CLINICAL RESEARCH

Improved control of brittle Parkinsonism by separate administration of levodopa and benserazide

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Abstract

A 59-year-old woman who had had Parkinsonism for 12 years was treated with orphenadrine and levodopa combined with a dopa carboxylase inhibitor. The initial response was good, but after several years' treatment her condition alternated between severe bradykinesia and incapacitating, violent chorea, interspersed with short periods of mobility. A new regimen was devised, using levodopa in capsules of 40 mg and benserazide in separate capsules of 10 or 25 mg. Levodopa 40 mg was taken at intervals of half to two and a half hours, usually with benserazide 10 mg but alone in the late morning and evening. Additional benserazide was required one hour after lunch. With this regimen her condition was greatly improved, though she still had an abnormal gait and spells of bradykinesia and chorea.

Separate, frequent small doses of levodopa and benserazide may give better control of brittle Parkinsonism.

Introduction

The combination of levodopa with a dopa decarboxylase inhibitor such as benserazide has improved the management of Parkinsonism by enabling optimum doses of levodopa to be used with fewer side effects. After several years' successful treatment this control may deteriorate, when the patient experiences rapid swings from a state of severe Parkinsonism to a state of incapacitating chorea. Control may often be re-established by "fine tuning" of the drug regimen by giving more frequent doses of small amounts of the fixed-ratio combination, but even finer tuning is required in certain patients.

The patient

The patient was a woman aged 59 years weighing 54 kg who had had Parkinsonism for 12 years. Levodopa combined with decarboxylase inhibitor had been used for the first time five years after the onset of the disease. The initial response had been good, but chorea started to appear intermittently after a few months and after three years of treatment she was admitted to another neurological unit for a trial of combined treatment with bromocriptine, which was unsuccessful.

Subsequently she took a combination of orphenadrine 300 mg and Sinemet-110 (levodopa and carbidopa monohydrate) five tablets daily in divided doses. She usually had one satisfactory period each day from 0800 to 0900, but thereafter her condition would alternate rapidly and unpredictably between severe bradykinesia of sudden onset and incapacitating and violent chorea, interspersed with short spells of mobility. During the phases of bradykinesia she was unable to move her limbs and could barely speak. During the phases of chorea the movements were so violent that she had to be left lying on her back surrounded by pillows for her own protection, either in bed or on the floor; this could persist for two or three hours. In the short spells of mobility she could write, feed herself, and walk, albeit with a bizarre athetoid movement of the right leg and trunk. A period of inpatient treatment with Madopar 62.5 and bromocriptine (levodopa and benserazide hydrochloride) did not improve her symptoms.

Treatment

Benserazide was made up in separate capsules of 10 or 25 mg and levodopa in capsules of 40 mg. Several different regimens were tried. Firstly, benserazide was given in three doses of 50 mg a day, which in most patients appears to provide adequate blocking of peripheral decarboxylase. The dose of levodopa was cautiously and progressively increased to a total of 40 mg every two hours, giving 400 mg per 24 hours. Though this was more than twice the dose of levodopa that had previously caused gross chorea, few short periods of partial mobility occurred and the episodes of chorea stopped; most of the time she was in a severely rigid and bradykinetic state, even when the doses of levodopa and benserazide coincided.

Modification of this regimen had interesting results, repeated on many occasions. The important features were that levodopa in 40 mg doses given by mouth without benserazide was relatively ineffective irrespective of the total amount of benserazide (150 mg) administered over 24 hours. The bradykinetic spells previously common immediately after lunch were consistently ameliorated by increasing the dose of benserazide immediately before or immediately after lunch. The

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	0700				1200				1800				2400			
Time of dose	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Levodopa 40 mg	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Benserazide 10mg	1	1*	1		1*	2	1	1	1	1*	1	1				
Orphenadrine 50mg			2				2				2					

Regimen established to provide smoothest effect, showing number of capsules of each drug taken. A total of 520 mg levodopa and 120 mg benserazide a day was required.

*Mealtime.

effect of a dose of levodopa could be enhanced by doubling the dose of benserazide given with it from 10 to 20 mg, but separating the doses by more than 45-60 minutes usually abolished this effect.

By a process of trial and error the regimen shown in the figure was adopted. Levodopa was taken in doses of 40 mg at intervals of half an hour to two and a half hours during the day. Most doses were accompanied by 10 mg benserazide. Levodopa was given alone in the late morning and on retiring, since combining it with benserazide at these times caused chorea. Additional benserazide was required one hour after lunch to avoid an akinetic spell in the afternoon. Orphenadrine 50 mg was given twice daily, and the timing of its doses did not appear to be critical. With this regimen the patient could take daily walks with her husband and help with shopping for the first time in two and a half years. Her gait remained highly abnormal, with bizarre athetoid movements of the right leg. Bradykinetic spells occupied about three hours of each waking day, usually in the early morning, after lunch, and in the early evening. Appreciable chorea, during which she could remain in her chair, occupied about two hours a day, mainly around 1130-1230 and 1630-1730, and could be provoked by delaying a meal.

Discussion

This patient's performance was greatly improved over a period of nine months by treating her with frequent small doses of benserazide and levodopa given separately. We observed that levodopa in the doses used was ineffective if given by mouth more than one hour before or one hour after a dose of benserazide irrespective of the degree of decarboxylase block in the peripheral tissues. Furthermore, coadministration of the same dose of levodopa with benserazide led to chorea, suggesting overdosage of levodopa.

The observations made in this patient are consistent with the view that the "on-off" syndrome is related to changes in levodopa concentrations and that the syndrome may be managed better by giving frequent small doses of levodopa and benserazide. Two clear factors emerge from this case report. Firstly, blocking local gut decarboxylase activity at the time of administration of levodopa is more important than peripheral blockade, and, secondly, absorption of levodopa is affected by food intake. This might result from stimulation of local gut decarboxylase activity or from changes in the rate of gastric emptying.

The four to one ratio of levodopa to benserazide appears to be appropriate for general use, and patients with brittle disease might be managed by frequent administration of Madopar 62.5 (50 mg levodopa and 12.5 mg benserazide) with small doses of levodopa or benserazide added to the regimen to obtain the "fine tuning" required. Further work is planned to validate these findings.

(Accepted 14 January 1982)

Nicotine concentrations in urine and saliva of smokers and non-smokers

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Abstract

Nicotine concentrations were measured in saliva and urine samples collected from 82 smokers and 56 non-smokers after a morning at work. Each subject answered a series of questions related to their recent intentional or passive exposure to tobacco smoke.

All non-smokers had measurable amounts of nicotine in both saliva and urine. Those non-smokers who reported recent exposure to tobacco smoke had significantly higher nicotine concentrations ($p < 0.001$) than those who had not been exposed; their concentrations overlapped those of smokers who had smoked up to three cigarettes before sampling. Among the cigarette smokers, the number of cigarettes smoked before sampling had the greatest influence on nicotine concentrations ($r = 0.62$ for saliva and $r = 0.51$ for urine). Neither the nicotine yield of cigarettes nor the self-reported degree of

inhalation had any significant effect on nicotine concentrations.

Introduction

For many years estimates of exposure to tobacco smoke have depended on information from questionnaires. More recently biochemical indices of smoke inhalation have been introduced¹⁻³; nicotine, being specific to tobacco smoke, provides a direct measure of smoke intake. Although peak nicotine concentrations just after smoking have a short half-life in blood, there is some accumulation and trough concentrations tend to build-up during the day.⁴ This suggests that salivary and urinary nicotine concentrations could be a useful non-invasive measure of exposure to tobacco smoke. Previous studies have concentrated on quantifying smoke intake among cigarette smokers, but smokers are not the only people to be exposed to smoke. Non-smokers may passively inhale other people's tobacco smoke and so develop small airway disease⁵ or be at greater risk from lung cancer compared with non-exposed non-smokers.⁶

We have compared the intake of tobacco smoke of smokers with that of two groups of non-smokers. One group had been exposed to smokers during their normal morning's work, the other had not. Exposure to tobacco smoke was assessed by a questionnaire and by measuring nicotine concentrations in saliva and urine.

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