The most severe parkinsonian patients are most improved with duodenal levodopa infusion compared with oral treatments

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Background

Two randomized controlled cross-over studies comparing duodenal infusion of a levodopa/carbidopa gel (Duodopa®) with oral treatments in patients with advanced Parkinson's disease (study 1 comparing infusion with Sinemet® CR, 12 patients, and study 2 comparing infusion with individually optimized conventional combination therapies, 18 patients) have shown significant improvement in median UPDRS scores and in percentage on-time on a global treatment response scale (TRS) based on hourly and half-hourly clinical ratings.

There have been studies on outcome prediction for deep-brain stimulation (DBS) of the subthalamic nucleus (Welter *et al*., 2002; Jaggi *et al*., 2004), but in spite of the evidence that infusion is beneficial to many patients, there has been no previous study reporting on predictive factors influencing degree of improvement with infusion compared to oral treatments in patients with on-off fluctuations.

Objectives

- To find predictive factors related to degree of improvement with infusion.
- To outline prediction models as potential future tools for optimizing recruitment of candidates for infusion.

Methods

Measures of severity were defined as total UPDRS score and scores for parts II and III, percentage functional on-time and mean squared deviation of ratings on the TRS, and as mean of diary questions about mobility and satisfaction (only study 2). Pearson correlation coefficients between measures of improvement (absolute, relative and ranked improvement) and other numerical variables were calculated, and Fisher's exact test was used to assess over-representation in categorical variables among patients with large improvement after infusion. Prediction models (classification algorithms and linear regression) were designed using data from study 2 and evaluated by using data from study 1.

Conclusions

- The main finding was that the more severe parkinsonian symptoms the patients had during their oral treatment, the more improved they became after infusion. This finding was reproducible between two clinical studies for different measures of severity and improvement
- The classification and numerical prediction methods were reasonably successful and have a potential to become useful for optimizing recruitment of candidates for infusion in the future

References

Study 1:

Nyholm D, Nilsson Remahl AI, Dizdar N, Constantinescu R, Holmberg B, Jansson R, Aquilonius SM, Askmark H.
Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets.
Clin Neuropharmacol 2003;26(3):156-163.

Study 2:

Nyholm D, Askmark H, Gomes-Trolin C, Knutson T, Lennernas H, Nystrom C, Aquilonius SM.
Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease.
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Welter ML, Houeto JL, Tezenas du Montcel S, Mesnage V, Bonnet AM, Pillon B, Arnulf I, Pidoux B, Dormont D, Cornu P, Agid Y.
Clinical predictive factors of subthalamic stimulation in Parkinson's disease.
Brain 2002;125(3):575-583.

Jaggi JL, Umemura A, Hurtig HI, Siderowf AD, Colcher A, Stern MB, Baltuch GH.
Bilateral stimulation of the subthalamic nucleus in Parkinson's disease: Surgical efficacy and prediction of outcome.
Stereotact Funct Neurosurg 2004;82:104-114.

Results

Generally, correlations were found between improvement measures and corresponding severity measures at baseline (oral treatment), indicating that patients with more severe symptoms were most improved after infusion (**Table 1**). Plotting the various improvement measures vs their corresponding baseline severity measures generally revealed good linearity in the relations as judged by visual inspection (cf. **Figure 1**). There were no correlations between improvement and age, age at disease onset, disease duration or years on levodopa treatment.

The accuracy of the best classification algorithm (3-nearest neighbours), compared to clinical classification of improvement, was 9/12 (sensitivity 7/7, specificity 2/5). Linear regression showed good fit (r^2 = 0.46) between absolute improvement in total UPDRS vs total UPDRS at baseline (**Figure 2**).

Table 1. Pearson correlation coefficients and p-values between improvement measures and corresponding severity measures

		Improvement measure					
		Absolute improvement		Relative improvement		Ranked improvement	
	Study:	1	2	1	2	1	2
Corresponding severity measure	UPDRS II at baseline	NS*+	0.79§ <0.001	NS*+	0.59§ 0.010	NS*+	0.75§ <0.001
	UPDRS III at baseline	0.69 0.013	0.63 0.005	NS	NS	0.61 0.036	0.67 0.003
	Total UPDRS at baseline	0.69* 0.73+ 0.013* 0.007+	0.57 0.013	NS*+	NS	0.72* 0.72+ 0.009* 0.008+	0.61 0.008
	TRS percentage on-time during oral treatment	-0.64 0.026	-0.76 <0.001	-0.85 <0.001	-0.77 <0.001	-0.61 0.036	-0.72 0.001
	TRS MSD during oral treatment	0.80 0.002	0.82 <0.001	NS	0.50 0.036	0.82 0.001	0.73 0.001
	Diary mean Mobility at baseline	NA	-0.50 0.036	NA	-0.60 0.009	NA	-0.48 0.042
	Diary mean Satisfaction at baseline	NA	NS	NA	NS	NA	NS

The table presents correlation coefficients between improvement measures in a certain variable, such as total UPDRS, and that same variable in the same study at baseline or during oral treatment. When the severity scale gave high scores to severe symptoms ('right scale'), the sign was positive and when the scale gave low scores to severe symptoms ('left scale') it was negative. Study 1 had N= 12 and study 2 had N = 18 patients (NS = not significant, NA = not available, * off-state, + on-state, § as during previous week).

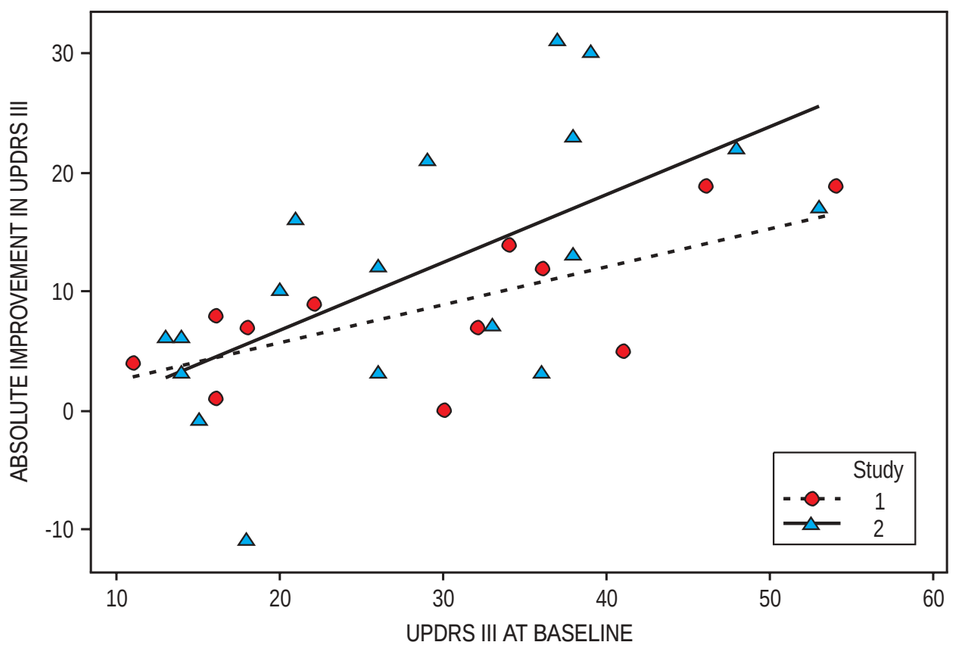

Figure 1. Plot of absolute improvement in UPDRS III vs UPDRS III at baseline, showing actual data and regression lines per study. Symbols represent individual patient scores. Difference between slopes is not significant.

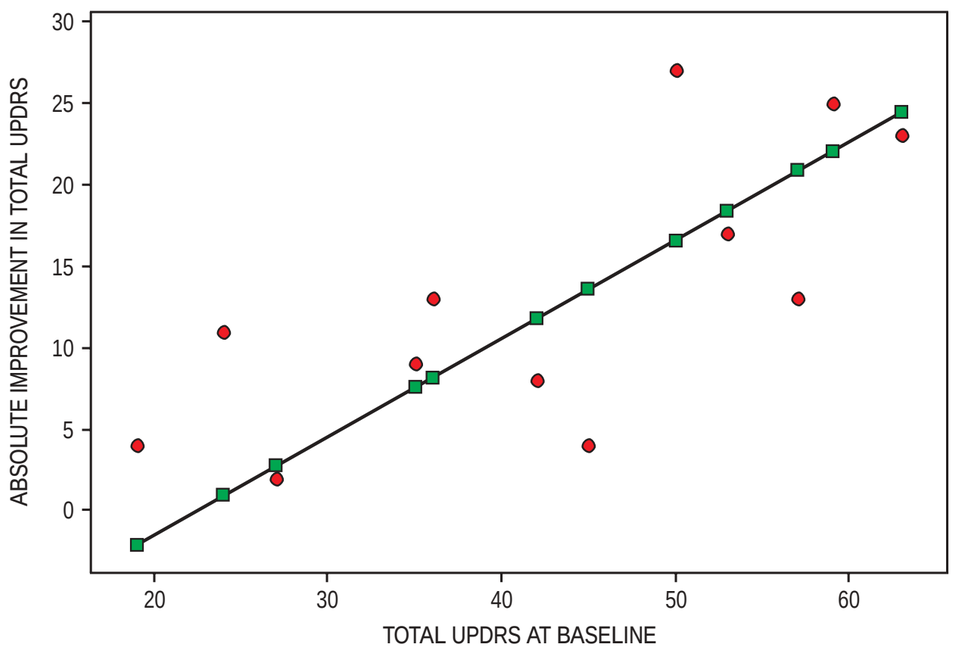

Figure 2. Actual (red circles) and predicted (green squares) absolute improvement with infusion in total UPDRS (part II on) score of the patients in study 1 based on a linear regression equation estimated from study 2 data vs total UPDRS score at baseline.

Discussion

An explanation for the finding that severity was a positive predictor for improvement after infusion, may be that patients with more severe symptoms have a narrower therapeutic window for levodopa treatment than those with less severe symptoms. Since the main advantage with infusion is a smoother plasma concentration profile compared to oral treatment, the time spent outside the therapeutic window will decrease more in patients with narrower therapeutic windows compared to those with broader windows.

In DBS-studies, Welter *et al*. (2002) found that preoperative UPDRS III score on levodopa correlated negatively to corresponding relative improvement with subthalamic stimulation on levodopa. Jaggi *et al*. (2004) concluded that preoperative levodopa response, young age and long disease duration were positive predictive factors. The present work indicates that selection criteria should be different for infusion since baseline severity was a positive predictive factor for improvement. Thus, infusion might be an interesting alternative to DBS in the more advanced patients and a study comparing these two treatments in this patient group would be welcome.