Analysis of response to enteral infusion of levodopa in patients with Parkinson's disease

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Background and objectives

A new evaluation of levodopa plasma concentrations and clinical effects during duodenal infusion of a levodopa/carbidopa gel (Duodopa®) in 12 patients with advanced Parkinson's disease (PD), from a study reported previously (*Nyholm et al, Clin Neuropharmacol 2003; 26(3): 156-163*) is presented. One objective was to investigate in what state of PD we can see the greatest benefits with infusion compared with corresponding oral treatment (Sinemet® CR). Another objective was to identify fluctuating response to levodopa (LD) and correlate to variables related to disease progression.

Description of the original study and investigator rating

12 patients received first either duodenal infusion or oral tablets during three weeks and were then crossed-over to the other treatment. Doses were individually adjusted for both treatments. Test days (3 non-consecutive days per treatment) involved and standardized video recordings hourly from 8 a.m. to 5 p.m. Video recordings consisted of three different tasks: “piano playing”, alternating hand movements, rising from a chair, and walking. This examination includes items 25, 27 and 29 of the UPDRS. One investigator then rated motor performance from -3 (severe parkinsonism) to +3 (severe dyskinesia) based on the video recordings. The details were described previously (*Nyholm et al. 2003*).

Patient characteristics at baseline

Patient No.	Sex	Age (yrs)	Age at onset of PD	No of years with PD	No of years on LD	Hoehn & Yahr stage at worst	“Off” -time	Dys-kinesias	Dose of LD at BL (mg/day)	Concomitant anti-PD medication
01	M	49	35	14	13	4	2	1	800	br, en, se
02	M	56	46	10	7	4	2	4	900	en, ro
03	M	69	40	29	26	4	1	1	1350	-
04	F	69	40	29	23	5	2	2	800	ap, en, pe
07	M	76	55	21	21	4	1	1	500	en
08	M	67	44	23	16	4	2	1	475	en, ro
09	M	39	31	8	4	3	1	1	900	en, se
11	M	67	59	7	6	3	3	1	1200	ca, to
13	M	48	37	10	8	3	2	1	900	ca
14	M	63	54	9	7	4	3	1	1350	br, en
15	M	61	47	14	14	4	1	3	1200	ap, br, to
16	F	70	50	20	18	4	2	1	600	-

"Off"-time: 1 = 1-25%; 2 = 26-50%; 3 = 51-75%; 4 = 76-100% of the day (Item 39, UPDRS, Part IV).
Dyskinesias: 1 = 1-25%; 2 = 26-50%; 3 = 51-75%; 4 = 76-100% of the day (Item 32, UPDRS, Part IV).
Concomitant anti-PD medication: am = amantadine; ap = apomorphine; br = bromocriptine; ca = cabergoline; en = entacapone; or = orphenadrine; pe = pergolide; pr = pramipexole; ro = ropinirole; se = selegiline; to = tolcapone
Table adopted from original paper (*Nyholm et al. 2003*)
Patient 2 had the cassette disconnected from the pump during one test day and patient 4 had the tube dislocated during two test days. Data from these days were excluded from all calculations.

Conclusions

- In this patient group, difference in MSE seems highest for those with intermediate stages of PD according to baseline variables
- Difference in MSE strongly correlates to MSE during the oral treatment
- Fluctuations during infusion measured as SD of the rating correlate with baseline variables related to progression

Calculations

Mean absolute error (MAE) and mean squared error (MSE) from symptom free state (= 0) of the clinical rating over the treatment periods (oral or infusion) were computed for each patient as measures of 'summary effect' for the given treatment. SD of the clinical rating when the levodopa plasma concentration was basically constant was used as a measure of response fluctuations. These measures were then correlated using linear regression to baseline values of:

- Years on levodopa (YLD)
- Years with PD (YPD)
- Age at PD onset (APO)
- UPDRS total in on state (UPDRStot)
- UPDRS part II in off state (UPDRSII)
- Sum of the integer value for off-time and dyskinesias according to the table above (FLUKT)
- Total daily dose levodopa (DOSE)

Also principal component analysis (PCA) was used to produce a combined baseline variable related to progression (PCA1BL). PCA uses eigenvectors of the covariance matrix to find the directions in variable space that maximises the variance and can be used to reduce the dimensionality of data. The first principal component contained 48 % of the total variance and was a linear combination of UPDRStot, UPDRSII, YPD, YLD, FLUKT and DOSE.

Differences between treatment-periods in terms of SD, MAE and MSE were computed as measures of 'improvement' and these were plotted and correlated to the above baseline variables and to SD, MAE and MSE from the oral treatment period. Calculations were performed in S-Plus 6.1 and Excel 2000.

Equations

Standard Deviation:

$$SD = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(p_i - \bar{p})^2}$$

Mean Squared Error:

$$MSE = \frac{1}{N}\sum_{i=1}^{N}(p_i - a)^2$$

Mean Absolute Error:

$$MAE = \frac{1}{N}\sum_{i=1}^{N}|p_i - a|$$

In this case a = 0;
the symptom-free state
and p_i is the rating at time i

Results

All of the measurements of MAE and MSE were higher on oral medication than on infusion for all the patients. MSE and MAE for both infusion and oral treatment (not shown) had significant linear correlations to YLD, YPD and UPDRStot (**Table**). When plotting the difference in MSE between oral treatment and infusion vs YLD, a maximal difference (benefit) of infusion over oral treatment for YLD at about 15 years was observed (**Figure 1**). Difference in MSE also had a strong correlation (R=0.80) to the MSE during oral treatment (**Figure 2**). Fluctuating response was seen in some patients although they had near constant levodopa plasma concentrations during infusion. Among the original baseline variables, the strongest correlation (R=0.77) was found between the fluctuations on infusion measured as SD of clinical rating to YLD (**Figure 3**). When the baseline variables were combined using PCA, correlations were stronger for either of SD (**Figure 4**), MAE and MSE to the first principal component than to any individual variable.

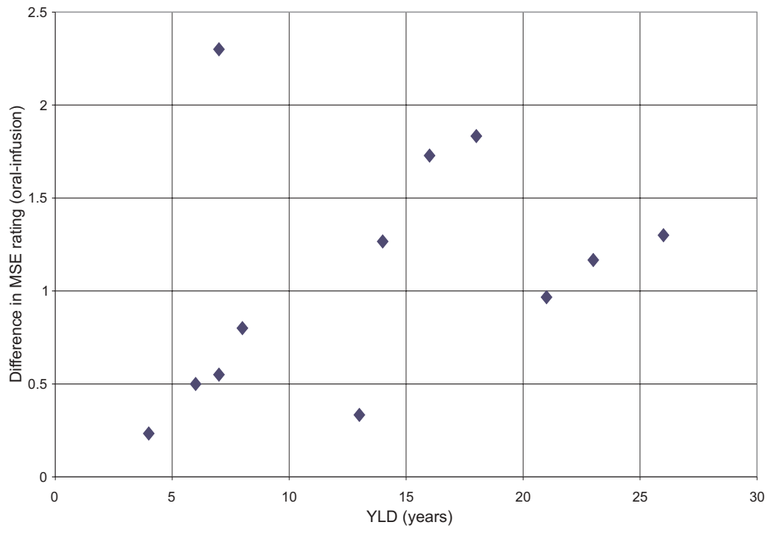

Figure 1. Difference in MSE vs. YLD.

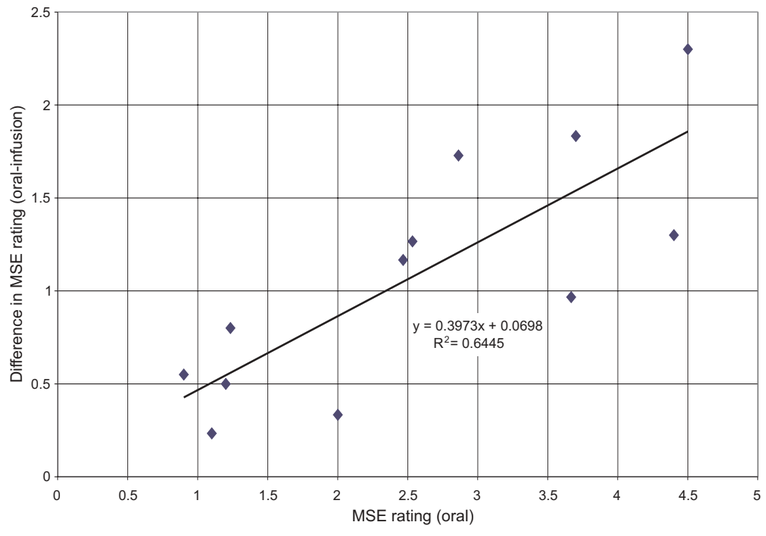

Figure 2. Difference in MSE vs. MSE during oral treatment.

Table of correlation coefficients

	SD infusion	MAE infusion	MSE infusion	SD difference	MAE difference	MSE difference
UPDRStot	0.594	0.652	0.657	NS	NS	NS
UPDRSII	0.634	0.628	0.673	NS	NS	NS
FLUKT	NS	NS	NS	0.794	NS	NS
YPD	0.664	0.643	0.598	NS	NS	NS
YLD	0.772	0.694	0.689	NS	NS	NS
DOSE	NS (negative)	NS (negative)	NS (negative)	NS (negative)	NS (negative)	NS (negative)
APO	NS	NS	NS	NS	NS	NS
SD oral	NS	0.721	0.605	0.711	NS	0.746
MAE oral	0.690	0.939	0.869	NS	NS	0.813
MSE oral	0.702	0.933	0.898	NS	NS	0.803
PCA1BL	-0.805	-0.722	-0.722	NS	NS	NS

R > 0.58 is significant 95 % for N = 12 patients.

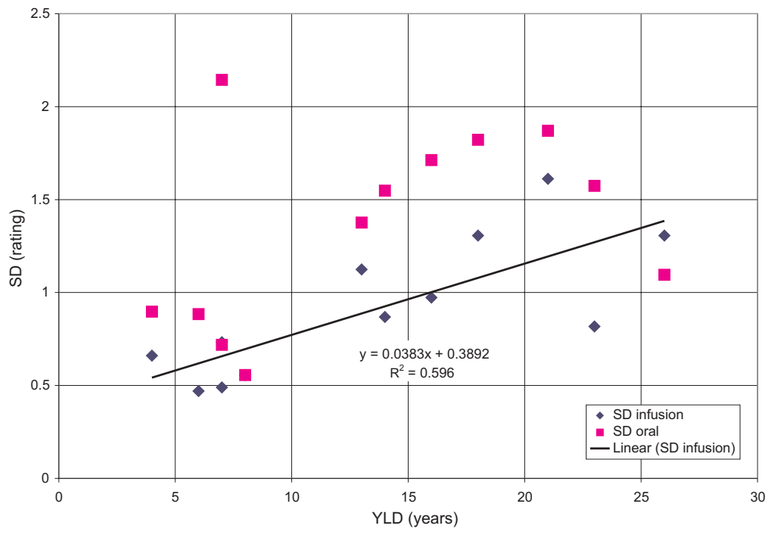

Figure 3. SD vs. YLD for both treatment periods.

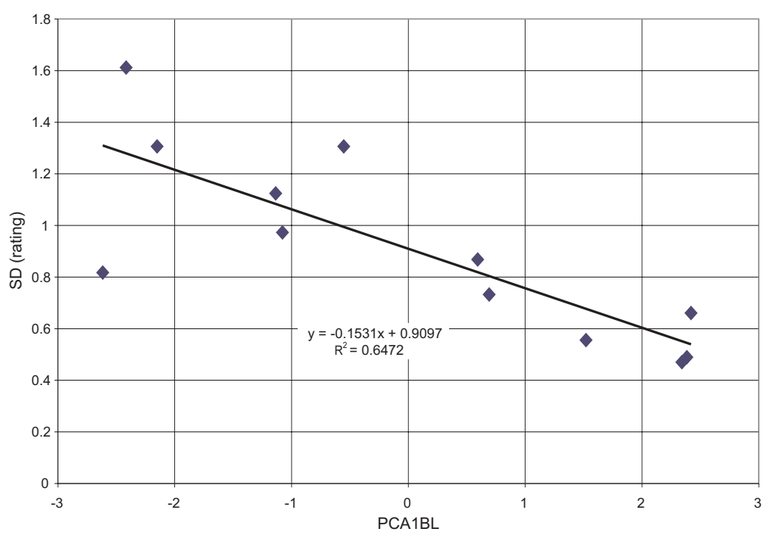

Figure 4. SD during infusion vs. first PCA component.

Discussion

Accumulating errors according to MAE or MSE as measures of 'summary effect' over treatment periods provides potentially useful information about clinical state. MSE seems to add more power to the more severe states and hence detects small improvements in the more advanced patients better than MAE. A disadvantage is that occasional extreme-values for the better patients will affect MSE more than MAE. Plotting these measures vs YLD is illustrative of disease progression over the years. An alternative approach would be to introduce weighting in the measures. For example, maybe higher weight should be added to the severe off states than to the severe dyskinetic states. Future work includes applying the presented calculations to more patients in other clinical studies including the "Direqt" study presented elsewhere at this conference.