Cancer Chemother Pharmacol (1982) 8:211–214

Cancer Chemotherapy and Pharmacology

Can Severe Vincristine Neurotoxicity be Prevented?

Z. R. Desai[1], H. W. Van den Berg[2], J. M. Bridges[1], and R. G. Shanks[2]

Departments of [1] Haematology and [2] Therapeutics and Pharmacology, Queen's University of Belfast, Grosvenor Road, Belfast, BT12 6BA, North Ireland

Summary. *Neurotoxicity in vincristine treatment has generally been considered a consequence of the cumulative dose of the drug, and liver dysfunction has been recognised as an indication to reduce the dosage. We demonstrate that neurotoxicity is also related to individual doses and that even when there is no other evidence of liver dysfunction, a raised level of serum alkaline phosphatase may predict severe neurotoxicity.*

Exposure to vincristine following IV injection of the drug was studied in 27 subjects by measuring the area under the vincristine plasma concentration time curve ($AUC_{0-\infty}$). A statistically significant relationship was found between the $AUC_{0-\infty}$ and the degree of neurotoxicity. The $AUC_{0-\infty}$ was related both to dose and to elevation of serum alkaline phosphatase, suggesting that elimination of the drug is impaired when serum alkaline phosphatase is raised. Among patients with elevated serum alkaline phosphatase, a small reduction in the dose of the drug resulted in lower vincristine plasma $AUC_{0-\infty}$ and less neurotoxicity.

Introduction

The major limiting factor in the use of vincristine is neurotoxicity. Almost all patients so treated will eventually lose their ankle jerks. Further loss of reflexes, paraesthesiae, motor weakness, and gait disorders may follow subsequent doses of the drug, but this progression is less predictable and the extent varies between patients [1, 2, 9]. It has become conventional in many centres to limit each dose of the drug to 2 mg, in an attempt to reduce the incidence of severe neurotoxicity, but the problem remains that some patients are more affected than others. Studies of the pharmacokinetics of vincristine were initiated to assess their relationship to the development of neurotoxicity. Plasma levels of vincristine were measured in 27 patients receiving the drug for a variety of haematological disorders, and the development of neurotoxicity observed.

Reprint requests should be addressed to Z. R. Desai

Materials and Methods

Twenty-four adults and three children undergoing treatment for leukaemia (9), lymphoma (14), multiple myeloma (2), and idiopathic thrombocytopaenic purpura (2) were studied. One adult had received vincristine 4 years previously, but no neurological abnormality was found prior to restarting therapy. There were eight female and 19 male patients, and ages ranged from 11 years to 68 years. The study was approved by the Ethical Committee of the Queen's University, Belfast, and each patient or guardian gave informed consent. All adult patients received bulk purgatives prophylactically to prevent constipation. Vincristine was administered IV according to protocols currently accepted as effective in the various disease states. Patients with multiple myeloma and idiopathic thrombocytopenia purpura received vincristine, 1 mg, while the dose of vincristine in patients with leukaemia and lymphoma was calculated at 1.4 mg/m^2 to a maximum of 2 mg, with the exception of two patients who received greater than 2 mg per individual dose on at least one occasion. The interval between injections ranged from 1 week to 4 weeks. Blood samples were collected through a heparinised indwelling venous catheter fitted with a three-way tap at 0 and at 5 and 30 min, and 1, 2, 3, 4, 5, 8, 12, 20, and 26 h after drug administration into lithium heparin tubes. Plasma was separated by centrifugation at 1,500 *g* for 10 min, and stored at −20° C until analysis. Samples for blood counts, checks of urea and electrolytes, and liver function tests were obtained at 0 min. The vincristine radioimmunoassay was performed by a modification of the method described by Teale et al. [7]. Exposure to vincristine was estimated by calculating the area under the vincristine plasma concentration time curve ($AUC_{0-\infty}$) by the trapezoidal rule.

Neurological examinations of patients were performed at least 2-weekly during initial treatment, and thereafter at least monthly for as long as treatment continued. The degree of neurotoxicity was assessed according to a modification of the recommendations of Sandler et al. [5].

0344-5704/82/0008/0211/$ 01.00

Table 1. Vincristine AUC, dose, patients, body surface area, and degree of toxicity[a]

	Grade 0 ($n = 2$)	Grade 1 ($n = 2$)	Grade 2 ($n = 17$)	Grade 3 ($n = 6$)
AUC[b] (ng/ml/h)	19 ± 4.2	18 ± 4.2	76.9 ± 39.4	182.6 ± 83.8
Total cumulative VCR dose (mg/m^2) at 2 months	2.40 ± 0.48	2.08 ± 0.30	4.29 ± 1.57	4.03 ± 2.00
Single dose VCR (mg/m^2)	0.68 ± 0.00	0.72 ± 0.05	1.17 ± 0.14	1.32 ± 0.16
Surface area (m^2)	1.45 ± 0.00	1.45 ± 0.21	1.69 ± 0.22	1.56 ± 0.26

[a] Results given as mean ± SD
[b] AUC in grades 0 + 1 pooled for statistical analyses: 0 + 1 to 2 $P = 0.001$; 2 to 3 $P = 0.004$

Grade 1 = Depression of Achilles reflexes only;
Grade 2 = Above findings, plus depression of other tendon reflexes and/or paraesthesiae;
Grade 3 = Above findings, plus motor weakness and/or gait impairment;
Grade 4 = Above findings, plus cranial nerve palsies and/or motor paralysis.

Grade 2 was modified to include mild weakness of the long extensors of the fingers, but with no other evidence of motor weakness. It has previously been reported as an early sign of motor neuropathy [2], and patients with this sign were still considered to in grade 2 for the purpose of this study. Motor involvement of other muscle groups resulted in a classification into group 3.

Patients were graded at 2 months according to the maximum severity of neuropathy (if any) manifested within that time. Results are expressed as means ± SD. The significance of differences between dose was calculated by Student's *t*-test, and between vincristine plasma $AUC_{0-\infty}$ by the Mann-Whitney *U*-test.

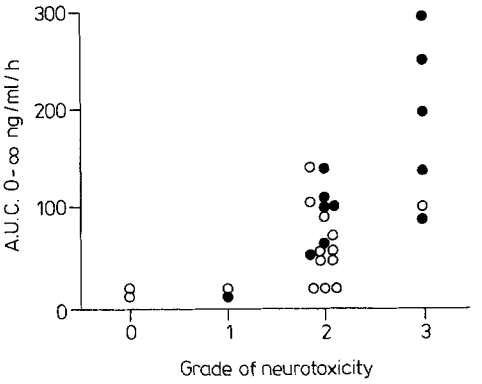

Fig. 1. The relationship between vincristine $AUC_{0-\infty}$ following initial therapy in 27 patients and the maximum degree of neuropathy observed during a 2-month observation period. ○, normal serum alkaline phosphatase at the time of vincristine therapy; ●, raised serum alkaline phosphatase at the time of vincristine therapy

Results

The relationship between vincristine $AUC_{0-\infty}$ determined following the first dose of vincristine and the maximum degree of neuropathy displayed by all subjects during the 2-month period of observation is shown in Table 1. The mean $AUC_{0-\infty}$ values for patients in grades 0 and 1 were pooled for analysis and were significantly lower than the mean $AUC_{0-\infty}$ for patients in grade 2 ($P = 0.001$), which was in turn significantly lower than mean $AUC_{0-\infty}$ for patients in Grade 3 ($P = 0.004$). Since patients displaying grade 2 or grade 3 neuropathy were comparable in terms of age, sex, total cumulative vincristine dose, and intervals between doses, an attempt was made to identify these factors that might account for the differing degree of neurotoxicity. Serum bilirubin and transaminase levels were not significantly different between the groups developing grade 2 or grade 3 neuropathy. Three patients in grade 2 were mildly jaundiced and none in grade 3. Transaminases were elevated in a further three patients in grade 2, and in an equal number in grade 3.

However, Fig. 1 shows that serum alkaline phosphatase (SALP) was raised in six of 17 patients in grade 2 (35%) and in five of six patients classified as grade 3 (83%). Serum γ-glutamyl transferase (GGT) was not routinely measured, but in 17 patients in whom it was, the GGT and SALP levels tended to parallel each other, except in one patient with elevated SALP. This man, with multiple myeloma, developed grade 1 neurotoxicity, and had low vincristine $AUC_{0-\infty}$ and normal bilirubin, transaminases and GGT. The elevated SALP in this case was presumably due to bone involvement.

Although the mean total cumulative dose of vincristine administered to patients who displayed grade 2 or grade 3 neuropathy was comparable (Table 1), the mean single dose of the drug was higher in patients who developed grade 3 neuropathy whether all patients are considered (Table 1) or only those with raised SALP (Table 2). Since patients in these grades generally received a fixed maximum dose of 2 mg per injection, the dose difference on a milligram per square metre basis reflects the smaller mean size of the grade 3 patients (Table 1), who consequently received an average of 12% more of the drug per square metre of BSA than patients in grade 2.

Patients with lymphoma have been reported to have a higher incidence of neurotoxicity than patients

Table 2. Effect of Serum alkaline phosphatase and dose on vincristine AUC[a]

	No. of patients	VCR dose/m^2	AUC (ng/ml/h)
Grade 2 Normal SALP	11	1.18 ± 0.16	65.0 ± 39.4
Grade 2 Raised SALP	6	1.15 ± 0.10	98.5 ± 31.8
Grade 3 Raised SALP	5	1.3 ± 0.15[b]	197.4 ± 84.5[c]

[a] Results given as mean ± SD
[b] $P < 0.05$ between patients in grades 2 and 3
[c] $P = 0.08$ with elevated serum alkaline phosphatase

with leukaemia [8]. Of our six patients with grade 3 neurotoxicity, five had lymphoma and one, leukaemia. The difference in mean $AUC_{0-\infty}$ between all leukaemia and lymphoma patients as measured on the first occasion of drug administration failed to reach significance. SALP at this time was elevated in seven of 14 lymphoma patients and in three of the nine leukaemia patients, and returned to normal more rapidly in the latter group. At a total of 41 injections of vincristine administered to these lymphoma patients over the following 2 months, the SALP was raised on 15 occasions (36%) with or without elevation of other liver enzymes, whereas SALP was elevated at only 4 (10%) of the 40 injections given to patients with leukaemia in that period.

Patients received a variety of drugs in addition to vincristine. However, no particular combination of drugs was used more frequently in grade 3 patients than in those who developed lesser degrees of toxicity, and three patients received vincristine with prednisolone alone, a combination not recognised as potentiating neurotoxicity.

Discussion

It is generally argued that vincristine neurotoxicity is related to the total cumulative dose of the drug [1, 2, 9], but among our patients the grade 3 neurotoxicity group had received no higher total dose of the drug than patients with grade 2 toxicity (Table 1). However, the six patients who developed grade 3 neurotoxicity had a significantly greater exposure to vincristine as measured by the plasma vincristine $AUC_{0-\infty}$; this appeared to be related both to the mean individual dose of the drug (Tables 1 and 2) and to the elevation of SALP (Table 2). The higher incidence of vincristine neurotoxicity in lymphoma patients than in those with other malignancies was described by Watkins and Griffin in 1978, who found no significant increase in the incidence of overt liver disease in these patients [8].

In the present study, severe (grade 3) neurotoxicity appeared to affect lymphoma patients more frequently than leukaemia patients, and SALP was elevated in a higher percentage of lymphoma patients. We have shown in the accompanying paper that raised SALP results in a significantly prolonged elimination half-life and higher $AUC_{0-\infty}$ of vincristine than in patients with SALP within normal limits, and although the difference in plasma $AUC_{0-\infty}$ in lymphoma and leukaemia patients as measured at the beginning of treatment failed to reach significance, it is probable that the lymphoma patients had higher $AUC_{0-\infty}$ with subsequent therapy, as SALP was elevated more frequently and over a longer period in this group than in the leukaemia patients, who tended to have a more prompt response to treatment.

It is possible that elevated SALP in our patients was a reflection of bone involvement by the primary disease process, but examination of other liver enzymes and bilirubin suggest that in the majority of cases the SALP was hepatic in origin. Since vincristine is excreted primarily via the biliary route [4], our data suggest that the high $AUC_{0-\infty}$ is consistent with impaired elimination of the drug. It has long been recognised that vincristine is more toxic in patients with gross liver dysfunction, and recommendations have been made that in this situation the dosage of vincristine be reduced [3, 5 6]. In this study, if patients with elevated SALP within grades 2 and 3 are compared, the patients with grade 2 toxicity received 12% less of the drug (Table 2) per individual dose. Therefore we would suggest that raised SALP is an important parameter in devising a chemotherapeutic schedule for individual patients. A reduction of the calculated dose of vincristine in patients with elevated SALP, even when bilirubin and transaminase levels are within normal limits, may prevent the development of severe neurotoxicity.

Acknowledgements. We thank Mr Christopher Patterson for statistical help.

Z. R. Desai is in receipt of a Clinical Research Fellowship from the Royal Belfast Hospital for Sick Children.

References

1. Bradley WG, Lassman LP, Pearce GW, Walton JN (1970) The neuropathy of vincristine in man. J Neurol Sci 10: 107
2. Casey EB, Jeliffe AM, Le Quesne PM, Millett YL (1973) Vincristine neuropathy: clinical and electrophysiological observations. Brain 96: 69

3. Dorr RT, Fritz WL (1980) Cancer chemotherapy handbook. Henry Klimpton, London, p 687
4. Jackson DV, Castle MC, Bender RA (1978) Biliary excretion of vincristine. Clin Pharmacol Ther 24: 101
5. Sandler SG, Tobin W, Henderson ES (1969) Vincristine-induced neuropathy. Neurology 19: 367
6. Shaw RK, Bruner JA (1964) Clinical evaluation of vincristine. Cancer Chemother Rep 42: 45
7. Teale JD, Clough JM, Marks V (1977) Radioimmunoassay of vinblastine and vincristine. Br J Clin Pharmacol 4: 169
8. Watkins S, Griffin JP (1978) High incidence of vincristine-induced neuropathy in lymphomas. Br Med J 1: 610
9. Weiss HD, Walder MD, Wiernik PH (1974) Neurotoxicity of commonly used antineoplastic agents. N Engl J Med 19: 127

Received November 6, 1981/Accepted January 26, 1982