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Cancer Chemotherapy and Pharmacology

Letter to the Editor

Dear Sir,

Re: The Relationship Between Serum Alkaline Phosphatase and Vincristine Neuropathy

We have read with interest the two papers on vincristine pharmacokinetics in the recent edition of Cancer Chemotherapy and Pharmacology [1, 2]. These papers confirm the relationship between the dose of vincristine, the area under the curve and the development of neurotoxicity. They also demonstrate the wide inter-patient variability in vincristine pharmacokinetics.

An association is shown between raised serum alkaline phosphatase levels, decreased vincristine clearance, and the development of severe neurotoxicity. On this basis the authors suggest that vincristine neuropathy could be prevented by a reduction of the dose of vincristine in patients with elevated serum alkaline phosphatase levels, even when bilirubin and transaminase levels are normal. However, the majority of the patients with raised serum alkaline phosphatase levels in this study, and five out of the six patients who developed severe neuropathy had lymphoma. It has previously been reported by Watkins and Griffin [3] that patients with lymphoma have an increased incidence of vincristine induced neuropathy. In their study 61% of patients with lymphoma developed vincristine induced neuropathy compared with 14% of patients with other diagnoses. There was no relationship between the clinical, biochemical, or histological evidence of liver infiltration in these patients and the development of neuropathy. Alternative explanations for the high incidence of vincristine induced neuropathy in patients with lymphoma include the disease state itself or interactions with other drugs.

To establish the relationship between serum alkaline phosphatase and vincristine clearance and neuropathy, it will be necessary to repeat these studies in a group of patients with the same disease and receiving identical therapy. Based on the data presented in these papers we are not convinced that there is a real relationship between raised alkaline phosphatase levels and decreased vincristine clearance. The evidence is insufficient to recommend modification of vincristine dosage on this basis.

References

1. Desai ZR, Van den Berg HW, Bridges JM, Shanks RG (1982) Can severe vincristine neurotoxicity be prevented? Cancer Chemother Pharmacol 8: 211–214
2. Van den Berg HW, Desai ZR, Wilson R, Kennedy G, Bridges JM, Shanks RG (1982) The pharmacokinetics of vincristine in man. Cancer Chemother Pharmacol 8: 215–219
3. Watkins S, Griffin JP (1978) High incidence of vincristine-induced neuropathy in lymphomas. Br Med J 1: 610

Yours sincerely,

M. L. Slevin, V. J. Harvey and P. F. M. Wrigley. October 14, 1982. ICRF Department of Medical Oncology St Bartholomews' and Hackney Hospitals, London, EC1A 7BE, Great Britain

Letter to the Editor

Dear Sir,

Re: The Relationship Between Serum Alkaline Phosphatase and Vincristine Neuropathy

Thank you for the opportunity to answer Doctors Slevin, Harvey and Wrigley's critisms of our papers.

We are grateful for the opportunity to clarify some points in our articles and in particular to further comment on the influence of patients' disease state on the occurrence of vincristine-neurotoxicity.

Of our six patients with severe neurotoxicity five had lymphoma. However, there were nine other lymphoma patients who developed less severe neurotoxicity, and our thesis is that the higher incidence of severe neurotoxicity in the five lymphoma patients can be related to the higher AUC 0-00 caused by (1) reduced excretion via the bile as indicated by elevated S.A.L.P., and (2) higher single dose of VCR, largely determined by body surface area (usual dose of VCR in adults = 2 mg).

A problem in comparing our study with that of Watkins and Griffin [1] is the criteria by which neurotoxicity is judged. In Watkin's study patients were considered to be neurotoxic when they spontaneously complained of parasthesiae, with or without numbness, wasting or muscle weakness, and no attempt was made to grade the severity of the neuropathy. Our patients were classified as having severe (grade 3) neurotoxicity only when objective weakness and/or gait disabilities developed, and those with parasthesiae and/or reflex loss were categorised as grade 2.

We feel that we have shown that elevation of S.A.L.P. results in significantly higher plasma VCR AUC levels in patients with a variety of disorders (Van den Berg et al. – Table 3) and that the plasma VCR AUC is related to the grade of neurotoxicity (Fig. 1 – Desai et al. [2, 3]).

Insofar as we found elevation of S.A.L.P. more frequent and persistent in patients with lymphoma than in our other subjects, it was, therefore, not unexpected that a higher proportion of these lymphoma patients should develop severe neurotoxicity.

Three of the nine lymphoma patients in grade 2 had elevated S.A.L.P. levels at the time of VCR administration – we suggest that the reason they did not become severely neurotoxic was because they received approximately 0.2 mg less VCR per single dose than similar grade 3 patients. This would not be incompatible with the findings by Watkins and Griffin that "VCR induced neuropathy in patients with lymphoma *seemed to be not only disease-related but also dose-related, for all those who received more than 0.075 mg/kg in the first month developed neuropathy*" (our italics). They also found evidence of liver disease in a higher proportion of patients with lymphoma compared to patients with other malignant disease, although this difference was not significant.

Serum alkaline phosphatase is a simple and commonly performed test in patients undergoing chemotherapy. We feel that the evidence presented in these papers is sufficient grounds for accepting a raised S.A.L.P. as an index of impaired vincristine excretion and thus suggest that to reduce neurotoxicity the individual dose levels of the drug in these patients be modified.

References

1. Watkins S, Griffin JP (1978) High incidence of Vincristine induced neuropathy in lymphomas. Br Med J 1: 610
2. Desai ZR, Van Den Berg HW, Bridges J, Shanks RG (1982) Can severe Vincristine neurotoxicity be prevented? Cancer Chemother Pharmacol 8: 211
3. Van Den Berg HW, Desai ZR, Wilson R, Kennedy G, Bridges JM, Shanks RG (1982) The pharmacokinetics of Vincristine in man: reduced drug clearance associated with raised serum alkaline phosphatase and dose limited elimination. Cancer Chemother Pharmacol 8: 215

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