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Short communication

Pulmonary distribution of vinorelbine in patients with non-small-cell lung cancer

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Abstract. Vinorelbine (Navelbine, NVB) is a new semisynthetic vinca alkaloid that is currently used in the treatment of advanced breast cancer and advanced non-small-cell lung cancer (NSCLC). In this study we investigated the tumoral and healthy pulmonary tissue concentrations of NVB in previously untreated NSCLC patients undergoing surgery. A total of 13 patients (mean age, 60 years; range, 42–70 years) were included and received NVB (20 mg/m^2) at 1 h (mean, 1.1 h; SD, 0.2 h; $n = 6$ patients) and 3 h (mean, 3.0 h; SD, 0.6 h; $n = 7$ patients) before tumor resection. A tumoral and adjacent healthy lung-tissue specimen as well as simultaneously sampled serum were analyzed for NVB by high-performance liquid chromatography (HPLC). NVB levels were much higher in tissue than in serum (up to 300-fold). The tissue/serum ratio increased between the 1-h sampling time (range, 0.1–100) and the 3-h time point (range, 10–300). In all patients but two, NVB concentrations were lower in tumors than in healthy lung tissue. The tumor/healthy tissue ratio ranged from 0.06 to 1.3 (median, 0.09) at 1 h and from 0.18 to 1.1 (median, 0.55) at 3 h. This ratio increased between the 1-h sampling time and the 3-h time point as a consequence of increasing tumor levels (median, 50.4 ng/g at 1 h and 278 ng/g at 3 h). In four patients, concentrations could be measured in necrotic and peripheral tumor zones, showing lower values in necrotic areas. Thus, these data indicate that NVB is highly distributed in lung tissue, with the disposition rate being slower in tumor tissue than in healthy parenchyma during the first 3 h.

Introduction

Vinorelbine (5′-nor anhydrovinblastine; Navelbine, NVB) is a new semisynthetic vinca alkaloid that differs chemically from its analogues by alterations on the catharanthine moiety [5, 12]. NVB is currently used in the treatment of advanced non-small-cell lung cancer (NSCLC) [1, 3, 9] and advanced breast cancer [2] but is also active in ovarian cancer [4]. The pharmacokinetic profile of NVB has recently been characterized in man using a high-performance liquid chromatographic (HPLC) method [7, 10]. It can best be characterized by a three-compartment model with a terminal half-life of about 42 h and a large volume of distribution (4050 l) [7]. The total clearance value is 1.1 l/min, with about 11% of the dose being eliminated by the kidney [7]. In a micropig model we found that biliary excretion accounted for about 26% of the delivered dose within the first 48 h [11]. Thus, as for other vinca alkaloids, the recovery of NVB remains incomplete, indicating the presence of metabolites and/or a sustained retention in tissue. In the rat, NVB showed a more intense tissue distribution than its analogues, particularly in the lungs [8]. No information is available about NVB human tissue disposition. Since lung tumors are a major target for NVB, we investigated the tumoral and healthy pulmonary tissue concentrations of NVB in previously untreated NSCLC patients undergoing surgery.

Patients and methods

Patients. A total of 13 patients with operable, histologically proven NSCLC entered this study. All patients gave written informed consent and this human investigation was approved by the local ethics comittee. Patients were required to be ≤70 years old and to have normal renal and hepatic functions, a white blood cell count of ≥3,500/μl, a granulocyte count of >1,500/μl, and a platelet count of >100,000/μl.

Treatment plan. Treatment consisted of NVB (20 mg/m^2) given by short i.v. infusion (15 min). The injection was done either 1 or 3 h before surgery.

Tissue and plasma sampling. Tumoral and adjacent healthy lung-tissue samples were obtained immediately after resection. The specimens were washed with phosphate buffer to remove the contaminating blood, cut into fragments weighing about 1 g, and then frozen at −70° C. Simultaneous blood samples were taken and immediately centrifuged at

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Table 1. Patient's characteristics

Patient number	Age (years)	Sex	Histology	Sampling time
1	69	M	Large-cell carcinoma	1.1 h
2	57	F	Adenocarcinoma	1.3 h
3	70	M	Squamous-cell	1.0 h
4	65	M	Adenosquamous	1.0 h
5	55	M	Squamous-cell	1.4 h
6	63	M	Squamous-cell	1.0 h
Mean (SD)				1.1 (0.2) h
7	55	M	Squamous-cell	2 h
8	65	M	Squamous-cell	2.7 h
9	42	M	Squamous-cell	3.5 h
10	61	F	Squamous-cell	3.5 h
11	60	M	Squamous-cell	2.7 h
12	55	M	Squamous-cell with adeno pictures	3.7 h
13	63	M	Squamous-cell	2.7 h
Mean (SD)	60 (8.1)			3.0 (0.6) h

1,000 *g* for 10 min, after which the serum was stored at –70° C until analysis.

Chemicals. Vinorelbine as the ditartrate salt (calibration standard) was kindly provided by Pierre Fabre Médicaments as a pure powder. Vinblastine (internal standard) was obtained commercially (Velbé, Eli Lilly). All solvents used were of HPLC grade.

Tissue extraction procedure. A frozen fragment weighing about 1 g was introduced into a cartridge of a model 6700 freezer-mill (Spex, industries, Edison, N. J., USA) and crushed for 1 or 2 min in liquid nitrogen. The powder was taken up with methanol-hydrochloric acid (pH 2; 20 : 80, v/v; 1 or 2 ml, depending on the weight). The mixed extracts were incubated overnight at 4° C, then centrifuged at 1,000 *g* for 10 min. A 1-ml aliquot of supernatant was sampled and extracted following the same procedure described below for serum.

Serum extraction procedure. This procedure has previously been described elsewhere [6]. Briefly, an aliquot (1 ml) of serum containing 100 ng vinblastine and 1 ml 66 m*M* phosphate buffer was added to 3 ml diethyl ether in a 6-ml screw-capped glass tube. After the ingredients had been mixed, the tubes were gently shaken for 30 min by rotation and then centrifuged for 10 min at 1,000 *g*. The upper organic phase was transferred to another glass tube and evaporated to dryness under a stream of nitrogen at 37° C. The residue was then dissolved in 120 µl methanol-hydrochloric acid (pH 2; 20 : 80, v/v), and 50 µl of the solution was injected into the chromatograph.

HPLC system. The HPLC system consisted of a model 126 programmable solvent-delivery device (Beckman, Fullerton, Calif.), a model 210 sample-injection valve with a 50-µl loop (Beckman), and a model 166 programmable wavelength detector (Beckman). Chromatograms were processed by a GOLD chromatographic data system (Beckman). The assay was carried out using a 250- × 4-mm (inner diameter) cyano-analytical column with a 5-µm particle size (SGE, Paris, France). Elution was performed under isocratic conditions with acetonitrile (55%) in 40 m*M* ammonium (pH 2.9) at a flow rate of 1 ml/min. Quantitation was based on UV detection at 268 nm. The detection limit of NVB was 1 ng/ml. NVB levels are expressed in terms of the median value plus the distribution range.

Results

In all, 11 men and 2 women were included in this study (mean age, 60 years; range, 42–70 years), and none of these patients had previously been treated either by chemotherapy or radiotherapy. The NVB injection was performed at 1.1 h (SD, 0.2 h; $n = 6$ patients) and 3.0 h (SD, 0.6 h; $n = 7$ patients) before surgergy. The patients' characteristics are shown in Table 1.

NVB levels (Table 2) were up to 300 times higher in tissue than in serum at 3 h after injection. The tissue/serum ratio was higher at 3 h (range, 10–300) than at 1 h (range, 0.1–100). Neoplastic and healthy tissue levels showed wide variation, and in all patients but two (one at 1 h and

Table 2. Serum concentrations and lung-tissue disposition of vinorelbine in patients with NSCLC as determined at 1 and 3 h after the injection

Patient number[a]	Serum concentration (ng/ml)	Tumor concentration ng/g tissue)	Healthy lung concentration (ng/g tissue)	Tumor: serum concentration ratio	Healthy tissue: serum concentration ratio	Tumor: healthy tissue concentration ratio
1 (1 h)	28.9	24.7	398	0.85	13.77	0.06
2 (1 h)	19.0	243	2,034	12.79	107.05	0.12
3 (1 h)	53.1	67.3	495.9	1.27	9.34	0.14
4 (1 h)	15.4	23.6	391	1.53	25.35	0.06
5 (1 h)	23.4	372.5	282	15.92	12.05	1.30
6 (1 h)	24.1	33.6	554	1.39	23.0	0.06
Range		23.6–372.5	282–2,034	0.85–15.92	9.34–107.5	0.06–1.30
Median		50.4	447	1.46	18.39	0.09
7 (3 h)	21.7	278	1,313	12.81	60.51	0.21
8 (3 h)	17.6	857	1,520	48.69	86.36	0.56
9 (3 h)	4.8	296	1,630	61.67	339.58	0.18
10 (3 h)	11.7	180	327	15.38	27.95	0.55
11 (3 h)	2.4	231	404	96.25	168.33	0.57
12 (3 h)	4.8	154	748	32.08	155.83	0.21
13 (3 h)	17.4	540	491	31.03	28.22	1.10
Range		180–857	327–1,630	12.81–96.25	27.95–339.58	0.18–1.10
Median		278	748	32.08	86.36	0.55

[a] Sampling time given in parentheses

Table 3. Vinorelbine (NVB) tumor concentrations measured in the central and peripheral zones

Patient number (sampling time)	NVB concentration in the central zone (ng/g tissue)	NVB concentration in the peripheral zone (ng/g tissue)
1 (1 h)	2.6	35.8
7 (3 h)	201	330
10 (3 h)	112	249
13 (3 h)	191	708

one at 3 h), NVB concentrations were lower in tumors than in healthy tissue. The tumor/healthy lung tissue ratio ranged from 0.06 to 1.3 (median, 0.09) at 1 h and from 0.18 to 1.1 (median, 0.55) at 3 h. This ratio increased between the 1-h sampling time and the 3-h time point as a consequence of increasing tumor levels that ranged from 23.6 to 372 ng/g tissue (median, 50.4 ng/g tissue) at 1 h and from 180 to 857 ng/g tissue (median, 278 ng/g tissue) at 3 h. In healthy tissue, NVB levels ranged from 282 to 2,034 ng/g tissue (median, 447 ng/g tissue) at 1 h and from 327 to 1,630 ng/g tissue (median, 748 ng/g tissue) at 3 h. In four patients NVB concentrations were measured in necrotic and vegetating tumor tissue, showing lower values in necrotic areas (Table 3).

Discussion

In humans, little information is available on the tumoral or healthy tissue distribution of anticancer drugs, more precisely, those of the vinca alkaloid family. To our knowledge, the tissue and tumoral disposition of vinca alkaloids has been studied only in brain metastatic tumors [14]. Lung cancer is the major target of NVB, which was selected because of both its antitumoral activity against human NSCLC cell lines and the high levels reached in animal lung tissue in relation to other vinca alkaloids.

In the present study, an important interindividual variation in the concentrations of NVB in lung tissue was observed; this occurs quite frequently in tissue investigations [13]. In addition, the tumor cell heterogeneity may explain this variation. Nevertheless, the NVB levels attained in pulmonary tissue (healthy or tumoral) were higher than those observed in serum and increased between the 1-h sampling time and the 3-h time point, indicating an accumulation in the lung. This increase was more pronounced in tumor tissue suggesting a slower disposition rate in malignant tissue than in healthy parenchyma. Furthermore, until the 3rd h, tumoral levels were lower than those measured in healthy lung tissue, amounting to roughly half of the latter values at 3 h. Inside the tumor, NVB levels were higher in the periphery than in the central zone. This discrepancy may be related to a better vascularization of the peripheral zone. In conclusion, this study indicates that NVB penetrates readily into pulmonary tissue and particularly into tumors, reaching levels considerably higher than those observed in serum. This property could partly explain the good activity of NVB in NSCLC.

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