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Changes in Electroretinogram and Serum Potassium During L-DOPA Treatment in Parkinsonism

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Summary. The relationship of L-DOPA plasma level, parameters of ERG and severity of extrapyramidal symptoms after a single dose of L-DOPA was investigated in 11 patients suffering from parkinsonism of idiopathic or arteriosclerotic origin.

After a drug-free night, each patient received his/her usual morning dose of L-DOPA. In the subsequent 3 h, the ERG recordings, blood levels and clinical ratings of extrapyramidal symptoms significantly dropped after a delay of 60 min in relation to the occurrence of the peak plasma L-DOPA level.

The initial "b" wave amplitudes as well as initial serum potassium values were abnormally high. There was a statistically significant correlation between the decrease of "b" wave amplitude (Δ"b") and the potassium "normalization index" (i.e. the ratio between the observed decrease of serum potassium and the pretreatment difference from the middle normal potassium value).

A definite interpretation of the data cannot be provided until more knowledge about the origin of "b" wave of ERG is available. It can be concluded tentatively that dopaminergic processes influence electrophysiological reactivity of the retina.

Key words: Electroretinogram in parkinsonism - Dopaminergic control L- DOPA pharmacokinetics - Electrolytic balance in parkinsonism

Introduction

There is considerable experimental evidence indicating that dopamine (DA) is a major neurotransmitter in the retina: presence of DA in the retina (Kramer 1971),

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increased tyrosine hydroxylase activity in retinal amacrine neurons following light stimulation (Iuvone et al. 1978), and presence of DA-sensitive adenylate cyclase activity in the retina (Brown and Makman 1973). Therefore, it can be hypothesized, that a record of retina action potential following light stimulation reflects to a certain degree the retinal dopaminergic activity (Filip and Balík 1978).

The origin of the "b" wave, the major component of human electroretinogram (ERG), is not yet fully understood. It was demonstrated that it originates in the bipolar cell layer of the retina (Armington 1974), where maximum dopaminergic activity can be found. The dopaminergic receptor in the retina is of Dl type, i.e. the preferred ligand is α-flupenthixol, in contrast to the striatal dopaminergic D2 receptor, which prefers binding with H^3-spiroperidol.

In order to ascertain if human ERG can reflect the changes in dopaminergic activity, a clinical study was designed, in which the relationship of L-DOPA pharmacokinetic variables, parameters of ERG and severity of extrapyramidal symptoms (EPS) after a single dose of L-DOPA was investigated. Taking into consideration the influence of electrolyte balance upon electrophysiological activity and that serum potassium is under dopaminergic control (Bevilacqua et al. 1980), serum levels of some ions were also estimated.

Material and Methods

Subjects

Patients (seven males, four females) treated longitudinally with L-DOPA to control parkinsonism of idiopathic or arteriosclerotic origin and not suffering from any other serious disease were used in the study. The patients age range was 52 to 78 years. Informed consent was obtained from all prior to the study.

Medication

L-DOPA was administered either as Dopaflex (Egyt, Hungary), i.e. a pure levodopa preparation or as Nakom (Lek, Yugoslavia), i.e. combined with carbidopa, a peripheral decarboxylase inhibitor. Drugs doses for each patient are shown in Table 1.

Procedures

After a drug-free night, each patient received his/her usual morning dose of L-DOPA. In the subsequent 3 h, blood sampling, ERG recordings and clinical ratings were performed at regular intervals (see Table 2). L-DOPA was estimated by a spectrofluorimetric method (Curzon et al. 1972). Maximum plasma level (C_{max}) and area under the curve of plasma concentration (AUC) were used as indicators of systemic availability of L-DOPA from the preparation used. Serum K^+, Na^+ and Cl^- were estimated by means of flame photometry.

The ERG was recorded under scotopic conditions (5 min dark adaptation). Artificial mydriasis was induced with homatropine. Henkes' contact lenses (without vacuum) were applied under local anaesthesia with Novesin. The stimulus energy was 2.0 J, the photostimulator lamp was placed 60 cm from the eye. The action potential of the retina was recorded by means of an EEG apparatus, the time constant was 0.3, paper velocity 6 cm/s. The records were evaluated without knowledge of identity of the particular curve.

For EPS assessment, the Rating Scale for Extrapyramidal Side Effects (Simpson and Angus 1970) and the Spiral Test were used. In our modification of the Spiral Test, the patient

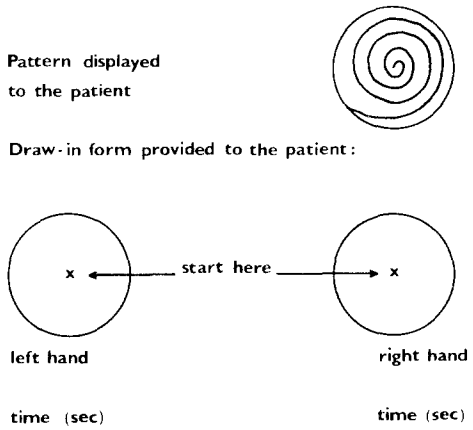

Fig. 1. Illustration of the spiral test technique

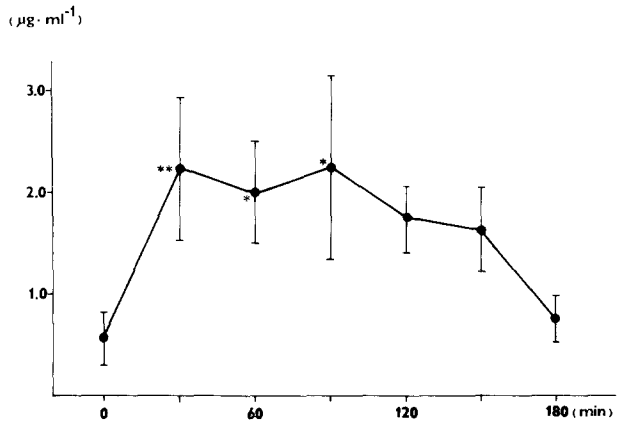

Fig. 2. The mean plasma concentrations (± SEM.) of L-DOPA in patients with Parkinson's disease after oral ingestion of a single maintenance dose. Statistically significant difference from pretreatment (zero time) values: * $P<0.05$ ** $P<0.01$

was asked to draw a spiral as similar as possible to the pattern provided (Fig. 1). The amplitude of the tremor was then evaluated on a 5-point raing scale. Moreover, the number of whorls drawn per 1 s was estimated. A mean score of both hands was used for data analysis

Statistical Evaluation

The values of the pharmacokinetic variables were computed for each single patient on an ADT 4316 minicomputer by means of non-linear regression analysis (Janků 1979). The changes of particular variables against pretreatment were compared with zero by means of the *t*-test. The statistical significance of correlation coefficients "*r*" was tested by means of the z-score.

Results

The plasma levels of L-DOPA peaked between 30 and 90 min after drug ingestion and thereafter declined slowly to initial values. (Fig. 2). There was a considerable variation in maximal L-DOPA concentration (C_{max}) as well as in corresponding

Patient	Dose of L-DOPA (g)	C_{max} ($\mu g \cdot ml^{-1}$)	AUC ($\mu g \cdot h \cdot ml^{-1}$)
F.M.	0.250 (NAK)	3.99	5.75
M.Š.	0.250 (NAK)	7.13	6.11
M.R.	0.250 (NAK)	7.33	7.33
A.S.	0.250 (NAK)	6.16	7.91
B.S.	0.250 (NAK)	3.78	3.42
M.H.	0.125 (NAK)	3.00	4.27
P.P	0.250 NAK)	5.28	7.43
Z.H.	0.375 (NAK)	0.97	1.46
A.M.	0.500 (NAK)	9.60	10.40
F.R.	0.125 (NAK)	1.50	1.58
O.S.	0.750 (NAK)	4.00	3.75

Table 1. Administered oral dose of L-DOPA and indicators of L-DOPA bioavailability

Time (min)	Experimental procedures
30	ERG, blood sampling, spiral test, Simpson-Argus score
0	Drug application
30	Blood sampling
60	ERG, blood sampling, spiral test
90	Blood sampling
120	ERG, blood sampling, spiral test
150	Blood sampling
180	ERG, blood sampling, spiral test, Simpson-Angus score

Table 2. Protocol of the investigation

areas under the curve of L-DOPA concentration (AUC) (Table 1) probably reflecting the "erratic nature" of L-DOPA absorption (Mearrick et al. 1974) which required that unequal doses of the drug were used for effective treatment of the disease. Similarly as in our previous study (Filipová et al. 1979), the baseline amplitude of the "b" wave in the ERG was abnormally high (455.69 ± 40.66 μV) decreasing continously during the course of the session to the final mean value 396.61 ± 35.46 μV. This decrease reached statistical significance $P < 0.05$) 120 min following L-DOPA administration i.e. with a delay of approximately 60 min in relation to the occurrence of the peak plasma L-DOPA level.

The Spiral Test scores declined in parallel with the "b" wave amplitude decrease. The difference against pretreatment was statistically significant at 60 min and 120 min of the experimental session ($P < 0.01$).

The Simpson-Angus total score also dropped significantly ($P < 0.01$) during the trial from the pretreatment mean value 17.56 ± 2.67 to 9.33 ± 1.80 recorded 180 min later.

The pretreatment serum potassium values were above the normal range (3.6–4.8 mmol/l) in 90% of the patients studied. Serum potassium decreased signifi-

Table 3. Abnormal potassium plasma levels in patients suffering from parkinsonism and their normalization after L-DOPA ingestion

Patient	Before L-DOPA deviation from normal value $\Delta_N K^+$ mmol/l	After L-DOPA deviation from pretreatment value ΔK^+ mmol/l	Normalization index $\Delta K^+/\Delta_N K^+$
M.S.	+5.0	−2.6	+0.5
M.R.	+6.0	−3.7	+0.5
A.S.	+0.6	−0.2	+0.3
B.S.	+2.8	−1.9	+0.7
M.H.	+4.7	−4.8	+1.0
P.P.	+1.3	−1.9	+1.5
Z.H.	+4.3	−3.1	+0.7
A.M.	+1.0	+0.3	−0.3
F.R.	+1.0	−0.8	+0.8
O.S.	+4.2	−2.8	+0.7
Mean	+3.09	−2.15	+0.65
S.E.M.	±0.63	±0.50	±0.15

cantly ($P<0.01$) 3 h after L-DOPA administration, but still remained above normal range in 66% of the patients (Table 3).

The decrease in serum potassium following L-DOPA administration can be considered as a return to normal values. Therefore, a new variable, the "normalisation index", indicating the ratio of the observed decrease of serum potassium (ΔK^+) and the pretreatment difference from the middle normal value ($\Delta_N K^+$) was introduced.

The value of the index is 1 when the serum potassium drops to the mean value of the normal range for serum potassium levels (4.2 mmol/l) during the experimental session. When the serum potassium remains above this level, the index value is below 1. The average value of the "normalisation index" in our experimental sample was 0.65 ± 0.15. According to the calculated confidence interval the value of the "normalisation index" falls with 95% probability between 0.31 and 0.99.

Neither serum Na^+ nor Cl^- changed significantly. The correlation between L-DOPA bioavailability variables (C_{max}, $C_{max/500}$, AUC, $AUC/_{500}$) on one side and clinical effects (Simpson-Angus scale, Spiral Test, change of ERG "b" wave amplitude and serum potassium "normalisation index") on the other were not statistically significant.

However, analyzing the correlation between the "normalisation index" and Simpson-Angus, Spiral Test and ERG results a statistically significant correlation coefficient ($r=0.805$, $P<0.01$) was found between the "normalisation index" and the decrease of "b" wave amplitude during the experimental session, Δ "b". The regression line of that relationship can be described by the equation:

$$\Delta \text{ "b"} = 20.61 - 117.56\ \Delta K^+/\Delta_N K^+$$

The value of the determination coefficient indicated that 64.8% of the variance of Δ "b" in our sample could be explained by this theoretical relationship.

Correlation between clinical symptoms of parkinsonism and the "normalisation index" were substantially lower and statistically not significant.

Discussion

Our results showed that there was a parallel between the diminution of clinical symptoms of parkinsonism after oral administration of L-DOPA and the reduction of the abnormal ERG response. However, in relation to the appearance of maximal concentrations of L-DOPA in plasma both changes occurred with a definite delay. Similarly, Doller and Conner (1980) found maximal plasma levels 1 h after peroral L-DOPA administration to rabbits with maximum striatal DA level 1 to 2 h later. Furthermore, Lloyd et al. (1975) found in their autopsy studies in patients with parkinsonism maximum DA concentration in putamen 2.5 to 3 h after the last L-DOPA administration. We assumed that the main factors contributing to the delay were L-DOPA crossing through the blood-brain (blood-retina) barrier and a process of formation of the active metabolite. This was also probably why we did not find any significant correlation between pharmacokinetic and clinical variables.

Until now there has been no data available in the literature on serum potassium elevation in patients with Parkinson's disease treated with L-DOPA. There is also a controversy to what extent serum potassium is controlled by dopaminergic mechanisms. An intraarterial application of metoclopramide, a dopaminergic antagonist, did not change serum potassium in rats (Sowers et al. 1980). On the other hand, Bevilacqua et al. (1980) have observed a decrease of plasma potassium following IV administration of metoclopramide in healthy volunteers.

Since we were unable to determine to what extent the reactivity of our patients was altered by their illness and/or treatment it was difficult to compare our results with these obtained in healthy volunteers. Therefore we share the opinion of Bevilacqua et al. (1980) that there were other factors (e.g. transfer of potassium from the extracellular into intracellular compartments) which might contribute to serum potassium regulation following dopaminergic blockade.

It cannot be excluded, however, that elevated serum potassium levels in patients with parkinsonism are rather related to changes in their muscular activity (rigidity and tremor). Provided this was true, the parallel changes of potassium "normalisation index" and "b" wave of ERG might represent two correlated phenomena dependent on a common underlying mechanism, i.e. dopaminergic blockade. However, taking into consideration that the changes of ion concentration in the bipolar cell layer of retina play a role in the origin of ERG (Armington 1974) the possibility exists that this correlation may mean a causal relationship, the ERG changes being a consequence of a shift in serum potassium. On the other hand, potassium is not free of effect upon dopaminergic system: it increases retinal tyrosine hydroxylase activity (Bustos et al. 1976) as well as the release of DA from retinal neurons (Sarthy and Lam 1979).

It is apparent that we are facing very complex mechanisms which are not yet fully understood. Numerous types of receptors have been discovered in the

retina recently and at least some of them can be affected by L-DOPA or its metabolites. Hence, our interpretation of clinical results can be only tentative until our knowledge of the origin of ERG is further elaborated.

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