Letters to the Editor

Ropinirole (SK and F 101468) in the treatment of Parkinson's disease

Ropinirole (4-[2-((diethylamino)ethyl)-1,3-dihydro-2H-indol-3-yl]amine), a selective D_2 agonist has been shown to have anti-Parkinsonian effects at doses between 0.6 mg twice a day and 2 mg twice a day in an open inpatient study. We report the results of a further open-label study in fourteen patients with idiopathic Parkinson's disease.

Participating in the study were seven patients with presumed Parkinson's disease (mean age 56.5 years, disease duration 4 years and mean Hoehn and Yahr Stage II) and seven patients with disabling levodopa-induced on-off oscillations (median age 66 years, disease duration 10 years and duration of levodopa treatment 4 years, daily levodopa dose 750 mg, median duration of disabling oscillations 1 year, mean Hoehn and Yahr stage when "off" III and when "on" II). Four of the patients treated with levodopa had severe idiosyncratic chorea and one patient had biphasic dyskinesias. Three patients were also receiving anticholinergic medication, three were taking L-deprenyl (selegiline); none of the patients had a history of psychiatric disorder or evidence of hepatic, renal or cardiovascular dysfunction.

Both groups were initially treated with 0.6 mg of ropinirole twice daily for one week. The dose was increased to 1 mg twice daily for the second week and further weekly increments of 1 mg twice daily to a maximum of 7 mg twice a day over an eight week period. If adverse reactions developed, patients continued on the previously tolerated dose for another week. In cases where less than 1 mg twice a day was made; if gastrointestinal side-effects or symptomatic orthostatic hypotension re-occurred, despite modification of ropinirole dosing, domperidone 20 mg twice daily was given in four cases, for the remaining trial period. If idosyncratic dyskinesias increased in the oscillating patients levodopa was concomitantly reduced. After each dose increase, patients were observed for standing and lying blood pressure and blood pressure were measured at baseline and then hourly for the following 6 hours.

Motor assessments were carried out on the day of dose increase before and two hours after dosing, using the Modified Webster scale and tapping and walking tests. Assessment of motor fluctuations were carried out using self-scoring diaries to record a percentage daily "on" time and severity of dyskinesias.

Of the previously untreated patients two showed improvement comparable with that seen with oral levodopa at doses of 12 mg and 6 mg a day respectively. The first patient had a Webster score which reduced from 14 to 10, a 44% increase in the number of finger taps and a 40% decrease in walking time. The second patient had an increase in the number of finger taps, but could not increase the dose further because of nausea despite domperidone. Two of the de novo patients dropped out before the treatment period was finished, one because of the absence of the second week and by further weekly increases of levodopa, one following symptomatic orthostatic hypotension after a single dose of 1 mg. Three patients had no response to the drug at daily doses of 10, 12 and 14 mg respectively. However, two of these patients subsequently failed to respond to apomorphine or chronic levodopa treatment raising the possibility of a diagnosis other than idiopathic Parkinson's disease.

Four of the seven patients with levodopa-induced on-off oscillations showed a worthwhile clinical response with a reduction of mean "off" hours per day from 3.9 (1-9.6-5) to 1.3 (0-4.2-1.2). A dose needed to obtain an optimal response was 5.8 mg per day (3.2-8 mg), but beneficial effects began at 2.3 mg daily (1.2-4). The duration and intensity of idosyncratic dyskinesias increased in three patients, but diminished to even below baseline level by a mean reduction of 15% of the total daily levodopa dose in two patients. Two patients treated with up to 10 mg a day in addition to their usual levodopa dose did not improve. In one, the mean "off" hours remained unaffected, while the other experienced prolonged episodes of disabling biphasic dyskinesias. One patient developed intolerable drooling and somnolence at 2 mg a day and discontinued the study. The second patient had a normal and symptomatic orthostatic hypotension controlled by domperidone. Laboratory test results, biochemistry and tests were normal throughout the eight week period.

We conclude that ropinirole has anti-Parkinsonian effect and that the optimum dose range for most patients may be 4-6 mg a day. Adverse reactions, limited to those seen with other dopamine receptor agonists and can be reduced by the use of domperidone and possibly more gradual dose increments than occurred in this trial. We would recommend in future that oral levodopa and subcutaneous apomorphine tests are carried out on previously untreated patients with Parkinson's syndrome before the assessment of a new dopaminergic agonist, as to exclude as far as possible patients with multi-system degeneration unresponsive to this group of drugs.


Cardiovascular autonomic function tests are three Valsalva and slow deep breaths necessary or will singles do?

In the assessment of autonomic neuropathy, two widely used tests of cardiovascular autonomic function assess the heart rate response to three consecutive Valsalva manoeuvres and to six consecutive deep breaths. We aimed to see whether the response to a single Valsalva manoeuvre was significantly different from that from the average of three and whether the response to a single deep breath was significantly different from that from the average of six deep breaths.

The study group consisted of diabetic patients, 25 male and 11 female, 15 insulin treated, mean age 54 years (range 30-82), mean duration of diabetes 17.4 years (range 3 months-51 years). All had symptoms which may have been due to diabetic neuropathy.

They underwent heart rate monitoring using a computer-assisted system for the collection and analysis of heart rate data for cardiovascular autonomic function tests (RR Medical Electronics, Letchworth, UK). A Valsalva manoeuvre was performed by the patient blowing into the tube of a sphygmomanometer and sustaining a pressure of 40 mm Hg for 15 seconds while the R-R interval was recorded, the result being expressed as the Valsalva ratio: the longest R-R interval during the manoeuvre. All the patients performed the Valsalva manoeuvre properly and, as far as could be ascertained, achieved an intrathoracic pressure which was adequately raised. Heart rate variability during deep breaths was also calculated by the patient resting quietly and breathing deeply in over five seconds and...
then out for over five seconds whilst recording the R-R interval. The maximum and minimum R-R intervals were converted to heart rates, with the difference between them being the heart rate variability.

Three Valsalva manoeuvres were performed consecutively for each patient as described by Ewing and the Valsalva ratio was calculated for each. The Valsalva ratio from the first manoeuvre was compared with the mean-of-three. Heart rate variability was obtained from a mean-of-six deep breaths and from a single deep breath performed in random order.

Twenty-three of 17 patients with a mean-of-three-derived Valsalva ratio less than 1:21 (abnormal according to previous criteria) had a single Valsalva ratio less than 1:21. Seventeen of the 19 patients with a mean-of-six-derived Valsalva ratio greater than 1:21 had a single Valsalva ratio greater than 1:21. Twenty-three of 24 patients with a mean-of-six-derived heart rate variability less than, or equal to, 10 beats per minute (abnormal according to previous criteria) also had a single breath-derived heart rate variability less than, or equal to, 10 beats per minute. Nine of 10 patients with mean-of-six-derived heart rate variability greater than 10 beats per minute (normal or borderline according to previous criteria) also had a single breath-derived heart rate variability greater than 10 beats per minute.

This single Valsalva ratio finds the same result as a mean-of-three-derived Valsalva ratio with a sensitivity of 16/17 (94%) and a specificity of 17/19 (89%). Similarly, a single breath-derived ratio gives the same result as a mean-of-six-derived heart rate variability with a sensitivity of 23/24 (96%) and a specificity of 9/12 (75%). The Valsalva data were further analysed by estimating the confidence interval of the three Valsalva ratio readings from each patient. In keeping with the hypothesis that one Valsalva manoeuvre is sufficient, within-subject variance (0.11) was extremely small in comparison to between-subject variance (4:17).

The mean (SEM) time taken to do a single Valsalva ratio and a single breath heart rate variability (5:70 (0.74) minutes) was significantly less than that to do three Valsalva ratios and derive the heart rate variability from a mean of six breaths (14:38 (0.68) minutes, p < 0.0001).

Benign relapsing meningomyelitis

Myelitis and encephalomyelitis are relatively common both as monophasic or relapsing diseases. Investigation of an infectious cause is essential at the first presentation particularly if the cerebrospinal fluid has inflammatory features. Multiple sclerosis would be the most common diagnosis in those cases with a relapsing course.

We describe a young man who presented at 10, 13 and 16 years with three stereotyped attacks of meningomyelitis. Aetiological investigations were negative and we found only one report on three similar cases in the literature.

The boy was born in 1972, lived in Paris and returned to Portugal when he was eight. He currently lives in a small village working as a shoemaker.

In December 1983 he presented with fever, vomiting and headache which was followed by drowsiness and an inability to walk. When first seen two weeks later he appeared to be very sleepy but cooperative. Neurological examination revealed a flaccid paraparesis, sensory loss from the T8 level, urinary retention and almost absent tendon reflexes with extensor plantar responses. He was febrile (40C) and the cerebrospinal fluid contained 0.70 g/l protein and 2.75 mmol/l glucose. Four days later he was paraplegic with a higher sensory level (T4) and some respiratory distress. He was treated with dexamethasone and to cover the possibility of tuberculosis infection, rifampicin and streptomycin was started. After two weeks there was gradual recovery of motor, bladder and sensory functions which was complete by four months.

In December 1985 he developed a second episode. After a short period of fever and myalgia he developed a flaccid and areflexic paraparesis with a sensory loss below T8, urinary retention and bilateral extensor plantar responses. Three days later he progressed to a tetraplegia with increasing respiratory difficulty and the neurological examination was entirely normal. During this admission he was treated with sulphasalazine and trimethoprim for an intercurrent urinary tract infection.

His third episode occurred in December 1988 when he presented with pyrexia, headache and drowsiness. When aroused he was confused and aggressive. Over the next few days a flaccid and areflexic tetraparesis again developed. There was no evidence of a sensory level but proprionic acid was impaired and urinary retention was present. The cerebrospinal fluid contained 64 X 10^6 cells/l (lymphocytes), 2.74 mmol/l glucose and 0.92 g/l protein. During recovery a spastic paraparesis emerged and a cerebellar syndrome with nystagmus, scanning speech, and bilateral dysmetria was noted. A few months later the neurological examination was again normal. During this admission he was treated with dexamethasone and ceftriaxone to cover the possibility of Lyme disease.

During the three admissions the following investigations were normal or indication of infection: serum: red and white cell blood counts, haematocrit, erythrocyte sedimentation rate, electrolytes, urea nitrogen, creatinine, glucose, liver and kidney function tests, rheumatoid factor, antinuclear antibodies and LE-cell tests, serum complement and immune complex levels; VDRL and FTA-ABS tests, Wright (Brucella serology, agglutination test) Rose Bengal Plate test, Widal and Weil-Felix reactions, Paul-Bunnel test, serological tests for hepatitis B surface antigen and antibody and human immunodeficiency virus (HIV1 and HIV2), CMV IgG and IgM complement fixation titre, complement fixation titres for other viruses (herpesvirus, adenovirus, parainfluenzae 1 and 3, measles, and respiratory syncytial virus) and convalescent periods, indirect immunofluorescent test for Lyme disease (Institut Pasteur, Paris) and serological tests for toxoplasma and bartonella antibodies.

In the CSF there were normal or negative results for: microscopic examination of stained specimens (Gram) and cultures for acid-fast bacilli, bacteria and fungi, and cryptococcus, complement fixation titres for virus in acute and convalescent periods,
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