THE EXPERIENCE OF AMANTADINE PHARMACOKINETIC MONITORING FOR INDIVIDUALIZING THE PHARMACOTHERAPY OF EXTRAPYRAMIDAL DISORDERS

D.A. Abaimov, V.V. Poleshchuk, L.A. Chigaleychik, E.Yu. Fedotova, S.L. Timerbaeva

Research Center of Neurology, Moscow

abaidenis@yandex.ru

Amantadine is the most known drug from the group of adamantanes. It has antiviral and, at the same time, anti-Parkinsonian activity (Illarioshkin, 2009). Mechanism of amantadine antiparkinsonian therapeutic action may be explained by stimulation of neuronal dopamine release and antagonism against NMDA-glutamate receptor, as well as by inhibition of pulses generation in motoneurons in the CNS. In neurology, amantadine is mainly used in the pharmacotherapy of Parkinson's disease (PD). Main clinical effects of amantadine are moderate reduction of major motor symptoms and levodopa-induced dyskinesia. Unfortunately, besides of all important positive properties, amantadine has quite a large number of side effects (especially in the elderly), the minimization of which requires the use of more sensitive therapeutic drug monitoring (TDM) technologies with the evaluation of the drug concentration in the blood of patients. The standard dose of amantadine is 200 mg per day; amantadine steady-state blood concentration is being reached during 4-7 days. Individual concentration values in the blood of the patients may be varied within the therapeutic range from 200 to 900 ng/ml (Pacifici et al., 1976). There is a proven correlation between blood levels of amantadine and its effect on extrapyramidal symptoms. This drug may interact with other substances, with both positive and negative clinical effects. For example, amantadine enhances the suppression of viral activity of interferon, potentiates anty-dyskinetic effects of levetiracetam in patients with PD, and may cause intense and recurrent paramnestic disturbances (such as déjà vu) while the use of phenylpropanolamine in the treatment of influenza. Amantadine side effects (such as nausea, dizziness and insomnia) occur quite frequently in patients (5-15%), especially in chronic amantadine administration (more than 6 weeks). Side effects of amantadine also include amphetamine-like effects: increased neuro-reflex excitability syndrome, anxiety, nightmares, etc. Amantadine concentration in the blood exceeding 1600 pg / mL is considered toxic (Arndt et al., 2005).

Treatment with high doses of amantadine is the cause of serious side effects such as heart attacks, suicide attempts, impotence, confusion, dysphonia, and alopecia. Drug interactions are directly dependent on serum concentrations of amantadine. Management of these effects requires the use of an adequate method of amantadine quantitative analysis.

Existing analytic methods, such as gas chromatography/mass spectrometry, are quite complex. Therefore, routine analysis of amantadine is rarely used in a clinical laboratories, and TDM of amantadine is not widely accepted. Creating a new method of amantadine analysis based on tandem liquid chromatography-mass spectrometry may allow simplifying sample preparation, reducing duration and cost of the analysis of single sample, as well as improving the selectivity and specificity of the method. In this regard, we have developed HPLC-mass spectrometric method for the analysis of blood plasma for pharmacokinetic maintenance of amantadine in PD patients. Our main task was to implement this method into clinical practice and to evaluate its usefulness in the selection of dose regimen in patients with extrapyramidal disorders.

MATERIALS AND METHODS

The study included 20 patients (12 female, 8 male) aged 56 to 70 years old (62 ± 6,1 years) suffering from PD and receiving amantadine. Selection of venous blood in heparinized tubes was carried out once at the maximum concentration selected [3], 3 hours after taking the drug; the tubes were centrifuged for 15 minutes at a speed of 3500 r.p.m to obtain blood plasma. Plasma samples were stored at the temperature -70°C in the hematology freezer until analysis. Prior to blood sampling procedure, patients signed informed consent to participate in the study.

Amantadine concentration in plasma was determined by liquid chromatography of the original copyright mass-spectrometric method. Amantadine was extracted from plasma by liquid extraction with diethyl ether. The concentration of drug in blood plasma was determined by liquid chromatography-mass spectrometry instrument Finnigan Surveyor LC Pump Plus in combination with mass spectrometry detector «LCQ Fleet MS» (quadrupole ion trap); Analytical Column - XTerra MS C18 firm Waters, USA (4,6 × 150 mm, 5 micron). The mobile phase consisted of two solutions: 10 mM ammonium acetate (solution A) and acetonitrile with 10% 10 mM ammonium acetate *v/v* (solution B). Solutions A and B were taken as a ratio of 60A: 40B. The work was conducted in isocratic elution mode. Total time of chromatography was 11 min. Mobile phase flow rate, 0.7 ml/min. Mass spectrometric detection was carried out by amantadine fragment-ion with *m/z* 134.9, which is formed as a result of the fragmentation of the parent molecular amantadine ion with *m/z* 152.2 by normalized collision energy of 20 eV. Ionization method was the electrospray in a positive ion mode. A more detailed description of the method can be provided by the authors upon request.

RESULTS AND DISCUSSION

In the studied group of patients with PD, mean concentration of amantadine was 388,5 ± 184,3 ng/ml. Concentration values ranged from 164.1 ng/mL to 758.3 ng/ml (348.68 [238.0; 540.7] ng/ml). Thus, most values were within the recommended therapeutic range of concentrations, which, according to the literature, is in the range from 200 to 600 ng/ml (Regenthal et al., 1999). Among the patients, we observed a small group (5 persons) at the initial stage of dose titration, whose concentration values of amantadine

were at the low range of the ‘therapeutic corridor’ and ranged from 164,1ng / mL to 252.8 ng / mL (241.94 [169 8, 252.2] ng / ml). The group of patients in the stationary state pharmacokinetics (amantadine taking over seven days required to reach the equilibrium concentration in the blood) was quite uniform. It has been found that patients taking amantadine 200 mg/day in their concentration values (515.6 [504.6; 524.4] ng/ml) did not significantly differ from the group of patients treated with amantadine 300 mg per day (540.7 [238.0, 568.9] ng/mL). This suggests in favor of the possibility of achieving the desired therapeutic effect at lower doses of amantadine (Fig. 1).

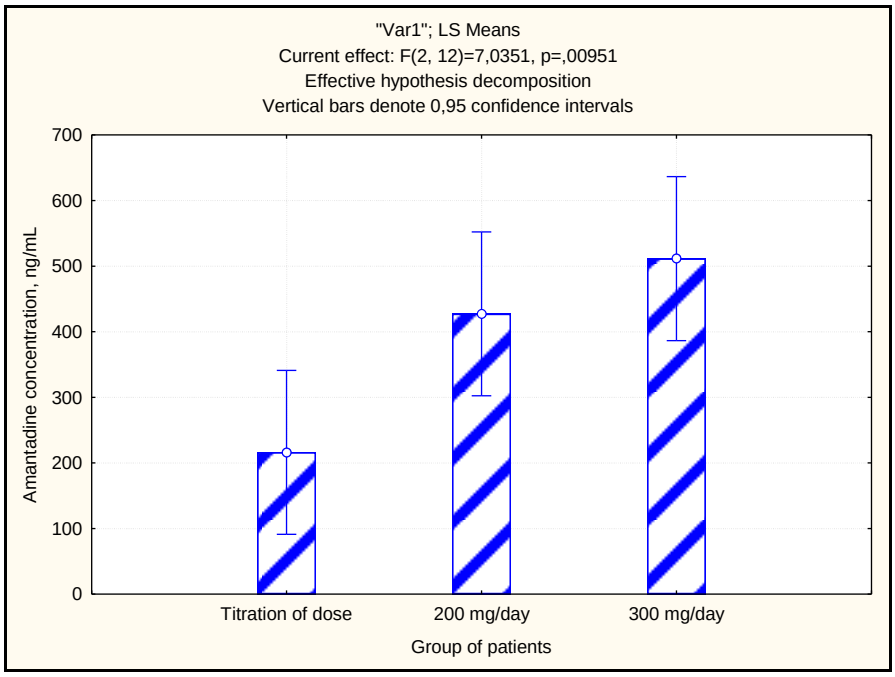

Figure 1. Concentration values of amantadine in patients with different dosing regimens.

CONCLUSIONS

1. We developed a metrologically validated LC-mass-spectrometric method for the quantitative determination of amantadine in human blood plasma.
2. With the use of this method, the amantadine blood concentrations was measured in the plasma samples from 20 patients with PD.
3. We demonstrated the usefulness of the method in individualizing the dosing and pharmacokinetic support of patients receiving amantadine both in mono- and polytherapy of PD.
4. Based on the individual pharmacokinetic parameters, we made some corrections of drug therapy in a number of patients.

REFERENCES

1. Arndt T., Guessregen B., Hohl A., Reis J. Determination of serum amantadine by liquid chromatography-tandem mass

spectrometry // Clin. Chim. Acta. 2005; 359: 125-131.
2. Illarioshkin S.N. Therapy of parkinsonism: capabilities and perspectives // Neurology and reumatology. Supplement of the Journal "Consilium Medicum". 2009; №1: 35-40 (in Rus.).
3. Pacifici G.M., Nardini M., Ferrari P. et al. Effect of amantadine on drug-induced parkisonism: relationship between plasma levels and effect // Br. J. Clin. Pharmacol. 1976; 3: 883-889.
4. Regenthal R., Krueger M., Koeppel C. et al. Drug levels: therapeutic and toxic serum/plasma concentrations of common drugs // J. Clin. Monitor. Comput. 1999; 15: 529-544.