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Short communication

Occurrence of circulating 7-deoxyaglycone metabolites of 4'-deoxydoxorubicin in man

Jeffrey Cummings, David J Kerr, and Stanley B Kaye

Department of Medical Oncology, University of Glasgow, 1 Horselethill Road, Glasgow G12 9LX, Scotland

Summary. In five cancer patients we have determined the pharmacokinetics of 4'-deoxydoxorubicin (4'-DOX), its alcoholic metabolite 4'-deoxydoxorubicinol and the occurrence of circulating 7-deoxyaglycone metabolites. The 7-deoxyaglycone of the alcohol metabolite, the major aglycone of Adriamycin (ADR) present in man, was not detected in any serum sample. The 7-deoxyaglycone of the parent drug, which appears in concentrations in excess of 30 ng/ml after ADR administration, was detected in only 2/5 patients in trace amounts. These preliminary data indicate a difference in biotransformation between ADR and 4'-DOX despite their close structural similarities.

Introduction

4'-Deoxydoxorubicin (4'-DOX) is a close structural analogue of Adriamycin (ADR) currently proceeding through phase I and II clinical trials [9]. The drug initially stimulated interest because it appeared not to induce cardiotoxicity in several animal species [5] and preliminary clinical trials suggested that it was also non-cardiotoxic in man [7]. The prominent mechanism of ADR toxicity to heart involves conversion to a semiquinone free radical and subsequent generation of reactive species derived from molecular oxygen [6]. In vitro experiments have shown that 4'-DOX is not reduced to a semiquinone free radical under conditions which produce ADR semiquinone, demonstrating metabolic differences between the two drugs which could account for different chemosensitivity to target tissues [4]. We have extended these in vitro studies concurrently to man and experimental animals, investigating the comparative pathways of metabolism of the two drugs [3]. In this report we describe our preliminary experience with 4'-DOX in man.

Materials and methods

Patients. Five subjects (four male, one female) were selected from a total of 20 who received 30 mg/m^2 as an i.v. bolus push injection in an EORTC coordinated phase II trial for advanced renal cancer. Each had normal liver function, and pharmacokinetic studies were performed after the first drug treatment. Blood samples (10-ml aliquots) were withdrawn through indwelling catheters positioned in the arm opposite to that used for drug injection before treatment and at 5 min, 10 min, 15 min, 20 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h and 48 h after drug administration. After bloods were collected, sera were separated and stored at −20° C.

Drug analysis techniques. Serum concentrations of 4'-DOX and all its principle fluorescent metabolites were determined by HPLC with sensitive fluorescence detection after extraction with chloroform:propan-2-ol (2:1) as previously reported [1]. Here daunorubicin was used as an internal standard and all samples, which were stored at −20° C, were thawed at room temperature and analysed immediately.

Pharmacokinetic analysis. 4'-DOX serum concentration time profiles were best-fitted to a bi-exponential decay (descriptive of a two-compartment open model, see Eq. 1) using an extended least squares computer programme (ELSFIT, version 3.0, obtained from Dr Lewis B Sheiner, University of California, San Francisco, USA).

$$\text{Serum concentration} = Ae^{-t\alpha} + Be^{-t\beta} \quad (1)$$

where A and B are defined as the theoretical zero time concentrations (ng/ml) in a central and peripheral compartment respectively and α and β are defined as apparent elimination rate constants (k_{el}). Other parameters are defined as follows:

$$\text{Half-life (t1/2)} = \frac{0.693}{k_{el}}$$

$$\text{Area under the curve (AUC)} = \frac{A + B}{\alpha\,\beta}$$

$$\text{Clearance (Cl)} = \frac{\text{Dose}}{\text{AUC}}$$

AUC of 4'-DOX metabolites was calculated by the trapezoidal rule and t½ by non-linear regression using ELSFIT.

Results and discussion

In a recent detailed report we described the pharmacokinetics of ADR and its metabolites in a large group of 25 cancer patients [2]. Three major metabolites were identified: adriamycinol (AOL), AOL 7-deoxyaglycone (AOL-

Offprint requests to: J. Cummings, Imperial Cancer Research Fund, Medical Oncology Unit, Western General Hospital, Edinburgh EH4 2XU, Scotland

Table 1. The pharmacokinetics of 4'-deoxydoxorubicin and its metabolites in cancer patients after i.v. administration of 30 mg/m² i.v. 4'-deoxydoxorubicin

	4'-Deoxydoxorubicin							4'-Deoxydoxorubicinol				4'-Deoxydoxorubicin 7'-deoxyaglycone			
	A (ng/ml)	$t_{1/2}\alpha$ (h)	B (ng/ml)	$t_{1/2}\beta$ (h)	AUC (ng/ml/h)	%	Cl (l/h/m²)	PC (ng/ml)	AUC (ng/ml/h)	%	$t_{1/2}$ (h)	PC (ng/ml)	AUC (ng/ml/h)	%	$t_{1/2}$ (h)
AD	927	0.01	15	6	266	86.6	112	6	24	8.6	19	29	17	5.5	1
JH	114	0.08	16	10	239	71.6	125	8	81	24.2	12	nd	nd	nd	nd
AL	201	0.13	41	3	192	60.0	156	32	145	40.0	30	nd	nd	nd	nd
AB	276	0.08	16	6	165	60.0	182	20	111	40.0	9	nd	nd	nd	nd
DR	1120	0.10	8	9	387	96.5	78	98	12	2.9	0.2	25	2.3	0.6	0.2

Pharmacokinetic constants are explained in "Materials and methods"
PC, peak concentration measured; %, individual AUC expressed as a percentage of the total AUC of parent drug plus metabolites combined; nd, not detected

DONE) and ADR 7-deoxyaglycone (ADR-DONE). Marked interpatient variations were observed in the pharmacokinetics of AOL-DONE: in 50% of all patients it was not detectable, and in two who developed cardiac problems it was present in large amounts (> 100 ng/ml). Values of $t_{1/2}$ varied between 0.1 and 24 h. ADR-DONE was detected in 60% of all patients and achieved concentrations in excess of 30 ng/ml in the majority of these, but was normally cleared in under an hour.

Table 1 contains the pharmacokinetics of 4'-DOX and its metabolites in patients. In keeping with the results of other studies, 4'-DOX was cleared quickly from serum in a bi-exponential manner with a short terminal half life ranging from 3 h to 10 h [7, 8]. 4'-Deoxydoxorubicinol (4'-DOL), the major metabolite, displayed a longer $t_{1/2}$ than its parent compound in 4/5 patients (9–30 h), but levels of this metabolite were extremely variable, ranging from as low as 6 ng/ml (peak concentration) to as high as 98 ng/ml (peak concentration). 4'-DOL-DONE was not detected in any patient serum sample. 4'-DOX-DONE displayed similar kinetic properties to ADR-DONE but was present in only trace amounts in only 2/5 patients (< 30 ng/ml).

In this preliminary report we confirm that biotransformation of 4'-DOX to 7-deoxyaglycones in man, as in experimental animals [3], is reduced compared with ADR, as evidenced by either lack of detection or detection of only trace amounts of circulating aglycones. These data are in accordance with the findings of other workers who have performed pharmacokinetic studies with 4'-DOX in man, where the only metabolite species identified was 4'-DOL [7, 8].

References

1. Cummings J (1985) Method for the determination of 4'-Deoxydoxorubicin, 4'-Deoxydoxorubicinol and their 7-deoxyaglycones in human serum by high performance liquid chromatography. J Chromatogr 341: 401
2. Cummings J, Milsteed R, Cunningham D, Kaye SB (1986) Marked inter-patient variation in Adriamycin biotransformation to 7-deoxyaglycones: evidence from metabolites identified in serum. Eur J Cancer Clin Oncol 22: 991
3. Cummings J, Willmott N, More I, Kerr DJ, Morrison JG, Kaye SB (1987) Comparative cardiotoxicity and anti-tumour activity of doxorubicin (Adriamycin) and 4'-deoxydoxorubicin and the relationship to in vivo disposition and metabolism in the target tissues. Biochem Pharmacol 36: 1521
4. Dickson AG, DeJordy JO, Boutin MG, Teres D (1984) Absence of generation of oxygen containing free radicals with 4'-Deoxydoxorubicin, a non-cardiotoxic anthracycline drug. Biochem Biophys Res Commun 125: 584
5. Gagnasso AM (1982) Summary of pre-clinical studies on IMI-58 (4'-Deoxydoxorubicin) up to April 1981. Farmitalia Carlo Erba, Milan
6. Myers CE, McGuire WP, Liss RH, Ifrim I, Grotzinger K, Young RC (1977) Adriamycin: the role of lipid peroxidation in cardiac toxicity and tumour response. Science 197: 165
7. Stanton GF, Raymond V, Wittes RE, Schulman P, Budman D, Baratz R, Williams L, Petroni GR, Geller NL, Hancock C, Kreis W, Young CW (1985) Phase I and clinical pharmacological evaluation of 4'-Deoxydoxorubicin in patients with advanced cancer. Cancer Res 45: 1862
8. Weenen H, Van Maanen JMS, De Planque MM, McVie JG, Pinedo HM (1984) Metabolism of 4'-modified analogs of Doxorubicin. Unique glucuronidation pathway for 4'-Epidoxorubicin. Eur J Cancer Clin Oncol 20: 919
9. Young CW, Raymond V (1986) Clinical assessment of the structure-activity relationship of anthracyclines and related synthetic derivatives. Cancer Treat Rep 70: 51

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