Br. J. clin. Pharmac. (1984), **18**, 959–962

Domperidone and levodopa in Parkinson's disease

J. S. SHINDLER, G. T. FINNERTY, K. TOWLSON, A. L. DOLAN, C. L. DAVIES[1] & J. D. PARKES
The University Department of Neurology, Kings College Hospital and Institute of Psychiatry, London SE5 and [1]MRC Unit of Clinical Pharmacology, Radcliffe Infirmary, Oxford

To study the absorption of levodopa and interaction with the extracerebral dopamine antagonist domperidone, 15 patients with idiopathic Parkinson's disease were given levodopa 500 mg p.o., alone, and with domperidone pre-treatment. Domperidone pre-treatment (10, 20, 40 mg, p.o., i.v. or i.m.) caused a mean 12% increase in peak plasma levodopa concentration, which occurred a mean of 10 min earlier than when levodopa was given alone. Parkinsonian disability scores were improved and peak clinical response occurred 16 min earlier with domperidone than without. Domperidone slightly increases the immediate bioavailability (over 4 h) and anti-parkinsonian response to a given dose of levodopa.

Keywords domperidone levodopa Parkinson's disease

Introduction

Dopamine stimulates gastric dopamine receptors (Schuurkes & van Nueten, 1981), and levodopa causes gastric stasis for 1–2 h. The main site of absorption of levodopa is the small intestine, and gastric stasis will delay the response to an oral dose of levodopa in Parkinson's disease (Bianchine *et al.*, 1971; Wade *et al.*, 1974). The clinical response to levodopa depends on many different factors, amongst the most important of which are differences in bioavailability of levodopa in different subjects and at different ages, due, at least partly, to gastric and bowel effects.

Delayed gastric emptying due to levodopa can be prevented by domperidone. Domperidone has been shown to block stomach wall dopamine receptors *in vitro* (van Nueten *et al.*, 1978). In addition, domperidone may prevent other peripheral effects of levodopa, in particular nausea and vomiting. However, since domperidone in normal doses does not cross the blood brain barrier (Laduron & Leysen, 1979), it should not impair the central therapeutic effect of levodopa in Parkinson's disease.

Previous studies have shown that metoclopramide in Parkinson's disease, although preventing vomiting and increasing the bioavailability of levodopa, slightly impairs its effectiveness (Mearrick *et al.*, 1974; Schachter *et al.*, 1980).

Methods

Fifteen patients, eight male and seven female, aged 57–75 years (mean = 63.7) with idiopathic Parkinson's disease of 5–18 years' duration were studied. All were responsive to, and established on, levodopa therapy. All subjects were investigated twice, at the same time of the day, with a 1–4 week interval between trials. Levodopa was stopped for 18 h before the trial, but other drugs and anti-parkinsonian medication were continued unchanged. No patient was taking selegiline.

Subjects were given levodopa 500 mg (Brocadopa 250 mg capsules) preceded (30 min) by domperidone 10–40 mg p.o., i.v. or i.m. on the first occasion; and levodopa alone on the second. This sequence (rather than random order) was used in an attempt to identify patients intolerant of levodopa despite peri-

pheral blockade by domperidone, and exclude them from further studies. In the event, all subjects tolerated both single and combined therapy without serious adverse effects.

The following observations were made at 15–30 min intervals before and for 4 h after levodopa was given: (i) Parkinsonian disability score (KCH rating scale: 0 = normal mobility, 12 = total disability; response determined by percentage of change from mean of scores from between −30 and 0 min). (ii) Nausea and vomiting (linear visual analogue self-rating scale). (iii) Supine and erect blood pressure, radial pulse. (iv) Blood samples were taken for levodopa analysis (high performance liquid chromatography coupled with electrochemical detection: LC-EC: MRC Unit of Clinical Pharmacology, Oxford: Freed & Asmus, 1979); and for domperidone analysis (radioimmunoassay: Janssen Pharmaceutical Limited).

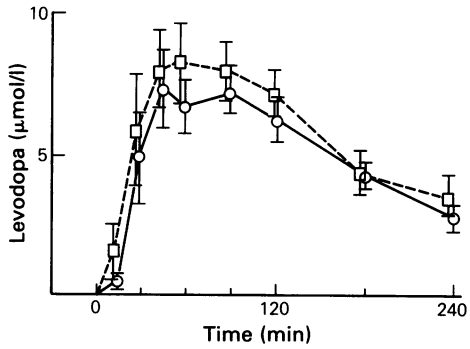

Figure 1 Mean (± s.e. mean) plasma levodopa concentration with levodopa alone (μmol/l) (○—○) and with domperidone pre-treatment (□---□).

Results

Clinical response

Eleven patients had a clearly defined clinical response to levodopa 500 mg. In these patients the mean peak fall in disability (percentage reduction in score units) was 24 with levodopa alone (with domperidone pre-treatment 35, $P < 0.5$, NS, Student's *t*-test). Mean time of peak response to levodopa was 66 ± 5.6 min after levodopa alone (50 ± 5.8 min with domperidone; $P < 0.1$, NS).

Peak dose dyskinesias occurred in six patients. The occurrence and severity of dyskinesias was unaltered by domperidone pre-treatment.

Two patients reported nausea and vomiting on levodopa alone, none with domperidone pre-treatment.

Following levodopa 500 mg alone, the mean maximum fall in erect blood pressure was 44 ± 3.2 mmHg (systolic) and 15 ± 3.7 mmHg (diastolic). Pre-treatment with domperidone did not alter the degree of hypotension.

Plasma levodopa concentration

Mean peak plasma levodopa concentration was 7.3 ± 1.4 μmol/l after levodopa 500 mg alone (8.2 ± 1.4 μmol/l with domperidone pre-treatment: $P < 0.5$, NS) (Figure 1). The mean time of peak plasma levodopa concentration with levodopa alone was 75 ± 11.8 min (65 ± 7.6 min with domperidone pre-treatment; $P < 0.25$, NS). Peak levels were higher in 11 subjects and earlier in 11 with domperidone than without.

With levodopa alone, seven out of 15 subjects had two peaks of plasma levodopa concentration, whilst only one subject had two peaks with domperidone pre-treatment.

The mean AUC for plasma levodopa over a 4 h period was 14% higher with domperidone than without.

The change in plasma levodopa concentration with domperidone was unrelated to the

Table 1 Effect of pre-treatment with domperidone (10, 20 and 40 mg p.o., i.m. and i.v.) on levodopa peak plasma concentration and overall absorption following levodopa 500 mg p.o.

Domperidone dose	*Mean peak plasma levodopa concentration following levodopa 500 mg p.o. (μmol/l)*			*AUC (plasma levodopa concentration: time over 4 h: units)*		
	−dp	*+dp*	*Ratio −dp:+dp*	*−dp*	*+dp*	*Ratio −dp:+dp*
10 mg p.o. ($n = 3$)	6.3	11.6	1.8	0.12	0.17	1.4
10 mg i.m. ($n = 3$)	9.1	12.8	1.4	0.14	0.19	1.4
20 mg i.v. ($n = 2$)	12.2	11.8	1.0	0.12	0.18	1.5
40 mg p.o. ($n = 3$)	8.5	9.0	1.1	0.12	0.13	1.1
40 mg i.m. ($n = 3$)	7.0	10.0	1.4	0.16	0.21	1.3

dose of domperidone, route of administration, or peak plasma domperidone concentration (Table 1). Peak plasma domperidone concentrations occurred 30–75 min following oral dosage and 15–30 min following i.m. dosage. Plasma domperidone levels were three to six times greater following i.m. than oral dosage.

Discussion

Delay in gastric emptying may delay and impair the response to levodopa in Parkinson's disease. Recently, Nutt *et al.* (1984) have confirmed and extended previous observations that when levodopa is given with food, there is delayed absorption and a lower peak plasma levodopa concentration that when levodopa is given alone. Likewise, high gastric acidity (Rivera-Calimlim *et al.*, 1970) and anticholinergic drugs (Fermaglich & O'Doherty, 1972; Morgan *et al.*, 1975) will delay gastric emptying. However, the most important cause of gastric delay in parkinsonism may be levodopa itself.

In this study, seven of 15 patients had two peaks of plasma levodopa concentration over a 4 h period when given levodopa alone, but with one exception a single peak when given domperidone pre-treatment. Similar results were found by Wade *et al.* (1974), who found two plasma peaks in 19 of 49 patients given a single oral dose of levodopa. These two peaks may possibly result from separate gastric and subsequent duodeno-jejunal absorption (Gundert-Remy *et al.*, 1983).

Levodopa causes nausea and vomiting in up to 80% of parkinsonian patients (Parkes, 1981), although the majority of subjects develop tolerance to sickness within 4–6 months of starting treatment, and the addition of decarboxylase inhibitors to levodopa reduces the incidence of sickness to about 15%. Levodopa-induced emesis can also be prevented by many different dopamine antagonists which block dopamine receptors in the chemoreceptor trigger zone, but drugs such as metoclopramide also prevent or reduce the therapeutic effect (Schachter *et al.*, 1980). This is not the case with domperidone. The anti-emetic effect of domperidone in levodopa-induced sickness may be due to gastric rather than central 'chemotrigger area' dopamine receptor blockade: we have observed that levodopa may not cause nausea in vagotomized subjects.

Domperidone slightly increases the initial bioavailability of levodopa and may increase the initial rate of absorption of levodopa in Parkinson's disease. Low doses of domperidone (10 mg p.o.) are as effective as high doses (20–40 mg p.o. or parenterally) in this respect, but no dose investigated prevented levodopa-induced hypotension.

Our thanks are due to Dr R. de Coster of Janssen Pharmaceutica NV, Belgium, Dr G. Lake-Bakaar and Mr R. Wright of Janssen Pharmaceutical Limited, GB, for supplies of domperidone and domperidone assays, and also to Mrs L. Gibson for invaluable secretarial help.

References

Bianchine, J. R., Calimlim, L. R., Morgan, J. P., Dujovne, C. A. & Lasagna, L. (1971). Metabolism and absorption of 3, 4 dihydroxyphenylalanine in patients with Parkinson's disease. *Ann. N.Y. Acad. Sci.*, **179**, 126–140.

Fermaglich, J. & O'Doherty, D. S. (1972). Effect of gastric motility on levodopa. *Dis. Nerv. Syst.*, **33**, 624–625.

Freed, C. R. & Asmus, P. A. (1979). Brain tissue and plasma assay of L-dopa and alpha-methyldopa metabolites by high performance liquid chromatography with electrochemical detection. *J. Neurochem.*, **32**, 163–168.

Gundert-Remy, U., Hildebrandt, R., Stiehl, A., Weber, E., Zurcher, G. & Da Prada, M. (1983). Intestinal absorption of levodopa in man. *Eur. J. clin. Pharmac.*, **25**, 69–72.

Laduron, P. M. & Leysen, J. E. (1979). Domperidone, a specific *in vitro* dopamine antagonist devoid of *in vivo* central dopaminergic activity. *Biochem. Pharmac.*, **28**, 2161.

Marsden, C. D. & Parkes, J. D. (1976). 'On-off' effects in patients with Parkinson's disease on chronic levodopa therapy, *Lancet*, **i**, 292–295.

Mearrick, P. T., Wade, D. N. & Birkett, D. J. (1974). Metoclopramide, gastric emptying and levodopa absorption. *Aust. N.Z. J. Med.*, **4**, 144–148.

Morgan, J. P., Rivera-Calimlim, L., Messiha, F., Sundaresan, P. R. & Trabert, N. (1975). Imipramine-mediated interference with levodopa absorption from the gastrointestinal tract in man. *Neurology (Minneap.)*, **25**, 1029–1034.

Nutt, J. G., Woodward, W. R., Hammerstead, J. P., Carter, J. H. & Anderson, J. L. (1984). The 'on-off' phenomenon in Parkinson's disease. *New Engl. J. Med.*, **310**, 483–488.

Parkes, J. D. (1981). Adverse effects of anti-parkinsonian drugs. *Drugs*, **21**, 341–353.

Peringer, E., Jenner, P., Donaldson, I. M. & Marsden, C. D. (1976). Metoclopramide and dopamine receptor blockade. *Neuropharmacology*, **15**, 463–469.

Rivera-Calimlin, L., Dujovne, C. A. & Morgan, J. P. (1970). Levodopa treatment failure: explanation and correction. *Br. med. J.*, **4**, 93.

Schachter, M., Bedard, P., Debono, A. G., Jenner, P., Marsden, C. D., Price, P., Parkes, J. D., Keenan, J., Smith, B., Rosenthaler, J., Horowski, R. & Dorow, R. (1980). The role of D_1 and D_2 receptors. *Nature*, **286**, 5769, 157–159.

Schuurkes, J. A. J. & Van Nueten, J. M. (1981). Is dopamine an inhibitory modulator of gastrointestinal motility? *Scand. J. Gastroenterol.*, **16** (suppl 67), 33–36.

Van Nueten, J. M., Ennis, C., Helsen, L., Laduron, P. M. & Janssen, P. A. J. (1978). Inhibition of dopamine receptors in the stomach; an explanation of the gastrokinetic properties of domperidone. *Life Sci.*, **23**, 453.

Wade, D. N., Mearrick, P. T. & Birkett, D. J. (1974). Variability of levodopa absorption in man. *Aust. N.Z. J. Med.*, **4**, 138–143.

(Received May 16, 1984, accepted August 20, 1984)