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THE DOSAGE OF ANTIPSYCHOTIC DRUGS IN THE UNIVERSITY DEPARTMENTS OF PSYCHIATRY IN FEDERATION OF BOSNIA AND HERZEGOVINIA

Svjetlana, Loga-Zec[1], S. Loga[2], Saida Fišeković[3]

[1] *Institute of Pharmacology, Clinical Pharmacology and Toxicology, Medical Faculty, University of Sarajevo,* [2] *Academy of Sciences and Arts of Bosnia and Herzegovina, Sarajevo,* [3] *Department of Psychiatry, Medical Faculty, University of Sarajevo*

Abstract

The aim of this pharmaco - epidemiological study was to establish which antipsychotic are currently in use and determine in what daily dosages these drugs are given to patients in three Psychiatric departments in the Federation of Bosnia and Herzegovina (Sarajevo, Tuzla, Mostar).

Majority of patients received classic antipsychotic medications. In Sarajevo most frequently administered was promazine, orally and parenteral, for total of 38 patients or 28, 6% of Sarajevo sample. In Tuzla most frequently administered antipsychotics were haloperidol and thioridazine for 20 and 21 patients, which are 19, 2%, and 20, 2% of total number of patients in Tuzla. In Mostar the leading antipsychotic is haloperidol, orally administered, and with which 29 patients were treated. This represent 31, 2% of total number of patients in Mostar.

Clozapine was applied in all three centres but in very small percentage of cases.

Treatment with daily doses antipsychotics in the Department of Psychiatry in University Clinical Centres in Federation of Bosnia and Herzegovina are mainly in accordance with international standards. Only problem is area of simultaneous use of multiple antipsychotics, both in acute and chronic cases, and frequent use of antiparkinsonics in chronic cases. Because of disseminated results, were considered that the continuous medical education will lead to improvement of treatment quality for the patients with schizophrenia.

Key words: antipsychotics, schizophrenia.

Introduction

Treatment of schizophrenia consists a combination of psychosocial therapy and antipsychotic drugs. Drug treatment should de individualized for each patient with close monitoring. Negative symptoms of schizophrenia tend to respond less well to drug therapy than do positive symptoms (1)

It is well known that low-potency antipsychotic are more sedative and they have strong antimuscarinic and antiadrenergic effects, but they cause less acute extrapyramidal symptoms than the high-potency agents with a reversed pattern of adverse-effects. Sedative and muscarinic effects usually diminish with continued use, although sedative effects may be useful for behavioral control in acute phase of illness (2).

Antipsychotic is classified in three groups:

- First group antipsychotic is sedative, mild antimuscarinc and extrapyramidal adverse effects. Type of antipsychotic used in this study were: chlorpromazine, methotrimeprazine and promazine;
- Second group are slightly sedative effect, strong antimuscarinic effects, and lower extrapyramidal adverse effects than antipsychotic first and third group (pericyazine, pipothiazine, thioridazine);
- Third group are weak sedative effect, slightly muscarinic effect, and very strong adverse effects (fluphenazine, perphenazine, prochlorperazine, etc)

Other antipsychotic which belong phenotiazine derives, have likeness with antipsychotic of third group. Type of antipsychotic we used were: butyrophenones derives (haloperidol, droperidol, trifluperidol) and derivatives thioxanthenes (chlorprotixene, chlopenthixol and flupenthixol).

Atypical antipsychotic sulpiride and clozapine are not included in this classification.

Antipsychotic do block receptor sites for noradrenalin (NA) and dopamine (DA). Antipsychotic that blocked more NA receptors is sedative, and antipsychotic which blocked more DA receptors is including in controlling hallucinations and delusions. Atypical antipsychotic is involved in blockade of serotonin receptors (5-HT). Usually antipsychotic increased excitability hypothalamic centers (3).

In Federation of Bosnia and Herzegovina are accepted modern attitudes in the treatment of psychotic patients. These attitudes imply treatment within the community, closing of the big hospitals and preference of out-patients clinics for the treatment of the patients. In this sense one question must be posed, and that is to what extent is accepted and applied modern pharmacological treatments of schizophrenia. These modern, contemporary treatments imply use of new antipsychotic drugs, because in the area of psychopharmacology there are dramatic changes in the world, in a sense that classic antipsychotic are in the retreat and currently new atypical antipsychotic drugs are in use, which have been shown as far more efficient and safer for the patients.
The aim of this study was to establish which antipsychotic are currently in use and determine in what daily dosages these drugs are given to patients.

Patients and methods

Sample was made of all patients admitted to University Hospitals in the Federation of Bosnia and Herzegovina (Sarajevo, Tuzla, Mostar), questionnaire was applied It consists: demographic data, questions from general criteria for schizophrenia according to ICD-10, antipsychotic, route of administration, dose and time of administration, data for other drugs that were taken in a same day.

Data were evaluated with statistical methods. Mean values for all registered results of individual tests were calculated. Statistical methods used in this study were: the analysis of variance, significant differences between mean values and tests for significant correlation between tests used in the study. Results are presented in text, tables and figures.

Results

Haloperidol daily doses

Table 1. Haloperidol - daily doses

	N (number of patients)	Median of daily doses	Std. Deviation	Std. Error	95% CI (Confidence Interval for Mean)		Min.	Max.
					Lower Bound	Upper Bound		
Sarajevo	16	6,3750	4,92443	1,23111	3,7510	8,9990	1,00	15,00
Tuzla	20	8,1500	3,83577	0,85771	6,3548	9,9452	3,00	15,00
Mostar	29	18,1379	15,01362	2,78796	12,4271	23,8488	2,00	75,00
Total	65	12,1692	11,75807	1,45841	9,2557	15,0827	1,00	75,00

The highest average daily dose of haloperidol were administered in Mostar 18,13mg, while similar daily doses are applied in Sarajevo and Tuzla 6, 37 mg and 8, 15 mg. (Table 1 and Chart 1).

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Chart 1. Haloperidol- daily doses

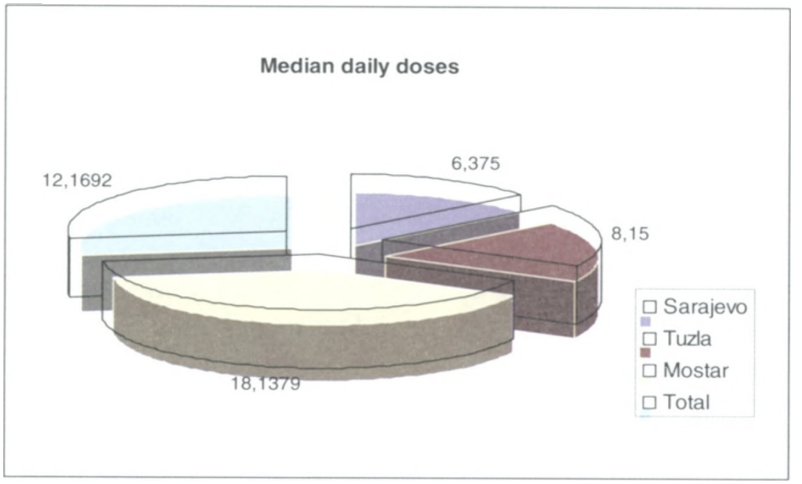


Table 2. Haloperidol – daily doses (ANOVA)

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1893,390	2	946, 695	8,440	**0,001**
Within Groups	6954,748	62	112,173		
Total	8848,138	64			

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There is a significant statistical difference between the centers by application by haloperidol daily doses applied at the **0,001** level (table 2).

Promazine daily doses

Table 3. Promazine daily doses

	N (number of patients)	Median daily doses	Std. Deviation	Std. Deviation	95% CI (Confidence Interval for Mean)		Min.	Max.
					Lower Bound	Upper Bound		
Sarajevo	26	211,5385	81,61825	16,00666	178, 5721	244,5048	100,00	400,00
Tuzla	11	197,7273	124,22487	37,45521	114, 2719	281,1827	75,00	450,00
Mostar	12	141,6667	100,18921	28,92214	78,0095	205, 3239	50,00	300,00
Total	49	191,3265	99,15673	14,16525	162,8454	219,8077	50,00	450,00

Average daily dose of promazine was 191,32mg, while the lowest daily dose is applied in Mostar 141, 66 mg, and highest in Sarajevo 211,538 mg (table 3).

Table 4. Promazine- daily doses (ANOVA)

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	40665,465	2	20332,733	2,169	,126
Within Groups	431273,310	46	9375,507		
Total	471938,776	48			

A significant statistical difference was not noticed between the tested centers regarding the applied daily promazine doses (table 4).

Clozapine daily doses

Table 5. Clozapine – daily doses

	N (number of patients)	Median daily doses	Std. Deviation	Std. Deviation	95% CI (Confidence Interval for Mean)		Min	Max
					Lower Bound	Upper Bound		
Sarajevo	3	266,6667	57,73503	33,33333	123,2449	410,0884	200,00	300,00
Tuzla	11	240,9091	125,63475	37,88030	156,5065	325,3117	75,00	450,00
Mostar	4	168,7500	94,37293	47,18647	18,5816	318,9184	75,00	300,00
Total	**18**	229,1667	111,55650	26,29412	173,6909	284,6424	75,00	450,00

Average daily dose of clozapine was 229, 16 mg, while the lowest daily dose is applied in Mostar 168, 75 mg, and highest in Sarajevo 266, 66 mg.
Within the total sample minimal daily dose of clozapine is 75 mg, and maximal daily dose is 450 mg (table 5).

Table 6. Clozapine- daily doses (ANOVA)

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	20.336,174	2	10.168,087	0,798	0,469
Within Groups	191.226,326	15	12.748,422		
Total	211.562,500	17			

A significant statistical difference was not noticed between the tested centers regarding the applied daily clozapine doses (table 6).

Discussion

In the USA conducted a comparative research regarding the applied antipsychotic in the period from 1989. until 1993. During the 1993 antipsychotic were prescribed to 299 patients (42%) from a total of 709 hospitalized patients. The treatment begins usually within the first 24 hours, while the hospitalization lasted around eighteen days. Highly potent antipsychotic were used 2, 4 times more frequently than the low potent; 13% of patients were treated with clozapine. Average daily doses of the applied antipsychotic equivalent to daily doses of chlorpromazine were 305 mg; and the maximal doses were 32% higher. Doses of highly potent antipsychotic (fluphenazine and haloperidol) are only 22%-33% above the mean values (4).
The doses in the United States are approximately double as the doses in the Europe (200-300 mg/day). Some of the side effects of clozapine, such as: convulsions, confusion and sexual dysfunction, are related to dose and blood levels. But, increase of body mass was not dependant on dose. Latest reports show that optimal blood levels of clozapine should be between 200 and 250 µg/ml, although a lot of patients had a good response even on lower concentrations (5).

The contemporary researches provided a strong evidences about the efficiency of second generation antipsychotic in the treatment of schizophrenia, and clearly indicated that cause much less extrapyramidal side effects (EPS) than the traditional medications (6). Also there are evidences that these medications have less potency to cause tardive dyskinesia (TD) than the first generation antipsychotic, and can be useful in the treatment of preexisting TD. In general patients tolerate much better these medications than older antipsychotic, with few important exceptions, including the risk of agranulocytosis in clozapine use and potential to increase body mass by many medications from this group. Due to their superior safety in terms of neurological side effects, it is considered that the second generation antipsychotic should be available as the first choice of treatment in schizophrenia, and preferred in first episode patients (7).
Conducted a study in the public hospitals in Hong Kong with obtained data about the treatment with antipsychotic medications in relation to the dose of antipsychotic, combined use of multiple antipsychotic, administration in divided daily doses and coadministration of antipsychotic with the medication for Parkinson's disease. Sample was consisted of 957 schizophrenic patients randomly selected. A census was made, and the questionnaire was consisted of items about demographic and clinical data, as well as description of all

medications that patients received on the day of census. Results of study indicates that the average dose of antipsychotic was 854 +/- 759 (mean: 600; range 0 - 4450) mg CPZeq. More than two thirds of patients received multiple medications simultaneously, while less than 20% take their medication in divided daily doses. Antiparkinsonics was used in 69, 6% of patients (8).

Apstrakt

Cilj ove farmako-epidemiološke studije je bio da se ispitaju doze neuroleptika, koji se aktuelno primjenjuju u tretmanu psihotičnih bolesnika u tri psihijatrijske klinike univerziteta u Federaciji Bosne i Hercegovine (Sarajevo, Tuzla i Mostar). Ispitani bolesnici pretežno su konzumirali klasične (tipične) antipsihotike. U Sarajevu 38 bolesnika (28,6% od ukupnog broja pacijenata) su koristili promazin, peroralno i peranteralno. U Tuzli najviše primjenjivani antipsihotici su haloperidol (20 ili 19,2%) i tioridazin (21 ili 20,2%), dok je u Mostaru najčešće propisivan haloperidol (29 ili 31,2%).

Klozapin je administriran u sva tri centra kod veoma malog broja pacijenata. Dnevne doze antipsihotika u svim centrima Federacije Bosne i Hercegovine su u granicama medjunarodnih standarda. Razlike se mogu primijetiti samo u slučajevima, kada se primijenjuje više lijekova i kada se koriste antiparkinsonici kod bolesnika na dozama održavanja.

Ključne riječi: antipshotici, shizofrenija.

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