Motor effects of broad beans (*Vicia faba*) in Parkinson's disease: single dose studies

P.A. Kempster*† MD, Z. Bogetic† MD, J.W. Secombe‡B Appl Sc, H.D. Martin‡ Bsc, N.D.H. Balazs‡Bsc and M.L. Wahlqvist† MD

Departments of Neurosciences, Medicine† and Biochemistry‡, Monash Medical Centre, Melbourne, Australia.*

Broad beans (*Vicia faba*) are a natural source of L-dopa. To investigate a possible role for this substance in the treatment of Parkinsonian motor oscillations, we carried out single dose studies of *Vicia faba* pod mixture plus carbidopa in six patients. Motor responses of equivalent magnitude to those of conventional L-dopa medication occurred in five cases with mean onset of 39 min and mean duration of 104 min. *Vicia faba* meals produced comparable L-dopa blood levels to fasting standard tablet doses and recovery studies yielded 0.25% L-dopa per weight of bean pod mixture. *Vicia faba* contains sufficient L-dopa to be pharmacologically active in patients with Parkinson's disease and can potentially be incorporated into dietary strategies to manage Parkinsonian motor oscillations.

Introduction

Pharmacological treatment of Parkinson's disease with L-dopa is the most practical and physiological way to ameliorate the underlying deficiency of endogenous dopamine release in the striatum. However, the pharmacokinetic properties of orally administered L-dopa lead to fluctuating blood levels, generating 'on-off' fluctuations of motor performance in susceptible patients. Diet, particularly protein intake, contributes to this effect and manipulation of dietary intake has been proposed as a method to reduce fluctuations of L-dopa delivery to the brain.

Food can also be a source of L-dopa. In 1913, Guggenheim first isolated dihydroxyphenylalanine in its levorotatory form after extracting it from *Vicia faba* beans[1]. He was also first to demonstrate a pharmacological action of L-dopa when he ingested some of his bean extract and became nauseated. He found the bean pods to be a richer source of L-dopa than the beans.

Vicia faba is a natural food which contains L-dopa in a different physico-chemical form to conventional tablet medication. We have studied the responses to single doses of broad bean mixture to investigate its possible use in the management of Parkinsonian motor oscillations.

Patients and methods

Six patients on chronic conventional L-dopa therapy complicated by moderate to severe motor oscillations were studied. Their mean age was 52 and the mean

Correspondence address: Dr P.A. Kempster, Neurosciences Department, Monash Medical Centre, 246 Clayton Road, Clayton, 3168, Melbourne, Australia.

Table 1. Summary of motor response characteristics to single *Vicia faba* mixture doses in each case. For comparison, modified Webster scale scores in relation to conventional L-dopa 100mg/decarboxylase inhibitor doses are shown (see text). N/D = not determined

Case No.	Age & Sex	*Vicia faba* (g)	Carbidopa (mg)	Onset (min)	Duration (min)	Modified Webster Scale			
							Vicia faba mixture	Pharmaceutical L-dopa	
						Off	On	Off	On
1	51F	100	0	30	30	23	2	23	2
2	41M	150	25	30	75	23	6	23	6
3	48M	100	50	75	60	18	7	18	4
4	54F	150	50	N/D	N/D	N/D	N/D	26	11
5	67M	200	50	20	285	26	1	28	1
6	72F	200	50	45	195	11	9	11	9

duration of disease was 16 years. Broad beans (*Vicia faba*) were purchased in season. Beans and pods were separated by hand while fresh, and the pods were cooked in a microwave oven for ten minutes. The cooked bean pods were then frozen and stored at −70°C until use. Immediately prior to serving, the bean pods were defrosted, fragmented in a food blender and weighed.

Clinical assessments

Each patient was given a dose of bean pod mixture (100–200 g) and carbidopa (25–50 mg) after overnight fasting. Normal anti-parkinsonian medication had been withheld for at least ten hours before. Bean pod mixture and carbidopa doses are shown in Table 1.

Motor response was measured by the following serial objective motor assessments at 15 min intervals:

(i) unilateral hand tapping count over 30 seconds
(ii) time taken to rise from a standard armless chair, walk six metres and return to the chair
(iii) quantitation of tremor and dyskinesia according to simple five point scales (0 = nil, 1 = mild, 2 = moderate, 3 = severe, 4 = violent/incapacitating) for each body side
(iv) scoring on a modified Webster disability scale (scoring for 12 areas of motor function giving a maximum disability score of 36)[2].

For the purposes of analysis of the modified Webster scale assessment of motor responses, 'on' phases are defined as at peak post-dose motor improvement and 'off' phases as pre-dose motor score (pre- and post-dose 'off' states did not differ significantly in any case). Amplitude of motor response was calculated by subtracting 'on' from 'off' scores. For comparison, 'on' and 'off' phase modified Webster scoring was carried out in relation to one of each patient's normal L-dopa/decarboxylase inhibitor doses (L-dopa 100 mg/carbidopa 25 mg or L-dopa 100 mg/benserazide 25 mg). In four cases, blood was sampled for plasma L-dopa assay before and at 30 min intervals after the *Vicia faba* dose until wearing off of motor response. Blood was immediately centrifuged and plasma samples were stored at −70°C.

L-dopa measurements

To plasma samples of 750 μL were added 25μL of 60% perchloric acid plus 50μL of an internal standard compound (dihydroxybenzylamine). Following centrifugation, 500 μL of supernatant was combined with 300 μL of TRIS buffer and 50 mg of Alumina. This was mixed, centrifuged and the supernatant was discarded. The precipitate was washed with distilled water and recentrifuged. To this precipitate was added 500 μL of 0.3N perchloric acid solution to elute L-dopa. Following further centrifugation, 20 μL samples of the supernatant were analysed by HPLC. The apparatus consisted of a BAS 200A liquid chromatograph and electrochemical detector at 0.70 volts oxidation potential. Isocratic elution was carried out at 1.0 ml/min at room temperature on a 10 cm Rainin Microsorb 3 micron ODS reverse phase column. The mobil ephase contained citric acid, sodium dihydrogen phosphate and acetonitrile adjusted to pH 2.5. The coefficient of intra-assay variability was 6%.

The ratio of L-dopa concentration at 4 hours post-dose to peak level has been shown to correlate with the time to wearing off of motor response[2] and this was used as a measure of the rate of decay of plasma L-dopa concentration.

For measurement of L-dopa recovery from *V. faba*, 1 g of bean pod mixture was homogenized under ice. This was washed with 20 ml of 0.1M hydrochloric acid containing 0.5% sodium metabisulphite. Following centrifugation, the supernatant was removed and the precipitate rewashed and recentrifuged. The process was repeated four times until no L-dopa could be detected in the supernatant. All supernatants were analysed for L-dopa by HPLC as described above and the total L-dopa content in the original bean pod mix sample was calculated.

Results

In five cases, a clear motor response to the bean mixture occurred. In case 4, severe 'off' phase disability necessitated an injection of apomorphine to allow the meal to be ingested and it was then difficult to differentiate the subsequent motor responses to apomorphine and *Vicia faba*. This case was excluded from the analysis of the motor assessments but included in the results of the pharmacokinetic studies. Several patients commented on the bland taste of the bean pods but only one described this as unpleasant. Mild nausea occurred 30 min after the meal in one case.

Peak motor improvement in the five patients with unequivocal responses to *V. faba* was similar to previously observed 'on' phases when taking conventional L-dopa medication. Mean modified Webster scale motor response amplitude was 15 for *Vicia faba* compared with 16 for conventional treatment (Table 1). The pattern and severity of dyskinesia was also similar for the two sources of L-dopa. Mean onset of response to *V. faba* was 39 min and mean duration was 104 min. Table 1 shows summarized motor response characteristics in each case and Figure 1 shows serial motor assessment and plasma L-dopa concentration results to compare *Vicia faba* with a conventional L-dopa medication response in case 5.

L-dopa assays

Results of pharmacokinetic studies are shown in Table 2. Mean time to peak L-dopa concentration was 53 min (30–60). Mean peak L-dopa level was 2.8 μg/ml (0.7 –

Table 2. Results of pharmacokinetic studies: peak plasma L-dopa concentration (c_{max}), time to reach peak level (T_{max}) and ratio of plasma L-dopa concentration at peak to four hours post-dose.

Case No.	T_{max} (min)	C_{max} (μg/ml)	[L-dopah] 4hrs/peak
3	60	1.0	0.29
4	60	0.7	0.20
5	30	6.3	0.21
6	60	1.6	0.25

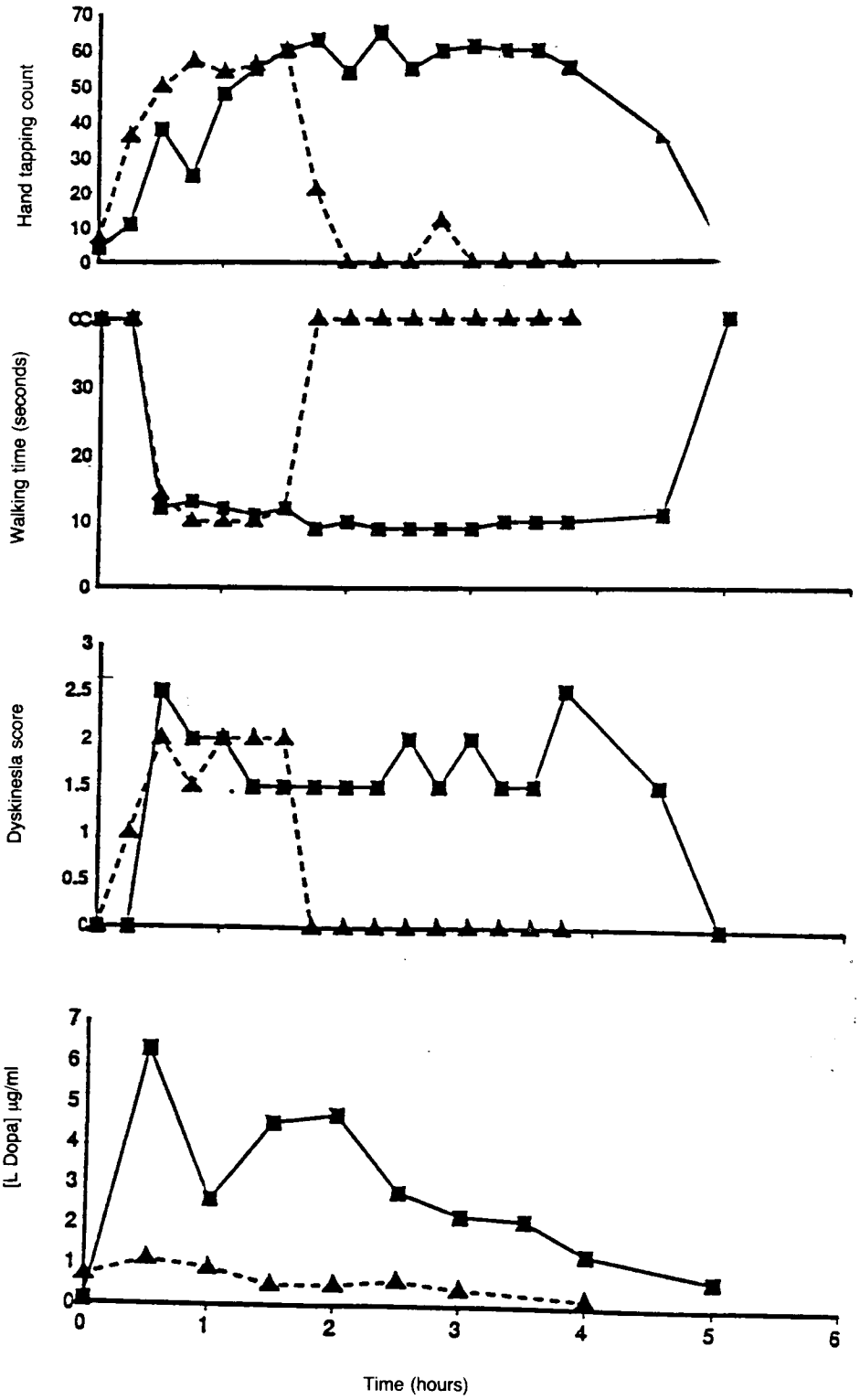

Figure 1. Serial motor assessments and plasma L-dopa assays in Case 5 for *Vicia faba*/carbidopa (squares) and a standard L-dopa 100 mg/carbidopa 25 mg tablet dose (triangles). These studies were performed under similar circumstances on consecutive mornings. Duration of motor response to *Vicia faba* was 285 mins, compared with 75 mins for conventional L-dopa medication. The prolonged motor response to *V. faba* corresponded to a much higher plasma L-dopa peak concentration in this case.

6.3) although the results reflected considerable variability in absorption of L-dopa from the *Vicia faba* mixture.

2.5 mg of L-dopa was extracted from the 1 g sample bean pod mixture, giving a L-dopa recovery of 0.25% per weight of *V. faba* pods (L-dopa 250 mg per 100 g of pod mixture).

Discussion

Broad bean pods contain a sufficient quantity of L-dopa to be pharmacologically active in patients with Parkinson's disease. To demonstrate this, we chose to study patients with pronounced motor oscillations. In such cases, fluctuation between distinct 'off' and 'on' motor states occurs. Clear and unequivocal responses to pharmacological agents such as L-dopa or apomorphine which are potent in causing central dopamine receptor stimulation allow the magnitude and time course of such motor responses to be accurately quantified by serial objective motor assessments. In five of the six patients studied, *Vicia faba* meals produced motor improvement accompanied by dyskinetic involuntary movements in the absence of other dopamine receptor stimulating pharmacological agents. Motor responses following *Vicia faba* ingestion were generally equivalent to but no better than responses to conventional oral L-dopa doses, suggesting that the motor benefits of *Vicia faba* can be attributed to their L-dopa content alone, rather than to other pharmacologically active naturally occurring substances. The pharmacokinetics of L-dopa from *Vicia faba* were comparable to those of fasting oral L-dopa/decarboxylase inhibitor tablet doses in terms of peak levels and decay of L-dopa concentration[2]. The pod mixture does not have the characteristics of a slow release L-dopa preparation[3]. Our finding of L-dopa recovery of 0.25% per weight of *Vicia faba* pods was identical to that of Guggenheim, who used stoichiometric methods to measure the L-dopa content of a sample of fresh bean pods[1]. Our pharmacokinetic data is consistent with L-dopa bioavailability from *Vicia faba* of that order of magnitude.

Most of the L-dopa contained in *Vicia faba* exists in a free form in the bean pods although small quantities of a dopa glucoside can be detected in both legumes and pods[4]. L-dopa also occurs naturally in significant quantities in several other leguminous species. It is present in the Georgia velvet bean (*Stizolobium deeringianum*)[5] and the legumes and seeds of the Indian medicinal plant *Mucuna pruriens*[6]. The L-dopa yield per weight of the latter plant is considerably greater than from *Vicia faba*.

Natural sources of L-dopa cannot compete with tablet formulations for convenience and predictable bioavailability. However, *Vicia faba* does have some potential advantages in reducing the interaction between oral L-dopa medication and diet. High protein meals will antagonize transmembrane passage of L-dopa across the gut and the blood-brain barrier[7] and dietary protein restriction has been shown to improve responsiveness to L-dopa in some patients[8].

Vicia faba is a relatively rich protein source (if both legumes and pods are ingested)[9] which has demonstrably positive effects on both plasma L-dopa concentration and motor function. It is inexpensive, both as a nutritional substance and as a pharmacological treatment. Rather than simply restricting oral protein intake, a diet which substitutes *Vicia faba* for other protein-rich foods, in conjunction with conventional L-dopa/decarboxylase inhibitor medicaton, may have a stabilizing effect on motor fluctuations and reduce food induced 'off' phases.

Anecdotal reports that patients may gain benefit from a broad bean rich diet[10] and findings on L-dopa absorption and motor response characteristics following single *Vicia faba* doses[11] suggest that this strategy is worthy of further study as an adjunct to the management of Parkinsonian motor fluctuations.

Acknowledgements – We are grateful for the assistance of Mr Len Edwards who provided practical advice on the preparation and effects of broad bean mixture. Mr Sam Lai assisted with the graphical production of the Figure.

References

1 Guggenheim M. Dioxyphenylalanine, a new amino acid from *Vicia faba*. Z Physiol Chem 1913;88:276.
2 Kempster PA, Frankel JP, Bovingdon M, Webster R, Lees AJ, Stern GM. Levodopa peripheral pharmacokinetics and duration of motor response in Parkinson's disease. J Neurol Neurosurg Psychiatry 1989;52:718–723.
3 Yeh KC, August TF, Bush DF, Lasseter KC, Musson DG, Schwartz S, Smith ME, Titus DS. Pharmacokinetics and bioavailability of Sinemet CR: A summary of human studies. Neurology 1989;39(suppl 2):25–38.
4 Andrews RS, Pridham JB. Structure of a dopa glucoside from *Vicia faba*. Nature 1965;205:1213–1214.
5 Miller ER. Dihydroxyphenylalanine, a constituent of the velvet bean. J Biol Chem 1920;44:481–486.
6 Damodaran M, Ramaswamy R. Isolation of L-3,4-dihydroxyphenylalanine from the seeds of *Mucuna pruriens*. Biochem J 1937;31:2149–2152.
7 Nutt JG, Woodward WR, Hammerstad JP, Carter JH, Anderson JL, 'On-off' phenomenon in Parkinson's disease: relation to L-dopa absorption and transport. New Eng J Med 1984;310:483–488.
8 Pincus JH, Barry KM. Protein redistribution diet restores motor function in patients with dopa-resistant 'off' periods. Neurology 1988;38:481–483.
9 Duke JA. Handbook of legumes of world economic importance. Plenum Press: New York 1981:275–279.
10 Spengos M, Vassilopoulos D. Improvement of Parkinson's disease after *Vicia faba* consumption. Book of abstracts, 9th International Symposium on Parkinson's disease 1988:46.
11 Rabey JM, Vered Y, Shabtai H, Graff E, Korczyn AD. Improvement of Parkinsonian features correlate with high plasma levodopa values after broad bean (*Vicia faba*) consumption. J Neurol Neurosurg Psychiatry 1992;55:725–727.

Motor effects of broad beans *Vicia faba* in Parkinson's disease: single dose studies

P.A. Kempster, Z. Bogetic, J.W. Secombe, H.D. Martin, N.D.H. Balazs, M.L. Wahlqvist

Asia Pacific Journal of Clinical Nutrition 1993; 2:85–89

蠶豆(VICIA FABA)對帕金森氏病運動神經的作用：單劑量研究

摘要

蠶豆(VICIA FABA)是左旋多巴的天然來源。作者對6個病人用蠶豆、 黃混合物加卡比多巴(CABIDOPA)進行單劑量研究，以探討蠶豆對治療帕金森氏病者運動神經震顫的可能作用。5個用蠶豆治療和用常規的左旋多巴治療的病人，獲得相同的運動神經反應，他們平均開始震顫的時間爲３９分鐘，平均震顫持續１０４分鐘。空腹時，蠶豆蓉與標準片劑產生類似的血左旋多巴濃度，進食１００克蠶豆、黃混合物可回收０.２５克左旋多巴。最后作者認爲， 蠶豆含有足够能使柏金森氏病起藥物作用的左旋多巴，并且認爲可能混在膳食中治療柏金森氏病人的運動神經震顫。