Convulsions induced by donepezil

Donepezil, a centrally acting acetylcholinesterase inhibitor, has been recently introduced for the symptomatic relief of cognitive impairment in patients with mild to moderate Alzheimer's disease. Several adverse events thought to be related to donepezil have been reported so far, the most common ones being gastrointestinal disturbances due to cholinomimetic effects of donepezil.¹ Convulsions have not been reported for donepezil to date. We report on a patient with mild Alzheimer's disease who presented with convulsions during treatment with donepezil.

The patient was a highly educated, ApoE4 homozygous, 72 year old man, who was diagnosed with dementia of probable Alzheimer's type (NINCDS-ADRND criteria) 14 months previously. His medical history, with the exemption of non-familial dementia, was unremarkable and his only medication was 100 mg aspirin daily. His mini mental state examination score was 22 points. He was treated with 5 mg donepezil once daily for 2 weeks, and then 10 mg a day for 23 days when he was admitted due to convulsions. The patient was unconscious for 40 minutes with urinary incontinence and bitten tongue. Blood analyses were normal. A contrast brain CT showed a mild degree of cortical atrophy with no structural lesions. EEG showed mild and diffuse neuronal dysfunction with the absence of grafoelements indicative of epilepsy. Donepezil was discontinued and no other therapy was instituted. Six weeks later 5 mg donepezil once daily was restarted. On day 52 of donepezil treatment the patient's caregiver had reported loss of consciousness and convulsions in our patient. The donepezil was discontinued and 100 mg indomethacin a day was prescribed. For the subsequent 8 months the patient has been convulsion free and his current mini mental state examination score is 19.

Convulsions in Alzheimer's disease are rare until late in the illness, when up to 5% of patients reportedly have infrequent seizures.² We think that convulsions reported in our patient could be due to donepezil. It has already reported that some centrally acting cholinesterase inhibitors—that is, tacrine, velnacrine, and physostigmine³⁻⁵ might induce convulsions in patients with Alzheimer's disease. The mechanism of convulsive action of acetylcholinesterase inhibitors is not clear. As donepezil seems a useful drug in some of the carefully selected patients with mild to moderate dementia of Alzheimer's type we think that this report will extend our knowledge of donepezil's safety profile.

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- 1 Rogers SL, Farlow MR, Doody RS, *et al.* A 24-week, double blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology* 1998;50:136-45.
- 2 Adams RD, Victor M, Ropper AH. *Principles of neurology*, 6th ed. New York: McGraw-Hill, 1997.
- 3 Lebert F, Hasenbroekx C, Pasquier F, *et al.* Convulsive effects of tacrine. *Lancet* 1996;347:1339-40.
- 4 Cutler NR, Sramek JJ, Murphy MF, *et al.* Implications of the study population in the early

evaluation of anticholinesterase inhibitors for Alzheimer's disease. *Ann Pharmacother* 1992;26:1118-22.

- 5 Taylor P. Anticholinesterase agents. In: Hardman JG, Limbird LE, Molinoff PB, *et al.*, eds. *Goodman and Gilman's the pharmacological basis of therapeutics*, 9th ed. New York: McGraw Hill, 1996:161-76.

Severe toxic neuropathy due to fibrates

The main adverse effects of lipid lowering agents in the fibrate family involve the gut, the skin, the liver, the blood, and the muscular system. Some of these complications are more frequent when renal failure exists.¹ Here we report a case of neuropathy secondary to long term treatment with fenofibrate in a patient without renal failure taking recommended doses.

A 60 year old man was seen in September 1996 complaining of leg pain for 6 months. His relevant medical history included coronary artery disease treated for 10 years with 6 mg molsidomine/ day and 60 mg isosorbide dinitrate/ day, high blood pressure and hyperlipidaemia treated respectively with 100 mg atenolol/ day and 200 mg fenofibrate/day for the past 5 years. He complained of paresthesias along the posterior aspect of both thighs, later complicated by progressive muscle weakness.

The physical examination disclosed a patient incapable of standing on his toes or heels. No proximal muscle weakness was present. The deep tendon reflexes were reduced in all limbs. There was no sensory loss to light touch, vibration sense, pain perception, and joint position sense. There was no disturbance of sphincter control or postural fainting and no impairment of potency to suggest dysautonomia. The rest of the physical examination was within normal limits. The EMG suggested an axonal sensorimotor neuropathy with reduced amplitude of nerve action potentials without any significant slowing of conduction velocity. There were spontaneous fibrillations in the right tibial anterior muscle. The complete blood cell count, erythrocyte sedimentation rate, fibrinogen, C reactive protein, and serum protein electrophoresis were normal. Muscle enzymes were normal and immunological studies (antinuclear factor, serum and urinary immunoelectrophoresis, circulating immune complexes, serum complement, ANCA) were negative. Antiparaneoplastic antibodies and antiglycolipid antibodies were not detected. Two CSF examinations were performed: the CSF contained 1 white cell/mm³, the protein concentration was 65 mg/dl, the glucose concentration was 2.5 mmol/l. Accessory salivary gland biopsy eliminated amyloidosis, sarcoidosis, and Gougerot-Sjögren's syndrome. Nerve biopsy confirmed axonal disease and disclosed a focal perivascular inflammatory lymphocytic infiltrate without vasculitis. No ultrastructural study was performed. An adverse drug effect was suggested in May 1997 and fenofibrate was discontinued. Three months later the patient indicated an improvement in the distance he could walk. In December 1997, he no longer complained of myalgia. Improvement in motor function was apparent; the patient could now stand on his toes and heels without help.

Axonal sensorimotor neuropathy was confirmed in this case by electrophysiological and histological findings. Other common causes of axonal neuropathy were excluded and a toxic cause was considered.² Because

the patient had been receiving all of his medications well before the beginning of the clinical manifestations, there was no chronological argument targeting any one drug in particular. However, a review of the literature suggested fenofibrate as the causative agent as neuropathies have been described after treatment with clofibrate and bezafibrate.³⁻⁵ In addition, none of the other drugs he was taking have been associated with neuropathy. The role of fenofibrate was confirmed by regression of the symptoms after discontinuation of this drug without the addition of any other treatment. There are no previous reports of histological findings in neuropathy due to fibrates. The delay between initial treatment with fenofibrate and the appearance of the symptoms as well as the time required for them to regress, suggest a cumulative toxic effect but no other predisposing risk factor such as high dosage or renal failure was present.

In conclusion, fibrates can be responsible for neuropathies even when given in approved doses and in the absence of renal failure.

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- 1 Kondel LC, Talbert RI. Adverse effects of hypolipidaemic drugs. *Med Toxicol* 1987;2:10-32.
- 2 McLeod JG. Investigation of peripheral neuropathy. *J Neurol Neurosurg Psychiatry* 1995;58:274-83.
- 3 Gabriel R, Pearce JMS. Clofibrate induced myopathy and neuropathy. *Lancet* 1976;ii:906.
- 4 Argov O, Mastaglia FL. Drug-induced peripheral neuropathy. *BMJ* 1979;1:663-6.
- 5 Ellis CJ, Wallis WE, Caruana M. Peripheral neuropathy with bezafibrate. *BMJ* 1994;309:929.

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Macs with multiple sclerosis

Rothwell and Charlton¹ have suggested that Scottish ancestry is associated with an increased susceptibility to multiple sclerosis. They make the novel observation that a higher than expected proportion of patients with multiple sclerosis had Scottish surnames as defined by the prefix Mc or Mac. They quote that the percentage of the population in the Highlands and Islands with a surname of Mc or Mac is 22.6%. They then suggest that this is the percentage with Mc or Mac in Orkney and Shetland but these islands are not part of the Highlands and Islands. In Orkney and Shetland, in fact, only 3.5% of the population have a surname beginning with Mc or Mac, which is much lower than the percentage in north east Scotland—namely 7.5%.

Rothwell and Charlton do make the point, however, that an increase in the proportion of surnames prefixed with Mc or Mac with latitude within Scotland is not associated with an increase in the prevalence of multiple sclerosis.