

## ORIGINAL ARTICLE

# Steady-state bioequivalence studies of two memantine tablet and oral solution formulations in healthy volunteers

Jaroslav Chládek<sup>1</sup>, Bořek Žaludek<sup>2</sup>, Petr Sova<sup>2</sup>, Aleš Franc<sup>2</sup>, Luděk Šišpera<sup>1</sup>, Jiřina Martínková<sup>1</sup>,  
Stanislav Mičuda<sup>1</sup>, Jolana Cermanová<sup>1</sup>

<sup>1</sup>Department of Pharmacology, Faculty of Medicine, Charles University, Hradec Králové, Czech Republic,

<sup>2</sup>Pliva-LACHEMA a.s., Brno, Czech Republic

Received 11<sup>th</sup> September 2007.

Revised 4<sup>th</sup> October 2007.

Published online 22<sup>nd</sup> November 2007.

### Summary

The bioavailability of memantine was compared using two tablet (Memantine LACHEMA 10 tbl. obd. and Akatinol® Memantine 10 tbl. obd., Study A) and two oral solution formulations (Memantine LACHEMA gtt. and Akatinol® Memantine gtt., Study B) containing 10 mg memantine hydrochloride in two randomized, two-period, two-sequence, crossover studies with 24 healthy volunteers. In both study periods, memantine concentrations were determined by gas-chromatography with electron-capture detection in plasma samples taken at the steady state after 22 days of once-daily dosing. The arithmetic mean (SD) pharmacokinetic parameters in the studies A and B were:  $AUC_{0-0.75\tau_{ss}}$  768 (141) vs. 727 (99) and 807 (154) vs. 836 (156) ng/ml h,  $C_{max,ss}$  37.3 (6.1) vs. 35.2 (4.5) and 39.2 (7.3) vs. 40.6 (6.7) ng/ml. Median values of  $T_{max}$  were in the range of 4 to 5 h. Both tablet and oral solution formulations were found bioequivalent (90%-confidence intervals for  $AUC_{0-0.75\tau_{ss}}$ ,  $C_{max,ss}$  and  $C_{\tau,ss}$  within 101–114% (Study A) and 92 and 104% (Study B)). For the peak-trough fluctuation, the bioequivalence intervals were 85–107% and 86–104%, respectively. By pooled analysis of both studies, the geometric mean (90% CI) relative bioavailability of memantine from tablets compared to oral solutions was 91% (85–98).

**Keywords:** memantine – pharmacokinetics – bioequivalence

## INTRODUCTION

Memantine (1-amino-3,5-dimethyladamantane hydrochloride, Fig. 1) is an uncompetitive

antagonist of glutamate at the N-methyl-D-aspartate (NMDA) receptor complex, whose dysfunction is involved in many neurodegenerative diseases associated with ageing, such as vascular dementia, Alzheimer's disease, stroke and Parkinson's disease (Le and Lipton 2001, Palmer 2001). Memantine appears to block the NMDA receptor in its open state, i.e. in the presence of pathologic neural toxicity associated with persistent activation of the NMDA receptor due to prolonged glutamate release without altering activation of the receptor during physiological neurotransmission. Several controlled clinical trials in patients with Alzheimer's disease have demonstrated the efficacy

---

✉ Jaroslav Chládek, Department of Pharmacology, Faculty of Medicine, Charles University, Šimkova 870, 500 01 Hradec Králové, Czech Republic

chladekj@lfhk.cuni.cz

+420-49-5816104

+420-49-5513022

---

of memantine on cognitive, functional, and global clinical criteria (Reisberg et al. 2003, Reisberg et al. 2006, Peskind et al. 2006). Clinical experience so far confirms the safety of use and good tolerability profile of memantine at the recommended daily dosages of 10 to 30 mg.

There are few published studies of memantine pharmacokinetics in humans. The available data show that memantine is well absorbed from the gastrointestinal tract and its pharmacokinetics are linear after single doses of 5 to 40 mg. After a single oral administration of 20–40 mg memantine, peak plasma concentrations of 40–90 ng/ml are observed at 3.5–7 h. The terminal half-life is as long as 53<sub>297h</sub> (Wesemann et al. 1983, Freudenthaler et al. 1998). The drug is predominantly (>90%) excreted via the kidney as unchanged drug and glucuronide conjugate. Memantine is a weak base with pK of 10.3 and urine pH has a considerable effect on its renal clearance (Freudenthaler et al. 1998). Renal and total clearances of memantine are reduced and dose reduction is recommended in patients with severe renal impairment (Periclou et al. 2006).

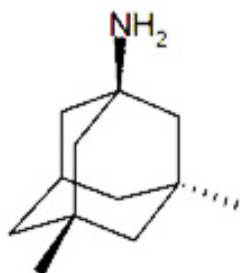


Fig. 1. Chemical structure of memantine.

The aim of the present work was to investigate the relative bioavailability of two new memantine oral formulations: Memantine LACHEMA tablet and oral solution versus reference formulations Akatinol® Memantine in two separate fixed-multiple-dose studies (10 mg memantine hydrochloride qd). The drug was administered to 24 healthy volunteers in a multiple-dose regimen under fasting conditions.

## MATERIALS AND METHODS

### Pharmaceutical formulations

The newly developed formulations containing 10 mg memantine hydrochloride were Memantin LACHEMA 10 tbl. obd. and Memantin

LACHEMA gtt. (both produced by Pliva-LACHEMA, a.s., Brno, The Czech Republic). The reference formulations were Akatinol® Memantine 10 tbl. obd. and Akatinol® Memantine gtt. (both produced by MERZ and Co., Frankfurt, Germany). Two separate studies were conducted: one with tablets (Study A) and the other with oral solutions (Study B).

### Subjects

Twenty-four healthy male subjects with the mean (range) basic characteristics: age 23 years (18–30), body weight of 77 kg (65–100), and height 181 cm (168–192) were enrolled in the tablet study (Study A). The characteristics of the subjects participating in the oral solution study (Study B) were quite comparable: age 23 years (19–26), body weight 77 kg (65–102) and height 181 cm (172–194). The subjects were non-smokers taking no other medication. The exclusion criteria were renal insufficiency, liver, gastrointestinal, cardiovascular, neurological, psychiatric and haematological diseases. The subjects were covered by special insurance policies and gave written consent to participate in the study.

### Study design

The studies were performed at the 1<sup>st</sup> Department of Internal Medicine, University Hospital and Department of Pharmacology, Charles University in Prague, Faculty of Medicine in Hradec Králové, The Czech Republic. The Ethics Committee of The Faculty of Medicine and University Hospital approved the study protocol. Both studies were performed in compliance with the Declaration of Helsinki and with principles of good clinical and laboratory practice.

Both studies were organized as open, fixed-multiple-dose, randomized, two-way cross-over studies in 24 healthy young male volunteers. The subjects, who had met the study entry criteria were dosed according to a randomisation schedule. The studies consisted of two phases with duration of 22 days each to allow for attainment of the steady-state. Subjects showed up at the study centre in the morning of each study day in order to have their drug intake. On day 22 of each study phase, the subjects were hospitalised at the 1<sup>st</sup> Department of Internal Medicine and remained there for 24 h. Blood samples (10 ml each) for plasma concentration measurements of memantine were collected from the antecubital veins immediately before drug administration and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16 and 24 h thereafter. The samples were collected into monovettes containing NH<sub>4</sub>-heparinate as an anticoagulant and centrifuged in a cooling centrifuge (8 °C, 3 000 g for 10 min). The plasma was pipetted into 2 ml plastic tubes and frozen at -20 °C. Within 24 h of collection, the

samples were placed in a  $-70\text{ }^{\circ}\text{C}$  freezer and stored until analysis (no longer than 6 months).

#### Analytical method

Plasma concentrations of memantine were determined using a fully validated gas chromatography assay with electron capture detection. The plasma sample was thawed and 1 ml was added to 0.5 ml of the internal standard solution (80 ng/ml rimantadine in 4mM  $\text{H}_2\text{SO}_4$ ) in a 10 ml glass tube. The sample was alkalised by the addition of 0.5 ml of 2M NaOH. Toluene (4.5 ml) was added and the tubes were shaken on a reciprocating shaker (100 strokes/min) for 30 min and then centrifuged at 2000 g for 10 min. The organic phase was transferred to 1 ml of 0.1M  $\text{H}_2\text{SO}_4$  in 10 ml glass tubes and the tubes were shaken and centrifuged as described above. The aqueous phase was frozen by placing the tubes in a ethanol bath at  $-25\text{ }^{\circ}\text{C}$  for 5 min and then the upper toluene layer was immediately removed. After heating the tubes in a water bath at  $25\text{ }^{\circ}\text{C}$  for 15 min, the aqueous phase was made alkaline by the addition of 1 ml of 2M NaOH. The final extractive benzoylation was carried out by shaking the solutions with 1 ml of a derivatization reagent ( $8.10^{-4}\%$  pentafluorobenzoyl chloride in toluene) for 30 min. After 10 min of centrifugation, the aqueous phase was frozen as described previously. The upper toluene layer was poured into a glass autosampler vial and analysed by GC-ECD.

#### Instrumentation and chromatographic conditions

The assay was developed using a 6890+ series gas chromatograph, equipped with a micro electron-capture detector, a split-splitless injector and a 7683 series autosampler (Hewlett-Packard, Wilmington, DE, USA). Data acquisition was accomplished using a personal computer Kayak XA equipped with Chemstation software (Hewlett-Packard, Wilmington, DE, USA). The carrier gas was hydrogen at the flow rate of 4 ml/min. The auxiliary gas was argon-methane (95:5, 99.9999%, Linde, Prague, The Czech Republic) at a flow rate of 26 ml/min. Hydrogen was generated using a model 75-34 generator (Whatman, Haverhill, MA, USA). Chromatography was performed on an HP-35 fused-silica capillary column (30 m x 0.32 mm I.D.), film thickness 0.25 mm (Hewlett-Packard, No. 19091G-113).

The operating temperature for the injector and detector was  $280\text{ }^{\circ}\text{C}$ . The oven temperature was programmed as follows: 1 min interval at  $143\text{ }^{\circ}\text{C}$ ,  $50\text{ }^{\circ}\text{C}/\text{min}$  up to  $193\text{ }^{\circ}\text{C}$ , then  $4\text{ }^{\circ}\text{C}/\text{min}$  up to  $221\text{ }^{\circ}\text{C}$ , then  $40\text{ }^{\circ}\text{C}/\text{min}$  up to  $240\text{ }^{\circ}\text{C}$  and held for 2.45 min. An equilibration period of 2 min was set to stabilise the temperature prior to the following injection. The split-splitless injector was operated in the splitless mode. The splitless period, split flow and purge flow were 0.75 min, 20 ml/min and

6 ml/min, respectively. For the autosampler, the fast injection mode and toluene as a washing solvent were used.

#### Pharmacokinetic and statistical analysis

From memantine plasma levels, the following pharmacokinetic parameters were estimated: the area under the curve over one dosing interval  $\tau=24\text{ h}$  at the steady-state ( $\text{AUC}_{0-\tau,ss}$ ) was calculated by means of the linear trapezoidal rule; the maximum concentration ( $C_{\text{max},ss}$ ), minimum plasma concentration ( $C_{\tau,ss}$ ), pre-dose concentration ( $C_{\tau,ss}$ ) and the time of  $C_{\text{max},ss}$  occurrence ( $T_{\text{max}}$ ) were obtained directly from the plasma profiles. Peak trough fluctuation (PTF) was calculated as follows:  $\% \text{ PTF} = 100 (C_{\text{max},ss} - C_{\tau,ss}) / C_{\text{av}}$ , where  $C_{\text{av}}$  is the average plasma concentration (the ratio of the  $\text{AUC}_{0-\tau,ss}$  to the length of the inter-dose interval  $\tau$  of 24 h).

The decision in favour of bioequivalence was based on the inclusion of the shortest 90%-confidence interval for the ratio of expected medians in the respective bioequivalence range, assuming a multiplicative model. Point estimates and 90% confidence intervals for the test-to-reference ratios of the parameters  $\text{AUC}_{0-\tau,ss}$ ,  $C_{\text{max},ss}$ ,  $C_{\tau,ss}$  and PTF were derived from confidence intervals for the differences of means of the logarithmically transformed values. A full model for the cross-over design was chosen as a model for the analysis of variance and including the factors: carry-over, volunteer (nested in sequence), treatment and period. For the parameter  $T_{\text{max}}$ , the point estimate and the 90% confidence interval were derived for the median difference by a method described elsewhere (Hauschke et al. 1990). In the present bioequivalence study, the bioequivalence interval 0.80–1.25 was suggested for the parameters  $\text{AUC}_{0-\tau,ss}$ . For  $C_{\text{max},ss}$  and  $C_{\tau,ss}$ , the respective interval was 0.70–1.43. The median difference in  $T_{\text{max}}$  should be within  $\pm 2\text{ h}$ .

## RESULTS

#### Validation of the assay for plasma memantine

The results of an in-study validation of the analytical method have demonstrated its excellent performance. The linearity of the calibration line was confirmed over the concentration range of 5.0–100 ng/ml. In both studies, each of 27 analytical batches included study samples, two sets of calibration standards (7 concentration levels and blank), spiked quality control samples in duplicate at three concentrations, and one biological quality control sample (a pool of plasma samples obtained during the study). The assayed concentrations of calibration standards were used to calculate between-day accuracy and imprecision. Relative

errors ranged from -0.9% to +1.2%. The coefficients of variation were less than 6.50%. For spiked quality control samples, the relative errors were in the range of -2.9% to +1.3% and the estimates of within-run and between-run imprecision (%CV) were less than 5.5%. The between-run imprecision of the assayed concentrations of the BQC was 4.7%. There was no plasma sample with a memantine concentration less than the lower limit of quantification of 5.0 ng/ml.

Spiked quality control samples at two concentrations (12 and 80 ng/ml) were used to evaluate the stability of memantine in human plasma. Memantine was stable in the plasma samples allowed to stay at room temperature for up to 6 h, during three freeze/thaw cycles, and during long-term storage at -70 °C for one year. The stability of memantine in extracts of plasma samples placed in the autosampler at laboratory temperature (20–23 °C) was proven for 48 h.

Table 1. Mean (SD) memantine pharmacokinetic parameters at the steady-state following multiple oral doses of 10 mg memantine hydrochloride qd in two tablet and two oral solution formulations.

		Tablets		Oral solutions	
		Memantine LACHEMA 10 tbl. obd.	Akatinol Memantine 10 tbl. obd.	Memantin LACHEMA gtt.	Akatinol Memantine gtt.
AUC <sub>0-τ ss</sub> *	ng/ml·h	768 ± 141	727 ± 99	807 ± 154	836 ± 156
C <sub>max,ss</sub>	ng/ml	37.3 ± 6.1	35.2 ± 4.5	39.2 ± 7.3	40.6 ± 6.7
C <sub>τ,ss</sub>	ng/ml	28.0 ± 6.0	25.9 ± 4.1	28.8 ± 6.1	29.2 ± 6.1
C <sub>ss</sub>	ng/ml	27.1 ± 4.6	25.5 ± 4.1	27.9 ± 5.6	29.4 ± 6.8
T <sub>max</sub> **	h	4 (2 – 10)	5 (3 – 12)	4 (1 – 12)	4 (1 – 10)
% PTF	%	29.8 ± 10.4	30.8 ± 8.9	31.3 ± 8.0	33.0 ± 8.4
t <sub>1/2</sub>	h	71.2 ± 42.2	64.2 ± 61.1	60.6 ± 40.5	51.1 ± 34.9
CL / F	L / h	13.4 ± 2.25	14.0 ± 1.96	12.9 ± 2.66	12.3 ± 2.1
V <sub>ss</sub> / F	L	1350 ± 826	1270 ± 1090	1110 ± 750	877 ± 419

\*τ is the inter-dose interval of 24 h

\*\* the median (range)

Table 2. Bioequivalence testing of memantine tablet and solution formulations.

Parameter	Tablets		Solutions	
	Point estimate	90%-CI	Point estimate	90%-CI
AUC <sub>0-τ ss</sub> ratio (%)	105	101 – 109	96	92 – 101
C <sub>max,ss</sub> ratio (%)	106	102 – 109	96	92 – 101
C <sub>τ,ss</sub> ratio (%)	108	101 – 114	98	92 – 104
% PTF ratio (%)	100	85 – 107	99	86 – 104
T <sub>max</sub> difference (h)	! 0.5	! 1.0 – 0.5	0.5	! 0.5 – 1

### Safety and tolerability

In both studies, the test and reference formulations were well tolerated. There was no premature withdrawal from the study by any subject. In the course of the studies, several subjects reported mild transient adverse effects possibly related to the drug administration. These adverse effects did not significantly influence the subjects' condition and all of them had been resolved at the follow-up examination.

Five subjects had transient sleep problems, five subjects experienced vertigo, eleven fatigue, five headache, two subjects reported accelerated psychic activity and two accelerated physical activity. Two subjects experienced unfocused vision, euphoria, irritability and enhanced sexual arousal. There were no pathological changes during physical examinations performed on the days of memantine administration and after the end of the study. There were no pathological changes on 12-lead

electrocardiograms. No clinically important changes in the results of clinical chemistry or haematology were observed.

### Steady-state pharmacokinetics of memantine

The geometric mean plasma concentration vs time data for memantine are presented in Fig. 2. The pharmacokinetic variables are summarized in Table 1. For all drug formulations, the mean pre-dose concentration  $C_{ss}$  was the same as the concentration at the end of the inter-dose interval of 24 h ( $C_{\tau,ss}$ ). The intra-individual variability of  $AUC_{0-\tau,ss}$ ,  $C_{max,ss}$  and  $C_{\tau,ss}$  in both studies was comparable and were less than 13%. The inter-individual variability of all these variables was within the range of 13 to 18%. For both the tablet and oral solution formulations, the peak-trough fluctuation (PTF) was the variable with the highest intra-individual (23% and 19%) and inter-individual variability (27% and 23%).

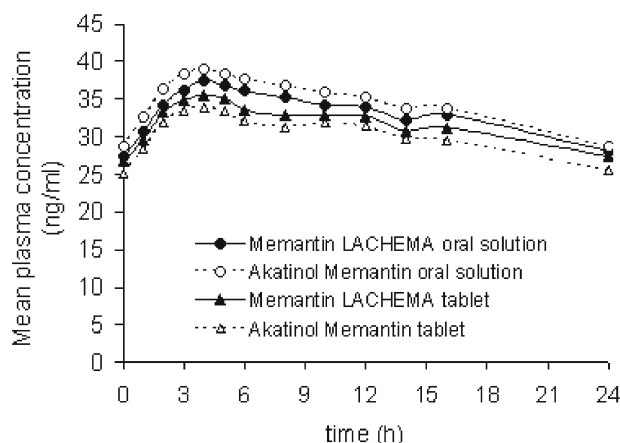


Fig. 2. Geometric mean plasma memantine concentrations versus time profiles at steady state following a multiple oral dose of 10 mg memantine hydrochloride in two tablet and two oral solution formulations.

These results indicate that the power to prove bioequivalence was higher than 95% for all parameters except of PTF (83%). The geometric mean half-lives of memantine in plasma were independent of formulation and ranged from 44 h to 61 h. However, the range of individual values of  $t_{1/2}$  was very large (21–180 h).

The results of the statistical analysis of bioequivalence obtained by parametric and nonparametric procedures are given in Table 2. It was concluded that the tablet formulation under

investigation, Memantin LACHEMA 10, was bioequivalent to the Akatinol® Memantin 10 tablet formulations with respect to all parameters tested. The same conclusion was accepted with regard to both oral solution formulations under comparison. By pooled analysis of the data from both studies, the geometric mean (90% CI) relative bioavailability of memantine from the tablet formulations compared to the solution formulations was 91% (85–98 %).

## DISCUSSION

This work reports on two separate bioequivalence studies, one with tablets and the other with oral solutions containing memantine hydrochloride. In vivo bioequivalence studies are waived for solutions on the assumption that release of the drug substance from the drug product is self-evident and that the solutions do not contain any excipient that significantly affects drug absorption. The oral solution formulation Memantin LACHEMA gtt. contains sorbitol, i.e. an excipient that may reduce drug absorption. Therefore, it was decided to prove its bioequivalence with the reference formulation in a bioequivalence study. This also raised the possibility of comparing the pharmacokinetics of memantine released from tablet and solution formulations.

Both studies were conducted at the steady state under fasting conditions. The multiple-dose design was selected for two main reasons. First, memantine has a very long half-life. A single-dose cross-over design would require sampling of blood over at least one week after administration. Second, plasma levels are higher at the steady state. Memantine was well tolerated by young healthy volunteers in a published study with a design similar to our studies (Freudenthaler et al. 1998). Attainment of the steady state was not verified by measurements of trough memantine concentrations on additional days preceding the measurement days. However, each drug administration was performed under supervision and the total period of continuous dosing (22 days) was approximately 7- to 10-times longer than the mean half-life. Moreover, the mean pre-dose concentrations agreed with the mean concentrations at the end of the inter-dose interval of 24 h.

The mean steady-state memantine plasma concentrations were quite comparable between all four formulations. The pharmacokinetic variables  $AUC_{0-\tau_{ss}}$ ,  $C_{max,ss}$  and  $T_{max}$  and estimated half-lives agree well with a previously published steady-state study with healthy volunteers (Freudenthaler et al. 1998). Taken together, these data indicate that memantine is well and rapidly absorbed from oral dosage formulations. The drug has a very large  $V_{ss}$  of 1000 L, approximately. It can be concluded that the long terminal half-life of memantine reflects its redistribution from tissues back to the plasma where the drug becomes available for renal excretion. Recently, Kornhuber et al (2007) have performed a population pharmacokinetic study of memantine in patients with neuropsychiatric diseases.

The steady-state clearance of memantine was influenced by the total body weight, drug formulation and co-medication eliminated via tubular secretion (Kornhuber et al. 2007). Patients receiving memantine solution (Akatinol

Memantine) had higher memantine concentrations and 47% less total clearance compared to those taking tablets. In our study, we observed only a 10% reduction in total clearance. The possible explanation is that, in a population study with naturalistic design, the bioavailability of memantine from tablets was less due to some other factors such as the dose and compliance. Periclou et al. (2006) investigated the pharmacokinetics of memantine after a single dose administration of 20 mg memantine in two tablets to healthy volunteers and estimated the steady-state maximum concentration after 10 mg bid using pharmacokinetic modelling (Periclou et al. 2006). A maximum concentration of 37 ng/ml observed in our study after 10 mg memantine once daily corresponds to the maximum steady-state concentration of 82 mg/l estimated by Periclou et al. (2006) for twice as high a rate of dosing, i.e. 10 mg twice daily.

In our study, the range of individual values for  $t_{1/2}$  was very large (21–180 h). Most probably, this was the result of difficulties in its estimation since the mean concentration vs time profiles showed double and triple concentration maxima (Fig. 2). We found that the intra-individual and inter-individual variability in the proposed characteristics of bioequivalence ( $AUC_{0-\tau_{ss}}$  and  $C_{max,ss}$ ) was low (less than 13% and 18%, respectively). The composite metric %PTF was the variable with the highest intra-individual variability of 23% (tablets) and 19% (oral solutions), respectively. The point estimates and 90%-confidence intervals for the test/reference ratios indicate that bioequivalence criteria were highly fulfilled for all characteristics. Moreover, low intra-individual variability of most characteristics resulted in very narrow confidence intervals. Administration of 10 mg memantine hydrochloride once daily over 44 days was safe and well tolerated. Adverse effects (fatigue, vertigo, headache, insomnia) were mild and transient.

In conclusion, according to the current valid criteria, the memantine tablet formulation Memantin LACHEMA 10 tbl. obd. is bioequivalent to Akatinol® Memantine 10 tbl. obd. and the oral solution formulation Memantin LACHEMA gtt. is bioequivalent to Akatinol® Memantine gtt. After multiple-dose administration of 10 mg memantine hydrochloride, the relative bioavailability of memantine from tablets compared to oral solutions was 91%. All formulations were well tolerated.

## ACKNOWLEDGEMENTS

This study was supported by a grant from the Czech Ministry of Industry and Trade No. FB-CV/09. We thank the subjects for their participation and excellent compliance with the protocol. We gratefully acknowledge the technical assistance of

Hana Krupičková, Ivana Tothová, Jana Prokopová  
and Ludmila Koželuhová.

## REFERENCES

- Freudenthaler S, Meineke I, Schreeb KH, Boakye E, Gundert-Remy U, Gleiter CH: Influence of urine pH and urinary flow on the renal excretion of memantine. *Br. J. Clin. Pharmacol.* 46:541–546, 1998.
- Hauschke D, Steinijans VW, Diletti E: A distribution-free procedure for the statistical analysis of bioequivalence studies. *Int. J. Clin. Pharmacol. Ther. Toxicol.* 28:72–80, 1990.
- Kornhuber J, Kennepohl EM, Bleich S, Wiltfang J, Kraus T, Reulbach U, Meineke I: Memantine pharmacotherapy: A naturalistic study using a population pharmacokinetic approach. *Clin. Pharmacokinet.* 46:599–612, 2007.
- Le DA, Lipton SA: Potential and current use of N-methyl-D-aspartate (NMDA) receptor antagonists in diseases of aging. *Drugs Aging* 18:717–24, 2001.
- Palmer GC: Neuroprotection by NMDA receptor antagonists in a variety of neuropathologies. *Curr. Drug Targets* 2:241–71, 2001.
- Periclou A, Ventura D, Rao N, Abramowitz W: Pharmacokinetic study of memantine in healthy and renally impaired subjects. *Clin. Pharmacol. Ther.* 79:134–43, 2006.
- Peskind ER, Potkin SG, Pomara N et al.: Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial. *Am. J. Geriatr. Psychiatry* 14:704–15, 2006.
- Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ: A 24-week open-label extension study of memantine in moderate to severe Alzheimer disease. *Arch. Neurol.* 63:49–54, 2006.
- Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ: Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. *N. Engl. J. Med.* 348:1333–41, 2003.
- Wesemann W, Sontag KH, Maj J: Zur Pharmakodynamik und Pharmakokinetik des Memantin. *Arzneimittelforschung* 33:1122–1134, 1983.