Pharmacokinetic and Pharmacodynamic Modeling of Levodopa in Parkinson Disease

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The concentration effect relationship (pharmacokinetic pharmacodynamic model, PKPD) of drugs used for Parkinson's disease is complex [1]. The benefits and adverse effects of drug treatment have to be considered in terms of short term and long term effects. Acute effects, observed over hours and days, reflect symptomatic benefit while chronic effects, observed over months and years, also reveal influences on the progress of the disease [2].

The acute effects of levodopa can be described by a standardized tapping rate. The time course of tapping after levodopa can be described by fast (short duration response) and slow (long duration response) effects plus a circadian component independent of levodopa administration. Data collected over 4 years after starting levodopa has been used to describe the evolution of the tapping response [3]. Using individual PKPD it has been possible to describe the time course of tapping rate on multiple occasions using the data from this 4 year study. It is striking that while there is a response to levodopa after the first dose the most important benefit arises from a much more slowly developing improvement in baseline tapping rate over a period of months to years ().

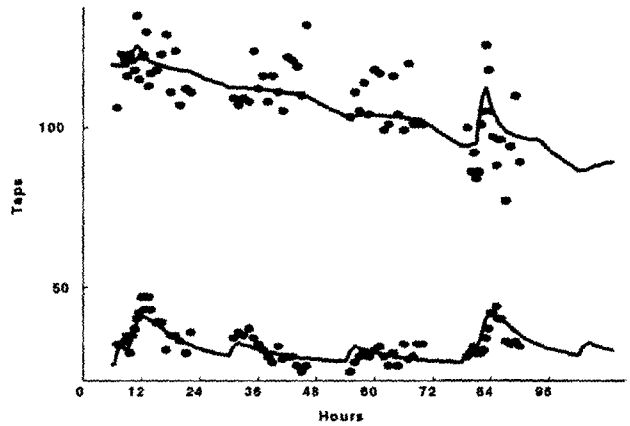

Figure 1 Tapping Rate (per minute) at 0 and 4 Years of Levodopa Treatment

As well as slow change in the baseline tapping rate there was also a slow increase in the maximum effect of levodopa (Emax) in many patients. There was no systematic change in the concentration sensitivity (EC50).

Effects on disease progression can be characterized by the change in the Unified Parkinson's Disease Rating Scale (UPDRS) after accounting for symptomatic effects. Using data from the Parkinson Study Group DATATOP studies [4-6] a population PKPD and disease progress model has been developed (Figure 2).

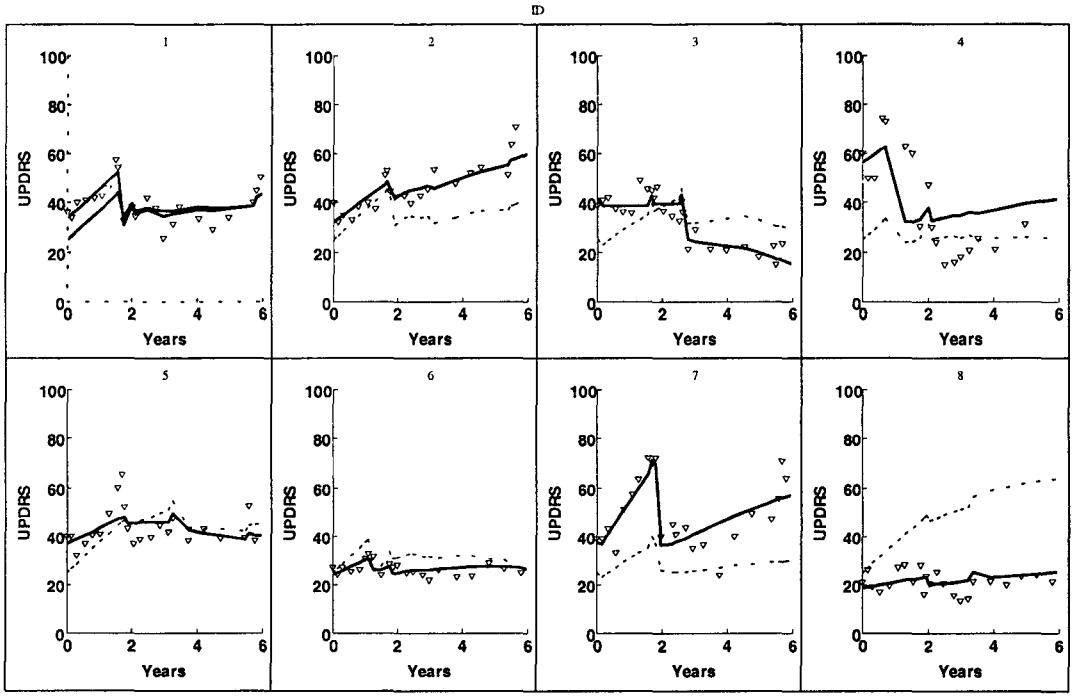

Figure 2 UPDRS Changes over 6 Years. Levodopa and Deprenyl Treatment Start at One Year (Subject 8 had Deprenyl only)

The symptomatic response to levodopa was best described, with a slow onset of effect and an increase in Emax over the first few years of treatment. These changes in UPDRS are very similar to those observed with tapping scores. The DATATOP cohort data also showed that levodopa and deprenyl appear to slow disease progression. The effect of levodopa was unexpected as it has been thought that the use of levodopa may accelerate the progression of

Parkinson's disease[7]. We have used PKPD models to simulate the outcome of a clinical trial to test this hypothesis [8] which will be reported in the near future.

Acknowledgments

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