Effect of Frusemide on Pulmonary Blood Volume and Circulatory Dynamics in Seven Subjects Convalescing from High-altitude Pulmonary Oedema

Case No.	Age	Body Surface Area (sq.m.)	Interval after Oedema (Weeks)	Pressures (mm. Hg)								H.R. per min.	C.I. (l./min./sq.m.)	S.I. (ml./beat/sq.m.)	P.V.R. (mm. Hg)	S.V.R. (l./min./sq.m.)	Ventricular Work (kg.m./min./sq.m.)		Blood Volume (ml./sq.m.)		
				Femoral Artery			Pulmonary Artery			R.A.	L.A.						Right	Left	Central	Pulmonary	Total
				S	D	M	S	D	M	Mean											
1	24	1.7	6 { B A	125 122	75 64	88 80	22 18	8 7	12 12	5 2.5	6 5	64 60	3.1 1.9	48 32	1.9 3.7	27 41	0.6 0.3	4.4 2.7	866 731	296 242	
2	24	1.9	8 { B A	120 106	65 60	80 78	24 23	11 9	17 16	3.5 2	3 2	72 72	3.3 2.4	46 33	4.2 5.8	23 32	0.8 0.6	4.8 3.1	435 391	250 229	
3	25	1.7	8 { B A	112 107	65 78	84 87	20 19	11 7	15 11	3.5 3	8 5	60 60	3.8 2.6	63 43	1.8 2.3	21 32	0.7 0.5	4.8 3.2	640 703	306 271	
4	24	1.6	3 { B A	104 108	68 81	81 90	22 21	10 10	16 14	1.5 1	4 1.5	72 72	3.9 2.7	54 38	3.1 4.6	20 33	0.9 0.6	4.8 3.5	600 528	264 180	
5	29	1.7	6 { B A	110 115	58 60	78 80	25 25	5 5	13 13	2 1.5	2 2	67 66	4.7 3.0	70 45	2.3 3.7	16 26	1.2 0.8	6.3 4.2	838 625	478 275	
6	29	1.6	4 { B A	130 130	80 80	100 100	24 24	7 10	17 17	5 5	7 6	75 75	5.6 3.4	75 45	1.8 3.2	17 28	1.1 0.7	8.3 5.0	871 688	398 309	3,600 2,200
7	28	1.5	5 { B A	124 126	78 79	95 98	25 18	7 8	15 14	5 2	5 3	75 75	4.7 3.4	63 45	2.1 3.2	19 28	1.0 0.7	6.7 5.1	635 612	298 261	3,700 2,700
Average	26	1.67	6 { B A	118 116	70 72	87 88	23 21	8 8	15 14	3.6 2.4	5.0 3.5	69 69	4.2 2.8	60 40	2.4 3.8	20 31	0.9 0.7	5.7 3.8	698 611	327 252	

B = Before frusemide. A = After frusemide. S = Systolic. D = Diastolic. M = Mean. R.A. = Right atrium. L.A. = Left atrium. H.R. = Heart rate. C.I. = Cardiac index. S.I. = Stroke index. P.V.R. = Pulmonary vascular resistance. S.V.R. = Systemic vascular resistance.

in another similar study in progress at present the average fall in the total blood volume value in eight patients was 20%. Furthermore, the total blood volume of five patients with congestive cardiac failure fell by 21% following the administration of 100 mg. of intravenous frusemide (Davidov, Kakaviatos, and Finnerty, 1967). In the present study it may therefore be surmised that the total blood volume might also have fallen in the other five cases. If reduction in total blood volume initiates circulatory changes the role of the pulmonary blood volume in the chain of events has to be ascertained. The discrepancy between the reduction in the levels in the pulmonary and central blood volumes by frusemide supports our previous observation that the response of the pulmonary blood volume to high-altitude hypoxia was independent of the central blood volume (Roy *et al.*, 1967). This may represent a form of homeostasis between the pulmonary and the extrapulmonary blood volumes.

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Preliminary Communications

Oral Phenylalanine and Tyrosine Tolerance Tests in Parkinsonian Patients

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Summary: Reduction of dopamine concentrations in the brains of patients with Parkinsonism, together with reported clinical improvement after the administration of dihydroxyphenylalanine, has led to the hypothesis that impaired hydroxylation of tyrosine may be associated with the disease. To test this hypothesis oral loading tests with L-phenylalanine and tyrosine were carried out in patients and controls. After phenylalanine lower blood levels of this were found in Parkinsonian patients than in controls, but tyrosine levels were the same. After

tyrosine lower levels of this were also found in patients compared with controls. It is suggested that these findings indicate a decreased rate of tyrosine utilization in Parkinson's disease together with intestinal malabsorption; the latter is supported by the finding of abnormal D-xylose tolerance in these patients.

INTRODUCTION

Increasing evidence supports the belief that abnormal aromatic amino-acids and catechol metabolism may be responsible for the manifestations of Parkinson's disease. Interest has centred chiefly on the role of dihydroxyphenylalanine, which is the precursor of both melanin (decreased in the substantia nigra of patients with Parkinsonism) and dopamine (found in reduced quantities in the substantia nigra and the corpus striatum of

these patients (Hornykiewicz, 1963). The administration of dihydroxyphenylalanine has been reported to alleviate rigidity and tremor in patients with Parkinsonism (Birkmayer and Hornykiewicz, 1962; Cotzias *et al.*, 1967), while decreased urinary dopamine and increased tyramine excretion have also been found (Barbeau *et al.*, 1961; Boulton *et al.*, 1967). Hence defective hydroxylation of tyrosine dihydroxyphenylalanine leading to its deficiency might be the biochemical error in Parkinsonism (Cotzias *et al.*, 1967). To investigate this, the response of patients with Parkinson's disease to phenylalanine and tyrosine loading tests has been examined and compared with that of non-Parkinsonian subjects.

MATERIAL AND METHODS

A total of 14 Parkinsonian patients were investigated; one was 40 years old and the others were aged 50–76 years. No attempt was made to divide them into possible aetiological groups. Two control groups were investigated. Group 1 consisted of young healthy subjects (aged 20–40 years) selected at random. Control group 2 were elderly patients (aged over 60 years) in the departments of neurology and ophthalmology. One of them suffered from motor neurone disease and another from atrophic presenile dementia. The others had been admitted to hospital because of cataract or glaucoma and showed no overt neurological disorders. One Parkinsonian patient had both clinical and laboratory evidence of hyperthyroidism. All the other patients and control subjects were found to have protein-bound iodine, cholesterol, and liver-function tests within normal limits, and had no signs of liver or thyroid disease.

L-Phenylalanine and L-Tyrosine Loading Tests.—The test substances were mixed with diluted apple sauce and given by mouth after an overnight fast. For the Parkinsonian patients all specific therapy was interrupted at least 48 hours previously. The loading doses were L-tyrosine 0.05 g./kg. and L-phenylalanine 0.1 g./kg. body weight (Yeda-Miles, Rehovoth). Blood samples were collected at zero, one, two, and four hours. Tyrosine and phenylalanine were examined by microspectrofluorometric methods (Wong *et al.*, 1964).

D-Xylose Tolerance Test.—After an overnight fast the first morning urine was collected and stored. The patients were given 5 g. of D-xylose mixed with water. The urine was collected during the next five hours and examined for xylose (Roe and Rice, 1948; Butterworth *et al.*, 1959).

RESULTS

L-TYROSINE LOADINGS

Eight Parkinsonian patients and six control subjects (group 2) received tyrosine. The results are shown in Table I and Fig. 1. The response of the Parkinsonian patient with hyperthyroidism (Case 8) differed from that of the other patients. In view of the known effect of the thyroid disease on results of tyrosine tolerance tests (Rivlin *et al.*, 1965; Besser, 1968) this patient was omitted from further consideration.

In six out of the remaining seven Parkinsonian patients the blood tyrosine level one hour after the loading dose was below one standard deviation limit from the mean of the control group. The difference between the mean of the two groups was statistically significant ($P > 0.02$; $t = 3.086$; d.f. = 11). This difference was no longer evident after two hours, while after four hours the mean tyrosine level in the Parkinsonian group was slightly but not significantly higher than in the control group.

L-PHENYLALANINE LOADING TESTS

Seven Parkinsonian patients were compared with seven control subjects of group 1, and nine control patients of group 2 (Table II and Fig. 2).

TABLE I.—L-Tyrosine Loading Tests

	Blood Tyrosine Levels (mg./100 ml.) by Hours			
	0	1	2	4
Parkinsonian patients:				
Case 1	1.5	2.0	2.6	2.5
" 2	1.4	2.4	4.9	3.6
" 3	1.2	3.1	4.3	4.0
" 4	1.2	2.4	3.6	3.5
" 5	1.3	2.2	2.4	2.8
" 6	1.0	2.0	2.0	2.3
" 7	1.2	3.9	3.8	2.7
" 8	1.3	5.3	5.8	4.1
Mean values $\pm$ S.D.* ..	1.26 $\pm$ 0.16	2.57 $\pm$ 0.69	3.31 $\pm$ 1.05	3.06 $\pm$ 0.64
Control group 2 (n=6).				
Mean values $\pm$ S.D. ..	1.25 $\pm$ 0.33	3.73 $\pm$ 0.65	3.65 $\pm$ 0.68	2.72 $\pm$ 0.61
t	Not significant	3.086	Not significant	Not significant
P		< 0.02		

* Case 8, with hyperthyroidism, was not included in the statistical evaluations.

Phenylalanine Levels.—The mean post-loading blood phenylalanine levels in the control group of the elderly subjects (group 2) were slightly lower than in control group 1, but the differences were not statistically significant. On the other

FIG. 1

FIG. 2

FIG. 3

FIG. 1.—L-Tyrosine loading test: blood tyrosine levels. Solid line and the shaded area represent the mean value $\pm$ S.D. of the control group. Parkinsonian patients are depicted by the broken lines. Case 8 (see Table I) with hyperthyroidism is not included in the graph. FIG. 2.—L-Phenylalanine loading test: blood phenylalanine levels. Solid line and shaded area represents the mean value $\pm$ S.D. of the control group 2. Parkinsonian patients are depicted by the broken lines. FIG. 3.—L-Phenylalanine loading test: blood tyrosine levels. Solid line and the shaded area represent the mean value $\pm$ S.D. of control group. Parkinsonian patients are depicted by the broken lines.

hand, blood phenylalanine levels of the Parkinsonian patients one and two hours after loading were significantly lower than those found in both control groups.

Tyrosine Levels.—The two control groups did not differ significantly in their blood tyrosine level after L-phenylalanine loadings (Table II). The Parkinsonian patients showed a very wide range of individual differences (Fig. 3, Table II). One patient (Case 3) showed throughout the tolerance test blood tyrosine levels much higher than those observed in the control groups. In another patient (Case 1) all the values were below the range observed in the control groups. As a group, however, the Parkinsonian patients did not differ significantly from the control groups.

TABLE II.—L-Phenylalanine Loading Test

	Blood Phenylalanine Levels (mg/100 ml. (by Hours))				Blood Tyrosine Levels (mg/100 ml. (by Hours))			
	0	1	2	4	0	1	2	4
Parkinsonian patients:								
Case 1 ..	1.8	7.3	7.2	3.8	1.0	1.6	1.7	1.5
" 2 ..	2.6	3.8	4.4	11.8	1.2	1.7	1.9	2.7
" 3 ..	1.8	14.7	10.7	6.1	1.3	2.8	4.0	3.7
" 4 ..	1.8	15.2	10.1	5.5	1.3	2.0	2.5	2.5
" 5 ..	2.6	9.3	10.1	6.3	1.4	2.3	3.0	2.8
" 9 ..	1.6	3.9	7.5	6.7	1.1	1.2	2.9	2.2
" 10 ..	1.8	10.8	10.8	5.0	1.2	2.2	2.9	2.4
Mean values	2.00	9.29	8.69	6.46	1.21	1.97	2.70	2.54
± S.D. (n=7)	± 0.42	± 4.65	± 2.40	± 2.55	± 0.14	± 0.52	± 0.77	± 0.67
Control group 1 (n=7)								
Mean values	2.11	16.14	13.86	8.27	1.31	2.01	2.33	2.24
± S.D.	± 0.46	± 3.24	± 2.32	± 2.51	± 0.07	± 0.32	± 0.46	± 0.38
Control group 2 (n=9)								
Mean values	2.30	14.60	13.20	7.28	1.20	1.94	2.33	2.46
± S.D.	± 0.19	± 4.04	± 2.50	± 1.00	± 0.18	± 0.21	± 0.30	± 0.74
Statistical analysis*								
Parkinsonian patients vs. control group 1	N.S.	3.192	4.084	N.S.	N.S.	N.S.	N.S.	N.S.
t		<0.01	<0.005					
P								
Parkinsonian patients vs. control group 2	N.S.	2.443	3.61	N.S.	N.S.	N.S.	N.S.	N.S.
t		<0.05	<0.005					
P								

N.S. = No significant difference.

* Statistical analysis was carried out with Student's *t*-test. In some measurements the variances within the Parkinsonian patients and the control groups differed significantly, and the analysis was carried out according to Dixon and Massey (1957) by a *t*-test modified for samples with unequal variances.

D-XYLOSE TOLERANCE TEST

D-Xylose tolerance tests (Table III) were performed on five Parkinsonian patients and five control subjects of a comparable age. The normal range of xylose excretion in our laboratory in young or middle-aged healthy subjects is 1.2–2.2 g. of xylose five hours after ingestion of 5 g. of xylose. Among the five control subjects (aged 60–65) two showed xylose excretion within this normal range, one had a slightly lower excretion (1.06 g./5 hours), while two had definitely decreased excretion (0.51 and 0.67 g./5 hours). In the Parkinsonian group only one subject was within the normal range, while the other four gave definitely abnormal results and their xylose excretion (0.14–0.47 g./5 hours) was below that observed in any of the control subjects of comparable age.

DISCUSSION

The most striking difference observed between non-Parkinsonian controls and Parkinsonian subjects was the low blood phenylalanine levels in the latter after phenylalanine loading tests. This suggests either an increased rate of metabolism or a decreased rate of intestinal absorption of phenylalanine.

In the first stages of the investigation our control group consisted only of young and middle-aged subjects (control group

1). When the difference between this group and the Parkinsonian patients (the majority of them old-aged) was observed, the possibility of the influence of some age-related factors was considered. Pelz *et al.* (1968) recently demonstrated an impaired intestinal absorption in many elderly subjects. All 50 people aged 62–97 years studied by this group showed decreased xylose absorption compared with a younger control group. Consequently we performed phenylalanine tolerance tests in a second control group, age-matched with our Parkinsonian patients. The phenylalanine blood levels in this control group did not differ significantly from those in the younger control group and were significantly higher than those observed in the Parkinsonian patients. Hence the different behaviour of the Parkinsonian patients in the phenylalanine loading tests was not due to age factors but was probably related to the disease itself.

The D-xylose tolerance tests performed on a small sample of Parkinsonian patients suggested intestinal malabsorption in four out of five patients examined. Most patients also had relatively low levels of tyrosine one hour after tyrosine administration, a finding which suggested that the absorption of this amino-acid may also be impaired in this disease.

The blood tyrosine levels after phenylalanine loading indicate the relative rates of formation of tyrosine from phenylalanine and its metabolism.

If the metabolism of tyrosine is normal in Parkinson's disease we would expect to find low blood tyrosine levels because of the presumably slow intestinal absorption of phenylalanine. We did not, however, observe any significant difference between the blood tyrosine levels of the controls and Parkinsonian subjects after phenylalanine loading, suggesting a decreased rate of tyrosine utilization. The postulated deficiency of tyrosine hydroxylase in Parkinson's disease is compatible with these observations. The low level of blood tyrosine one hour after

TABLE III.—D-Xylose Tolerance Tests

Parkinsonian Patients			Control Group		
Case No.	Age	Xylose Excretion (g./5 Hours)	Subject	Age	Xylose Excretion (g./5 Hours)
2	60	1.29	A	65	0.67
11	62	0.42	B	62	1.26
12	63	0.14	C	64	0.51
13	65	0.47	D	62	1.07
14	67	0.46	E	60	1.47
Range		0.14–1.29			0.51–1.47

its administration by mouth in Parkinsonian patients (suggestive of malabsorption of this amino-acid) could explain why, even if deficient tyrosine hydroxylation exists, the levels of this amino-acid did not rise higher than in normal controls. Thus all our observations in Parkinsonian patients may be explained by the hypothesis of the coexistence of intestinal malabsorption of phenylalanine and tyrosine, and a deficiency of tyrosine hydroxylation. Nevertheless, these findings may also have other explanations based on an increased rate of metabolism of phenylalanine and tyrosine in the patients. It is hoped that investigations by intravenous loading tests of phenylalanine (and thus bypassing the intestinal barrier) may clarify the situation.

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Medical Memoranda

Anterior Interosseous Nerve Palsy

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Spontaneous paralysis of the muscles innervated by the anterior interosseous nerve is an extremely rare condition. We could find only 11 documented cases in the literature. It was first described by Parsonage and Turner (1948). It is interesting to note that in nearly all the cases reported the treatment was conservative, with variable results. Fearn and Goodfellow (1965) were the first to operate on such a case, and the result was stated to be good.

The anterior interosseous nerve arises from the median nerve as the latter passes between the two heads of the pronator teres and accompanies the anterior interosseous artery to reach the anterior surface of the interosseous membrane in the forearm. Here it lies in the interval between the flexor pollicis longus and the flexor digitorum profundus. Variation in the anatomy has been seen at operation but has not been mentioned in standard textbooks.

In some of the reported cases it was found that the anterior interosseous nerves were compressed by fibrous bands which passed between the deep head and the superficial head of the pronator teres. One author reported a fibrous band beneath the flexor digitorum sublimis.

Recently a case of spontaneous palsy of the anterior interosseous nerve was seen and treated by us at the East Glamorgan General Hospital.

CASE HISTORY

A 40-year-old woman was seen at the casualty department of the East Glamorgan Hospital. She stated that she worked as a metal-ring cutter, and that while pulling a lever she experienced pain in the right shoulder. She was treated conservatively with analgesics for one week, and for a further week with splinting and physiotherapy. There was no improvement in her condition, and she was therefore referred to the orthopaedic department. Here it was noted that she could not flex the interphalangeal joint of the right thumb nor the terminal interphalangeal joint of the right index finger. There was no wasting of the right thenar eminence. The reflexes were normal and there was no sensory changes. No point of deep tenderness was found anywhere on the arm or forearm.

Electromyography showed paralysis of the flexor pollicis longus and partial paralysis of the flexor digitorum profundus. This confirmed the presence of an isolated lesion of the anterior interosseous nerve. Three weeks later there was no improvement, and exploration of the nerve was undertaken.

At operation a musculofibrous band running across the anterior interosseous nerve from the deep head to the superficial head of the pronator teres muscle was found. Further dissection showed that this band bifurcated at the level of the elbow and that one head was attached to the capsule of the elbow joint. This band was completely removed and the wound was closed in layers.

Almost full return of power of flexion to the terminal phalanges of the thumb and index finger occurred within 10 days.

COMMENT

Our knowledge of isolated anterior interosseous nerve palsy is limited. The nerve is situated deep in the forearm and is therefore rarely injured, but there have been occasional reports of its being damaged as a result of fractures of the radius and ulna (Warren, 1963).

Mechanical compression by fibrous bands has been reported by Fearn and Goodfellow (1965), but according to Vichare (1968) it is rare.

It seems to us that because there exists an uncertainty about the aetiology, and because the results of conservative treatment are unpredictable, early surgical exploration after a preliminary course of conservative treatment is justifiable.

In the case reported there was no recovery after four weeks of conservative treatment. Paralysis of the muscles supplied by the anterior interosseous nerve was clearly shown by electromyography. At operation it was evident that the nerve was compressed by a fibromuscular band—this is the first time a fibromuscular band has been reported. Division of this band was followed by the return of movement of the paralysed muscle within 12 hours, and complete recovery occurred within two weeks.

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