.098 0.08–0.12	636 430–790	7.18 5.8–8.3	8440 5500–9900	0.61 0.44–0.86	8.06 6.3–11.3

K_{el}, elimination rate constant; Co, concentration extrapolated back to the end of the loading infusion; $t_{1/2}$, half-life; Cl, total body clearance; V_d, volume of distribution. Values quoted as means with range beneath

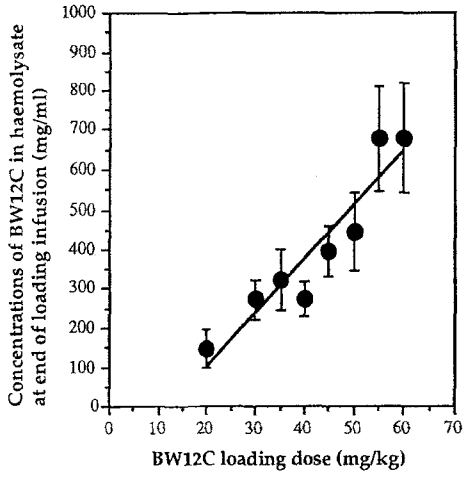

Fig 4. Relationship between whole blood BW12C concentration (±2 SE) immediately after the end of the loading infusion and BW12C loading dose

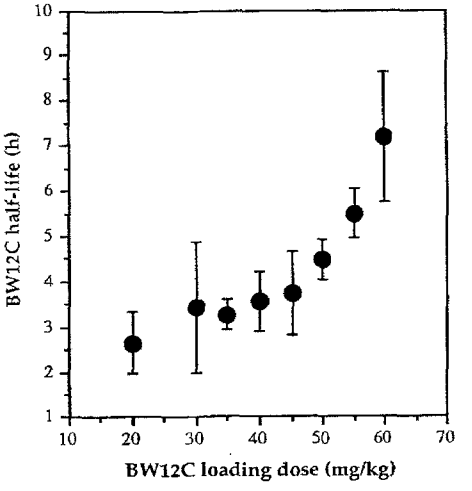

Fig 5. Effect of BW12C loading dose on the half-life (±2 SE) of BW12C

Four patients experienced vomiting (WHO grade 3); 3 of these patients had received doses of 55 mg/kg or greater. Vomiting was dose limiting at doses greater than 50 mg/kg.

MMC toxicity was limited to myelosuppression, and this was not obviously more pronounced than with MMC alone. There were no cases of neutropoenic sepsis or bleeding secondary to thrombocytopoenia.

Out of the group of 26 patients treated, 1 patient with liver disease showed a partial response after two cycles and another patient with anastomotic recurrence showed a complete response after two cycles.

Chromatography

Figure 2 shows typical chromatograms of BW12C extracted from whole blood. Figure 2A shows a chromatogram of haemolysate from a patient prior to treatment; there are no detectable peaks after the solvent front. Figure 2B shows control haemolysate spiked with BW12C (750 μg/ml) and containing internal standard BW80C (185 μg/ml); both compounds are clearly resolved from each other. Figure 2C shows whole blood haemolysate from a patient who received 60 mg/kg BW12C i. v., 60 min after the end of infusion. BW12C was meaurable in haemolysate to a limit of detection of approximately 10 μg/ml. In addition to BW12C itself, two minor metabolites are just noticeable, eluting at about 6 and 7 min respectively.

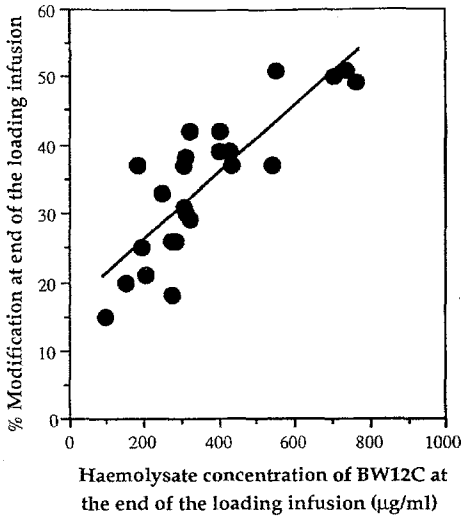

Fig 6. Relationship between the whole blood BW12C concentration at the end of the loading infusion and the modification of the haemoglobin at that time point

Pharmacokinetics

Whole blood concentrations of BW12C and plasma concentrations of MMC were quantified over the complete measurable time course for each patient. Figure 3 shows pharmacokinetic profiles for a typical patient who was treated with a 40-mg/kg 1-h loading infusion of BW12C followed by a maintenance infusion of 6 $mg \cdot kg^{-1} \cdot h^{-1}$ for 3 h. BW12C haemolysate concentrations rise sharply during the loading infusion and can be seen to remain fairly steady during the maintenance period (Fig. 3A). After the end of infusion the kinetics can be best described by a monoexponential decay curve, though due to the sampling protocol it was not possible to determine the curve over three complete half-lives. Figure 3B shows the pharmacokinetics of MMC (20 mg/m^2) given at the end of the completed BW12C infusion as a single i. v. bolus injection. The MMC plasma concentrations can be seen to decay repidly in a biphasic manner.

The pharmacokinetic parameters for BW12C in whole blood for each treatment are detailed in Table 1. BW12C concentration after the end of the loading infusion can be seen to increase approximately linearly with increase in

Table 2. Summary of plasma pharmacokinetics of MMC (20 mg/m²) given in combination with escalating doses of BW12C (20–60 mg/kg)

BW12C Loading dose (mg kg^{-1})	No. of treatments	MMC pharmacokinetic parameters			
		Co (μg ml^{-1})	$t_{1/2}\alpha$ (min)	$t_{1/2}\beta$ (min)	$AUC_{0\to\infty}$ ($\mu g \cdot ml^{-1} \cdot h^{-1}$)
20	2	3.00 2.6–3.4	10.24 5.0–15.5	45.7 45–46	1.435 1.38–1.49
30	2	2.17 1.8–2.5	7.37 6.9–7.8	36.5 33–40	0.953 0.92–0.99
35	2	2.32 2.3–2.3	9.96 6.6–13.3	72.1 65–79	1.274 1.12–1.43
40	8	2.65 1.9–3.5	7.38 3.0–13.0	41.2 25–60	0.992 0.81–1.26
45	3	2.28 1.4–3.1	5.13 4.1–5.8	50.6 45–54	1.031 0.97–1.11
50	2	1.85 1.5–2.2	8.14 7.7–8.6	52.2 51–54	1.099 1.06–1.14
55	2	2.13 1.8–2.5	7.60 5.4–9.8	66.2 63–69	1.305 1.21–1.40
60	2	1.78 1.4–2.1	7.54 5.5–9.5	47.8 46–50	0.979 0.96–1.00
Mean ±2 SE	23	2.37 0.25	7.66 1.28	48.8 5.25	1.092 0.081
MMC alone	5	3.75 2.0–6.0	4.62 1.7–6.8	43.0 21–53	1.429 1.05–1.77

dose as shown in Fig. 4. BW12C appears to exhibit dose-dependent pharmacokinetics, the half-life lengthening with increasing dose above 35 mg/kg (Fig. 5). While there is an indication of a slight increase in half-life at doses up to 45–50 mg/kg, there is clearly a dramatic increase above 45–50 mg/kg. There is a linear relationship between percent modification of haemoglobin and BW12C whole blood levels, as shown in Fig. 6. Analysis of urine samples revealed that for a 24-h collection period after the start of infusion, the amount of parent drug eliminated in the urine was only 0.7% (range 0.07–2.68%) of the total dose. A number of BW12C metabolites could be seen in the urine, and together with parent drug they accounted for 12.2% (range 5.5–23.0) of the total dose.

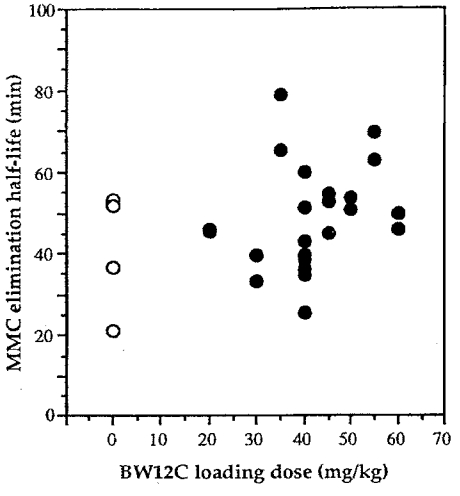

Fig 7. Effect of BW12C loading dose on the elimination half-life of MMC for patients treated with the combination of drugs (●). Also plotted are data for patients treated with MMC only (○)

MMC plasma pharmacokinetics are detailed in Table 2. These have been calculated from data obtained from the first treatment only. MMC pharmacokinetic parameters appear to be independent of BW12C dose. A plot of MMC elimination half-life versus BW12C loading dose is shown in Fig. 7 to illustrate this observation. For all patients treated with the combination of drugs, MMC was shown to have a mean (±2 SE) $t_{1/2}\alpha$ of 7.7±1.3 min, a $t_{1/2}\beta$ of 48.8±5.3 min, an $AUC_{0\to\infty}$ of 1.09±0.08 $\mu g \cdot ml^{-1} \cdot h^{-1}$ and a clearance of 18.9±1.3 $l \cdot h^{-1} \cdot m^{-2}$.

Discussion

The pharmacokinetics of BW12C and MMC given in combination were successfully determined using the procedures and HPLC techniques described. BW12C haemolysate pharmacokinetics as measured in this study were best described by a 1-compartment model, rather than a 2-compartment model as previously reported [5]. It was not possible to demonstrate either the presence or the absence of a second compartment with the blood sampling regimen chosen in the present study. Note that this was a maximum of 5 h from the end of infusion. The previously reported β-phase half-life was 8.5 h. Futhermore, the postulated existence of a second compartment is of little im-

portance, as it was thought to be due to the loss of an acid-labile metabolite rather than the parent drug. The fact that the loss of left shifting effect on the haemoglobin OSC is a first-order process provides further evidence suggesting that a second compartment is due to an artefact. The pharmacokinetic parameters clearly show non-linearity: for example, the half-life increased from 2.1 h at a dose of 20 mg/kg to 7.2 h at a dose of 60 mg/kg. Similar effects had previously been observed [5] in healthy volunteers, albeit at lower dose levels, and a saturation of the elimination pathway was proposed as an explanation for such findings. Little information is available on the metabolism of BW12C, but it is obvious from these and other available data that it is metabolized prior to excretion, rather than by direct renal clearance. However, the enzymes involved and the nature of the metabolites remain unknown, but at the very high blood levels achieved (up to 800 μg/ml) saturation of an elimination pathway is feasible. Dose-limiting toxicity of nausea and vomiting was observed at BW12C doses of 55 and 60 mg/kg, corresponding to whole blood levels of 700 μg/ml and higher and to greater than 50% haemoglobin modification; thus a dose of 50 mg/kg was considered to be the maximum tolerated for a 1-h i.v. infusion for use in further studies.

MMC pharmacokinetic parameters were in good agreement with those in previously published single-agent trials [4, 9, 15, 16]. MMC elimination rates were unaffected by the combined treatment with BW12C, though there was a correlation between BW12C dose and MMC clearance, Co and AUC.

Clinically there was no evidence of any increased toxicitiy of MMC when given in combination with BW12C, and neither was there any evidence of improved efficacy of the treatment.

The study is continuing with a different dosage schedule. The effects of BW12C on normal and tumour tissue oxygenation are being investigated with the aid of an oxygen electrode probe. This is vital in order to determine whether BW12C is producing the desired hypoxia required to enhance the activity of the bioreductive drugs with which it is given in combination.

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