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Venlafaxine for treatment of chemotherapy-induced neuropathic pain

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ABSTRACT

Peripheral neuropathy (PN) is a common toxicity of frequently used chemotherapy agents. Pain in these patients may sometimes be a difficult problem to manage. To palliate symptoms we administered venlafaxine in our patients suffering from chemotherapy induced peripheral neuropathy. 12 patients with cancer, 10 of whom had unremitting painful chemotherapy-induced peripheral neuropathy and 2 had been suffering from severe paresthesia, numbness, walking difficulty without pain, used 75 mg venlafaxine extended release capsules for 8 weeks. Symptoms and adverse effects were evaluated before and after treatment. Median VAS score declined to 0 at the 8th week from its baseline median value of 45. This decline in pain severity was significant (P≤0.001). Other symptoms did not improve. As a side effect, drowsiness increased from 0% of cases reported baseline to 75% at the 8th week (P=0.041). Two patients gave up due to the toxicity. Venlafaxine seems to effectively improve chemotherapy induced neuropathic pain with moderate manageable toxicity. This observation warrants further study for comparison with other antidepressants. [Turk J Cancer 2004;34(3):110-113]

KEY WORDS:

Neuropathy, pain, chemotherapy, cancer

INTRODUCTION

Peripheral neuropathy (PN) is a common toxicity of frequently used chemotherapy agents such as platinum analogues, vincristine and taxanes. Peripheral neuropathy has been reported to occur in almost 50% to 90% of patients treated with cisplatin, up to 90% of patients treated with cisplatin plus paclitaxel, and almost half of the patients receiving vincristine (1-3). It is well recognized that chemotherapy-induced neuropathic pain sometimes may be severe and disabling, compromise quality of life, and may cause further compliance problems in cancer treatment. Therefore, early recognition of PN and effective treatment should be an important component of oncology patient care. Various drugs are used to treat chemotherapy-induced neuropathic pain. However, at present, there is no established, standard treatment to control neuropathic pain (1,4).

Venlafaxine hydrochloride is a structurally novel antidepressant that inhibits neuronal serotonin and norepinephrine re-uptake. There is anecdotal experience suggesting that venlafaxine was efficacious for decreasing neuropathic pain in diabetic patients (5-7). Venlafaxine has no anticholinergic effect and could have better compliance than other antidepressants. Based on these observations we used venlafaxine in our patients suffering from chemotherapy induced peripheral neuropathy. This report is the documentation of the first 12 patients.

PATIENTS AND METHODS

We administered venlafaxin HCl in 10 patients who had unremitting painful chemotherapy-induced peripheral neuropathy and 2 patients who had paresthesia, numbness, walking difficulty but no pain. None of the patients were receiving chemotherapy at the time of venlafaxin HCl administration. Six patients had stable disease, 4 patients were in remission, and 2 patients had progressive disease and were on supportive treatment. Before venlafaxin HCl was started, peripheral sensory neuropathy was demonstrated with physical examination and electromyography in all of them. During the first week of the treatment patients were administered daily 37.5 mg venlafaxine peroral and 75 mg extended release capsules (Efexor, Wyeth) daily thereafter. The patients were observed and symptoms were reevaluated after eight weeks of treatment. Before the treatment, all patients were evaluated with standard visual analogue scale (VAS) (a 100 mm horizontal line marked "no pain" at one end and "worst possible pain" at the other). Follow up assessment with VAS was done at 2nd, 4th and 8th weeks. Paresthesia and numbness were measured by the patients' judgment as mild, moderate or severe. Walking difficulty was evaluated to be present or not. On each visit the patients were asked about any possible adverse effects. Specially to evaluate toxicity, we asked patients to note whether they having any of the following symptoms during each week; sleepiness or sleeping difficulty, nausea, vomiting, drowsiness and dry mouth.

Statistical Analysis

Change in pain score and severity of toxicity over time was assessed by Friedman's test or Cochrane's Q where appropriate. A p value of < 0.05 was considered as significant. SPSS 10.0 was used for the statistical analysis.

RESULTS

Our study group consisted of 50% male, and the median age was 54. Causative chemotherapy regimens and diagnoses are detailed in table 1. Median VAS score declined to 0 at the 8th week from its baseline median value of 45 and this decline in pain severity was significant ($p<0.001$). Details are presented in table 2. VAS scores in time are also presented in figure 1. Other symptoms of neuropathy

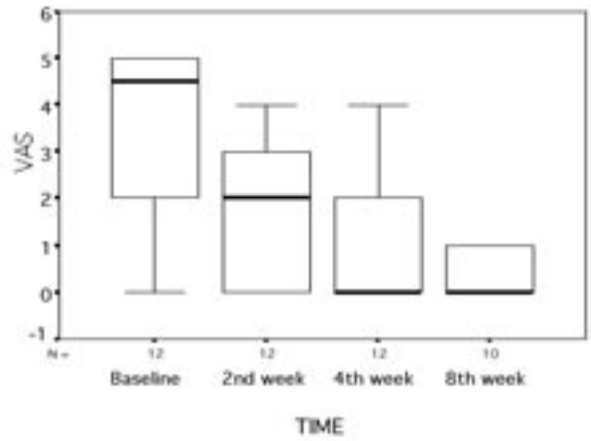

Fig 1. Pain intensity over time

however, did not show improvement. As a side effect, drowsiness increased from 0% at baseline, up to 75% at the 8th week (P=0.041). Two patients stopped taking venlafaxine after 4 weeks because of toxicity. The toxicities were moderate nausea and severe sleepiness. One of those patients was the one with paresthesia, numbness and walking trouble without pain. The symptoms did not improve under venlafaxine treatment in that patient. The other one had severe paresthesia, numbness and walking trouble with neuropathic pain. After 4 weeks the patient stopped taking venlafaxine because of mild emesis, severe sleepiness

Table 1
Demographics

	n(%)	Min, Median, Max
Age		25, 54, 68
Sex		
Male	6 (50.0)	
Female	6 (50.0)	
Chemotherapy Received		
Carboplatin-paclitaxel	6 (50.0)	
Cisplatine-etoposide	2 (16.7)	
Cisplatin-5FU	2 (16.7)	
Etoposide-cisplatin-5FU	1 (8.3)	
Vincristine	1 (8.3)	
Diagnosis		
Ovary carcinoma	6 (50.0)	
Nasopharynx carcinoma	2 (16.7)	
Lung carcinoma	2 (16.7)	
Hepatocellular carcinoma	1 (8.3)	
Medulloblastoma	1 (8.3)	

Table 2
Pain and toxicity change in time

	n(%)	Min, Median, Max	P value
Pain Score (VAS)			<0.001
Baseline		00, 45, 50	
2nd week		00, 20, 40	
4th week		00, 00, 40	
8th week		00, 00, 10	
Paresthesia and numbness*			0.100
Baseline		0.0, 2.0, 3.0	
8th week		0.0, 1.0, 3.0	
Difficulty in walking			0.171
Baseline	3 (25.0)		
8th week	5 (41.7)		
Nausea			1.000
Baseline	1 (8.3)		
8th week	2 (16.7)		
Drowsiness			0.041
Baseline	0 (0.0)		
8th week	9 (75.0)		

* Over an ordinal scale from 0 to 3

although neuropathic pain improved. No serious adverse effects were observed in other patients.

DISCUSSION

Little is known about the mechanism responsible for the development of chemotherapy induced neuropathy. It is predominantly a sensory or sensory-motor neuropathy but in some cases is accompanied by dysfunction of the autonomic nervous system. Neurotoxicity depends on the total cumulative dose and the type of drug used. The neurotoxic effects can appear immediately during or shortly after administration of the drug (8). These effects can also become evident with a long delay following cessation of chemotherapy (1,4). The recovery from symptoms is often incomplete and a long period of regeneration is required to restore function.

Various drugs are used to treat chemotherapy induced neuropathy. Data is very limited in cancer patients. Mostly drugs used to palliate symptoms of patients with diabetic neuropathy such as amitriptyline and gabapentin are also tried for cancer patients in daily practice (9,10). But there is no gold standard and adverse effects and compliance problems are common.

Venlafaxine HCl was dramatically effective in reducing the pain of chemotherapy induced neuropathy in our patients. However it did not help other symptoms of neuropathy. Our findings are compatible with other trials reporting response to venlafaxine in neuropathic pain of different etiologies. In a recent report, venlafaxine effectively reduced local neuropathic pain following breast cancer treatment (11). In this trial a slow crescendo increased dose from 18.75 mg to 75 mg was used. Pain intensity measured by VAS decreased from the median 49 to 0 in this trial which is very similar to our results. However in the trial of Tasmuth et al. (11), results were not statistically significant because the placebo response was very strong in the control group. In our trial we used a faster increased dose from 37.5 to 75 mg in one week. That did not cause major compliance problems in our patients.

Side effects were manageable and only 2 patients gave up because of adverse effects. This rate is slightly better than other commonly used drugs such as amitriptyline. In a report by Kalso et al. (12) 4 patients out of 15 withdrew amitriptyline because of side effects.

This report includes a very small number of cases and placebo effect could not be eliminated since there was no control group. However, results are hopeful and warrants further study for comparison with other antidepressants or placebo. Neuropathic symptoms other than pain does not improve with venlafaxine. Mechanisms of these symptoms and other drugs to palliate them should take major interest in further studies.

References

1. Armstrong T, Gilbert MR. The Female Patient: Chemotherapy induced peripheral neuropathy. Chatham, Ob/Gyn ed., 2002;27-30.
2. van der Hoop RG, van der Burg ME, ten Bokkel Huinink WW, et al. Incidence of neuropathy in 395 patients with ovarian cancer treated with or without cisplatin. Cancer 1990;66:1697-702.
3. Postma TJ, Vermorken JB, Liefting AJ, et al. Paclitaxel-induced neuropathy. Ann Oncol 1995;6:489-94.
4. Quasthoff S, Hartung HP. Chemotherapy-induced peripheral neuropathy. J Neurol 2002;249:9-17.
5. Kiayias JA, Vlachou DE, Lakka-Papadodima E. Venlafaxine HCl in the treatment of painful peripheral diabetic neuropathy. Diabetes Care 2000;23:699.
6. Davis JL, Smith RL. Painful peripheral diabetic neuropathy treated with venlafaxine HCl extended release capsules. Diabetes Care 1999;22:1909-10.
7. Lithner F. Venlafaxine in treatment of severe painful peripheral diabetic neuropathy. Diabetes Care 2000;23:1710-1.
8. LoMonaco M, Milone M, Batocchi AP, et al. Cisplatin neuropathy: clinical course and neurophysiological findings. J Neurol 1992;239:199-204.
9. Goodnick PJ. Use of antidepressants in treatment of comorbid diabetes mellitus and depression as well as in diabetic neuropathy. Ann Clin Psychiatry 2001;13:31-41.
10. Morello CM, Leckband SG, Stoner CP, et al. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med 1999;159:1931-7.
11. Tasmuth T, Hartel B, Kalso E. Venlafaxine in neuropathic pain following treatment of breast cancer. European J Pain 2002;6:17-24.
12. Kalso E, Tasmuth T, Neuvonen P. Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer. Pain 1996;64:293-302.