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Use of drugs for diabetic neuropathy in a group of Turkish diabetic patients

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ABSTRACT

Diabetic neuropathy is a disease of peripheral nerves that occurs in at least 50% of patients who have had diabetes for 25 years. A study to figure out the probable markers of early diabetic neuropathy was carried out. The major point to be investigated was the use of drugs for diabetic neuropathy either in the presence or absence of the diagnosis of diabetic neuropathy by a performed EMG. This research was carried out in 2002 in Afyon province, Turkey. A questionnaire of 36 questions was administered. A total of 204 diabetic patients were involved in the study where 72 (35.3%) were male and 132 (64.7%) were female. Only 3 of the patients were Type1 diabetes mellitus. The mean duration of diabetes mellitus was 6.92 ± 5.60 years. There were no patients using carbamazepine, metoclopramide or diphenhydramine, where one (0.5%) was using amitriptyline, 46 (22.7%) were using B1+B6 or combined vitamins, and only six (3%) were using gabapentin. Our study demonstrates the necessity of diagnosis and treatment of diabetic neuropathy.

Keywords. Diabetic neuropathy, treatment

INTRODUCTION

Diabetes mellitus is a common condition and diabetic neuropathy is a disease of peripheral nerves that occurs in at least 50 percent of patients who have had diabetes for 25 years (1). The syndrome includes symmetrical distal polyneuropathy, asymmetrical proximal motor neuropathy, focal asymmetrical mono- or polymononeuropathies, or autonomic neuropathy (1). The aetiology is uncertain. However, there are four hypotheses. These are; hyperglycemia-polyol-myoinositol hypothesis, microvascular hypothesis, structural changes at the node of Ranvier, and vasculitic neuropathy (1-4).

The clinical features, which are classified under four items, may present with a wide range of symptoms. The first, symmetrical distal polyneuropathies, includes pain and paresthesias usually in the lower extremities, decreased vibration and position sense, sensory ataxia, loss of ankle jerks, painful or painless foot ulceration, dissociated sensory loss of pain and temperature sensation, development of Charcot joints in the lower extremities, painless distension of the bladder and Argyll Robertson pupils. Sudden asymmetrical weakness of the pelvic musculature, and slowly progressive weakness of the proximal limb-girdle musculature are named as asymmetrical proximal motor neuropathies. The third, focal asymmetrical mono- or polymononeuropathies, includes paralysis of extraocular muscles, painful dysesthesias involving the lower thorax or upper abdominal wall, weakness of intercostal abdominal muscles, and involvement of nerves at risk of compression. The fourth item, autonomic neuropathies, include postural hypotension, resting tachycardia, silent myocardial infarction, atonic, painless distended bladder with overflow incontinence, male impotence with failure of ejaculation, reduced vaginal lubrication and dyspareunia in the female, incoordination of oesophageal peristalsis, gastric hypomobility, pylorospasm, intestinal hypomobility and constipation, intestinal incoordination and diarrhoea, anorectal dysfunction with incontinence, meiosis and failure of reaction to light- an Argyll Robertson-like pupil (1).

Progressive nerve degeneration is reflected in reduction in amplitude of compound muscle action potential and a progressive slowing of conduction velocity in multiple nerves (5). Therefore, in addition to a detailed neurological examination, electromyography is a necessary diagnostic test in the diagnosis of diabetic neuropathy.

Intensive diabetic therapy markedly delays or prevents the clinical manifestation of diabetic neuropathy (6). Maintenance of ideal body weight is another requirement. There are many drugs used for symptomatic treatment in diabetic neuropathy. Tricyclics such as amitriptyline, carbamazepine, and gabapentin are used for painful neuropathy. Intravenous lidocaine can be used for patients with intractable pain. Fluorohydrocortisone, indomethacin, a combination of diphenhydramine and cimetidine, and liquorice containing glycyrrhizic acid can be used for autonomic dysfunction and postural hypotension. Bethanechol can be used to promote detrussor contraction, and to accelerate delayed oesophageal emptying. Imipramine may prevent retrograde ejaculation, and impotence may be treated with Sildenafil citrate. Metoclopramide may be used for delayed gastric emptying, and tetracycline for diarrhoea (1,7).

The aim of this study was to define the drugs used for diabetic neuropathy in a primary care setting, and whether these drugs are used with or without EMG confirmation. Another objective of the study was to define whether there are drugs which are prescribed to diabetic patients but have no proven therapeutic value for diabetic neuropathy.

METHODS

This research was carried out in 2002 in Afyon, Turkey. Afyon has a central population of 150,000 and a total population of approximately 840,000. The subjects involved in the study were chosen from a diabetes mellitus centre working in cooperation with the Afyon General Hospital. The centre is working for the care of the voluntarily submitted diabetes mellitus patients who are the members of three of the four social security organizations in Turkey, and has been established two years ago. There are nearly five hundred patients who are being periodically examined in the centre.

The research group was composed of diabetes mellitus patients who had admitted to the diabetes centre during a three month period. All of the patients gave oral informed consent. The study included 204 patients.

Interviews were performed face-to-face by a family physician, who is a staff member of the centre, and a staff nurse who is trained in diabetes mellitus. A questionnaire of 36 questions was administered. The questionnaire inquired about age, level of education, occupation, addiction of tobacco, social security, type of diabetes mellitus, the drugs which are used for diabetes mellitus and the other drugs which are permanently used, duration of diabetes mellitus from the onset of disease, presence of other chronic diseases and their names, and 16 other questions to define the presence of diabetic neuropathy.

The drugs, which are used by the patients, are classified into nine groups as: oral anti-diabetics, insulin, amitriptyline, carbamazepine, metoclopramide, diphenhydramine, B1 and B6 vitamins, gabapentin, and as others to attain a better evaluation. The questions to define the presence of diabetic neuropathy are taken from the questions which Feldman et al. have used (8).

The results were stored and processed on a computer running SPSS version 10.0. Standard deviation was used for means.

RESULTS

In the study group, there were 72 (35.3%) men and 132 (64.7) women. The average age was 59.75 ± 21.57. The patients' levels of education were as follows: 26.9% were illiterates, 11.4% could read and write, 43.8 were primary school graduates, 5.5% were secondary school graduates, 6.0% were high school (lycee) graduates, and 6.5% were university graduates. The general distribution of social security types was as follows: 51% government employees' social security, 39.7% social security of self-employed professionals, 3.1% social security organization of employees, and 6.2% were using other social security organizations. There were 1.6% type 1 diabetes mellitus patients and the remaining 98.4% was type 2 diabetes mellitus. Only 12.7% had tobacco addiction in the study group.

There were only 27.1% of patients with no additional chronic disease, however 66.8% of them had a chronic disease. Hypertension was the most commonly seen additional chronic disease, which was present in 98 (48%) patients. The second and third most common chronic diseases were: 17 (8%) coronary heart disease patients and 14 (6%) hyperlipemia patients. The list of concomitant diseases is in Table1. The average duration of diabetes mellitus was 6.92 ± 5.60 years.

The answers to the questions administered for defining diabetic neuropathy were as follows: 27.1% had numbness in legs or feet, 30.5% had burning pain in legs or feet, 5.9% have feet too sensitive to touch, 34.7% get muscle cramps, 24.6% have prickling feeling in legs or feet, only 2% feel hurt when the bed covers touch their feet, 2.5% patients are not able to tell hot water from cold, 2.5% patients have open sores on their feet, 53% feel weak most of the time, 24.4% have worse symptoms at night, 27.4%'s legs are hurt when they walk, 74% can sense their feet while they walk, 22.7% have dry feet or skin with cracks, only 3.4% have performed EMG, 1% have been told that they have diabetic neuropathy, and 1% had an amputation.

There were 165 (80.9%) patients using oral antidiabetics, 37 (18.1%) using insulin, and 1 (0.5%) patient was using both insulin and oral antidiabetics. There were no patients using carbamazepine, metoclopramide or diphenhydramine, where 1(0.5%) was using amitriptyline, 46(22.7%) were using B1+B6 or combined vitamins, and only 6(3%) are using gabapentin (Table2). The list of the other drugs used by the patients is in Table 3.

DISCUSSION

It has been projected that 300 million individuals would be affected with diabetes by the year 2025 (9). The progression of diabetic retinopathy and nephropathy can be slowed or prevented with tight glucose and blood pressure control. Neuropathy remains a major problem causing significant impairment (10). It has been stated in various studies that diabetic patients have neuropathy in varying percentages such as: 7-25% in one year after the onset of disease, 50% 25 years after the onset of disease (11,12). In our study group, all of the patients have diabetes mellitus over a period of one year, and two patients have diabetes mellitus for more than 25 years. Diabetic neuropathy is a progressive process that starts from the onset of the disease. It may be either symptomatic or without the presence of any notable symptoms, which in case do not eliminate the presence of the disease. When we consider the percentages of the symptoms that are probably the markers of neuropathy, we have a wide range of percentages varying from 2% to 53%. It is not possible to state the certain number of patients with neuropathy without performing EMG on the patients. However there may be patients with some kind of presenting symptoms and yet not considered to have neuropathy on a performed EMG.

The major point that we should be interested in might be the evaluation of the presence of other possible causes of neuropathies. Forty-six patients (22.6%) in our study group are using either B1+B6 or combined vitamins. It has been shown in many studies that these vitamins are of no use in diabetic neuropathy, but only useful in the neuropathies due to the lack of these vitamins (11,12). Most physicians still prefer to prescribe vitamins in case of possible diabetic neuropathy symptoms.

There were no patients using carbamazepine, in the study group; indicating that probably carbamazepine is not a drug of choice for painful neuropathy by physicians, and on the other hand the patients were probably not evaluated for the presence of painful neuropathy, or the patients' perception of pain was so low that it was not mentioned as a complaint. The use of drugs such as amitriptyline and gabapentin are low as well, likely due to similar conditions. There are

several studies that have shown the effectiveness of both of the drugs in painful diabetic neuropathy with relief of pain varying from 50% to 67% (13,14). It has been stated that carbamazepine was the first of this class of drugs to be studied in clinical trials and has been longest in use for treatment of neuropathic pain (15). Antidepressants and anticonvulsants are used widespread for the relief of pain in diabetic neuropathy, with the expression that gabapentin is an expensive drug although it offers a symptomatic treatment with less adverse effects when compared to amitriptyline (13,16). In our study group there were only 7 (3.4%) patients using any of these three drugs, which is probably not compliant with the actual number of patients with painful diabetic neuropathy as we observe symptoms reaching to 53%, which indicates that approximately 100 patients could be receiving symptomatic treatment.

In conclusion, questions regarding diabetic neuropathy should be asked of the patients in order to define the presence of symptoms and drugs should be prescribed for relief of pain. In order to improve the life quality of the patients, a physician should prescribe drugs for neuropathy following the diagnosis of diabetic neuropathy.

REFERENCES

1. Gilroy J. Basic Neurology. (Third edition). McGraw-Hill, New York 2000, pp 523-525
2. Sima AA: Pathological definition and evaluation of diabetic neuropathy and clinical correlations. Can J Neurol Sci. 1994; 21: 13-17.
3. Vanderpump M, Taylor R. New concepts in diabetes mellitus II: complications. Postgrad Med J 1994; 70: 479-485.
4. Krendel DA, Costigan DA, Hopkins LC: Successful treatment of neuropathies in patients with diabetes mellitus. Arch Neurol 1995; 52: 1053-1061.
5. Bril V: Role of electrophysiological studies in diabetic neuropathy. Can J Neurol Sci. 1994; 2: 8-12.
6. The Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on development and progression of neuropathy. **:** Ann Intern Med 1995; 15;122: 561-568.
7. Çorapçıoğlu D. Tip 2 Diyabet kronik komplikasyonlarında tedavi prensipleri. In: Bağrıaçık N, Hatemi H, Yılmaz T, İlkova H, Satman İ, Dinçağ N (eds), Year Book of Turkish Diabetology 1999-2000. Türk Diyabet Vakfı ve Türk Diyabet Cemiyeti, İstanbul 2000, pp 219-222.
8. Feldman EL, Stevens MJ, Thomas PK, et al. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care 1994;17:1281-1289.
9. Pradeepa R, Deepa R, Mohan V. Epidemiology of diabetes in India--current perspective and future projections. J Indian Med Assoc 2002; 100:144-148.
10. Bailes BK. Diabetes mellitus and its chronic complications. AORN J 2002; 76: 266-276.
11. Güvener N. Diabetik Nöropati. In: İliçin G, Ünal S, Biberoğlu K, Akalın S, Süleymanlar G (eds), Temel İç Hastalıkları Cilt 2 Eki. Güneş Kitabevi, Ankara 1997, pp 21-25.
12. 12. Straub RH, Rokitzki L, Schumacher T, Hillmann C, Palitzsch KD, Scholmerich J. No evidence of deficiency of vitamins A, E, beta-carotene, B1, B2, B6, B12 and folate in neuropathic type 2 diabetic women. Int J Vitam Nutr Res 1993; 63: 239-240.
13. Ahmad M, Goucke C. Management strategies for the treatment of neuropathic pain in the elderly. Drugs Aging 2002; 19: 929-945.
14. Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Sahagian GA. Randomised double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Arch Intern Med 1999;159:1931-1937

15. Backonja MM. Use of anticonvulsants for the treatment of neuropathic pain. Neurology 2002; 59 (Suppl 2): S14-17.
16. Dallocchio C, Buffa C, Mazzarello P, Chiroli S. Gabapentin vs. amitriptyline in painful diabetic neuropathy: open label pilot study. J Pain Symptom Manage 2000; 20:280-285.

TABLE 1. ***List of concomitant diseases***

Concomitant diseases	No. of records	Percentage
Anaemia	2	0.9
Arthritis	7	3.4
Asthma	1	0.5
Benign Prostate Hyperplasia	1	0.5
Chronicle Obstructive Pulmonary Disease	2	0.9
Congestive Heart Failure	2	0.9
Coronary Artery Disease	17	8.3
Depression	1	0.5
Diabetic Neuropathy	2	0.9
Diabetic Nephropathy	1	0.5
Diabetic Retinopathy	2	0.9
Glaucoma	1	0.5
Goitre	2	0.9
Hepatitis B	1	0.5
Hyperlipemia	14	6.8
Hyperparathyroidism	1	0.5
Hypertension	98	48
Hyperthyroidism	1	0.5
Lumbago	1	0.5
Mental Retardation	1	0.5
Osteoporosis	6	2.9
Peptic Ulcer	3	1.4
Psychosis	1	0.5
Urolithiasis	1	0.5

TABLE 2. ***List of separately inquired drugs***

Separately inquired drugs	No. of records
Oral antidiabetics	165

Insulin	37
Amitriptyline	1
Carbamazepine	0
Metoclopramide	0
Diphenhydramine	0
Vitamins	46
Gabapentin	6

TABLE 3. Use of other drugs

Other Drugs	*No. of records*	*Drug*	*No. of records*
Acebutolol hydrochloride	1	Levothyroxine sodium	1
Acetylsalicylic acid	23	Losartan	3
Alendronic acid	3	Losartan+hydrochlorotyazide	3
Amiodarone	1	Metaprolol tartarate	4
Amlodipine	16	Mianserin hydrochloride	1
Atenolol	2	Montelucast	1
Atorvastatin	15	Opipramole hydrochloride	1
Bisoprolol fumarate	1	Perindopril+indapamide	3
Calcitriol	1	Perindopril terbutalamin	5
Calcium carbonate	4	Propylthiouracil	1
Digoxin	3	Pyribedil	2
Diltiazem hydrochloride	1	Quinapril hydrochloride	2
Dipyridamol	1	Quinapril+ hydrochlorothiazide	3
Doxazosin	4	Ramipril	5
Famotidine	1	Salbutamol sulfate	1
Fosinopryl sodium	1	Silasopyril	1
Fluvastatin	5	Spironolactone+hydrochlorotyazide	1
Gemfibrosil	1	Terbutaline sulfate	1
Gingko glycosides	11	Thioridazine hydrochloride	2
Haloperidol	1	Trandolopryl	3
Indapamide	5	Trimetazine hydrochloride	2
Irbesartan	1	Valsartan	3
Iron III hydroxate polymaltose	1	Valsartan+hydrochlorothiazide	4
Isosorbide-5-mononitrate	4	Verapamil hydrochloride	2
Lasidipyne	3	Warfarin sodium	1
Latanoprost	1		