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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).

RESULTS

In general, the demographic characteristics of the patients were similar in the experimental and control groups. The adverse effects observed in bought groups were of type A (i.e. pharmacological side-effects). In group of patients treated with individualized doses of amitriptyline the adverse effects were reported in following maner: 10 patients reported it on day 14th (33.3%), 12 patients on 28th day (40.0%), 6 patients on 42nd and 56th day, by each day (20.0% each). Significantly higer number of patients complaing on adverse effects were in the controle group: 16 patients on day 14th (53.3%), 17 patients on day 28th (56.7%), 42nd and 56th day for 8 patients, each day (26.7%) (Table 1).

Table1. Number of patients with adverse effects of amitriptyline per days of research

Adverse effects	Days of research							
	14		28		42		56	
	E	C	E	C	E	C	E	C
Present	10	16	12	17	6	8	6	8
Not present	20	14	18	13	14	12	14	12

E- Experimental group of patients- patients with individual dosing of medication
C-Control group of patients- patients with common dosing of medication

In experimental group 69 complains 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 complain on twelve different types of adverse effects. 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 (Table2).

Table 2. No. adverse effects observed

	Days							
	14		28		42		56	
Adverse effects	E	C	E	C	E	C	E	C
Dry mouth	8	12	10	13	6	7	6	7
Nausea	2	3	3	3	1	2	1	6
Constipation	2	2	2	3	4	5	4	4
Tachycardia	2	3	1	2	1	1		
Blurred vision		2	1	2				
Urinary retention		1		2				
Sweating	1	2	1	3				
Fatigue	2	5	3	5	1	3	1	2
Tremor	1	1	1	5				
Confusion				1				
Postural hypotension	3	5	1	2				
Arrhythmia				1				
Total	21	36	23	42	13	18	12	19
χ^2 (d.f.=1)	P=0.0384*		P=0.0135*		P=0.3586		P=0.5562	

E- Experimental group of patients- patients with individual dosing of medication
C-Control group of patients- patients with common dosing of medication; *-Significant difference

Adverse effects were less frequent in group of patients with individualized treatment. These were especially observed in first four weeks of treatment when difference was statistically significant (14th day U=318.50, p<0.05; 28th day U=310.00, p<0.05) (Table 3; Figure 1).

Table3. Distribution of mean score values (with standard deviation) of CGI scale for adverse events per days of research

Visits (days)	Groups of patients	
	E	C
Visit 1 (day 14)	1.36±0.55	1.80±0.80
Visit 2 (day 28)	1.46±0.62	1.93±0.82
Visit 3 (day 42)	1.20±0.40	1.33±0.47
Visit 4 (day 56)	1.20±0.40	1.36±0.49

E- Experimental group of patients- patients with individual dosing of medication
C-Control group of patients- patients with common dosing of medication

Table4. Distribution of values of Vilkoksons test of equivalent pairs of CGI scale for adverse events per days of research

Days of research	Group of patients	
	E	C
14 and 28	Prob z >0.94 P<0.01	Prob z >0.90 P>0.05
28 and 42	Prob z >1.95 P>0.05	Prob z >3.07 P<0.01
42 and 56	Prob z >0.00 P>0.05	Prob z >0.40 P>0.05

E- Experimental group of patients- patients with individual dosing of medication
C-Control group of patients- patients with common dosing of medication

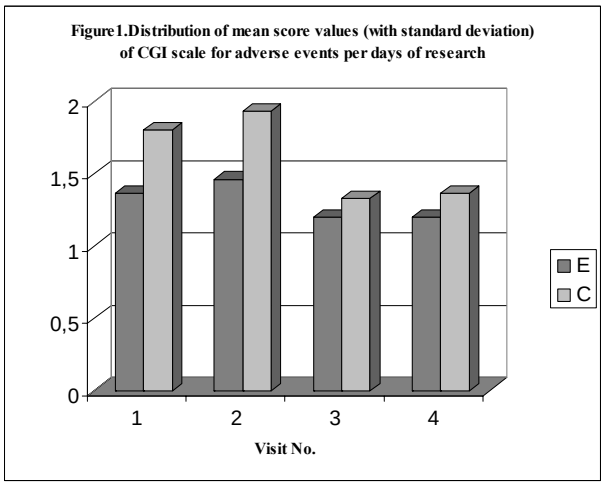

Figure 1. Distribution of mean score values (with standard deviation) of CGI scale for advanse events per days of research

Following weekly score changes in the same groups of patient, showed by Wilkoxon signed- rank test, we did not notice significant difference between 28th end 42nd, and between 42nd and 56th day of treatment (Table4).

DISCUSSION

Whether plasma steady-state concentrations of amitriptyline and nortriptyline are correlated with clinical effects remains a controversial issue (Perry et al. 1994). Most clinicals determine doses of amitriptyline empirically but with coast of significant incidence of adverse effects (Corona et al. 1990; Jakovljević 2009). In the present study we compared modified Bayesian method of dose individualization with empiric treatment. Analyzing of the results according to CGI scale for adverse events, showed that, during the treatment period, adverse events were less frequency in experimental group. This was particularly obvious in the first four weeks of treatment, when statistically significant difference ($p<0.05$) was observed. Because the adverse effects of tricyclic antidepressants are dose dependent (Vandel et al. 1997; Pidrman & Krpalek 1998), the modified Bayesian method might result in better safety profile. Clinicians treating major depression have sometimes had difficulty in achieving full clinical improvement. One of the reasonable alternatives in that situation should be a selection of proper method of dose individualization of antidepressants (Lôo et al. 2004).

CONCLUSION

We showed that the modified Bayesian method used in the present study had less adverse effects than empiric treatment. If larger clinical trials, using more patients as well as other antidepressants, confirm our findings this method could be widely recommended as an easy-to-use tool in everyday psychiatric practice dealing with major depressive disorder.

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