Cancer Chemother Pharmacol (1992) 29: 480–484

Cancer Chemotherapy and Pharmacology

Clinical pharmacokinetics of mitoxantrone after intraperitoneal administration

J. Dieter Nagel[1], Freek J. Varossieau[2], Ria Dubbelman[2], Wim W. ten Bokkel Huinink[2], and J. Gordon McVie[3]

[1] University Clinic of Bonn, Department of Pediatric Oncology and Hematology, Adenauerallee 119, W-5300 Bonn, Federal Republic of Germany
[2] Netherlands Cancer Institute, Department of Experimental Therapy, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
[3] Cancer Research Campaign, 2 Carlton House Terrace, London, SWIY 5AR, U.K.

Received 20 June 1990/Accepted 14 October 1991

Summary. The pharmacokinetics of intraperitoneally (i.p.) injected mitoxantrone was determined in plasma and peritoneal dialysate taken from five patients presenting with cancer confined to the peritoneal cavity over a sampling period of 1 week. The drug was given through a Tenckhoff catheter as a 15-min infusion and the peritoneal dialysate was removed after a dwell time of 4 h; the doses delivered varied between 20 and 50 mg/m^2. Dose-limiting local toxicity was moderate. The HPLC technique used for mitoxantrone determinations proved to be sensitive within the range of 0.3–4,000 ng/ml. Median values obtained for the pharmacokinetic parameters of mitoxantrone in peritoneal dialysate were: $t_{1/2\beta}$ (distribution), 56.4 min (range, 16.8–235.8 min); $t_{1/2\gamma}$ (elimination), 128 h (range, 28.3–171.0 h); Vd_{ss} (volume of distribution at steady state), 24.8 l (range, 17.0–232.5 l); Δ'_{ss} (volume of distribution at steady state corrected for the body surface area in square meters), 14.4 l/m^2 (range, 10.6–129.2 l/m^2); and clearance, 0.25 l/h (range, 0.16–0.59 l/h). For plasma the median values were: $t_{1/2\alpha}$ (absorption), 58.8 min (range, 45.6–87.0 min); $t_{1/2\beta}$ (distribution), 2.5 h (range, 1.4–6.3 h); $t_{1/2\gamma}$ (elimination), 44.1 h (range, 9.1–91 h); Vd_{ss}, 2,152 l (range, 352–19,733 l); Δ'_{ss}, 1,345 l/m^2 (range, 220–11,606 l/m^2); and clearance, 117 l/h (range, 51–1,609 l/h). After 168 h the median plasma concentration was 1 ng/ml. The median peak concentration in peritoneal dialysate was 490 ng/ml. Considering the moderate toxicity observed and the concentrations achieved in the peritoneal dialysate, removal of the dialysate after certain dwell times seems reasonable to be a reasonable approach for the optimization of i.p. treatment with mitoxantrone.

Introduction

Intraperitoneal (i.p.) administration of mitoxantrone to patients presenting with refractory ovarian cancer has resulted in surgically defined responses, including complete remissions, in an adjuvant setting [3, 5, 10, 16]; responses have been obtained even in previous nonresponders to i.p. cisplatin [10].

Several phase I and II studies [3, 5, 10, 11] have reported local toxicity (abdominal pain, adhesion formation) rather than systemic toxicity as the dose-limiting factor. Various attempts have been made to decrease the local toxic effects of mitoxantrone, particularly to prevent adhesion formation. Limited experimental data suggest that the use of nonsteroidal antiinflammatory agents might be successful [9]. Other investigators have removed the peritoneal dialysate, which contains at least a fraction of the amount of mitoxantrone delivered, after dwell times of 24 [7] or even 8 h [8] or have considered delivering lower doses more frequently [10] to reduce local toxicity. The approach of removing the peritoneal dialysate after certain dwell times is supported by the pharmacokinetic properties of the agent, including a high affinity for tissue [1, 2, 6, 13, 18] and favorable ratios of $AUC_{(peritoneal\ dialysate)}$ over $AUC_{(plasma)}$ [3, 5, 11].

The aim of the present study was to investigate whether the pharmacokinetics of mitoxantrone would remain favorable and whether its local toxicity could be decreased if dwell times were reduced to only 4 h. The sampling intervals for previous data did not exceed 48 h after i.p. administration, at which time a measurable amount of drug could be detected in both plasma and peritoneal dialysate. To obtain better insight into the pharmacokinetics of mitoxantrone, longer sampling periods were considered [17]. In the present study, we determined the pharmacokinetics of mitoxantrone over an interval of up to 1 week after i.p. administration.

Patients and methods

Patients. Individuals presenting with metastatic cancer confined to the peritoneal cavity that was sensitive to mitoxantrone were eligible for this study. Since only the pharmacokinetics in respect to reduced dwell times and local toxicity were at issue, patients that were heterogeneous according to histology and previous chemotherapy were accepted. Additional

Offprint requests to: J. D. Nagel

Table 1. Patients' characteristics

Patient, sex, age (years)	Dose		Drug removed mg (%)	Pain	Previous chemotherapy		Primary malignancy	Previous laparatomies (*n*)
	mg/m²	mg			i.v.	i.p.		
A, F, 47	20	32	4.94 (15.4%)	–	CDDP, CPP, HMM	Mitoxantrone, 2	Ovarian carcinoma	2
B, F, 54	25	40	7.57 (18.9%)	–	CPP, MTX, 5-FU	Mitoxantrone, 5	Breast cancer	1
C, M, 44	25	45	3.21 (7.1%)	–	–	–	Peritoneal mesothelioma	0
D, F, 56	30	60	17.49 (29.2%)	(+)	5-FU, MTX HMM, CPP ADR, CDDP	Carboplatin Mitoxantrone, 6	Ovarian carcinoma	2
E, F, 55	50	85	12.11 (14.2%)	+	CDDP, CPP ADR, HMM	Carboplatin Mitoxantrone, 1	Ovarian carcinoma	3

CDDP, Cisplatin; CPP, cyclophosphamide; HMM, hexamethylmelamine; MTX, methotrexate; 5-FU, 5-fluorouracil; ADR, doxorubicin

Table 2. Pharmacokinetic parameters of mitoxantrone in peritoneal dialysate

Patient	$t_{1/2\beta}$ (min)	$t_{1/2\gamma}$ (h)	Vd_{ss} (l)	Δ'_{ss} (l/m²)	C (l/h)	$\frac{AUC_{perit.dialy.}}{AUC_{plasma}}$
A	63.0	28.3	17.0	10.6	0.45	381
B	235.8	128.0	22.3	13.9	0.16	713
C	56.4	171.0	232.5	129.2	0.24	479
D	16.8	144.0	51.0	25.5	0.25	270
E	17.4	63.0	24.8	14.4	0.59	2,729

Table 3. Pharmacokinetic parameters of mitoxantrone in plasma

Patient	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)	Vd_{ss} (l)	Δ'_{ss} (l/m²)	C (l/h)
A	49.2	2.6	12.0	352	220	171
B	87.0	1.6	44.1	2,152	1,345	113
C	45.6	6.3	91.0	10,091	5,606	51
D	58.8	1.4	47.0	644	322	117
E	82.8	2.5	9.1	19,733	11,606	1,609

eligibility criteria included a Karnofsky performance status of $\geq 60\%$, a WBC of $\geq 3{,}000/\mu l$, a platelet count of $\geq 100{,}000/\mu l$, serum creatinine levels of ≤ 2.0 mg/dl, serum bilirubin values of ≤ 1.5 mg/dl, and a minimal life expectancy of >6 months. All subjects exhibited ascites; in addition, patient D displayed pleural effusion and patient E, peritoneal carcinomatosis. The first patient received a dose of 20 mg/m². Since no local toxicity as judged by the occurrence of abdominal pain was observed, doses were escalated up to 50 mg/m².

Treatment. Mitoxantrone was given in 2 l saline as a 15-min infusion through a Tenckhoff catheter. After a dwell time of 4 h the solution was withdrawn. Blood samples were taken via an indwelling cannula at 5, 10, 15, 30, and 60 min and then at 1-h intervals for the first 12 h and at 24-h intervals for up to 168 h thereafter. Ascites samples were simultaneously drawn via the Tenckhoff catheter. The catheters were washed with saline after each mitoxantrone treatment to eliminate possible contamination of the samples with drug that might have adsorbed to the inside of the catheters.

Chemicals. Mitoxantrone was supplied by Lederle Nederland B.V. as a sterile solution of mitoxantrone hydrochloride (2 mg/ml). Buffer I consisted of 0.16 M ammonium formate (pH 2.5; Fluka Chemie AG, Buchs, FRG), and buffer II comprised 0.16 M ammonium formate (pH 6.5) and 8 mM heptane sulphonic acid (Aldrich Chemie, Steinheim, FRG). Acetonitrile was purchased from Merck (article 3, Darmstadt, FRG), and mitoxantrone hydrochloride (Lot PC 0517, 83.7% free base) and ametantrone hydrochloride were generously donated by Cyanamid Company (Pearl River, NJ, USA).

Blood sampling. Blood samples were drawn into citrate tubes and centrifuged immediately. The supernatant was pipetted into a clean tube and stored at –20° C. Prior to processing, the plasma samples were thawed; 1 ml plasma was then transferred into a silicone-coated tube and 1 ml buffer I containing an appropriate amount of ametantrone as an internal standard was added (e.g., 10, 100, or 1,000 ng). After mixing of this solution, 1 ml 0.1 M borax buffer (pH 9.6) was added and further mixed, following which 8 ml chloroform/isopropanol (4 : 1, v/v) was added and vortexed vigorously. After centrifugation for 15 min at 4,000 *g*, the aqueous layer was discarded and the organic layer was transferred to a clean tube and evaporated at 37° C under air. The residue was dissolved in 200 µl buffer II prior to analysis and 175 µl of this solution was injected onto the column. The rate of drug recovery for this procedure was $89\% \pm 2.1\%$.

Ascites sampling. Ascites samples drawn from the belly were collected in citrate tubes and stored at –20° C. The samples taken during the first 24 h

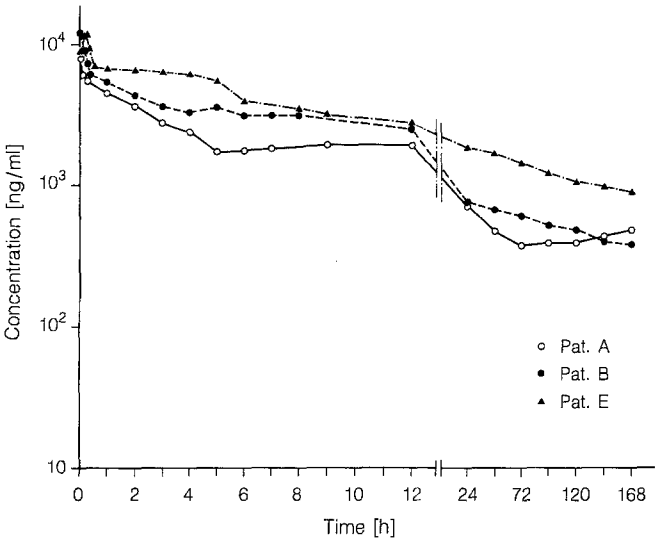

Fig. 1. Time-concentration curves calculated for mitoxantrone in peritoneal dialysate from patients A, B, and E

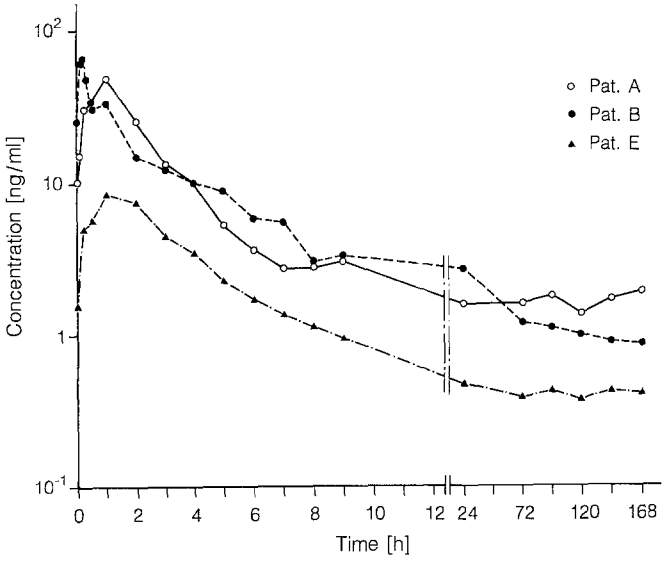

Fig. 2. Time-concentration curves calculated for mitoxantrone in plasma from patients A, B, and E

were diluted 10 times with buffer II and an appropriate amount of ametantrone was added (4,000 ng). The specimens obtained during the rest of the sampling period were diluted 5 times with buffer II, and 1,000 ng ametantrone was added. Of the diluted sample, 100 µl was injected onto the column.

High-pressure liquid chromatography. The high-pressure liquid chromatography (HPLC) system consisted of a Perkin-Elmer Series 2 solvent delivery system (Perkin-Elmer Company, Norwalk, Conn., USA), a Perkin-Elmer ISS-100 autosampler fitted with a cooled tray (0° C), a Spark MUST column switcher (a gift from Spark Holland B. V.), and an ISCO V4 variable-wavelength detector (ISCO Inc., Lincoln, Neb., USA) set at 658 nm. The preconcentration column was a Chrompack cartridge column (10 × 3 mm; C18 material; particle size, 45 µm; Chrompack, Middelburg, The Netherlands). The analytical column was an Alltech Solvent Miser column (150 × 2.1 mm; C18 material; particle size, 5 µm; Alltech Europe Inc., Eke, Belgium). The preconcentration eluent consisted of buffer II, and the analytical eluent contained 27% acetonitrile and 73% buffer I (v/v) and 8 mM heptane sulphonic acid. The flow rates were 1.25 and 0.35 ml/min, respectively. After injection, the compounds concentrated on the preconcentration column. After 3 min washing, the eluents were switched and the compounds were washed onto the analytical column. In this way, almost all of the sample could be injected onto the column. The total analysis time was 11 min. Nonlinear regression analysis was used to calculate the pharmacokinetic parameters.

Results

Five patients presenting with peritoneal metastases were entered in the study; their representative data are shown in Table 1. Four of them had previously received chemotherapy, including i.p. mitoxantrone. The primary tumor involved ovarian carcinoma in three cases and breast cancer and abdominal mesothelioma, respectively, in the other two subjects. Routine biochemistry was normal in all but patient D, who exhibited increases in alkaline phosphatase and γ-glutamyl transpeptidase (γ-GT). No patient showed decreased renal function as determined by blood creatinine and urea levels. The number of laparotomies undergone by our subjects prior to the present study ranged from 0 to 3. Abdominal pain did not occur in patients A–C, who received mitoxantrone 20–25 mg/m^2. Patients D (30 mg/m^2) and E (50 mg/m^2) experienced moderate abdominal pain without requiring analgesics.

The pharmacokinetic data are summarized in Table 2 for peritoneal dialysate and in Table 3 for plasma. Figure 1 illustrates the mitoxantrone concentrations measured in peritoneal dialysate for patients A, B, and E, and Fig. 2 shows the corresponding plasma drug concentrations.

The maximal drug concentrations in peritoneal dialysate were achieved directly after the end of the infusion, the median value being 8,700 ng/ml dialysate. The concentration declined continuously, reaching 10% of the maximal value within 24 h. For peritoneal dialysate, the median values found were: $t_{1/2\beta}$ (distribution), 56.4 min (range, 16.8–235.8 min); $t_{1/2\gamma}$ (elimination), 128 h (range, 28.3–171.0 h); Vd_{ss} (volume of distribution at steady state), 24.8 l (range, 17.0–232.5 l); Δ'_{ss} (volume of distribution at steady state corrected for the body surface area in square meters, 14.4 l/m^2 (range, 10.6–129.2 l/m^2); and clearance (C), 0.25 l/h (range, 0.16–0.59 l/h). After 168 h, high drug concentrations could be detected in peritoneal dialysate, with the median value being 490 ng/ml.

The maximal plasma concentrations were achieved within 1 h of the end of the infusion, the median value being 34 ng/ml plasma. The concentration declined continuously, reaching 10% of the maximal value within 8 h. For plasma, the median values found were: $t_{1/2\alpha}$ (absorption), 58.8 min (range, 45.6–87.0 min); $t_{1/2\beta}$ (distribution), 2.5 h (range, 1.4–6.3 h); $t_{1/2\gamma}$ (elimination), 44.1 h (range, 9,1–91 h); Vd_{ss}, 2,152 l (range, 352–19,733 l); Δ'_{ss}, 1,345 l/m^2 (range, 220–11,606 l/m^2); and clearance (C), 117 l/h (range, 51–1,609 l/h). After 168 h, mitoxantrone could be detected in plasma, the median concentration being 1 ng/ml. The ratio $AUC_{(peritoneal\ dialysate)}/AUC_{(plasma)}$ ranged from 270 to 2,729 (median, 479). In all, 7.1%–29.2% of the delivered drug was removed after the dwell time of 4 h (Table 1). The analytical method used

in this study proved to be sensitive within the range of 0.3–4,000 ng/ml.

Discussion

Both the terminal (elimination) half-life ($t_{1/2\gamma}$) and the volumes of distribution (Vd_{ss}, Δ'_{ss}) determined in the peritoneal dialysate indicated that mitoxantrone bound extensively to the peritoneal tissues and confirmed previous findings that the drug is distributed into a deep tissue compartment from which it is slowly released [1, 2, 6, 13, 18]. After the dwell time (4 h), no sudden change in the slope of the concentration-time curve occurred, suggesting that the distribution of mitoxantrone in the peritoneal cavity was almost completed within this period. The high drug concentrations found in the peritoneal dialysate after 168 h indicated that mitoxantrone stayed in the peritoneal cavity for a long time and reflected its low systemic absorption. This observation was supported by the plasma concentrations.

The mean peak plasma concentration after the i.p. administration of mitoxantrone was about 10–15 times lower than those previously determined after i.v. administration. Smyth et al. [13] found a mean peak plasma concentration of 550 ng/ml after i.v. administration of 14 mg/m^2, and in a previous study [18] we reported a mean peak value of 352.6 ng/ml following an i.v. dose of 15 mg/m^2. The mean ratio for the peak concentrations (peritoneal dialysate/plasma) was 255. Ehninger et al. [7] and Loefller and Freund [8] reported even higher ratios for the peak concentrations in peritoneal dialysate and plasma (564 and 620, respectively). The ratios of $AUC_{(peritoneal\ dialysate)}$/$AUC_{(plasma)}$ ranged from 270 to 2,729 and again indicated a low systemic absorption of mitoxantrone from the peritoneal cavity. Similar ratios have been reported by other investigators. Blochl-Daum et al. [5] found a value of 1,108 and that determined by Alberts et al. [3] was 800. Earlier studies conducted by our group [11] have also revealed a highly variable ratio ranging between 258 and 24,639.

After the dwell time of 4 h, 7.1%–29.2% of the delivered drug was removed. Interestingly, the more often patients had received i.p. mitoxantrone previously, the higher the percentage removed. In patient D, who had received i.p. mitoxantrone six times previously, 29.2% of the agent was removed, and in patient C, who had not previously received i.p. mitoxantrone, only 7.1% was removed. Due to the small number of patients studied, explanations for these results are difficult to find.

The heterogeneity of the patients' characteristics, the differences in prior chemotherapy (i.v. vs i.p.), and the different doses delivered may account for the observed interindividual variability, which has also been demonstrated in previous studies [7]. Nevertheless, one can reasonably assume that due to the high affinity of mitoxantrone for tissue, large proportions of the delivered dose remain in the peritoneal cavity following the removal of the peritoneal dialysate after a dwell time of 4 h. The mitoxantrone concentrations that were achievable in the peritoneal cavity after a dwell time of 4 h exceeded those required to produce an antitumor effect against ovarian carcinoma in an experimental setting [3, 4]. Considering that toxicity was only moderate, even at doses of 30 or 50 mg/m^2, the removal of the peritoneal dialysate after a given dwell time seemed to be a reasonable approach for the optimization of i.p. treatment with mitoxantrone.

Presently, i.p. mitoxantrone is widely used as second-line treatment for mainly small-volume refractory ovarian cancer following the i.v. and/or i.p. administration of cisplatin rather than being considered a standard therapy option. The i.p. administration of mitoxantrone should be further evaluated in investigative settings, whereby the peritoneal dialysate is removed after certain dwell times. Determinations of tumor and tissue drug concentrations after the i.p. injection of mitoxantrone, as after i.v. administration [12, 14, 15], will provide further insight into this modality of treatment.

References

1. Alberts DS, Peng YM, Leigh S, Davis TP, Woodward DL (1983) Disposition of mitoxantrone in patients. Cancer Treat Rev 10: 23–27
2. Alberts DS, Peng YM, Leigh S, Davis TP, Woodward DL (1985) Disposition of mitoxantrone in cancer patients. Cancer Res 45: 1879–1884
3. Alberts DS, Young L, Mason N, Salmon SE (1985) In vitro evaluation of anticancer drugs against ovarian cancer at concentrations achievable by intraperitoneal administration. Semin Oncol 12: 38–42
4. Alberts DS, Surwit EA, Peng Y-M, McCloskey T, Graham V, McDonald L, Roe D (1988) Phase I clinical and pharmacokinetic study of mitoxantrone given to patients by intraperitoneal administration. Cancer Res 48: 5874–5877
5. Blochl-Daum B, Eichler HG, Rainer H, Jakesz R, Salzer H, Ehninger G (1987) Clinical and pharmacokinetic evaluation of intraperitoneal mitoxantrone: phase I study (meeting abstract). Proc Am Soc Clin Oncol 6: A77
6. Ehninger G, Proksch B, Heinzel G, Woodward DL (1986) Clinical pharmacology of mitoxantrone. Cancer Treat Rep 70: 1255–1261
7. Ehninger G, Aapro MS, Rainer H, Blochl-Daum B (1987) Intracavitary treatment with mitoxantrone: In: Mouridsen HT, Arlin ZA (eds) The role of mitoxantrone in malignant diseases. Pharmalibri, Morristown, New Jersey, pp 19–24
8. Loeffler T, Freund W (1986) Pharmacokinetics of intraperitoneal mitoxantrone (meeting abstract). Proc Am Assoc Cancer Res 27: 175
9. Markman M, Vasilev S, Howell SB, et al. (1986) Inhibition of peritoneal cavity fibrin deposition induced by the intraperitoneal administration of cisplatin and cytarabine. Clin Res 34: 567 A
10. Markman M, George M, Hakes T, Reichman B, Hoskins W, Rubin S, Jones W, Almadrones L, Lewis JL, Jr (1990) Phase II trial of intraperitoneal mitoxantrone in the management of refractory ovarian cancer. J Clin Oncol 1: 146–150
11. McVie JG, Rodenhuis S, Dubbelman R, Varossieau FJ, Ten Bokkel Huinink WW (1987) Clinical pharmacokinetics of intraperitoneal mitoxantrone in ovarian cancer (meeting abstract). Proc Am Soc Clin Oncol 6: A156
12. Roboz J, Paciucci PA, Silides D, Greaves J, Holland JF (1984) Detection and quantification of mitoxantrone in human organs. Cancer Chemother Pharmacol 13: 67–68
13. Smyth JF, Macpherson JS, Warrington PS, Leonard RC, Wolf CR (1986) The clinical pharmacology of mitoxantrone. Cancer Chemother Pharmacol 17: 149–152
14. Stewart DJ, Green RM, Mikhael NZ, Montpetit V, Thibault M, Maroun JA (1986) Human autopsy tissue concentrations of mitoxantrone. Cancer Treat Rep 70: 1255–1261

15. Stewart DJ, Green R, Monpetit V, Hugenholtz H, Richard M, Mikhael N, Maroun J (1986) Human tissue (TIS) concentration (CONC) of mitoxantrone (M) (meeting abstract). Proc Am Assoc Cancer Res 27: 167
16. Ten Bokkel Huinink WW, Kroes J, Dubbelman R, Franklin H, McVie JG (1986) Intraperitoneal mitoxantrone (M) in refractory ovarian cancer, a dose-finding study (meeting abstract). Proceedings, 5th NCI-EORTC Symposium on New Drugs in Cancer Therapy, October 22–24, Amsterdam
17. Ten Bokkel Huinink WW, Nagel D, Varossieau F, Dubbelman R, McVie JG (1987) Intracavitary chemotherapy. In: Hatt KJ, Robinson R, Robinson G, McGrath K (eds) Proceedings of the 3rd United Kingdom Novantrone Symposium on the Current Status of Clinical Research. November 26, London Media Medica, Chichester, pp 99–101
18. Van Belle SJP, De Planque MM, Smith IE, Van Oosterom AT, Schoemaker TJ, Deneve W, McVie JG (1986) Pharmacokinetics of mitoxantrone in humans following single agent infusion or intraarterial injection therapy or combined-agent infusion therapy. Cancer Chemother Pharmacol 18: 27–32