Cancer Chemother Pharmacol (1982) 9: 85–88

Cancer Chemotherapy and Pharmacology

O,p'-DDD (Mitotane) Levels in Plasma and Tissues During Chemotherapy and at Autopsy

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Summary. *The distribution of o,p'-DDD in various body compartments of patients being treated for metastatic adrenocortical carcinoma was studied. A highly significant semilogarithmic relationship was found between plasma and adipose tissue concentrations during therapy and between levels in plasma and adipose tissue and between plasma and brain at autopsy. A linear relationship was found at autopsy between concentrations in adipose tissue and those in various other tissues, such as tumour and brain. The semilogarithmic relationship can be explained by the assumption of two plasma pools for o,p'-DDD, one with low affinity and high capacity and one with high affinity and low capacity.*

Plasma concentrations must be carefully monitored to obtain an impression of the tumour concentration and to detect impending central nervous system intoxication.

Introduction

o,p'-DDD[1] has been used for more than 20 years in the chemotherapy of metastatic adrenocortical cancer (AC). Temporary remissions have been reported in large series of patients [7, 8]. Lasting remissions after cessation of o,p'-DDD therapy have also been described [3–5, 13, 15].

The effects of treatment in these various studies are difficult to compare because of the differences in the natural history of the disease, the prescribed doses, and patient compliance. The availability of the drug is influenced by its mode of administration [11]. Moy [12] found no correlation between tissue levels at autopsy and tumour response (7 cases). However, the interval between the withdrawal of o,p'-DDD therapy and autopsy varied widely between patients. Other authors have reported on the tissue and plasma levelds of o,p'-DDD in one patient [14] and the plasma levels in four patients [6].

Plasma concentrations of the drug are relatively low in comparison with tissue wet-weight concentrations [14], the greatest accumulation of the drug occurring in adipose tissue [12].

In a previous study we found, with the exception of one patient, no tumour regression in ten cases when the serum concentrations of o,p'-DDD were below 10 μg/ml [9]. We observed progressive neurological toxicity when the plasma levels of o,p'-DDD increased to over 20 μg/ml. These symptoms disappeared after temporary discontinuation of the therapy, which also resulted in a concomitant fall in plasma o,p'-DDD levels.

In the study reported in the present paper, we investigated the relationship between the concentration of o,p'-DDD in plasma and adipose tissue during chemotherapy, and these and other tissues, particularly brain tissue, obtained at autopsy.

Materials and Methods

Seventeen biopsies of subcutaneous adipose tissue were taken from ten patients during o,p'-DDD therapy. Blood samples were taken at least 10 h after the previous dose of o,p'-DDD. Ten patients with AC were autopsied within 7 days after the last dose o,p'-DDD. In seven of these cases plasma concentrations had been determined in the week preceding their death.

In plasma, o,p'-DDD was measured according to the method of Moolenaar et al. [10]. The inter-assay variation was 2.5% ± 1.1%. Recovery of o,p'-DDD added to plasma was 96.5% ± 3.2% at levels between 0.9 and 20 μg/ml. The tissues were homogenised and extracted with acetone after addition of an p,p'DDD internal standard. The acetone-dry residue was extracted with heptane. This extract was then analysed for o,p'-DDD as described for plasma. Results were expressed as μg/ml plasma or μg/g wet tissue. Regression and significance of the correlation between the various tissue concentrations were calculated using the usual techniques as described by Armitage [1].

Results

The o,p'-DDD concentrations found in plasma and adipose tissue during oral chemotherapy of ten patients are given in Table 1. The o,p'-DDD concentrations in plasma and various tissues obtained from ten other patients at autopsy are given in Table 2.

The relationship between the concentrations of o,p'-DDD in adipose tissue and in plasma of the first group of patients is shown in Fig. 1. The data points derived from five patients in whom sampling was repeated two or three times in the course of treatment are connected by lines. The relationship between the two parameters became approximately linear when the adipose tissue concentrations were plotted on a logarithmic scale (Fig. 2a). A significant correlation was found for 17

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1 o,p-DDD: Mitotane systematic name: ortho-paradichlorodiphenyldichloroethane; 1,1-dichloro-2, 2-bis (*p*-chlorophenyl)ethane; (Calbiochem); (Bristol-Myers)

0344-5704/82/0009/0085/$ 01.00

Table 1. o,p'-DDD concentration in plasma and subcutaneous adipose tissue in patients during chemotherapy

Patient no.	Mitotane concentration in		Duration of treatment (days)
	Plasma (μg/ml)	Subcutaneous adipose tissue (μg/g wet wt)	
1	15.3	2,006	78
	18.4	3,900	225
2	4.1	808	48
	4.7	898	56
	11.7	1,960	100
3	3.7	480	22
	14.7	2,030	150
4	16.0	3,860	75
	17.0	3,620	161
5	8.7	2,120	27
6	7.8	1,100	31
7	18.6	4,190	725
8	16.1	3,150	9
	17.3	3,619	177
	20.0	5,710	1,123
9	17.9	2,958	655
10	24.5	7,205	730

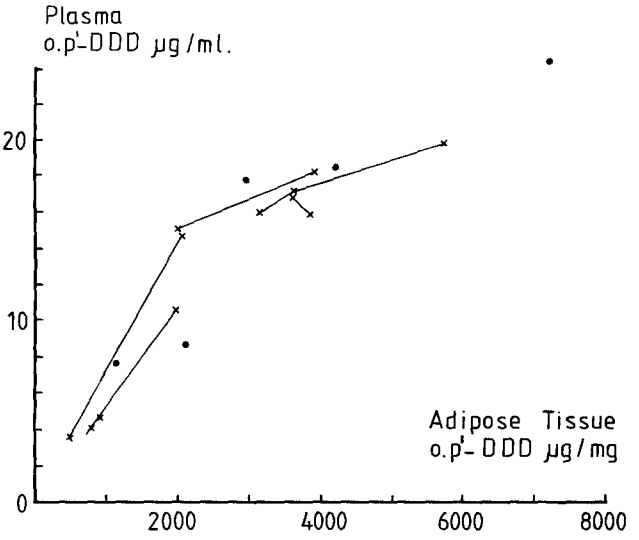

Fig. 1. Relation between o,p'-DDD concentrations in plasma and in subcutaneous adipose tissue, recorded in 17 biopsies from 10 patients during treatment

Table 2. o,p'-DDD concentrations in plasma (μg/ml) and tissues (μg/g wet wt) in ten patients at autopsy

	Patient no.									
	1	2	3	4	5	6	7	8	9	10
Duration of treatment (days)	32	55	110	116	120	175	250	560	900	1,050
Plasma	6.1	6.6	24.1	5	11.3	–	–	16.1	21.4	–
Subcutaneous adipose tissue	1,358	1,462	5,011	666	1,437	12.5	276	3,507	6,700	4,900
Mesenteric adipose tissue	1,373	1,787	5,046	600	2,163	11.0	180	3,314	–	3,500
Tumour: primary site or local recurrence	32 22 (27)	37.5	–	–	–	7.7	15.7	–	–	140
Lung metastasis	–	–	98.1 70.0 70.1 (76) 70.5	–	22.5 20.8 (21) 18.4	–	–	70.7 61.9 (63) 56.2	141	–
Lung	–	11	40	–	–	2.0	9.5	20	–	–
Liver metastasis	–	–	–	–	84 68 (73) 67	2.2	16	71.2	139	–
Liver	–	40	97	–	27.5 35.8 (31) 29.6	9.5	10.5	59	–	–
Kidney	–	15	45	–	25	–	9	28	–	36
Adrenal	–	320	735	–	296 268 (291) 284	8.5	69	–	–	–
Brain	–	–	54	8	18	3.5	11.5	25	56	34

( ): Mean values of multiple determinations

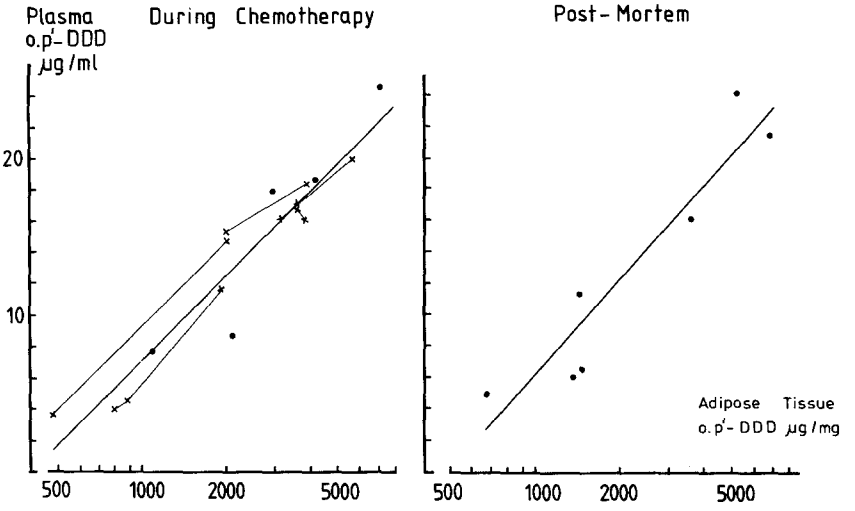

Fig. 2. Semilogarithmic relation between o,p'-DDD concentrations in subcutaneous adipose tissue and in plasma during therapy (*left*) (17 biopsies in ten patients) and at autopsy (*right*); ($n = 7$)

Table 3. Correlation coefficients and formulae of the regression lines between the o,p'-DDD concentrations in subcutaneous adipose tissue and other tissues at autopsy

	n	*r*	
Mesenteric adipose tissue	9	0.9578	y = 0.8458 x + 246.3
Lung	5	0.9528	y = 0.0065 x + 3.2
Kidney	6	0.9377	y = 0.0062 x + 9.1
Adrenal	5	0.9873	y = 0.1414 x + 52.9
Liver	6	0.9864	y = 0.0168 x + 8.3
Brain	8	0.9531	y = 0.0075 x + 5.0
Primary tumour, or local recurrence	5	0.9468	y = 0.0187 x + 16
Liver metastases	4	0.9689	y = 0.0215 x − 14
Lung metastases	5	0.9892	y = 0.0274 x + 1.8

n, number of cases; *r*, correlation coefficient

individual measuring points, expressed as the regression line $Y = 18.2 \log X - 47.5$, $r = 0.9544$ and $P < 0.01$. A similar relationship was found between concentrations of o,p'-DDD found in plasma and adipose tissue samples obtained at autopsy (Fig. 2b), where $n = 7$, $Y = 19.7 \log X - 52.5$ $r = 0.9228$ and $P < 0.01$. In Table 3 the relationship between o,p'-DDD concentrations in subcutaneous adipose tissue and in other tissues at autopsy are given. The linear correlations between the various tissue concentrations proved to be significant ($P < 0.01$).

Discussion

For obvious reasons the estimation of the relationship between o,p'-DDD concentrations in plasma and various tissues such as tumour and brain is not possible during chemotherapy. Only the relationship between the o,p'-DDD concentration in adipose tissue biopsies and plasma is studied during therapy (Fig. 1).

As seen in Fig. 2a, a semilogarithmic relationship between the adipose tissue and plasma concentrations is a good approximation.

In four patients, the lines connecting multiple sampling points obtained from individual patients (patients 1, 2, 3, and 8 in Table 1) are parallel to the regression line drawn through all 17 data points (Fig. 2a). In the fifth patient (patient 4), in spite of the fact that sampling took place some months apart, the two data sets gave similar points on the graph.

The relationship between plasma and subcutaneous adipose tissue at autopsy also fitted a semilogarithmic relationship (Fig. 2b, $P < 0.01$). A similar semilogarithmic relationship was found between plasma and brain concentrations of o,p'-DDD at autopsy ($n = 5$, $Y = 21.5 \log X - 14.7$, $r = 0.9868$ and $P < 0.01$).

There were too few plasma sampling points to derive correlations between plasma and other tissue concentrations at autopsy (Table 3). There was a good linear correlation between adipose tissue and other tissues.

Furthermore, the similarity of the regression functions of plasma and adipose tissue concentrations obtained during therapy and at autopsy, in combination with the good linear correlation between the concentration in adipose tissues and other tissues post mortem, suggests that a similar semilogarithmic relationship may exist between o,p'-DDD concentrations in plasma and in other tissues (especially brain) in vivo.

The semilogarithmic relationship between plasma and adipose tissue levels found in this study was unexpected and could be explained by the assumption of two plasma pools: one pool with a low capacity and high affinity for the (lipophilic) o,p'-DDD e.g., the lipoproteins, and a second pool with a high capacity but low affinity, e.g., albumin. At rising plasma o,p'-DDD concentrations the 'lipid pool' is saturated while the relative contribution of the 'albumin pool' increases. It is presumed that the albumin pool is mainly responsible for the loading of adipose tissue.

The relationship found between the plasma and tumour concentrations stresses the importance of plasma monitoring during therapy. The semilogarithmic relationship between plasma and tissue concentrations explains the small therapeutic range.

Acknowledgements. This study was supported by a grant from the Koningin Wilhelmina Fonds for Cancer Research (no. F 71.09).

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Received October 12, 1981/Accepted June 30, 1982