ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 46 (1998) 223–228

European Journal of Pharmaceutics and Biopharmaceutics

Research paper

Comparative single- and multiple-dose pharmacokinetics of levodopa and 3-*O*-methyldopa following a new dual-release and a conventional slow-release formulation of levodopa and benserazide in healthy subjects

U.E. Gasser[a,*], Ch. Crevoisier[b], M. Ouwerkerk[c], G. Lankhaar[c], J. Dingemanse[c]

[a]*Roche Pharma (Schweiz) AG, Reinach, Switzerland*
[b]*F. Hoffmann-La Roche Ltd., Basel, Switzerland*
[c]*Clin-Pharma Research AG, Birsfelden, Switzerland*

Received 1 September 1997; accepted 12 January 1998

Abstract

A multiple-dose study was performed to assess the pharmacokinetic profile of a new levodopa/benserazide dual-release formulation (DRF) in comparison with a conventional slow-release formulation (SRF). The study was of an open label, randomized, two-way cross-over design and was conducted in 18 subjects. Assessment of the two formulations was at day 1 (single-dose) and at day 7 after a 5-day t.i.d. pre-treatment (100 mg levodopa and 25 mg benserazide) in fasting state. The pharmacokinetic parameters reflecting bioavailability, accumulation and metabolism of levodopa were determined. The levodopa pharmacokinetics of the new DRF showed rapid absorption (t_{max} = 1.1 h), followed by sustained levodopa plasma concentrations, similar to the SRF. Following multi-dose administration, the peak plasma concentration of the new DRF was 90% higher compared to the SRF (C_{max} = 2.1 and 1.1 μg/ml, respectively). The bioavailability was significantly increased by 40% ($AUC_{0-\infty}$ = 6.1 and 4.3 μg × h/ml, respectively). The new DRF was well tolerated as shown by the low incidence of mild side effects. In conclusion, the results of this study confirmed the levodopa dual-release properties of this new levodopa/benserazide formulation.

Keywords: Parkinson's disease; Levodopa; Dual-release formulation; Pharmacokinetics; Multiple dose

1. Introduction

Levodopa remains the most effective drug in the management of Parkinson's disease. Due to rapid absorption and disposition of levodopa, its plasma concentrations rapidly rise and fall after drug intake. In view of the suggested relationship between plasma concentrations and clinical effects of levodopa [1–4], improvement of clinical efficacy was aimed to be achieved by the development of slow-release formulations (SRFs). These preparations are characterised by more sustained plasma levels of the drug than those obtained with immediate-release formulations (IRFs) [5,6], and such treatment may possibly delay the occurrence of fluctuations in the therapeutic effect. Madopar® HBS and Sinemet® CR were the first examples of SRFs, with good clinical efficacy in de novo patients [7], in the treatment of night-time problems and early morning symptoms [8–10]. They are often also useful for combating wearing-off and on–off fluctuations [11–13] which represent the major challenge in the management of Parkinson's disease. The main problems associated with these SRFs are their variable bioavailability and, consequently, the possibility of variable efficacy [14,15]. In addition, peak plasma levels of levodopa are reached later, 2–4 h after administration and peak concentrations of levodopa are lower than with IRFs [5,6,16]. These facts make it necessary for the patient to sometimes

* Corresponding author. Roche Pharma (Schweiz) AG, Schönmattstrasse 2, CH-4153 Reinach, Switzerland. Tel.: +41 61 7154216; fax: +41 61 7154331. e-mail: urs.gasser@roche.com

0939-6411/98/$19.00
PII S0939-6411(98)00022-8

use an IRF as the first dose in the morning, and often also a combination of IRF and SRF during the day, in order to elicit a rapid onset of effect.

In order to counterbalance the drawbacks of the existing IRFs and SRFs, a dual-release formulation (DRF) of levodopa and benserazide, in the dose ratio 4:1, was developed. This new dosage form, consisting of a breakable 3-layer tablet (immediate-release layer, barrier and slow-release layer), results in dual-release characteristics and, therefore, would combine the advantages of early peak plasma levels of levodopa at around 1 h (similar to the peak time of IRFs) with sustained plasma levels (similar to SRFs) [5,6].

The objective of the present multiple-dose study in healthy subjects was to assess the pharmacokinetic profiles of levodopa and 3-*O*-methyldopa (3-OMD) following the new DRF and to compare them with those following conventional SRF.

2. Subjects and methods

2.1. Clinical procedure

An open-label, multiple-dose, randomized, 2-way crossover clinical trial was performed in healthy subjects. Ethics Committee approval was obtained from the Freiburg Ethics Committee, Freiburg, Germany, and all subjects gave their written informed consent before any screening procedures were performed. Before study entry, the subjects underwent a general physical examination including measurements of blood pressure, heart rate, ECG and body weight. A blood sample was drawn for the assessment of clinical laboratory tests. Thirteen male and five female healthy subjects with a mean age of 28 years (range: 19–34 years) were enrolled into the study. All subjects were within ±15% of their ideal body weight.

This study consisted of two study periods of 7 days each, separated by a wash-out period of at least 7 days. After eligibility screening, the subjects were randomized to receive by oral administration first either the DRF (Madopar® DR; Roche Pharma (Schweiz), Reinach, Switzerland) or the SRF (Madopar® HBS; F. Hoffmann-La Roche, Basel, Switzerland) for 7 days. They then crossed over to the other treatment.

For the DRF period, one tablet (containing 200 mg levodopa and 50 mg benserazide) was administered on day 1 in the morning, half a tablet three times daily (at 0700, 1500 and 2300 h; total daily dose of 300 mg levodopa and 75 mg benserazide), on the subsequent 5 days (days 2–6), followed by one tablet on day 7 in the morning. For the SRF period, two capsules (one capsule contains 100 mg levodopa and 25 mg benserazide) were administered on day 1 in the morning and one capsule three times daily (at 0700, 1500 and 2300 h; total daily dose of 300 mg levodopa and 75 mg benserazide) on the subsequent 5 days (days 2–6), followed by two capsules on day 7 in the morning. Vital signs and adverse events were recorded at regular intervals after drug intake. On days 1 and 7, the subject fasted overnight (starting from 2000 h on the previous day) and remained fasted for 4 h. Standardized meals were provided at 4 and 10 h after drug intake. On both days, the subjects consumed 200 ml water 2 h after drug administration. Starting from 2000 h on the previous day to 24 h after drug intake, smoking and the consumption of alcohol and xanthine-containing beverages were not allowed. After completion of the last treatment period, a follow-up physical examination was conducted.

2.2. Sample collection and analysis

Blood samples were obtained for up to 12 h following drug administration on day 1 at the following time-points: baseline, 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h. On each of the five subsequent days, morning trough (0700 h) blood samples were taken. On day 7, blood samples were taken after the last dose administration at the same times as on day 1, and 24 and 36 h samples were collected in addition. On days 1 and 7, blood was taken from an indwelling cannula, placed in a forearm vein of the volunteer. On days 2–6, blood samples were collected by venipuncture. Blood samples of 7 ml were collected into tubes containing EDTA as an anti-coagulant and 0.1 ml 1 N metabisulfite solution as an anti-oxidant. Samples were put on ice immediately and were centrifuged for 10 min at $3000 \times g$ and 4°C. Plasma was transferred into a polypropylene tube and stored at −40°C. Samples were analysed for levodopa and 3-OMD. The levodopa and 3-OMD concentrations were determined by high-performance liquid chromatography (S3-ODS 2 column). The samples were separated using a mixture of methanol/phosphate buffer with EDTA, and octane sulfonic acid as additives to build ion-pairs. Levodopa and 3-OMD were detected by electrochemical detection. The lower level of quantification was 5 ng/ml for levodopa and 7 ng/ml for 3-OMD. The calibration curves for levodopa and 3-OMD were linear in the range 50–2200 and 100–4000 ng/ml, respectively. The inter- and intra-day variability of the assay were 5 and 4%, respectively.

2.3. Pharmacokinetic characteristics

Pharmacokinetic parameters of levodopa and its metabolite 3-OMD were derived by compartmental-free analysis using Topfit 2.0 [17]. For day 1, the following parameters were derived: the peak plasma concentration (C_{max}), the time to reach peak plasma concentration (t_{max}) (both observed values), the apparent elimination half-life of levodopa ($t_{1/2}$) as determined by log-linear regression analysis of the terminal portion of the plasma concentration–time curve, the area-under-the-curve of levodopa (AUC_{0-12} and $AUC_{0-\infty}$) by the linear trapezoidal rule (AUC_{0-12}) and extrapolation to infinity ($AUC_{0-\infty} = AUC_{0-12} + C_{12} \times t_{1/2}/0.693$), where C_{12} is the plasma concentration at 12 h. The area-under-the-curve of 3-OMD was calculated as AUC_{0-12}. The

mean value of the trough levels prior to morning administration on days 4 to 7 was calculated. For day 7, C_{max}, t_{max}, $t_{1/2}$ (only levodopa), $AUC_{0-\infty}$ (levodopa), AUC_{0-36} (3-OMD), peak–trough swing (PTS), peak–trough fluctuation (PTF) and accumulation ratio (R_{AC}, only levodopa) were calculated. PTF relates the peak–trough difference ($C_{max} - C_{trough}$) to the mean dosing interval concentration (AUC_{0-8}/τ, where τ is the dosing interval of 8 h), whereas relating the peak–trough difference to the trough concentration yields PTS. The accumulation ratio (R_{AC}; only for levodopa) was estimated by $AUC_{0-\infty}$(day 7)/$AUC_{0-\infty}$(day 1). The metabolic ratio (MR) was calculated by AUC_{0-12}(3-OMD)/AUC_{0-12}(levodopa) on days 1 and 7. Mean, median, standard deviation (SD) and 95% confidence intervals around the mean (95% CI) were calculated for all pharmacokinetic parameters.

3. Results

3.1. Safety

A total of eight adverse events (mild tiredness, mild headache and mild nausea) were reported by five subjects. Two abnormalities in laboratory values (haemoglobin and haematocrit) were found at the post-study check of one volunteer. Both values returned to normal a few days later.

3.2. Pharmacokinetics

Single dose administration of the DRF on day 1 was characterised by a rapid absorption (t_{max} 1.1 h) and a marked peak plasma concentration (C_{max} 1.7 μg/ml) of levodopa when compared to the SRF with a C_{max} of 1.0 μg/ml and a t_{max} of 2.3 h (Table 1 and Fig. 1). After administration of the DRF, the $AUC_{0-\infty}$ was significantly larger by 38% as compared to the SRF. The apparent elimination half-life amounted to 1.2 and 1.5 h following DRF and SRF administration, respectively.

Similar findings were obtained after multiple dosing. On day 7, the differences between the two formulations in terms of $AUC_{0-\infty}$ and C_{max} were still apparent (Table 1 and Fig. 1). $AUC_{0-\infty}$ of levodopa after DRF was significantly higher by 42% as compared to the SRF. This was also indicated by higher mean values of PTS and PTF for the DRF. Peak and trough levels of levodopa were in the expected range (Table 1) following multiple dose administration of DRF and SRF. For both formulations, there was a 50% accumulation of levodopa as evidenced by R_{AC} (Table 1).

Following multiple dosing for 7 days, a considerable accumulation of 3-OMD was observed after intake of the formulations (Fig. 2). The C_{max} was more than doubled and the AUC was accordingly higher (Table 2).

4. Discussion

The objective of the present study was to describe the pharmacokinetics of levodopa and 3-OMD in healthy subjects after single and multiple doses (100 mg t.i.d. for 6 days) of a new DRF and a conventional SRF.

In clinical practice, Parkinsonian patients receive 'tailor-made' dosage regimens, individualized according to the patient's therapeutic response to levodopa. The dose of levodopa is different in stable patients with no clinically relevant daily changes in motor performance and in patients with predictable fluctuations in motor state, related to levodopa levels. Stable and fluctuating patients usually take 2 to 4 doses (daily dosage 150–500 mg) and 3–8 doses (daily doses 300–1200 mg) of levodopa per day, respectively [18]. Therefore, the dosage regimen in this study (200 mg levodopa) essentially reflects the regimen in stable patients, and is therefore based on therapeutically effective doses in Parkinsonian patients. A previous multiple-dose study in healthy subjects receiving thrice daily doses of 200 mg of levodopa (SRF) showed, however, a high number of adverse events probably related to levodopa such as nausea and vomiting [6]. The rationale for the dosage regimen (three times 100 mg levodopa and 50 mg benserazide) during the treatment intervals (days 2–6) was to compromise a thrice daily administration of levodopa and benserazide in order to inhibit the decarboxylase activity efficiently and to reduce the occurrence of adverse events in the healthy subjects.

There is virtually no difference in the accumulation ratio of levodopa from DRF and SRF, whereas fluctuations within a dosing interval on day 7 are higher following the DRF because of higher peak and lower trough levels of levodopa. It has been reported that fluctuations in levodopa concentrations can be related to motor response fluctuations [2]. Fluctuations of the peripheral levodopa pharmacoki-

Table 1
Pharmacokinetic parameters of levodopa (mean (SD)) following single-dose administration on day 1 and multiple-dose administration on day 7 (n = 18)

Levodopa	C_{max} (μg/ml)	t_{max} (h)	AUC_{0-12} (μg × h/ml)	$AUC_{0-\infty}$ (μg × h/ml)	$t_{1/2}$ (h)	Trough (μg/ml)[a]	PTF	PTS	MR
DRF, day 1	1.7 (0.6)	1.1 (0.6)	4.3 (1.7)	4.4 (1.7)	1.2 (0.3)				
DRF, day 7	2.1 (0.6)	1.1 (0.9)	5.9 (1.8)	6.1 (1.8)	2.6 (1.9)	0.059 (0.052)	3.3 (0.7)	36 (37)	1.5 (0.5)
SRF, day 1	1.0 (0.4)	2.3 (1.3)	3.1 (1.1)	3.2 (1.1)	1.5 (0.6)				
SRF, day 7	1.1 (0.3)	2.0 (0.9)	4.2 (1.2)	4.3 (1.3)	1.9 (1.2)	0.096 (0.066)	2.2 (0.6)	28 (38)	1.5 (0.7)

[a]Trough values were averaged over days 4–7.

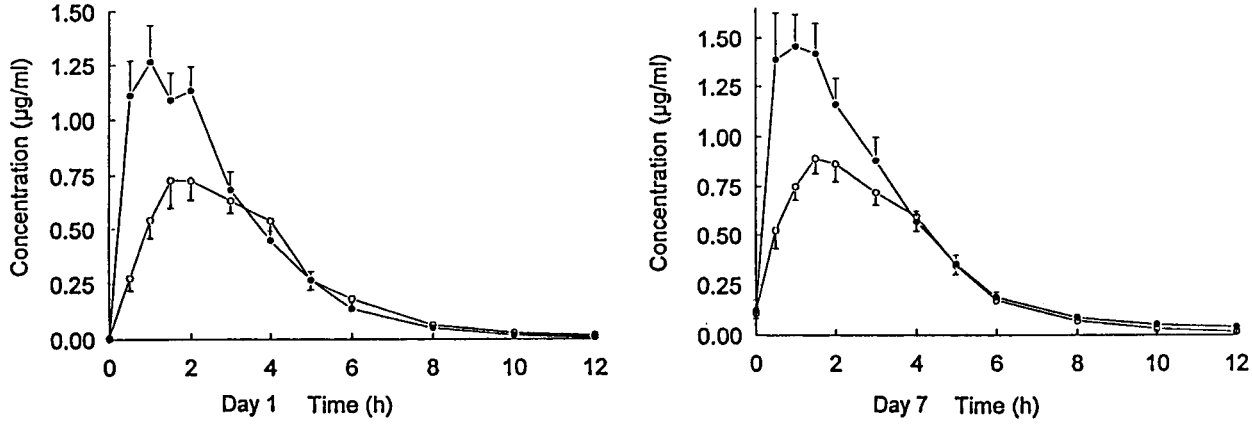

Fig. 1. Mean levodopa plasma concentration–time curves of the DRF (closed symbols, +SEM) and the SRF (open symbols, –SEM) following single-dose administration on day 1 and multiple-dose administration on day 7 (n = 18).

netics are, however, not sufficient to predict the complex mechanisms of response fluctuations in Parkinsonians. Motor fluctuations are primarily dependent on central effects such as effect site concentrations and storage capacity of dopamine and receptor desensitisation [2]. In any case, fluctuations in plasma levodopa concentrations following DRF are less pronounced than those following IRF [6].

As a result of the slower absorption of levodopa from SRF, steady-state concentrations were lower at peak and higher at trough compared to treatment with DRF. Higher trough levels of levodopa from SRF were already previously reported [6]. Higher trough levels may explain the advantages of SRFs over IRFs in the treatment of nocturnal disabilities in Parkinson's disease [8–10].

The bioavailability of levodopa after both single (day 1) and multiple (day 7) doses of DRF is 40% higher than that following SRF. It is of interest to note that a 6-day t.i.d. regimen of 100 mg levodopa had no effect on the relative bioavailability of the DRF. In contrast to our study, the relative bioavailability of the SRF (vs. the IRF) was 60% after a single dose [5] and 85% after multiple doses [6]. As suggested elsewhere, benserazide pre-treatment had no effect on the extent of levodopa absorption following DRF [19], whereas pre-treatment with benserazide enhanced the AUC of levodopa by one-third after a single dose administration of an IRF [5]. This suggests that the DRF has different inhibitory effects on decarboxylase compared to the SRF. It seems that a formulation with combined rapid- and slow-release properties, such as the new DRF, inhibits the decarboxylase more efficiently than mono-release formulations.

Our study revealed that mean trough levels of levodopa (days 4–7) were 0.06 and 0.10 μg/ml and maximum plasma levels (day 7) were 2.1 and 1.1 μg/ml for DRF and SRF, respectively. The pharmacodynamic response to levodopa is characterised by a threshold level of levodopa which must be exceeded to obtain clinical efficacy [1]. The threshold levels reported in Parkinsonians [20] and our multi-dose kinetic data in healthy subjects suggest that plasma concentrations of levodopa need to be higher in most of the fluctuating Parkinsonian patients, and this could be achieved by higher doses of the controlled-release forms (SRFs and DRF) and/or shorter dosing intervals.

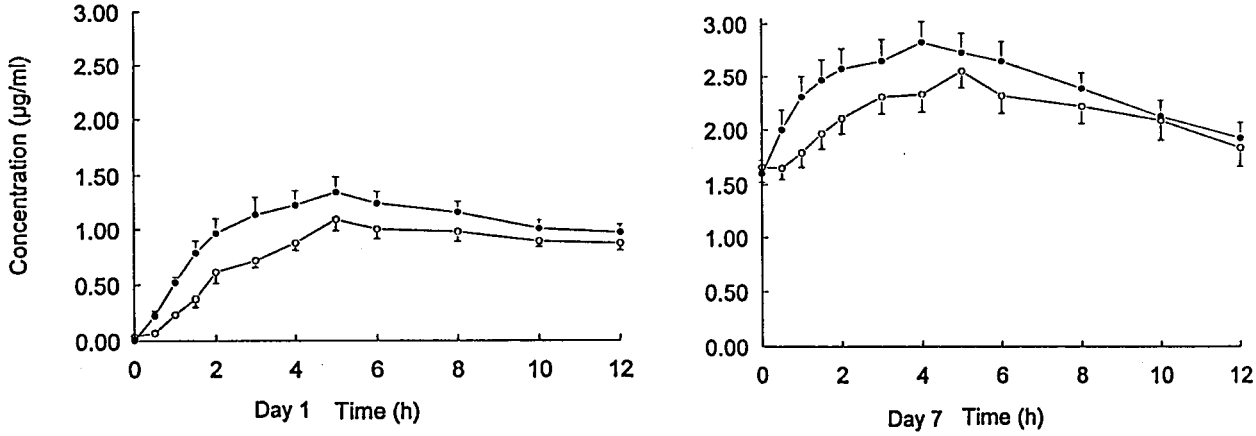

Fig. 2. Mean 3-OMD plasma concentration–time curves of the DRF (closed symbols, +SEM) and the SRF (open symbols, –SEM) following single-dose administration on day 1 and multiple-dose administration on day 7 (n = 18).

Table 2

Pharmacokinetic parameters of 3-OMD (mean (SD)) following single-dose administration on day 1 and multiple-dose administration on day 7 ($n = 18$)

3-OMD	C_{max} (μg/ml)	t_{max} (h)	AUC_{0-12} ($\mu g \times h/ml$)	AUC_{0-36} ($\mu g \times h/ml$)	$t_{1/2}$ (h)	PTF	PTS	MR
DRF, day 1	1.5 (0.6)	5.6 (2.3)	12.5 (4.9)		11.5 (6.5)			2.9 (0.5)
DRF, day 7	3.2 (0.8)	3.7 (1.6)	28.9 (7.9)	56.6 (17.7)	11.8 (3.3)	1.1 (0.4)	1.1 (0.7)	5.6 (1.7)
SRF, day 1	1.2 (0.4)	5.8 (2.3)	9.5 (2.6)		15.8 (9.2)			3.4 (1.8)
SRF, day 7	2.7 (0.7)	4.9 (2.3)	25.8 (7.1)	51.5 (15.6)	12.9 (4.3)	0.8 (0.5)	0.7 (0.4)	6.8 (1.6)

Due to a higher accumulation of 3-OMD, the metabolic ratio expressed as the AUC_{0-12} ratio of 3-OMD and levodopa is about 3 on day 1 and about 6 on day 7 for both formulations. Being a large neutral amino acid, 3-OMD may compete with levodopa for blood–brain barrier uptake [21]. Parkinsonian patients who have a poor response to levodopa have higher plasma levels of 3-OMD [4,22]. Since in our study the metabolic ratio is similar following administration of the two formulations, clinical deterioration induced by high circulating 3-OMD levels would be expected to be similar in Parkinsonian patients receiving either DRF or SRF.

5. Conclusions

The results of the present single- and multiple-dose study revealed for the new formulation a bi-phasic pharmacokinetic profile which can be characterised by a rapid absorption and sustained concentrations of levodopa. Matching specific pharmacokinetic properties of both, IRFs and SRFs raises expectations that the new DRF would have the potential to combine the advantages of a rapid onset of efficacy and a sustained effect. The new DRF containing levodopa and benserazide had a superior bioavailability compared to the SRF, both after single- and multiple-dose administration, and was well tolerated in healthy subjects. Results of the first clinical study with the DRF showed that the new galenical concept and its characteristic pharmacokinetic profile could be transformed into clinical benefits in Parkinsonian patients following substitution of the DRF for IRFs and/or SRFs [23].

References

[1] S. Harder, H. Baas, H. Bergemann, L. Demisch, S. Rietbrock, Concentration–effect relationship of levodopa in patients with Parkinson's disease after oral administration of an immediate release and a slow-release formulation, Br. J. Clin. Pharmacol. 39 (1995) 39–44.

[2] S. Harder, H. Baas, S. Rietbrock, Concentration–effect relationship of levodopa in patients with Parkinson's disease, Clin. Pharmacokinet. 29 (1995) 243–256.

[3] P.A. Kempster, J.P. Frankel, M. Bovingdon, R. Webster, A.J. Lees, G.M. Stern, Levodopa peripheral pharmacokinetics and duration of motor response in Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 52 (1989) 718–723.

[4] M.D. Muenter, N.S. Sharpless, G.M. Tyce, Plasma 3-*O*-methyldopa in levodopa therapy of Parkinson's disease, Mayo Clin. Proc. 47 (1972) 389–395.

[5] Ch. Crevoisier, B. Hoevels, G. Zürcher, M. Da Prada, Bioavailability of levodopa after Madopar HBS administration in healthy subjects, Eur. Neurol. 27 (suppl. 1) (1987) 36–46.

[6] A. Grahnén, S.A. Eckernäs, C. Collin, A. Ling-Andersson, G. Tiger, M. Nilsson, Comparative multiple-dose pharmacokinetics of slow-release levodopa products, Eur. Neurol. 32 (1992) 343–348.

[7] U.K. Rinne, J.O. Rinne, Madopar HBS in the treatment of early Parkinson's disease, in: A. Agnoli, G. Campanella (Eds.), New Developments in Therapy of Parkinson's Disease, John Libbey CIC, Rome, 1991, pp. 17–22.

[8] E.N.H. Jansen, J.D. Meerwaldt, Madopar HBS in Parkinson patients with nocturnal akinesia, Clin. Neurol. Neurosurg. 90 (1988) 35–39.

[9] E.N.H. Jansen, J.D. Meerwaldt, Madopar HBS in nocturnal symptoms of Parkinson's disease, Adv. Neurol. 53 (1990) 527–531.

[10] C. Trenkwalder, M. Wagner, T. Gasser, W. Poewe, W.H. Oertel, Long-term treatment with slow-release levodopa (Madopar HBS) in Parkinsonian patients with nocturnal disabilities, in: A. Agnoli, G. Campanella (Eds.), New Developments in Therapy of Parkinson's Disease, John Libbey CIC, Rome, 1991, pp. 22–27.

[11] W.H. Poewe, A.J. Lees, G.M. Stern, Treatment of motor fluctuations in Parkinson's disease with an oral sustained-release preparation of levodopa: clinical and pharmacokinetic observations, Clin. Neuropharmacol. 9 (1986) 430–439.

[12] U.K. Rinne, Madopar HBS in the long-term treatment of Parkinsonian patients with fluctuations in disability, Eur. Neurol. 27 (suppl. 1) (1987) 120–125.

[13] F. Stocchi, I. Giorgi, D. Bravi, S. Ruggieri, A. Monge, L. Bramanta, A. Agnoli, A multicenter trial with Madopar HBS in fluctuatory Parkinsonian patients, in: A. Agnoli, G. Campanella (Eds.), New Developments in Therapy of Parkinson's Disease, John Libbey CIC, Rome, 1991, pp. 29–32.

[14] R. Kurlan, J.G. Nutt, W.R. Woodward, K. Rothfield, D. Lichter, C. Miller, J.H. Carter, I. Shoulson, Duodenal and gastric delivery of levodopa and parkinsonism, Ann. Neurol. 23 (1988) 589–595.

[15] E. Schneider, B. Ziegler, Levodopa-Therapie und Ernährung beim Parkinson-Syndrom, Neurol. Psychiatr. Schweiz 2 (1991) 109–115.

[16] K.C. Yeh, T.F. August, D.F. Bush, K.C. Lasselet, D.G. Musson, S. Schwartz, M.E. Smith, D.C. Titus, Pharmacokinetics and bioavailability of Sinemet CR: summary of human studies, Neurology 39 (suppl. 2) (1989) 25–37.

[17] G. Heinzel, R. Woloszczak, P. Thomann, TopFit 2.0 Pharmacokinetic and Pharmacodynamic Data Analysis System for the PC, Gustav Fischer, Stuttgart, 1993.

[18] M. Contin, R. Riva, P. Martinelli, P. Cortelli, F. Albani, A. Baruzzi, Pharmacodynamic modeling of oral levodopa: clinical application in Parkinson's disease, Neurology 43 (1993) 367–371.

[19] J. Dingemanse, C.H. Kleinbloesem, G. Lankhaar, Ch. Crevoisier, U.E. Gasser, Pharmacokinetic studies with a new dual-release formulation of levodopa, a novel principle in the treatment of Parkinson's disease, Eur. Neurol. 39 (1998) 119–124.

[20] M.V. Nelson, R.C. Berchou, P.A. LeWitt, D. Kareti, M.P. Galloway, Pharmacodynamic modeling of concentration–effect relationships

after slow-release carbidopa/levodopa (Sinemet CR4) in Parkinson's disease, Neurology 40 (1990) 70–74.
[21] L.A. Wade, R. Katzman, 3-*O*-Methyldopa uptake and inhibition of levodopa at the blood–brain barrier, Life Sci. 17 (1975) 131–136.
[22] L. Rivera-Calimlim, T. Deepak, R. Anderson, R. Joynt, The clinical picture and plasma levodopa metabolite profile of parkinsonian nonresponders, Arch. Neurol. 34 (1977) 228–232.
[23] J. Ghika, J.P. Gachoud, U.E. Gasser and the l-Dopa Dual-Release Study Group, Clinical efficacy and tolerability of a new Levodopa/Benserazide Dual-Release formulation in Parkinsonian patients, Clin. Neuropharm. 20 (1997) 130–139.