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. 2003, 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 either enteral 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 examiners used 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).

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 (UPDRS0)
- 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 maximise 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.

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.