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Short communication

Effect of cancer chemotherapy on dapsone N-acetylation in man

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Summary. The effect of cancer chemotherapy on dapsone (DDS) N-acetylation was explored in 28 patients with various malignancies. There was a significant ($P = 0.01$) increase in plasma monoacetydapsone/dapsone (MADDS/DDS) ratios within 24 h of the start of chemotherapy (CT), indicating an acceleration of N-acetylation.

Introduction

Cancer patients are subject to concurrent medication with potential interactions. Most of the information available on such interactions is based on animal work, with relatively few human studies. Previous studies have concentrated on the effect of cytotoxic agents on microsomal oxidation, and very little work has involved conjugation reactions such as acetylation [2, 6, 7]. Knowledge of such interactions will facilitate dose adjustments of the interacting drugs such that undue toxicity can be avoided while the efficacy of drugs used is maintained.

N-Acetylation exhibits bimodality in man. Approximately 55% of a Caucasian population are slow acetylators and the rest are rapid acetylators [4]. A growing number of commonly used drugs including dapsone (DDS) are metabolised by the same enzyme system [3]. In some instances it has been possible to relate efficacy or toxicity to the acetylation phenotype [1]. Using DDS as a marker, this study investigates the acute effect of cytotoxic drug administration on DDS N-acetylation in an attempt to explore the metabolic interactions involving cytotoxic agents.

Patients, materials and methods

Patients. A group of 28 adults at Guy's Hospital receiving chemotherapy (CT) for various malignant conditions consisted of 16 men and 12 women of mixed ethnic background. The age range was 20–78 years (median, 45 years). None of the patients were on any drugs known to be polymorphically N-acetylated.

N-Acetylation phenotyping. Patients were given 100 mg DDS p.o. Blood was obtained 1–4 h post-dosing and immediately separated; plasma was stored at −20° C pending analysis by high-performance liquid chromatography [5]. Monoacetydapsone/dapsone (MADDS/DDS) ratios of <0.30 indicated slow acetylation and those of $\geqslant 0.30$, rapid acetylation. Phenotype testing was carried out before and approx. 24 h after the start of CT. Patients were maintained on their usual diets and medications.

Results

Table 1 presents data on each subject regarding the type of malignancy, CT regimen and MADDS/DDS ratios before and after CT. Standard doses of chemotherapy were used as described elsewhere. The dose of ifosfamide was 4.0 g/m^2. There was a significant increase in MADDS/DDS ratios (Wilcoxon's rank-sum test; $P = 0.01$). It is noteworthy that the four patients receiving single-agent ifosfamide experienced significant rises in these ratios.

Discussion

Data on metabolic interactions between cytotoxic and other drugs have mainly focused on microsomal oxidation [2, 6, 7]. Much of the available information tends to come from animal experiments and in vitro systems, which require careful extrapolation to humans because of the differences in drug-metabolising enzymes. Conjugation pathways such as N-acetylation have recently been shown to be important not only in determining the response to certain drugs but also in the development of certain spontaneous disorders in man [1].

The present study shows that different standard CT combinations and ifosfamide increase the MADDS/DDS ratio, indicating increased N-acetylation; the time course (within 24 h) and the known non-inducibility of cytosolic N-acetyltransferase make enzyme induction highly unlikely as an explanation. However, by inhibiting microsomal N-oxidation, cytotoxic agents could possibly increase the amount of drug available for N-acetylation, which is known to be non-saturable. N-Oxidation accounts for approximately 60% of the DDS dose [4]. For exploration of this hypothesis, the rate of the formation of oxidation metabolites should be determined under similar circumstances. However, the difficulty is that N-oxidation products of DDS are unstable and there are as yet no reliable assay techniques for their quantification. Alternatively, the effect of cancer CT can be investigated using another marker for N-acetylation that is predominantly metabolised by this pathway.

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Table 1. Results of the study

Patient	Diagnosis	CT	MADDS/DDS ratio	
			Before CT	After CT
1	Non-Hodgkin's lymphoma	CHOP	0.91	0.33
2	Hodgkin's disease	MOPP	0.45	0.31
3	Hodgkin's disease	MOPP	0.28	0.19
4	Non-Hodgkin's lymphoma	CHOP	0.59	0.92
5	Non-Hodgkin's lymphoma	CHOP	0.70	1.00
6	Hodgkin's disease	MOPP	0.18	0.50
7	Non-Hodgkin's lymphoma	CHOP	0.40	0.35
8	Hodgkin's disease	MOPP	1.23	1.17
9	Non-Hodgkin's lymphoma	CHOP	0.40	0.26
10	Non-Hodgkin's lymphoma	CHOP	1.06	2.81
11	Non-Hodgkin's lymphoma	CHOP	0.17	0.25
12	Non-Hodgkin's lymphoma	COP	0.11	0.22
13	Carcinoma of the uterus	IFX	0.62	2.15
14	Non-Hodgkin's lymphoma	CHOP	0.14	0.19
15	Hodgkin's disease	OPEP	0.66	0.76
16	Non-Hodgkin's lymphoma	CHOP	0.21	0.22
17	Non-Hodgkin's lymphoma	CHOP	0.18	0.25
18	Non-Hodgkin's lymphoma	CHOP	0.12	0.15
19	Soft-tissue sarcoma	IFX	0.29	1.65
20	Small-cell lung cancer	ACV	1.31	1.55
21	Carcinoma of the tongue	IFX	0.08	0.30
22	Non-Hodgkin's lymphoma	CHOP	0.40	0.17
23	Carcinoma of the tongue	IFX	0.39	1.05
24	Non-Hodgkin's lymphoma	COP	0.24	0.32
25	Hodgkin's disease	BACOP	0.58	0.72
26	Non-Hodgkin's lymphoma	CHOP	0.63	0.62
27	Hodgkin's disease	BACOP	0.56	0.91
28	Hodgkin's disease	BACOP	0.13	0.34

A or H, adriamycin; B, bleomycin; C, cyclophosphamide; E, VP16-213; IFX, ifosfamide; M, methotrexate; O, vincristine; P, prednisolone

The clinical significance of this observation has yet to be determined; it remains to be seen which enzyme system is directly influenced by CT (i.e. N-acetyltransferase or cytochrome p-450). Hence drugs predominantly disposed by the involved pathway might potentially be affected, and the therapeutic consequences would depend on factors such as the therapeutic index of the drugs.

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