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Toxicity, Pharmacokinetics and Metabolism of Iododoxorubicin in Cancer Patients

Klaus Mross, Ulrich Mayer, Tobias Langenbuch, Kirsten Hamm, Konrad Burk and Dieter Hossfeld

25 patients, mostly pretreated, received 55 courses of iododoxorubicin as a single intravenous bolus every 2 weeks. The starting dose was 2 mg/m² with seven steps to reach the dose-limiting toxicity level. 3 patients treated with 90 mg/m² had WHO grade 4 myelotoxicity; 2 of these patients had not had cytostatic chemotherapy. 3 of 7 patients treated with 75 mg/m² had grade 3–4 myelotoxicity; 4 had grade 1–2. Non-haematological toxicities were minor. Acute cardiotoxicity and objective tumour responses were not observed. Plasma and urine levels of iododoxorubicin and five metabolites were assayed in 16 patients. Metabolism to iododoxorubicinol was rapid and plasma clearance was dose-dependent and rapid. Plasma levels and the area under the curve for iododoxorubicin increased with dose. The mean residence time was 3.9 h in patients without liver metastasis and 10.4 h in patients with liver metastasis. Renal excretion was minor. The maximally tolerated dose was 90 mg/m².
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INTRODUCTION

THE INTRODUCTION of an iodine atom at the 4′ position of the daunosamine sugar of doxorubicin lowers the acid dissociation constant (p*K*a 6.4) of iododoxorubicin, which is therefore nearly unprotonated at physiological pH [1], and makes the drug more lipophilic than its parent [2]. Thus the penetration of cell membranes should be more rapid with iododoxorubicin. In preclinical screens iododoxorubicin had broad antitumour activity against several mouse and human tumours *in vivo* and *in vitro* [3,4] and against several human xenografts [5]. Additionally, the compound inhibited anthracycline-resistant tumour cells [6] and there was incomplete cross-resistance between iododoxorubicin and doxorubicin [7]. Preclinical toxicology showed that the major target organ for iododoxorubicin was bone marrow and the well-known side-effects of anthracyclines were reduced with this drug [5,8]. The reduction of the C-9 carbonyl by aldoketo-reductases yields iododoxorubicinol [9,10], which is also cytotoxic [11]. The parent as well as the

Table 1. Patients' characteristics

Courses	55
M/F	19/6
WHO performance status	
0–1	15
2	8
3	3
Previous treatment	
None	3
Radiotherapy	2
Chemotherapy	12
Radiation + chemotherapy	8
Tumour types	
Lung (small and non-small cell)	5
Colorectal	3
Stomach	3
Adenocarcinoma, unknown primary	3
Sarcoma	3
Liver	3
Others	5

alcohol metabolite undergoes reduction by a glycosidase to form deoxy-aglycones. Biphasic disposition curves of iododoxorubicin in mice were reported with a shorter elimination half-life than doxorubicin. High drug levels were found in liver and spleen and concentrations of iododoxorubicin were higher and clearance was faster in tumour tissue, spleen, lung, gut, brain, pancreas and ovary [12].

We have studied iododoxorubicin given as a single intravenous bolus injection repeated every 2 weeks to reach a high dose-intensity, which is the best way to evaluate the efficacy of an anticancer agent [13]. We report the maximally tolerated dose (MTD), toxicity profile, pharmacokinetics, metabolism and antitumour effect of iododoxorubicin in patients with advanced tumours given this schedule.

PATIENTS AND METHODS

Patients

Patients who entered the study were required to have a microscopically confirmed diagnosis of solid tumour, refractory to conventional therapy or with no effective therapy option. Other eligibility criteria included: (1) life expectancy of at least 8 weeks; (2) WHO performance status of 3 or less; (3) age 18–75; (4) at least 3 weeks since previous chemotherapy and/or myelosuppressive radiotherapy; (5) adequate bone marrow white blood cell (WBC) count over 4.0×10^9/l, platelets over 130×10^9/l and liver function (normal bilirubin), and serum creatinine under 2.0 mg/dl; and (6) no other illness of sufficient severity to prevent full compliance. All patients gave written consent according to federal guidelines (Table 1).

Treatment plan

Iododoxorubicin was obtained from Farmitalia Carlo Erba as a freeze-dried powder containing 5 or 10 mg. The starting dose was 2 mg/m^2 every 2 weeks. The drug was reconstituted in 5 ml sterile water and given via a central line as rapid bolus (1–2 min).

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The publication includes parts of the thesis of U. Mayer.

Before treatment, all patients had a complete history and physical examination, haemogram, full chemistry profile, urinalysis, electrocardiogram and heart echographic examination. Measurable tumour lesions were documented if possible. Complete blood counts and chemistry profiles were repeated twice a week or more if indicated. Tumour was measured after two cycles according to WHO guidelines. Toxicity was graded according to WHO criteria. Dose-limiting toxicity was defined as toxicity of grade 3 or higher observed in at least 2 patients out of 3 (3 patients at each dose level was the target number of patients). More patients have been accrued at the same dose level in case of a grade 2 (or even higher) toxicity. 4 more patients (total 7) had to enter the study at the dose level considered to be MTD, which was defined as the highest safely tolerable dose that caused 50% grade 3 and/or 20% grade 4 toxicity.

Dose escalation

3 patients should have been included per dose level. Dose escalation in individual patients was not allowed. The dose was escalated as shown in Table 2. When toxicity data became available from the other two phase I study centres (National Cancer Institute, Milan and Institute Gustav-Roussy, Villejuif), no more patients entered at 2, 6.6 and 14 mg/m^2; the increment for each dose level was determined in light of available information from the data centre in Milan. Dose escalation was rapid to prevent patients being exposed to non-toxic and thus probably ineffective doses.

Pharmacokinetics

Blood sampling and urine collection. Blood was obtained from a central line before injection, at 1, 5, 10, 15, 30, 45 and 60 min and at 2, 4, 6, 9, 12, 18, 24, 30, 36, 42 and 48 h after injection. The blood was collected into heparinised polypropylene tubes and immediately centrifuged on the ward at room temperature at 2000 *g* for 5 min. The plasma samples were divided into 1.3 ml aliquots. Urine samples were collected in black polypropylene containers. After 6 h the volume was measured and a small sample (1 ml) was transferred to a polypropylene tube. All plasma and urine samples were stored at −20°C. After thawing, all samples were centrifuged at 15 000 *g* at room temperature to remove clotted material.

High-performance liquid chromatography (HPLC). HPLC of iododoxorubicin and its metabolites was as described [14]. The internal standard, daunorubicin, was added to all samples before solid–liquid extraction. All samples were prepared in duplicate.

Table 2. Dose escalations

Dose (mg/m^2)	No. of patients	No. of evaluable courses
2	2	5
4	3	9
6.6	1	3
14	1	3
28	3	8
50	4	9
75	8	15
90	3	3

Table 3. Haematological toxicity

	Dose (mg/m²)			
	2–28	50	75	90
No. of patients	10	4	8	3
No. of cycles	28	9	14	3
Haemoglobin (g/dl)				
Grade 0 (>11.0)	28	6	4	0
Grade 1 (9.5–10.9)	0	3	5	0
Grade 2 (8.0–9.4)	0	0	4	2
Grade 3 (6.5–7.9)	0	0	1	1
Leucocytes (× 10⁹/l)				
Grade 0 (>4.0)	28	2	0	0
Grade 1 (3.0–3.9)	0	0	3	1
Grade 2 (2.0–2.9)	0	6	4	0
Grade 3 (1.0–1.9)	0	1	4	0
Grade 4 (<1.0)	0	0	3	2
Neutrophils (× 10⁹/l)				
Grade 0 (>2.0)	28	3	3	0
Grade 1 (1.5–1.9)	0	4	2	1
Grade 2 (1.0–1.4)	0	2	1	0
Grade 3 (0.5–0.9)	0	0	5	0
Grade 4 (<0.5)	0	0	3	2
Platelets (× 10⁹/l)				
Grade 0 (>100)	28	0	11	1
Grade 1 (75–99)	0	0	0	0
Grade 2 (50–74)	0	0	2	0
Grade 3 (25–49)	0	0	0	0
Grade 4 (<25)	0	0	1	2

For each patient's series, a full calibration line, including five different concentrations, was set up. Up to 1 h all samples were diluted with heparinised plasma from a healthy donor in various concentrations, allowing the whole series to run at the highest sensitivity level without any changes in the set-up of the detector and chromato-integrator. A least-square fit of area under the peak ratio of drug/internal standard vs. concentration was used to construct the calibration line; r^2 was more than 0.99 in all experiments. Recovery from plasma samples ranged from 72–100%, depending on the compound being analysed. The assay limit of detection was 0.05–0.1 ng/ml. The precision during within-day and between-day runs ranged from 3 to 14% (coefficient of variance). The whole assay procedure was evaluated according to good laboratory practice [15].

Pharmacokinetic variables. Each set of concentration-time ($c[t]$) values for iododoxorubicin and iododoxorubicinol was fitted to the appropriate polyexponential equation with the program JANA (Statistical Consultant Inc., Lexington). Based on these initial estimates, we decided to describe the results for iododoxorubicin according to a three-compartment model and those for iododoxorubicinol according to a two-compartment model. The r^2 of least-square fit for iododoxurubicin was always better than 0.99, and for iododoxorubicinol better than 0.95. The final pharmacokinetic calculations were done with MedUSA, a program specifically designed for us (Medical Usage of Scientific Algorithms, version 1.5, SCIAN Software Inc., Toronto). We introduced the estimates of A, B and C from JANA for all calculations. All fittings were done to the two and three exponential equation, respectively (plasma concentration = $A \times e^{-\alpha t} + B \times e^{-\beta t} + C \times e^{-\gamma t}$). We calculated the following pharmacokinetic indices: peak plasma concentration (PPC), apparent volume of distribution at steady state (Vd_{ss}), plasma clearance (Cl_0), area under the $c(t)$ curve (AUC) by the trapezoidal rule and the terminal elimination, mean residence time (MRT) and half-lives of distribution ($t_{1/2\alpha}$), intermediate ($t_{1/2\beta}$) and elimination ($t_{1/2\gamma}$) phase. Because of irregular $c(t)$ curves of the aglycones no fit according to a model was done. Instead, AUC and $t_{1/2\gamma}$, calculated by use of all concentration values from 12 h to the last measurable value by least-square fit, were determined.

RESULTS

Of the 25 patients, 20 patients had received either chemotherapy or combination radio-chemotherapy (Table 1). 13 patients have been treated with two or more different chemotherapies; 7 patients had received chemotherapy according to one protocol until progressive disease. A total of 55 courses of iododoxorubicin were administered. 1 patient was not evaluable for toxicity because of bone marrow infiltration, which was not known before start of treatment. Patients received a median of 2 cycles of treatment (range 1–3). There were no drug-related deaths. Dose escalations are shown in Table 2.

Toxicity

Non-haematological toxicities were as expected: nausea/vomiting and stomatitis/mucositis were seen in 2 patients (grade 1 and 3, respectively). 1 patient with advanced stomach cancer treated with 75 mg/m² developed (bilirubin elevation) grade 1 hepatotoxicity after the second treatment course. He had severe haematological toxicity with grade 4 leucocytes and platelets and grade 2 anaemia. The pharmacokinetics of this case are reported below. No acute cardiotoxicity was observed. The highest cumulative dose was 225 mg/m² in 1 patient. All other patients received 150 mg/m² or less.

Granulocytopenia as well as thrombocytopenia were the dose-limiting myelosuppressive toxicities developing at a mean of 9 days (S.D. 3, range 6–13) and consistently resolving by day 14 (5, 8–22) (Table 3). No severe bleeding complication occurred although in 1 patient platelet nadir was 10 × 10⁹/l with slight mucosal bleeding in the nasal cavity. This patient received platelet-rich plasma transfusions. The episodes of anaemia were dose-related. 2 patients required blood transfusions. Granulocytopenia and leukopenia were clearly dose-related and dose-

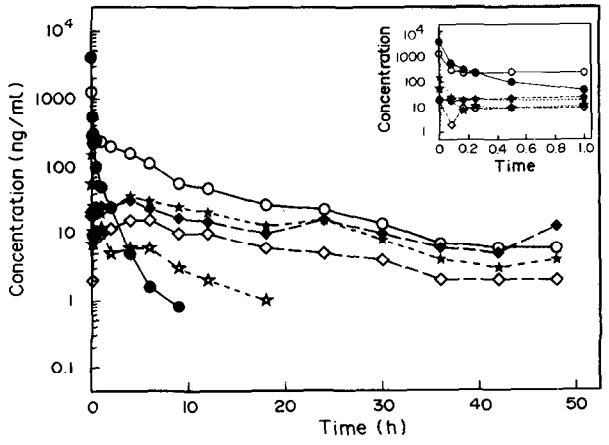

Fig. 1. Typical $c(t)$ curve for iododoxorubicin and its metabolites in a patient without liver metastasis receiving 75 mg/m² intravenous bolus. Inset shows same data during the distribution phase up to 1 h. • = iododoxorubicin, ○ = iododoxorubicinol, ◇ = AOLON, ◆ = 7d-AOLON, * = AON and ☆ = 7d-AON.

Table 4. Pharmacokinetic indices

Dose (mg/m²)	Patient	Age	Diagnosis	Metastasis	Dose (mg)	PPC (μg/l)	Vd_{ss} (l/kg)	AUC (μg h/l)	Cl_p l/min	MRT (h)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	$t_{1/2\gamma}$ (h)	AUC*	AUC† %
90	1	66	Adenocarcinoma	Skin, lung	175	3551	40.6	1049	2.5	19.0	1.8	20.2	18.8	4114	34.2
	2	55	NSCLC	Liver, lung	150	1630	50.4	654	3.9	13.0	6.3	86.9	38.9	4524	16.9
	3	68	Liver		190	1744	49.7	893	2.9	21.0	1.7	8.2	17.6	5196	20.8
75	4	61	Stomach	Liver	110	3176	30.7	572	3.8	8.1	3.8	93.5	19.3	2367	31.5
	5	60	Rectum	Abdomen	150	1048	6.4	436	5.0	1.5	1.8	8.5	2.7	2863	17.9
	6	24	Sarcoma	Abdomen	140	1438	7.9	220	10.1	0.8	3.2	36.2	2.7	2270	10.7
	7	67	Stomach	Liver	120	3011	37.0	2287	0.8	51.0	2.1	7.2	41.2	4999	84.3
	8	42	Sarcoma	Liver	150	1177	21.8	194	11.2	2.3	3.7	52.3	9.5	2705	7.7
	9	58	Colon	Liver	120	2064	22.1	615	3.5	3.3	1.4	26.0	12.5	3850	19.0
	10	55	Adenocarcinoma	Lung	110	3813	3.2	409	5.2	0.7	1.6	33.4	2.8	2644	18.3
50	11	60	Ovary	Abdomen	75	505	35.6	151	9.6	3.7	4.5	170	14.1	2965	5.4
	12	68	Adenocarcinoma	Liver, lung	95	712	28.4	123	12.4	2.6	1.3	21.8	5.4	3471	3.7
	13	53	Lung	Pelvic	100	897	9.3	115	12.6	0.9	0.8	11.3	1.2	2075	5.9
	14	51	Lung	Liver	105	1122	7.6	147	9.9	1.0	1.2	11.8	2.1	2816	5.5
25	15	33	Sarcoma	Liver	52	178	53.9	16	47.5	1.3	1.1	38.8	3.7	2696	0.6
	16	61	Blastoma	Lung	56	260	21.1	143	5.2	4.8	1.1	10.1	4.8	2631	6.2

*Iododoxorubicin plus iododoxorubicinol.
†Due to iododoxorubicin.

limiting. 1 patient had a temperature of 38.7°C during the neutropenic period (neutrophils under 0.1 × 10^9/l), which resolved after antibiotic therapy within 4 days. X-ray of the thorax was normal. There was no indication of an infection in the genitourinary tract.

Antitumour activity

There was no objective tumour response to iododoxorubicin. In 3 patients with lung cancer (2 small cell), stable disease was observed for short periods (4–8 weeks in total). These patients were treated with 28 mg/m² (n = 1) and 50 mg/m² (n = 2), respectively, times three. 1 patient with bladder cancer paraaortal lymph-node metastasis achieved stable disease for half a year after 3 cycles of iododoxorubicin at 4 mg/m².

Pharmacokinetics and metabolism

Plasma pharmacokinetics of iododoxorubicin and its metabolites were measured in 16 patients during the first cycle. First analyses were done after the development of the procedure, the pharmarokinetic studies starting in patients treated with 28 mg/m². Following administration, iododoxorubicin concentrations declined tri-exponentially with a very rapid $t_{1/2\alpha}$ (Fig. 1 and Table 4), a rapid $t_{1/2\beta}$ and an elimination phase which, in the patients without liver metastasis was short (mean 6.7 h, range 1.2–18.8) and in those with liver metastasis, significantly longer (16.7 h, 2.1–38.9). There was a significant relation with an r^2 of 0.98 for the correlation coefficient between dose and the AUC of iododoxorubicin but no relation between the iododoxorubicin dose and the AUC of doxorubicinol or with the sum of the AUCs of iododoxorubicin and iododoxorubicinol (Fig. 2). The percentage of iododoxorubicin from the sum of the AUCs from iododoxorubicin and iododoxorubicinol was correlated with the administered dose (Fig. 3). Dose and plasma clearance were inversely related (Fig. 4). The $t_{1/2\gamma}$ of iododoxorubicin was longest in those patients receiving the highest dose (90 mg/m²) and in those patients with liver metastasis (Table 4). Vd_{ss} was also highest in these patients. Metabolism was dominated by the formation of doxorubicinol by aldo-ketoreductases and was very rapid. High levels were detectable minutes after the injection. The $c(t)$ curves of doxorubicinol were crossed those of iododoxorubicin within minutes (Figs 1 and 5); $t_{1/2\gamma}$ of doxorubicinol were unique with a mean of 12.7 h (range 7.2–24.7; all $c(t)$ curves of this metabolite after administration of 75 mg/m² are shown in Fig. 6). The AUCs of iododoxorubicinol were several times higher than those of the parent drug; the mean AUC for doxorubicinol was 2598 μg h/l (range 1815–4303). The aglycones were of minor importance for AUC. The AUC of

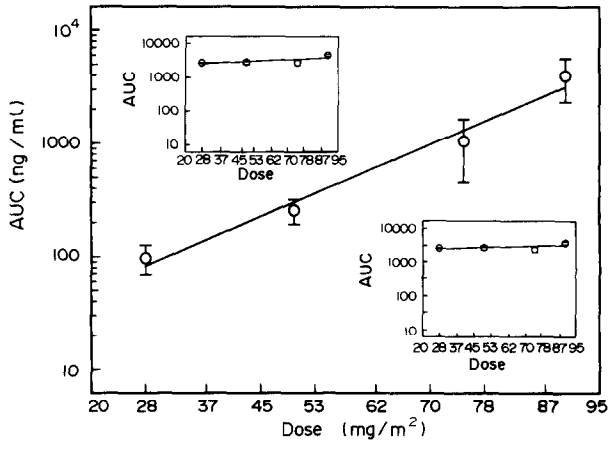

Fig. 2. Relation between iododoxorubicin dose and mean iododoxorubicin AUC (r^2 = 0.98). Data from Table 4 with S.D. from mean. Insets depict poor correlation (r^2<0.5) between iododoxorubicin dose and AUCs of iododoxorubicin and iododoxorubicinol (upper left) and between iodoxorubicin dose and AUC of doxorubicinol (lower right).

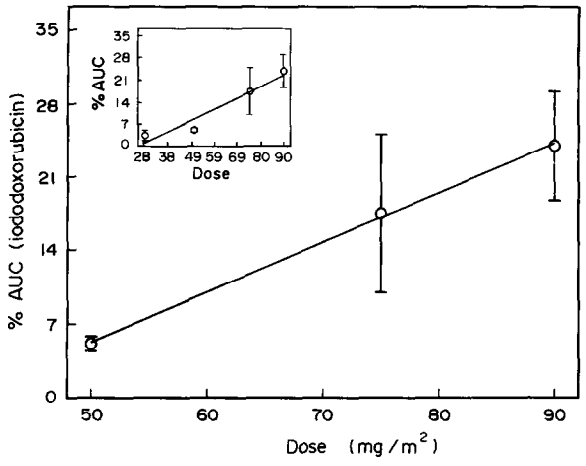

Fig. 3. Relation between percentage of AUC iodoxorubicin from AUC (iodoxorubicin plus iodoxorubicinol) and iodoxorubicin dose. Inset shows same relation including 28 mg/m² dose level (only two estimates).

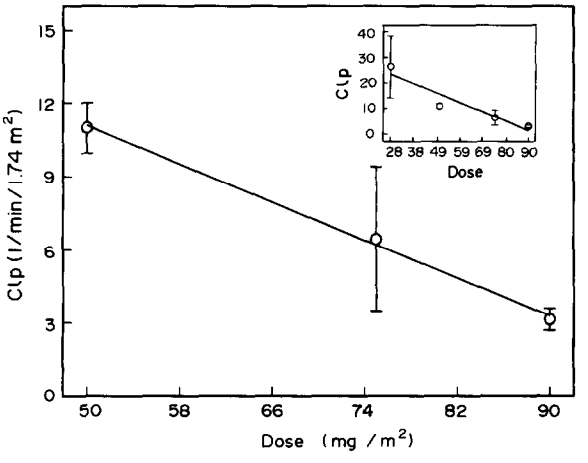

Fig. 4. Inverse relation between iodoxorubicin dose and mean Cl_p (r^2 = 0.97). Data from Table 4 with S.D. from mean. Inset shows same relation including the 28 mg/m² dose (only two estimates).

AOLON was highest of all the aglycones with a mean of 279 μg h/l (47–528), followed by 7d-AOLON with a mean 162 μg h/l (13.7–522). The AUCs of AON and 7d–AON were 177 (41–502) and 70 mg h/l (2.9–334). The longest $t_{1/2}$ was found for AOLON with a mean of 18.9 h (5–42.5), followed by 7d-AOLON with a mean of 18.7 h (4–70.3). Next was AON, mean 13.7 h (7.2–28.1), and 7d-AON, mean 11.7 h (1.6–42.4).

The urinary excretion of iododoxorubicin was minor. Only a mean of 0.7 (1.0)% was excreted unchanged. 8.1 (12.4)% was excreted as doxorubicinol (1.6–39.9%). No aglycones were identified in urine samples.

1 patient (no. 7) with stomach cancer and liver and regional lymph-node metastasis, treated with iododoxorubicin 75 mg/m², had a remarkable deviation in some of his pharmakokinetic indices (Fig. 6). The AUC of iododoxorubicin was 7 times higher than the mean, Cl_p was markedly reduced by a factor of 7 and $t_{1/2}$ and MRT of iododoxorubicin were prolonged when compared with all patients. Metabolism was not unusual: the AUC of doxorubicinol and the generation of aglycones was normal, except for 7d-AON which was 20 times higher than the mean of the whole group. This patient had a liver-metastasis with no clinical chemistry signs of compromised liver function. The toxicity was remarkable with grade 4 myelotoxicity and a slightly increased bilirubin after the second course (pharmacokinetics were done during the first cycle).

When all patients with liver metastasis were analysed separately, MRT and $t_{1/2\gamma}$ were significantly longer compared with those without liver metastasis. All these patients had normal bilirubin, cholinesterase, albumin and total protein as well as a normal coagulation profile. There was no indication that liver functions would be significantly altered in these patients, except in 1 who had elevated aminotransferases. A correlation between the extent of liver metastasis and unusual pharmacokinetic results was not found.

DISCUSSION

This phase I study has shown that the dose-limiting toxicity of iododoxorubicin myleosuppression, which was as predicted [7] affected all three cell lines (erythrocytes, platelets and WBC) with WBC and granulocyte nadirs occurring between 6 and 13 days. Full haematological recovery was observed between days 8 to 22, with a mean at day 14. In unpretreated patients without liver metastasis a second cycle should be given at days 15–21 to allow a high intensity treatment which is probably the best way

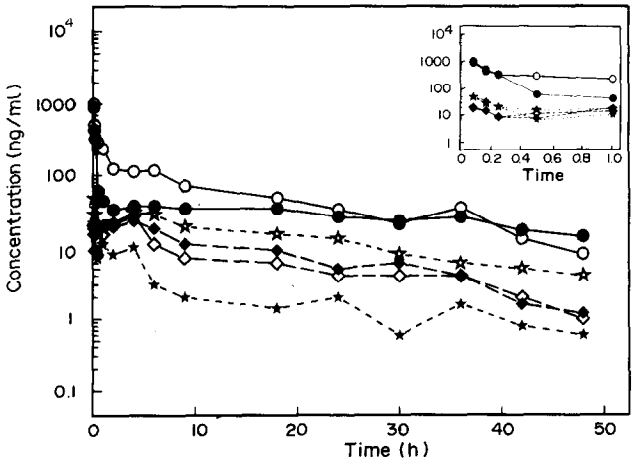

Fig. 5. c(t) curve for iodoxorubicin and its metabolites in patient with liver metastasis receiving 75 mg/m². Inset shows same data within the distribution phase up to 1 h.

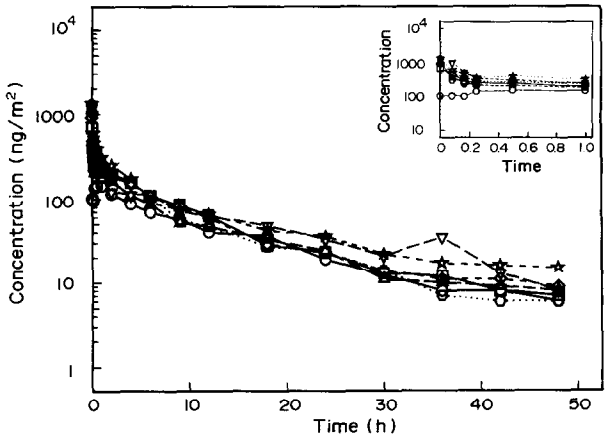

Fig. 6. c(t) curves for iodoxorubicinol in all patients (n = 7) treated with 75 mg/m². Inset shows same data during the distribution phase up to 1 h after injection.

Table 5. Pharmacokinetic indices of metabolites after iododoxorubicin administration

Patient	Iododoxorubicinol		AOLON		7d-AOLON		AON		7d-AON	
	AUC	$t_{1/2}$	AUC	$t_{1/2}$	AUC	$t_{1/2}$	AUC	$t_{1/2}$	AUC	$t_{1/2}$
1	3065	17.2	378	15.7	286	4.0	502	12.1	–	–
2	3870	17.5	47.2	15.5	94.2	59.2	–	–	2.8	1.6
3	4303	14.3	417	21.4	168	20.6	203	17.0	107	9.7
4	1815	24.5	74	14.1	303	17.1	131	8.2	26	7.7
5	2427	10.9	114	11.4	104	8.9	126	7.2	51	–
6	2050	10.0	350	30.7	47	14.1	271	11.5	17.4	–
7	2712	13.6	130	–	126	14.8	54	21.3	334	14.8
8	2511	12.6	528	42.5	109	7.2	143	21.3	118	42.0
9	3235	15.5	432	39.2	522	70.3	247	28.1	–	–
10	2235	11.3	440	17.8	193	15.1	441	12.5	49	5.0
11	2814	8.2	422	18.6	131	13.7	118	21.1	108	13.2
12	3348	10.0	309	19.9	195	11.0	51	9.2	56	19.6
13	1960	8.7	119	5.0	13.7	11.8	41	10.1	35	–
14	2669	7.2	428	13.7	145	12.6	149	11.9	8	13.2
15	2680	11.9	1070	24.0	91.4	4.3	60	20.2	6.3	6.4
16	2478	8.3	277	14.7	127.4	9.3	126	8.3	5.3	1.4

AUC: μg h/l and $t_{1/2}$ in h.

to evaluate the efficacy of an anticancer agent [13]. Whether the treatment intervals become prolonged after several courses requires investigation in future studies. Other side-effects such as nausea/vomiting and alopecia were uncommon. Iododoxorubicin was well tolerated, much better than doxorubicin would be, even at the highest dose level. We never observed postinfusion venous irritations [16], but this could have been underestimated because in most patients the drug was given via a central line, at least during the first course. Neither cardiac rhythm problems nor cardiomyopathy occurred. Chronic cardiotoxicity cannot be evaluated within a phase I study because of the lack of repeated administrations. The major metabolite of doxorubicin, doxorubicinol is produced by cardiac tissue and contributes significantly to the chronic cumulative cardiotoxicity of doxorubicin therapy [17]. Iododoxorubicinol was by far the most prominent metabolite after iododoxorubicin administration but dose and iododoxorubicinol formation were not correlated. It remains to be seen whether cardiotoxicity is less common with iododoxorubicin predicted by preclinical studies [5,8]. Mice may be an ambiguous model for the prediction of cardiotoxicity; because the metabolism of mice and men is different [11], much less iododoxorubicinol is generated in mice. Most of our patients had received previous chemotherapy, but were still in good general condition. Many had liver metastasis but their blood chemistry was not compromised. Overall liver function as judged by clinical chemistry, was normal. Notwithstanding, differences in toxicity and pharmacokinetics were found in patients with liver metastasis (see below).

The pharmacokinetics of iododoxorubicin is best described by a three-compartment model. The r^2 for such a fit was always better than the fit for a two-compartment model. This behaviour is in line with data for doxorubicin and epirubicin [18]. The extremely short $t_{1/2\alpha}$ as well as the short $t_{1/2\beta}$ phase most probably reflected rapid uptake of this lipophilic drug into tissues and blood cell components. Its large Vd_{ss} (25 $t_{1/2\gamma}$ l/kg) also reflected extensive tissue uptake with minimal excretion. $t_{1/2\gamma}$ was influenced by two factors. First, it became longer at high doses, and in those patients with liver metastasis. In patients not compromised by liver metastasis or confronted by administration of large amounts of drug, $t_{1/2\gamma}$ as well as MRT were short compared with doxorubicin and epirubicin [18]. Urinary excretion was less than 1% for idodoxorubicin whereas nearly 8% is excreted via the kidneys as iododoxorubicinol. The other metabolites in plasma, the aglycones and the 7-deoxy-algycones, were not detectable in urine. An inverse relation was found for Cl_p and dose, suggesting limited excretion or metabolism capacities: Cl_p was lower at higher dosages and vice versa. The AUCs increased linearly with dose and was correlated with myelotoxicity.

The major metabolism of iododoxorubicin is by aldo-keto-reductases, a group of ubiqitous cytosolic enzymes of different tissues and cells [10,19,20]. The appearance of iododoxorubicinol, in which the C-13-carbonyl of iododoxorubicin has been reduced, was extremely rapid. In most patients the metabolite concentration at the end of injection was also the peak concentration which suggests that some iododoxorubicin is converted to the alcohol within the vascular space by blood cells. Human erythrocytes can metabolise iododoxorubicin thus [9]. This process starts immediately during drug administration and therefore rapid separation of blood cells from plasma is necessary to avoid large errors during the initial phase of pharmacokinetics. Nevertheless some error will occur even if the sample is centrifuged immediately. We have not found a relation between AUC iododoxorubicinol and the dose, suggesting that the metabolism has a limited capacity of generation of iododoxorubicinol. This result is still in contrast to previous data [11].

In fact, a strategy to escalate the dose according to the sum of the AUCs of iododoxorubicin and iododoxorubicinol would not be possible if our data were used. Only the AUC of iododoxorubicin increased linearly. The same was found for the AUC of iododoxorubicin and iododoxorubicinol when analysed. The percentage of AUC iododoxorubicin from the sum of the

AUCs was significantly correlated with the dose of iodoxorubicin, whereas the absolute amount of AUC (iodoxorubicinol) not correlated with the total dose being administered to the patients. We found a large variation in iododoxorubicinol formation, possibly related to the red cell counts and the total activity of aldo-ketoreductase in the liver, which is thought to be the major source of this conversion enzyme besides erythrocytes [10,20]. Although the aglycones do not play a major role in terms of AUC values, all known aglycones, including the 7-deoxy-aglycones, were detectable. This has also been shown for doxorubicin and epirubicin [18]. Aglycones were not described by Gianni *et al.* [11], mainly because only very sensitive assays can detect these metabolites, which are thought to be important measures indicating highly reactive intermediates during metabolism with the generation of free radicals [21,22]. $t_{1/2}$ values of all four aglycones were difficult to calculate because of irregular $c(t)$ curves. Use of only the last measured points from 12 h onward resulted in $t_{1/2}$ ranging from about 10 to 20 h. The irregular $c(t)$ curves for aglycones points to the possibility of an enterohepatic circulation, as described for doxorubicin [17,23] and epirubicin [17].

The altered pharmacokinetics, especially the observed longer $t_{1/2\gamma}$ of iododoxorubicin combined with lower Cl_p in the patient with liver metastasis who had severe myelotoxicity, suggests that close clinical monitoring of such patients is necessary. We recommended study of pharmacokinetics and metabolism in patients with liver metastasis with and without hepatic dysfunction in the forthcoming phase II trials. Early pharmacokinetic and disposition studies of doxorubicin, which showed the importance of biliary excretion and hepatic metabolism in clearance, led to the concept of doxorubicin dose reduction in patients with documented hepatic dysfunction hyperbilirubinaemia [24]. This practice is well established but pharmacokinetic and pharmacodynamic relations are poorly defined. The question remains open as to how well the data on which the clinical concept of dose reduction is predicted actually supports this practice. Drug monitoring should help answer this question unambiguously for iododoxorubicin but further investigations are necessary for the classical anthracyclines. Limited sampling procedures offer the possibility of pharmacokinetic studies in phase II trials [25].

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