Concentration-effect relationship of levodopa in patients with Parkinson's disease after oral administration of an immediate release and a controlled release formulation

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- 1 The relationship between plasma concentration of levodopa and motor-response was investigated in 12 patients with Parkinson's disease who showed marked response fluctuations, after a single oral dose of an immediate release (IR) formulation (100 mg levodopa/25 mg benserazide) and a controlled release (CR) formulation (300 mg levodopa/75 mg benserazide), using a double-blind, randomized, cross-over design.
- 2 The sum score of the Columbia University Rating Scale (CURS Σ) was used for pharmacodynamic assessment. A sigmoidal $E_{\max}$ -model was fitted to the data using a semiparametric pharmacokinetic/dynamic approach.
- 3 The dose-corrected AUC of levodopa after the IR-formulation was 27.5 ($\pm$ 9.1 s.d.) ng ml⁻¹ h per mg and 23.2 ($\pm$ 4.6 s.d.) ng ml⁻¹ h per mg after the CR-formulation. $C_{\max}$ was 1714 ($\pm$ 1027 s.d.) ng ml⁻¹ after the IR-formulation and 1494 ($\pm$ 383 s.d.) ng ml⁻¹ after the CR-formulation.
- 4 With both preparations, the maximal response to levodopa ($E_{\max}$) was a decrease in the CURS Σ rating of about 27 scores. Estimates of the EC_{50} of levodopa were 495 ($\pm$ 144 s.d.) ng ml⁻¹ (IR) and 1024 ($\pm$ 502 s.d.) ng ml⁻¹ (CR), respectively (95%-CI: 1.51–2.66, point estimator 1.95). The mean duration of the motor response was 1.9 ($\pm$ 0.5 s.d.) h (IR) and 2.8 ($\pm$ 0.7 s.d.) h (CR), respectively (95%-CI: 1.12–2.04, point estimator 1.53).
- 5 The difference in the responsiveness after the CR-formulation might be due to the increase in the concentrations of 3-*O*-methyldopa which rose from 5410 ($\pm$ 2360 s.d.) ng ml⁻¹ pre-dose to 6126 ($\pm$ 2660 s.d.) ng ml⁻¹ post-dose after the IR-form and from 5146 ($\pm$ 2292 s.d.) ng ml⁻¹ pre-dose to 6873 ($\pm$ 2830 s.d.) ng ml⁻¹ post-dose after the CR-form (95%-CI for the difference $C_{\max}$ – $C_{\min}$: 2.04–3.88, point estimator 2.63).
- 6 Although the peak response (i.e. $E_{\max}$) was not different after the two formulations, a gain in the duration of the motor response, which might be provided by sustained plasma concentrations of levodopa after the CR-preparation was offset partially by the apparent doubling of the threshold level (EC_{50}).

Keywords levodopa controlled release concentration/effect-analysis Parkinson's disease

Introduction

Studies on the concentration-effect relationship of levodopa in patients with Parkinson's disease have demonstrated an immediate onset of the motor response to levodopa when a threshold plasma concentration was exceeded and the appearance of off-

reactions when plasma concentrations declined below this level [1–3]. Controlled release (CR) preparations of levodopa should provide prolonged plasma concentrations above this 'therapeutic' threshold [4–6]. However, fluctuations were reported also with

CR-preparations even when elevated plasma concentrations were maintained [5, 6].

We have investigated whether the concentration-effect relationship of levodopa is influenced by the rate of drug absorption by comparing an immediate release (IR) and a controlled release formulation. The global score of the Columbia University Rating Scale (CURS Σ) was used for pharmacodynamic assessment [7, 8].

Methods

The study was performed in accordance with the declaration of Helsinki, the protocol was approved by the ethics committee of the University Hospital Frankfurt/Main, and written informed consent was obtained from all participants.

Study design

The study followed a double-blind, randomized, cross-over design. Twelve patients with advanced Parkinson's disease were included in the study. All were defined as 'fluctuators' according to the following criteria: A history of pronounced decrease in the efficacy of levodopa between two single doses with a maximum duration of the motor response after a single dose of 3 h. In each patient at least four single doses of levodopa per day were required to achieve sustained clinical improvement. The main exclusion criteria were co-treatment with other drugs causing dopamine release or affecting monoamine oxidase, treatment with antacids, sympathomimetics and neuroleptic drugs. The demographic characteristics of the patients are shown in Table 1.

Patients were stabilized over 4 weeks on an initial morning dose of 100 mg levodopa/25 mg benserazide (Madopar[®]). All other anti-Parkinson drugs were withdrawn. Study medication was an immediate release (IR) formulation (capsule) containing

100 mg levodopa/25 mg benserazide (Madopar[®]) and levodopa in a controlled release (CR) formulation (capsule with slow-release pellets, dose 300 mg levodopa/75 mg benserazide).

Assessment

After an overnight wash-out period from previous levodopa medication, a single dose of the study medication was given in random order together with 100 ml water. Blood samples were drawn at 15 min intervals from 0 to 3.5 h and at 30 min intervals from 3.5 to 6.0 h after dosage. Venous blood samples were drawn via an indwelling venous catheter in an antecubital vein into heparinized tubes which were centrifuged immediately (2000 rev min⁻¹). Plasma was stored at -70°C.

Simultaneously with plasma sampling, an assessment of the effect of levodopa on disability was made using the Columbia University Rating Scale global score (CURS Σ) which is a measure for all main motor symptoms in Parkinson's disease (gait, dexterity right/left, tremor and rigidity). CURS Σ is constructed from 25 items characteristic for motor disability in Parkinson's disease [7, 8]. Each item is evaluated on a 5 point scale from 0 (best) to 4 (worst). In addition, dyskinesia was scored using a semiquantitative global rating scale [9]. According to the cross over design the investigation was repeated using the other preparation 1 week after the first study.

Levodopa and 3-*O*-methyldopa (3-OMD) were measured in the plasma samples by an h.p.l.c. method with electro-chemical detection [10]. The lower limit of detection was < 1 ng ml⁻¹ for levodopa and 5 ng ml⁻¹ for 3-OMD. Intra-assay variability was 2.8% (levodopa) and 2.0% (3-OMD), respectively. Inter-assay variability was 7.0% for levodopa and 6.5% for 3-OMD.

Pharmacokinetic and pharmacokinetic/dynamic analysis

The AUC of levodopa was calculated using the TOPFIT program [11] by non-compartment analysis (logarithmic trapezoidal rule) and corrected to a dose of 1 mg. $C_{\max}$ and $t_{\max}$ values for levodopa and $C_{\min}$ (pre-dose levels) and $C_{\max}$ values for 3-OMD were noted directly from the data, and the magnitude of the post-dose increase in 3-OMD concentrations was calculated by subtraction of pre-dose from peak concentration.

A PK/PD analysis was made of individual plasma levodopa/CURS Σ -data from 0–6 h using a semiparametric approach [12, 13]. Concentration and effect data were fitted simultaneously by the $E_{\max}$ -model:

$$E = (E_{\max} * C^N) / (EC_{50} + C^N),$$

where $E_{\max}$ is the maximum decrease in the CURS Σ after levodopa, EC_{50} is the plasma drug concentration at half-maximal effect and N is the Hill-coefficient which describes the shape and steepness of the curve. To collapse the apparent hysteresis loop in the

Table 1 Demographic data of the patients

Age (years)	Mean ($\pm$ s.d.) range	60 (10) 41–79
Sex	Male Female	7 5
Weight (kg)	mean ($\pm$ s.d.)	70 (14)
Duration of Parkinson's disease (months)	Median Range	132 84–264
Severity of disease according Hoehn & Yahr [22]: Stage 1: 0; stage 2: 1; stage 3: 4; stage 4: 7; stage 5: 0		

plasma drug concentration-effect curves, plasma drug concentrations C_p were convolved to effect site concentrations C_e semiparametrically using the disposition function $k_{e0} e^{-k_{e0}t}$ [12]. The parameter of this transformation, the rate constant k_{e0} of equilibration of the effect site with the plasma is estimated as that value causing the least sum of squared differences between observed effects and those predicted by the E_{max} -model to occur at the corresponding effect site concentration. Minimization of k_{e0} and the parameters of the E_{max} -model by least squares was based on the simplex algorithm [14]. The equilibration half-life (t_{eq}) was calculated from $\ln(2)/k_{e0}$. The goodness of fit was assessed by Pearson's correlation-coefficient. An example of an observed plasma drug concentration-effect curve and the estimated effect-site-concentration-effect curve is shown in Figure 1.

The duration of the levodopa effect was derived from the effect-time profiles by calculation of the mean residence time MRT (0, 6 h) for the decline of the CURS Σ , using the TOPFIT program. Differences between the two preparations with respect to pharmacokinetic and pharmacodynamic parameters were assessed by 95%-confidence intervals (CI) according to Tukey.

Results

The IR-preparation was well tolerated by all patients. After administration of the CR-preparation, one patient developed severe dyskinesias and was withdrawn from the study. Another patient showed no effect. Thus, effect data were available for analysis in 10 patients.

Pharmacokinetic parameters

The dose-corrected AUC of levodopa after the IR-formulation was $27.5 (\pm 9.1 \text{ s.d.}) \text{ ng ml}^{-1} \text{ h per mg}$

and $23.2 (\pm 4.6 \text{ s.d.}) \text{ ng ml}^{-1} \text{ h per mg}$ after the CR-formulation (95% $\pm$ CI 0.71–1.04, point estimator 0.90). After administration of the IR-formulation C_{max} was $1714 (\pm 1027 \text{ s.d.}) \text{ ng ml}^{-1}$ and occurred at 0.75 h (median, range 0.25–2.0 h). After the CR-formulation, C_{max} $1494 (\pm 383 \text{ s.d.}) \text{ ng ml}^{-1}$ and t_{max} was 2.5 h (median, range 1.25–3.25 h) (Figure 2). The 95% CI for C_{max} was 0.67–1.38, the point estimator 0.96. Concentrations of 3-O-methyldopa rose from $5410 (\pm 2360 \text{ s.d.}) \text{ ng ml}^{-1}$ pre-dose to $6126 (\pm 2660 \text{ s.d.}) \text{ ng ml}^{-1}$ postdose after the IR-form and from $5146 (\pm 2292 \text{ s.d.})$ pre-dose to $6873 (\pm 2830 \text{ s.d.}) \text{ ng ml}^{-1}$ postdose after the CR-form (95% CI for the difference $C_{max} - C_{min}$: 2.04–3.88, point estimator 2.63).

Concentration-effect-analysis

The mean plasma concentration-effect relationship and that for one individual are illustrated in Figure 3. Figure 4 shows the effect-time profile after the two formulations. Following both formulations, the maximal response to levodopa (E_{max}) was a reduction in the CURS Σ by about 27 scores. The pretreatment CURS Σ was not different between the two preparations (Table 2). Hysteresis was present in all plasma drug concentration-effect plots after the IR-preparation and in 6/10 after the CR-preparation. In these cases, the equilibration half-life between the plasma and the effect compartment was similar after both preparations and averaged about 20 min. The EC_{50} of levodopa was estimated at $495 (\pm 144 \text{ s.d.}) \text{ ng ml}^{-1}$ when the IR-preparation was given and increased to $1024 (\pm 502 \text{ s.d.}) \text{ ng ml}^{-1}$ when the CR-preparation was given (95%-CI: 1.51–2.66, point estimator 1.95). The slope factor showed a wide variability with a range from 1 to 36. The mean duration of the motor response MRT (0, 6 h) was 1.9 ($\pm 0.5 \text{ s.d.})$ h (IR) and 2.8 ($\pm 0.7 \text{ s.d.})$ h (CR), respectively (95%-CI: 1.12–2.04, point estimator 1.53). The dyskinesia score was not different between the two formulations (IR: $1.9 (\pm 0.5 \text{ s.d.})$; CR: $1.8 (\pm 0.3 \text{ s.d.})$).

Figure 1 Plasma drug concentration-effect (●) and estimated effect-site concentration-effect relationships (○) in subject 11 after administration of the IR-formulation (Estimates: $E_{max} = 14$; $EC_{50} = 523 \text{ ng ml}^{-1}$; $N = 13$; $t_{eq} = 52 \text{ min}$).

Figure 2 Plasma concentrations of levodopa after administration of single doses of an IR-preparation containing 100 mg levodopa/25 mg benserazide (◇) and a CR-preparation containing 300 mg levodopa/75 mg benserazide (◆) (mean values, $n = 10$).

Discussion

Fluctuating control with akinesias at the end of the dosing interval remains a major problem in long-term therapy with levodopa in Parkinson's disease. It has been established that the kinetics of levodopa in patients with fluctuating response are not different from those in stable patients [15, 16], indicating a pharmacodynamic origin of the poor control [1]. The pharmacodynamic response to levodopa is characterized by a threshold level of plasma levodopa which

must be exceeded to obtain clinical efficacy. The short elimination half-life of levodopa (1 to 2 h) warrants short dosing intervals and patients are often treated with more than four single doses per day. The duration of plasma levodopa concentration above the threshold depends on the size of the dose, but peak concentrations of levodopa might be accompanied by dyskinesias [3, 17, 18]. These problems are the rationale for using controlled-release preparations of levodopa [4]. However, a decrease in the efficacy of levodopa and a need to increase the daily dose by threefold have been described when CR-preparations are compared with IR-preparations [5]. Accordingly, after a single dose, we observed a 2–3 fold decrease in drug responsiveness – as indicated by the increased EC_{50} – when the controlled release preparation was given. Although the magnitude of the therapeutic response was not different after the two medications, the gain in duration of the motor response was limited to about 50% despite the threefold higher dose of the CR-formulation. The loss of

Figure 3 Plasma drug concentration-effect relationship after administration of IR-levodopa (100 mg levodopa/25 mg benserazide $\diamond$) and CR-levodopa (300 mg levodopa/75 mg benserazide $\blacklozenge$) (a) mean values, $n = 10$ (b) patient 6.

Figure 4 Effect (CURS)-time-profile of levodopa after administration of a single dose of IR-levodopa containing 100 mg levodopa/25 mg benserazide ($\diamond$) and a CR-preparation containing 300 mg levodopa/75 mg benserazide ($\blacklozenge$) (mean values, $n = 10$).

Table 2 Pharmacokinetic/dynamic parameters of levodopa (mean $\pm$ s.d., $n = 10$)

Levodopa	IR-levodopa	CR-levodopa	95% CI (pe*)
Pre-dose CURS	40.6 $\pm$ 10.4	39.8 $\pm$ 9.2	0.87–1.20 (0.94)
E_{max} (Δ CURS)	27.2 $\pm$ 9.5	26.1 $\pm$ 8.2	0.80–1.16 (0.95)
EC_{50} (ng ml $^{-1}$)	495 $\pm$ 144	1024 $\pm$ 502	1.52–2.66 (1.95)
N	5.5 $\pm$ 4.1	10.0 $\pm$ 10.4	0.56–4.40 (1.56)
t_{eq} (min)	22 $\pm$ 18	19 $\pm$ 13**	
MRT (0, 6 h)	1.90 $\pm$ 0.48	2.84 $\pm$ 0.69	1.12–2.04 (1.53)

*point estimator, ** $n = 6$.

efficacy cannot be attributed to poor absorption of levodopa after the CR-preparation as the relative bioavailability of levodopa was about 90%.

This is the first study which provides an intraindividual comparison of the response to IR and CR levodopa by means of a PK/PD model. Contin *et al.* [1] found a lower EC_{50} of levodopa in stable patients compared with patients with fluctuating response after single dose administration of an IR-preparation. Although the concentration/effect-analysis was limited to hand tapping as an effect parameter, the mean EC_{50} reported in that study for the patients with fluctuating response was 600 ng ml⁻¹ and the slope factor was above 5, values which are in good agreement with the results obtained with the same dose of IR-levodopa in our study. The equilibration half life of the effect compartment has been reported to about 30 min and a similar value was observed in our study when the IR preparation was given. Nelson *et al.* [2] investigated the pharmacokinetic/dynamic relationship of levodopa after single dose administration of a CR-preparation. The mean EC_{50} was about 900 ng ml⁻¹ for improvement of walking speed and 1600 ng ml⁻¹ for the results of a finger tapping test. These data are also in agreement with the estimates in our study for the CR-preparation. However, all of these estimates of threshold levels refer to concentrations in the hypothetical effect compartment in which true equilibrium is only achieved under steady state conditions and with a low fluctuation index. Not surprisingly, improvement of the therapeutic response to levodopa has been reported in patients with poor control when intravenous or intraduodenal infusions of levodopa were given, compared with the oral administration of IR-forms [3, 18]. Considering that IR levodopa formulations cannot establish a stable steady state drug concentration within an acceptable dosing

interval due to the short elimination half-life of levodopa it seems doubtful whether such a threshold can be the target drug concentration at trough (e.g. during therapeutic drug monitoring) as suggested by Contin *et al.* [1]. Conversely, the data from the present study indicate that threshold concentrations of levodopa need to be higher for therapy with CR-formulations, and this does not allow for any marked prolongation of the dosing interval.

We cannot explain the decrease in responsiveness to levodopa after the CR-formulation. However, acute tolerance to levodopa does not appear to be the underlying cause as proteresis (i.e. clockwise hysteresis) was not present in the plasma drug concentration-effect plots, and this phenomenon has not been reported by other authors who applied PK/PD-modeling to levodopa [1–3].

Levodopa is metabolized to 3-*O*-methyldopa by catechol-*O*-methyltransferase (COMT). The role of 3-OMD with regard to the therapeutic response to levodopa is controversial. We observed an enhanced (2 to 3-fold) pre- to post-dose rise of plasma 3-OMD concentrations after the CR-form. Competition between 3-OMD and levodopa for blood-brain transport has been proposed [3, 19] and implicated as responsible for the inadequate dose-response to CR-levodopa [5]. However, it was reported [20] that the rate of levodopa appearance in the CSF is not correlated with the fractional increase of 3-OMD concentrations in the CSF, thus excluding competitive inhibition for the transport system. As the concomitant use of COMT inhibitors and levodopa is currently under clinical investigation [21], pharmacokinetic-/dynamic modeling with this combination might clarify whether elevated 3-OMD concentrations contribute to the loss in levodopa responsiveness after administration of CR preparations.

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