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Clinical pharmacokinetics of mitoxantrone in hyperthermic, isolated perfusion of the leg

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Summary. The clinical pharmacokinetics of mitoxantrone in hyperthermic, isolated perfusion of the leg were studied in five patients exhibiting solitary, localized malignant melanoma. Mitoxantrone was given as four 1-min infusions at 15-min intervals into the arterial line of the perfusion system at a total dose of up to 14 mg/m^2. The mean half-lives for mitoxantrone in the blood circulation of the leg were: $t_{1/2\alpha}$ (distribution phase), 25.5 s, and $t_{1/2\beta}$ (elimination phase), 14.9 min. The mean volume of distribution at steady state in the leg was 25.6 l. In the arterial part of the perfusion, the mean AUC was 155.9 mg min l^{-1}, and that in the corresponding venous part was 91.6 mg min l^{-1}. Leakage of the drug from the leg into the systemic circulation amounted to 1.2% of the total delivered dose; 91% of the delivered dose remained in the leg after the perfusion had been completed. The mean elimination half-life of mitoxantrone in the systemic circulation was 123 min and the corresponding AUC for systemic concentrations was 8.59 mg min l^{-1}. The present data revealed a high uptake of mitoxantrone into the leg and low systemic drug concentrations due to minor leakage, suggesting that mitoxantrone might be a good candidate for use in isolated, hyperthermic limb perfusion.

Introduction

Satisfactory results in patients suffering from malignant melanoma can be obtained only for primary tumors displaying minor invasion and an early clinical stage. For advanced melanomas and patients exhibiting local or regional metastases, no effective therapeutic approach is available [2, 11, 12].

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The intent of chemotherapeutic treatment by isolated regional perfusion is to achieve a high drug concentration in the tumor-bearing limb and a minimal concentration in the systemic circulation, thus leading to higher drug concentrations in the tumor and low systemic toxicity. Chemotherapy by isolated regional perfusion has proved to be of benefit for patients presenting tumors that are restricted to a limb [8, 12, 13]. Hyperthermia is an attractive concept for incorporation in such treatment, as malignant melanoma cells are significantly thermosensitive and are lethally affected by supranormal temperatures [5, 7, 9]. Mitoxantrone has shown an antitumor effect on human malignant melanoma cells in vitro [18], and its cytotoxic effect is enhanced under hyperthermic conditions [10, 20].

The aim of the present study was to gain information on basic pharmacokinetic parameters of mitoxantrone such as its half-lives, volumes of distribution and AUC values in the perfused leg; to determine the range of systemic leakage of this drug and the related systemic toxicity; to determine the optimal mode of application (single vs repeated dosing, bolus vs short-term infusion); and to assess the total delivered dose of 14 mg/m^2 in terms of its relationship to body surface rather than to body weight or limb volume.

Patients and methods

Five patients (three men and two women) aged 28–64 years who presented with solitary melanoma localized to the leg were studied. None of them had been exposed to prior systemic chemotherapy. All subjects displayed normal renal and liver function as judged by serum creatinine, urea, bilirubin, albumin and coagulation profiles. None of the patients suffered from any form of angiopathy. As primary therapy, all subjects underwent surgical excision of the primary tumor and of all detectable metastases and iliac lymph node dissection. Hyperthermic perfusion of the affected leg was carried out as an adjuvant form of therapy.

Lower limb perfusion was performed through the external iliac vessels. The perfusion catheters were connected to an extracorporeal circuit consisting of a disposable Bently pediatric-size, bubble oxygenator equipped with an integrated heater and a low-flow rotary pump. An Esmarch bandage was tied around the hip to prevent collateral circulation through cutaneous or subcutaneous blood vessels.

As soon as the tissue had reached a temperature of at least 40° C, mitoxantrone was introduced via a perfusor as a 1-min infusion into the arterial part of the perfusion system at a total dose of 14 mg/m², which was given as four divided single doses at 15-min intervals. Patients received a total amount of 24–28 mg mitoxantrone. The perfusion was continued for 1 additional h at tissue temperatures of 42° C. Blood samples were taken first from the arterial arm and 30 s thereafter from the venous arm of the perfusate every 5 min for up to 1 h, beginning after the first injection of mitoxantrone. Blood samples were taken from the systemic circulation via an indwelling cannula at 5-min intervals for up to 75 min, and a final specimen was drawn at 4 h. Samples were transferred to a 10-ml heparinized tube and were centrifuged immediately at 2500 rpm for 10 min. The plasma was separated, frozen and stored at −20° C until analysis.

Mitoxantrone was supplied in 30-mg (2 mg/ml) vials by Lederle Laboratories (Wolfratshausen, FRG). Determinations were carried out by high-pressure liquid chromatography using chromatographic conditions and sample preparation as described elsewhere [17]. Pharmacokinetic parameters were obtained using a compartment-model-independent analysis [4, 15].

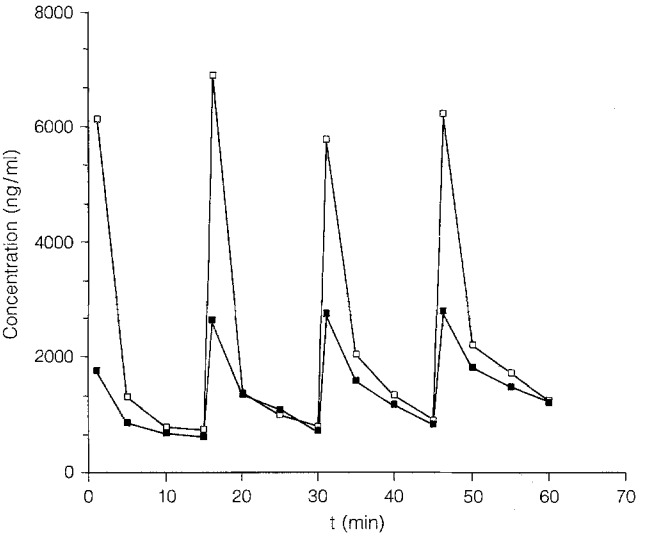

Fig. 1. Mitoxantrone concentrations in the arterial (□) and venous (■) lines of the perfusion system

Results

The pharmacokinetic data obtained in the present study are shown in Tables 1 and 2. As an example, Fig. 1 shows the plasma concentrations of mitoxantrone in the arterial and venous lines of the perfusion circuit and Fig. 2 illustrates the systemic plasma concentrations; the data used in both figures were obtained from patient 1.

The peak plasma concentration in the arterial line of the perfusion circuit occurred at about 1 min following each injection (Fig. 1) and was followed by a rapid decline. At 10 min after each injection, the mean arterial plasma drug concentrations in the leg corresponded to 11.7%, 14.3%, 19.8% and 22.9% of the respective peak concentrations. This increase reflects the accumulation of mitoxantrone in the leg. The mean AUC for the arterial concentrations in the leg was 155.9 mg min l^{-1} (Table 1). The peak plasma concentration in the venous line of the perfusion circuit was also noted at about 1 min after each injection (Fig. 1) and was also followed by a rapid decline. At 10 min following the first through the fourth injections, the mean venous plasma drug concentrations in the leg amounted to 39%, 40.3%, 44.2% and 51.1% of the respective peak concentrations, again reflecting the accumulation of mitoxantrone in the leg. The mean AUC for the venous concentrations in the leg was 91.6 mg min l^{-1} (Table 1).

The mean half-life for the distribution of mitoxantrone into the blood circulation of the leg ($t_{1/2\alpha}$) was 25.5 s. For the elimination of mitoxantrone from the blood circulation into the tissues of the leg ($t_{1/2\beta}$), the mean half-life was 14.9 min (Table 1). Thus, 1.2 l blood/min were cleared of drug. The mean volume of distribution at steady state (V_{dss}) calculated for the perfused leg was 25.6±4.5 l, and the mean distribution coefficient (Δ'_{ss}) was 0.355+0.05 ml/g (Table 1). The times of equilibration of the drug concentrations in the leg between the arterial and the venous systems showed intra- and interindividual differences, ranging from 4.3 to 20.1 min.

Table 2 shows the leakage of mitoxantrone from the leg into the systemic circulation and the amount of drug that was removed after completion of the perfusion. The mean leakage was 311 µg, corresponding to 1.2% of the delivered dose. Following the perfusion, 1.9 mg was removed with the perfusate, representing 7.3% of the

Table 1. Pharmacokinetics of mitoxantrone in 5 patients exhibiting solitary localized melanoma of the leg during hyperthermic, isolated perfusion of the affected limb

Patient number	$AUC_{ven.}$ (mg min l^{-1})	$AUC_{art.}$ (mg min l^{-1})	$AUC_{centr.ven.}$ (mg min l^{-1})	$t_{1/2\beta}$ (min)	$t_{1/2\alpha}$ (s)	$t_{1/2centr.}$ (min)	V_{dss} (l)	Δ'_{ss} (ml/g)
1	106.86	174.99	9.09	13.9	25.2	121.1	24.5	0.326
2	83.03	148.36	7.52	15	25.8	115	25.5	0.326
3	74.42	136.97	6.36	11	24.7	134.9	20.6	0.333
4	87.08	129.36	9.66	17.8	25.2	117.4	33	0.423
5	106.56	189.72	10.32	16.7	26.8	124.2	24.6	0.3
Mean	91.59	155.88	8.59	14.9	25.5	122.5	25.6	0.355
SD	±14.54	±25.63	±1.62	±2.6	±0.8	±7.8	±4.5	±0.05

Data represent AUC values for the venous ($AUC_{ven.}$) and arterial ($AUC_{art.}$) lines of the perfusion system and for the venous mitoxantrone concentrations of the body ($AUC_{centr.ven.}$); half-lives of mitoxantrone, including that for the overall elimination from the leg ($t_{1/2\beta}$), distribution in the leg ($t_{1/2\alpha}$) and overall elimination from the body compartment ($t_{1/2centr.}$); volumes of distribution at steady state (V_{dss}); and distribution coefficients (Δ'_{ss})

Table 2. Leakage of mitoxantrone into the systemic circulation, drug removed after perfusion and drug remaining in the leg after the completion of perfusion, expressed as absolute quantities and as percentages of the total delivered dose

Patient number	Leakage		Drug removed		Drug remaining	
	(μg)	(%)	(μg)	(%)	(mg)	(%)
1	314.9	1.2	2247	8.3	24.4	90.5
2	222.6	0.9	1530	6.4	22.2	92.7
3	306.2	1.3	1280	5.3	22.4	93.3
4	225.1	0.8	1857	6.6	25.9	92.6
5	485.5	1.9	2532	9.7	23	88.4
Mean	310.9	1.2	188.9	7.3	23.6	91.5
SD	±106.7	±0.4	±510	±1.7	±1.6	±2

delivered dose. Thus, 91.5% of the total dose remained in the leg.

The systemic plasma drug concentrations showed a gradual increase, reaching maximum levels at 55–60 min after the start of the perfusion (Fig. 2) and declining rapidly thereafter. At 3 h following the systemic peak concentration, corresponding to about 4 h after the first injection, the mean systemic drug concentration amounted to only 3.9%±1% of the peak. The mean elimination half-life of the drug from the systemic circulation was 123 min and the respective mean AUC value was 8.59 mg min l^{-1} (Table 1).

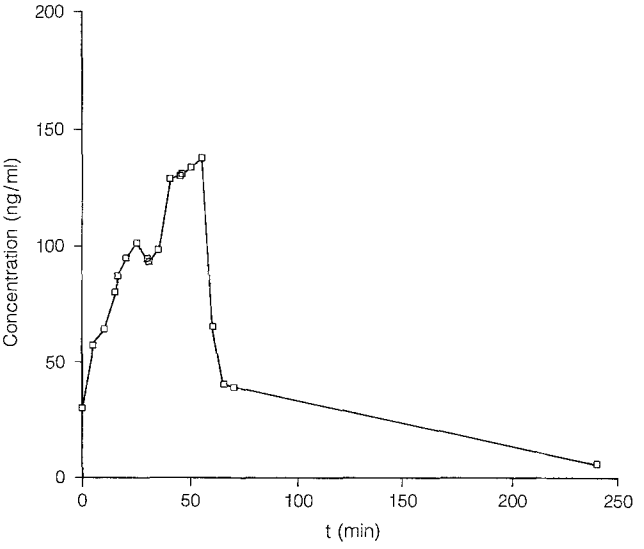

Fig. 2. Systemic mitoxantrone concentrations

Discussion

The rapid distribution of mitoxantrone into the blood circulation of the leg ($t_{1/2\alpha}$, 25 s) was followed by fast elimination from the blood circulation ($t_{1/2\beta}$, 15 min), reflecting uptake by the leg tissues (Table 1). At the end of the perfusion, about 91% of the total delivered dose remained in the leg (Table 2). The large volume of distribution (V_{dss}, 25.6 l, Table 1) reflected the high tissue affinity of mitoxantrone, which correlated with data previously obtained following systemic and intraperitoneal administration [1, 6, 16].

Calculation of the distribution volume calculated by the extrapolation method ($V_{d\ extrap}$), the distribution volume during the elimination phase ($V_d\beta$), the volume of distribution of the central compartment (V_c; above data not shown), and the V_{dss} values suggested that the data reflected a multicompartmental model and that a large proportion of the total amount of drug delivered was trapped in a central compartment of the leg. The distribution coefficients at steady state (Δ'_{ss}) of the five patients studied lay close together (Table 1), which might have been due to the absence of disease apart from melanoma, particularly that of angiopathy, in all subjects.

Systemic toxicity was attributable to leakage of the drug out of the leg. Leakage was very low, with the mean representing 1.2% of the total delivered dose (about 0.2 mg/m^2; Table 2), which explained why moderate nausea was the only systemic toxicity observed. The discrepancy between the 1.2% leakage value and the observation that the systemic AUC value corresponded to about 10% of that for the leg (Table 1) might have been due to the specific conditions used for the hyperthermic perfusion.

Although no local toxicity occurred at doses of up to 14 mg/m^2, the aspect of local toxicity may become important when the doses are increased. Since mitoxantrone showed a high tissue affinity as reflected by the large volumes of distribution (Table 1) and since 91.5% of the total delivered dose remained in the leg after the end of the perfusion (Table 2), repeated dosing such as that used in the present setting seemed to be advantageous in reducing local toxity. In other words, based on the favourable pharmacokinetic properties of mitoxantrone, reducing the local toxicity seems to be more advantageous than striving for maximal peak concentrations, especially when the doses are increased.

Equilibration times, i.e. the times at which both the arterial and the venous lines exhibit about the same drug concentrations, differed from 4.3 to 20.1 min. Repeated continuous infusions over a period corresponding to one complete circulation of the whole system (that is 2.5–3 min) would lead to the fastest possible equilibration of the system, which would be accomplished nearly at the end of the infusion. A reduction in peak concentrations would be the result. Drug administration should be repeated when the system has become equilibrated. A 15-min interval between treatments seemed reasonable according to our data.

The calculated theoretical maximal drug concentration (about 3650 μg/l) in the venous part of the leg exceeded that actually measured (about 2500 μg/l), thus indicating that the system was not yet equilibrated according to the maximal achievable drug concentrations. Therefore, further treatments would continue to increase the achievable peak concentrations. However, it should be borne in mind that a limb perfusion lasting for >60 min is not easy to perform due to practical reasons. Therefore, the four treatments chosen for the present study seemed to be reasonable.

The dose given can be related to body weight, body surface or limb volume. Mendoza et al. [14] have found that doses that are related to limb volume are on average 45% lower for arms and 15% higher for legs as compared with those given according to body weight. The interindividual variability found in the AUCs values in the present study (Table 1) support suggestions that the dose be calculated based on limb volume as described by Wieberdink et al. [19] and implemented by Benckhuijsen et al. [3].

In conclusion, hyperthermic perfusion of the leg with mitoxantrone provided promising pharmacokinetic data. The total dose delivered should preferably be related to the limb volume and could exceed 14 mg/m^2. Repeated dosing involving four continuous infusions of 2.5–3 min given at 15-min interval seemed to be the best mode of administration. Clinical long-term data are needed to confirm the benefit of this mode of treatment with mitoxantrone, since the clinical follow-up of patients treated on this regimen has thus far been only 2 years.

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