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COMPARISON OF SAFETY BETWEEN INDIVIDUALIZED AND EMPIRIC DOSE REGIMEN OF AMITRIPTYLINE IN THE TREATMENT OF MAJOR DEPRESSIVE EPISODE

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SUMMARY

To accomplish therapeutic goal it is necessary to adjust the dose of medication to be right for every single patient. This procedure of dose adjustment is individualized dose regimen. First of all, pharmacokinetic aspects should be revised, including parameters such as resorption, distribution, metabolism and secretion of drug. For these purposes, the authors developed and clinically assessed the modified Bayesian method supported by original basic computer program. The aim of research was to compare frequency of adverse events in cases of individualized and empiric dose regimens of amitriptyline in the treatment of major depressive episode. Sixty subjects (32- 65 years old), with major depressive disorder (International Classification of Disease, 10th revision), were randomly assigned and single- blinded to take individualized (experimental group, n=30) or empiric (control group, n=30) doses of amitriptyline for 8 weeks. CGI scale and originally designed questionnaire were used for adverse events assessment. In experimental group, 69 complaints on nine different types of adverse effects were recorded during eight-week treatment period. Severe adverse events, such as confusion or arrhythmia, were not registered in this subgroup. In control group, 111 complaints on twelve different types of adverse effects were recorded. Most common were anticholinergic effects, but during the third and fourth week from baseline, some severe adverse events were observed: tremor (16%), fatigue (16%), in one of the subjects confusion occurred and arrhythmia in another. Analyzing of the results according to CGI scale for adverse events showed that, during the treatment period, adverse events were less frequent in experimental group. This was particularly obvious in the first four weeks of treatment, when statistically significant difference ($p<0.05$) was observed.

Key words: *creative psychopharmacotherapy - individualized treatment - personalized medicine*

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INTRODUCTION

Amitriptyline is a tricyclic antidepressant approved for the treatment of major depression. Adult typical dosages are 25 to 150 mg daily. Generally it is accepted that exist correlation between plasma concentrations of amitriptyline and therapeutic effect in major depressive disorder (Ulrich & Lauter 2002). To accomplish therapeutic gold it is necessary to adjust dose of medication to every single patient (Filaković & Petek 2009; De Leon 2009). This procedure of dose adjustment is individualized dose regimen. First of all, pharmacokinetic aspects should be revised, including parameters such as resorption, distribution, metabolism and secretion of drug, too (Benet et al. 1996, Eugene & Po See Ch 2008).

SUBJECT AND METHODS

The most frequently used is Bayesian method of dose individualization using nomograms, specific for a particular patient (Potter et al. 1980), but in Serbian population this method can not be used because appropriate nomograms do not exist (Mihajlović 2004). The most precise, multiple-point method and simple to apply, the single dose method, have serious limitations (Barbui & Hotopf 2001). So for these purposes, the authors developed and clinically assessed the modified Bayesian method supported by original basic computer program. The program calculates doses using following parameters: therapeutic steady-state concentration of 80 ng/mL, patients sex, weight, age, creatinin plasma concentration, albumin plasma concentration and volume of the liquid in the "third space" with additional adjustment to the Serbian population (Jankovic et al. 1999). The aim of research was to compare frequency of adverse events between individualized and empiric dose regimen of amitriptyline in the treatment of major depressive episode. Sixty subjects (21 men and 49 women, between 32- 65 years old), with major depressive disorder (International Classification of Disease, 10th revision), were randomly assigned and single- blinded to take individualized (experimental group, n=30) or empiric (control group, n=30) doses of amitriptyline for 8 weeks, in a psychiatric clinical setting. The frequency of adverse effects was recorded. CGI scale for adverse effects and originally designed questionnaire were used for adverse events assessment. Treatment response was scored in range from 0 (marked improvement and no side-effects) to 4 (unchanged or worse and side-effects outweigh the therapeutic effects).