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The effect of verapamil on the pharmacokinetics of adriamycin

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Summary. The concurrent administration of adriamycin (intravenous) and verpamil (oral) is of considerable interest because of experimental data suggesting that resistance to adriamycin may be overcome by this means. The potential for a pharmacokinetic interaction between the two drugs has therefore been investigated in five patients with small cell lung cancer treated with combination chemotherapy comprising adriamycin, VP16, vincristine and cyclophosphamide. The data indicate that a significant interaction takes place. Adriamycin peak levels, terminal half-life and the volume of distribution at steady state are higher, whereas plasma drug clearance and the volume of the central compartment are lower with co-administration of verapamil. There was no evidence of enhanced drug toxicity in this study; however, the data should be considered in the interpretation of clinical trials in which adriamycin and verapamil are used together, both in terms of toxicity and tumour response.

Introduction

The calcium channel blocker, verapamil, can enhance the efficacy of the cytotoxic agent adriamycin in vitro [8, 16, 17, 18]. The underlying mechanism is unknown but may be related to inhibition of active drug efflux in resistant tumour cells [8]. Moreover, in vitro data indicate that enhancement of adriamycin toxicity by verapamil in normal granulopoietic cells does not occur [19]. There have been two preliminary reports of clinical trials combining verapamil and adriamycin. Ozols et al. [12] have shown that verapamil does not enhance the myelotoxicity or gastrointestinal toxicity of adriamycin and that serum verapamil levels of up to 300 ng/ml can be achieved in patients with refractory ovarian cancer, similar to efficacious verapamil concentrations used in some tissue culture systems. Presant et al. [13] indicated in a further study that oral verapamil (480 mg/day) did not enhance the toxicity of intravenous adriamycin (60 mg/m^2), and encouraging responses were seen in three patients with measurable disease which was previously unresponsive to adriamycin alone.

Adriamycin undergoes extensive hepatic metabolism and biliary excretion [15] and has an estimated hepatic extraction ratio of 0.4–0.5 [1]. Verapamil has vasodilator properties and has been shown to increase hepatic blood flow [10]. A randomised clinical trial involving verapamil in the treatment of small cell lung cancer is planned and a pilot study with five patients has been performed. We report here the data from this study with particular reference to the influence of verapamil on the kinetics of adriamycin in patients with small cell lung cancer.

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Materials and methods

Five patients (three male, two female, median age 52 years) with histologically confirmed small cell lung cancer limited to one hemithorax were studied. No patient had received prior chemotherapy, was taking any drugs likely to affect hepatic blood flow or the activity of the hepatic mono-oxygenase system. All patients had a WHO performance status of 1 and normal renal and hepatic function as judged by standard biochemical parameters. In addition, all patients were examined by hepatic ultrasonography and found to be free of metastases. All chemotherapeutic agents were administered intravenously. Day 1 cytotoxic therapy consisted of adriamycin (40 mg/m^2), vincristine (1.4 mg/m^2), cyclophosphamide (750 mg/m^2) and VP16 (100 mg/m^2), followed by VP16 (100 mg/m^2, day 2) and VP16 (100 mg/m^2, day 3). Treatment was repeated at 3-weekly intervals provided haematological parameters were satisfactory. In addition the patients were given oral verapamil with one or other of the first two courses of cytotoxic therapy, in random order. Verapamil was given for 7 days (80 mg TDS for 3 days, followed by 120 mg QDS for 4 days) and was continued for 24 h after bolus injection of adriamycin. Adriamycin was administered 1 h after the morning dose of verapamil and intermittent venous sampling was conducted thereafter for 48 h. The blood samples were centrifuged (2000 rpm for 5 min) and the serum (adriamycin) or plasma (verapamil) was separated and stored at −20 °C until analysis. Three of the five patients had 24-h Holter ECG monitoring performed after each treatment with adriamycin.

Drug assays and statistical tests. Adriamycin and its metabolites (adriamycinol and their 7-deoxyaglycones) were measured in serum using a sensitive and specific reversed-phase isocratic high-performance liquid chromatographic (HPLC) assay devised in our laboratory [5]. Verapamil and its metabolite norverapamil were estimated by an HPLC assay with fluorescence detection [4].

The pharmacokinetic profiles of adriamycin were most appropriately described by a model incorporating three compartments for drug disposition. Parameter estimates were obtained by non-linear least squares fitting using an "in-house" programme based on the Marquhardt algorithm [2]. Once the parameters had been determined it was possible to calculate the apparent volume of each compartment, the steady-state volume of distribution and the individual rate constants k_{12}, k_{21}, k_{13}, k_{31} and k_{10} and hence plasma drug clearance. Student's paired *t*-test, with Bonferroni correction where appropirate, was used for all comparisons. Results are expressed throughout as mean ± SD.

Results

Paired kinetic data were available for all five subjects. The mean (± SD) adriamycin decay curves are shown in Fig. 1. The verapamil treatment group has higher peak levels of adriamycin, with an elevated AUC and a longer terminal half-life. The kinetic parameters for individual patients are summarised in Table 1. Combined treatment with verapamil increases peak levels of adriamycin and the steady-state volume of distribution and prolongs the terminal half-life, whereas the volume of the central compartment and plasma clearance of adriamycin are reduced. Due to the small number of patients involved in this cross-over study, the errors involved in statistical analysis are relatively large, and there appear to be significant differences in peak drug level ($p < 0.03$) and terminal half-life ($p < 0.01$).

The main metabolite formed was adriamycinol, with negligible amounts of the 7-deoxyaglycone of adriamycin. The degree of metabolism was assessed by comparing the ratio $AUC_{adriamycin}/AUC_{adriamycin} + AUC_{adriamycinol} \times 100\%$. However, there was no difference between the two groups (adriamycin, 73%±5%; adriamycin + verapamil, 76%±7%).

Mean (± SD) trough verapamil levels are shown for the 24 h following administration of adriamycin in Fig. 2.

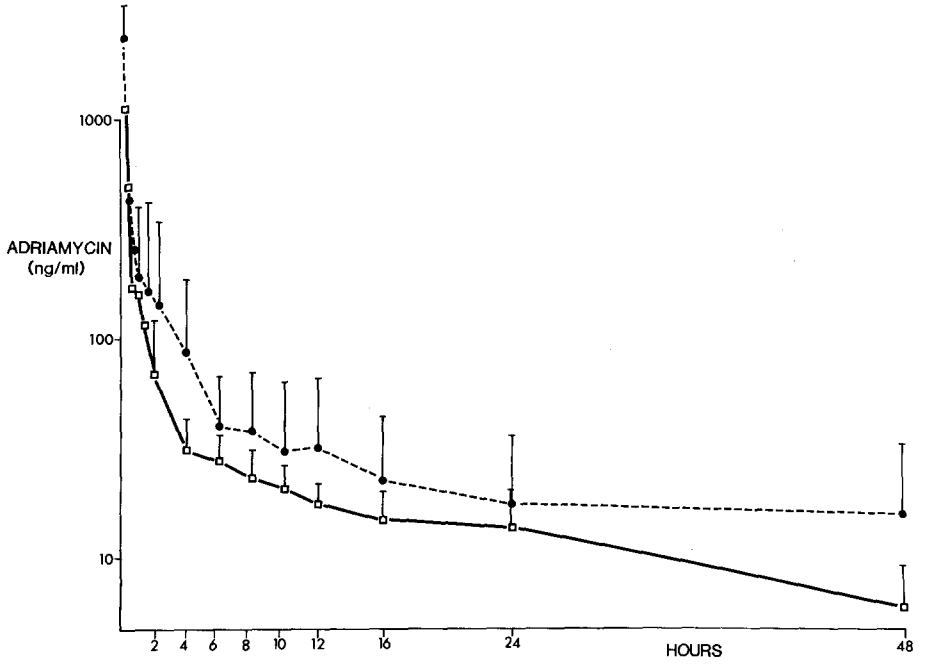

Fig. 1. Concentration-time curve for intravenous administration of adriamycin alone (□) or after treatment with verapamil (●). The vertical *bars* denote 1 SD

Table 1. Pharmacokinetic parameters for adriamycin ± verapamil

Subject	AUC (ng ml^{-1} h)		Terminal half-life (h)		Clearance (l h^{-1})		Steady-state volume of distribution (L)		Peak drug levels (ng/ml)	
	A+V	A	A+V	A	A+V	A	A+V	A	A+V	A
1	1663	842	22.5	14	27.5	33	325	233	3898	2486
2	984	797	44	33	38	53	2435	1376	2635	1211
3	4458	1199	38	26	12.4	59	444	1143	1207	805
4	1095	871	40	32	31	45	3828	2751	1418	1109
5	1000	789	18	15	71.5	78	767	444	1731	1143
Mean	1840	900	32.5	23.6	36.1	53.6	1560	1189	2178	1351
SD	1489	171	11.5	9.0	21.9	16.8	1526	993	1105	653
P^a	<0.3		<0.01		<0.08		<0.15		<0.03	

A, adriamycin alone; A+V, adriamycin+verapamil

[a] Paired Student's *t*-test

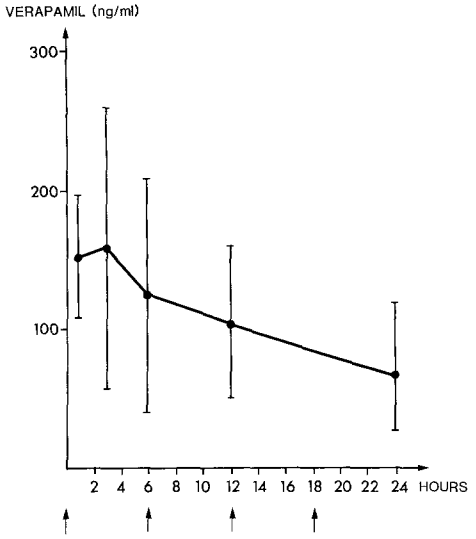

Fig. 2. Concentration-time curve for plasma verapamil following oral administration of verapamil 120 mg QDS. *Arrows* denote time of verapamil doses

The mean steady-state drug level for verapamil was 100 ± 32 ng/ml, with a calculated plasma clearance of approximately 200 $l hr^{-1}$. Norverapamil levels were usually lower than those of the parent compound, with mean steady-state levels of 95 ± 28 ng/ml. There were no apparent differences in the kinetic parameters depending on the order of administration of verapamil, but patient numbers are too small for this fact to have statistical validity.

The incidence of side effects was similar for each course of chemotherapy, independent of verapamil administration. The nadir white cell count (day 10–14) was 1.2×10^9 l for both groups. There were no significant cardiac dysrhythmias nor was there prolongation of the P-R interval with verapamil.

Discussion

It would appear from this preliminary study on a small number of patients that there is a significant pharmacokinetic interaction between adriamycin and verapamil. Adriamycin peak levels, terminal half-life and the volume of the peripheral compartments are higher, whereas plasma drug clearance and the volume of the central compartment are lower, with co-administration of verapamil. Despite having pretreated patients with oral verapamil for a period of time adequate to have achieved steady-state levels, there is an apparent, but not statistically significant, trend for verapamil levels to fall over the 24 h (Fig. 2). There is no obvious explanation for this fluctuation in the pharmacokinetics of verapamil, although it could be due to circadian variation or to an effect exerted by adriamycin.

There is some evidence to suggest that cyclophosphamide and vincristine [6] alter hepatic drug metabolism; however, we attempted to control this by using a cross-over design so that three patients had verapamil with the first course of chemotherapy and two patients with the second course. This should cancel any potential ordering effects from, say, having two courses of cyclophosphamide before repeating the adriamycin kinetic study, which might obfuscate the effects of verapamil.

The reduction in adriamycin clearance is associated with a prolonged terminal half-life and elevated AUC. Verapamil has been shown to inhibit the hepatic mono-oxygenase activity in rodents [14] and inhibit the metabolism of some lipid-soluble drugs in man [3, 9]. There was no evidence of altered routes of drug metabolism in this study based on comparison of the ratio $AUC_{adriamycin}/AUC_{adriamycin} + AUC_{metabolite}$. The major contributory metabolite detected was adriamycinol, which is produced by a ubiquitous cytoplasmic NADPH-dependent reductase. Deoxyaglycone metabolites, formed by the hepatic mono-oxygenase system, were virtually undetectable in both situations, despite the higher peak levels of adriamycin associated with verapamil co-administration. It is possible that verapamil reduces adriamycin clearance through an inhibitory effect on the mono-oxygenase activity.

Verapamil is a vasodilator and has been shown to increase hepato-renal blood flow in man [10] and tumour blood flow in rodent hind limb tumours [7]. Although it is difficult to extrapolate from these studies to the present data, a similar mechanism may contribute partially to the alteration of the steady-state volume of distribution of adriamycin with verapamil. A further small contribution may be made to the elevated volume of distribution by verapamil's reduction of the cellular efflux of adriamycin. However, in vivo both of these effects would be expected to be relatively small.

There was no apparent enhancement of toxicity during the brief study period with the adriamycin-verapamil combination as judged by nadir white cell counts.

Although serial assessment of cardiac function was not possible, we saw no important acute electrocardiographic or haemodynamic changes, despite the elevated peak levels of adriamycin. In two other phase I trials involving the simultaneous use of adriamycin and verapamil [12, 13], no evidence for enhanced adriamycin cardiotoxicity was seen. Moreover, left ventricular function has been assessed echocardiographically in a randomised clinical trial of two comparable patient groups receiving adriamycin ± continous oral verapamil. The results suggest that verapamil may in fact prevent adriamycin-induced cardiomyopathy by virtue of its cardioprotective (vasodilatory) properties [11]. Clearly, serial scintigraphic or ultrasonic measurement of left ventricular function will be an important part of any future phase II clinical trials of adriamycin combined with verapamil.

In summary, in addition to the enhancement by verapamil of the activity of adriamycin in tissue culture systems, there may also be, a contributory pharmacokinetic interaction between the two drugs in vivo. This should be taken into consideration in the analysis of clinical data with respect both to toxicity and to tumour response.

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