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Clozapine for Treating Pharmacoresistant Schizophrenia among Elders

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Abstract

Introduction: Pharmacoresistant schizophrenia is not a rarity. It is defined as un successfull treatment of schizophrenia by two different sort of antipsychotics with different mechanism of action, lasting up at least six weeks with dosage which is equivalent to 1000 mg per day of chlorpromazine in the period of last five years. Clozapine is used as a "rescue"antipsychotic when previous treatment of schizophrenia fails.Objective of the study is to examine safety and effectiveness of clozapine in treating pharmacoresistant schizophrenia among elders.

Material and Methods: Five patients with pharmacoresistant schizophrenia treated with clozapine. Psychiatric scales PANSS and CGI-S were used initially before starting with clozapine treatment, then after 4 and 8 weeks and after 12 weeks of clozapine use. White blood cells and agranulocytes count was monitored initially before starting with clozapine treatment, then after 4 and 8 weeks and finally after 12 weeks of using clozapine. Side effects caused by clozapine were monitored after 12 weeks of clozapine use.

Results: Clozapine decreased the main symptomatology of pharmacoresistant schizophrenia in old age patients with no serious deterioration of white blood cells count. Side effects of clozapine in old age patients were tolerable although sedation, hypotension, agitation, weight gain and deterioration in metabolit parameters were not rare in studied group of senior patients.

Conclusion: Clozapine can be used as rescue antipsychotic for treating the pharmacoresistant schizophrenia in elderly. However, monitoring of side effects of clozapine used in elderly and watchful awareness is unevitable.

Keywords: Pharmacoresistant schizophrenia; PANSS; CGI-S; Clozapine; Side effects; Elders

Intoduction

Pharmacoresistance in treating schizophrenia is defined as unsuccessfull treatment of schizophrenia by two different sorts of antipsychotics with different mechanism of action, lasting up at least six weeks with dosage which is equivalent to 1000 mg per day of chlorpromazine in the period of last five years [1,2]. In clinical practice, less strict definitions of pharmacoresistancy are used, according to Češková definition pharmacoresistancy means unssucces in previous treatment of a patients bytwo different sorts of antipsychotics with different mechanism of action, lasting up 3 – 4 weeks [2]. It is important to revise the psychiatric diagnosis, to differentiate from comorbid psychiatric diagnoses, nonadherence of a patient, underdosing the therapy, evaluation of time when patient got the antipsychotics [2,3]. Clozapine is recommended in treating pharmacoresistant schizophrenia with respect to side effects of clozapine and when benefit to risk ratio is considered [4-6]. Treatment of schizophrenia should be complex (psychopharmacology, psychotherapy, educative programs for patients, rehabilitation of social and communication skills,promoting the adherence to treatment, monitoring of early side effects of treatment, self helping groups etc) and complex therapy of schizophrenia should not be based only on pharmacotherapy [7-9]. This complex approach can influence effectiveness of treatment as a whole. When pharmacoresistency in a patient with schizophrenia has been proved, then augmentation of dosage, combination of antipsychotics, combination with auxilliary medication, clozapine, electroconvulsions or repetitive transcranial magnetic stimulation can be helpful in treatment [2,9,10]. Treatment with clozapine is adviced in treatment of pharmacoresistant schizophrenia worldwide [2,5,6]. However, clozapine is associated with many serious side effects which should be taken into account – such as severe and potentially lethal neutropenia, eosinophilia, seizures, myocarditis, weight gain, diabetes, metabolic syndrome, hypersalivation, fever, constipation, ileus, urinary incontinence, sweating [11]. There are no contraindications for using clozapine in elderly, however, clozapine treatment in the elderly requires a careful geriatric assessment [12]. Clozapine used in elderly at a relatively low mean dose seems to be safe, tolerated, and effective, agranulocytosis is more frequent than in younger adults and should be monitored carefully [12,13].

Objective

Objective of the study is to examine safety and effictive of clozopine in treating pharmacoresistant schizophrenia among eldres

Materials and Methods

Subjects

Five women (n=5) who have been hospitalized for pharmacoresistant schizophrenia in inpatient psychogeriatric ward in Mental hospital Kroměříž, Czech republic, in years 2010-2011. All the subjects fulfilled diagnostic criteria for paranoid schizophrenia according to the DSM-IV, diagnosis of paranoid schizophrenia was settled by trained psychogeriatrist. All the subjects agreed in participation in the researched. All the subjects were 65 years of age and older.

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All the subjects failed in prior treatment with two different sorts of antipsychotics used for 8 weeks (fulfilled criteria of pharmacoresistant schizophrenia). All the subjects were actually treated with clozapine in antipsychotic monotherapy for the first time (no patient was treated with clozapine any time before) and all the subjects had significant positive symptoms of schizophrenia at the beginning of treatment with clozapine.

Ethical considerations

All the subjects agreed with participation in research as well as taking the blood for laboratory checks (informed consent). No ethical or financial hazard connected with this research is known to the author of the study.

Design of study

Retrospective observatory study estimating years 2011 and 2012. The study was open and unblinded.Methods: psychiatric scales PANSS (Positive and Negative Symptoms of Schizophrenia) and CGI-S (Clinical Global Impression- Severity of illness) were used initially before starting with clozapine treatment, then after4. and 8. weeks and finally after 12 weeks of using clozapine. White blood cells (WBC) and agranulocytes count were monitored strictly according FDA rules weekly, but for purposes of the study only initial WBC and WBC from 4th, 8th and 12th week were analyzed statistically. Differences in WBC were monitored and compared to critical value of WBC 2.2 [10^9/l]. Titration of clozapine: initial dose 12.5 mg per day, increased by 12.5 mg daily up to clinically efficient and tolerated daily dose.Potential side effects caused by clozapine (side effects according AISL databasis – Automatized Information system of Registered Drugs in the Czech republic) were monitored after 12 weeks of treatment with clozapine. Data were statistically analyzed by software STATISTICA, 2007: chi2 test, Multivariate analysis (ANOVA). Significance: p=0.05.

Results

Five patients treated with clozapine due to pharmacoresistant paranoid schizophrenia, women, have been studied. The average age of a patient was 67.8 years, the average course of paranoid schizophrenia was 35.2 years. The average number of hospitalizations due to paranoid schizophrenia in a patient was 12. More than 10 different antipsychotics were used in patients history before this study, 40% of patient were nonadherent in any time to treatment (Table 1).

All patients were switched to clozapine, which was titrated gradually to the target daily dosage according clinical result of treatment and tolerability by a patient. The final average dosage of clozapine was 360 mg daily. The initial average total score in Positive and Negative Symptoms of Schizophrenia scale (PANSS) was 102.2 (it shows severity of schizophrenia expressed by symptoms), the average total score in PANSS scale after 4 weeks of treatment with clozapine was 86.5, the average total score in PANSS scale after 8 weeks of treatment with clozapine was 56.6, the average total score in PANSS scale after 12 weeks of treatment with clozapine was 48.2. The initial average total score in Clinical Global Impressionscale (CGI) was 13.0, the average total score in CGI after 4 weeks of treatment with clozapine was 10.4, the average total score in CGI after 8 weeks of treatment with clozapine was 7.6 and finally the average total score in CGI after 12 weeks of treatment with clozapine was 5.0. Clinical improvement in psychopatology during therapy with clozapine (expressed by dicrease of total score both in PANSS and CGI) was clinically evident and statistically significant (Table 2).

White blood cells count with special regards to leukocytes count and agranulocytes count was checked in all patients regularly.The initial average leukocytes count was 5.7 [10^9/l], the average leukocytes count after 4 weeks of treatment with clozapine was 5.8 [10^9/l], the average leukocytes count after 8 weeks of treatment with clozapine was 5.7

Patient	Age	History*	Hospitalization**	Former therapy***	Former adherence****
1.	68	40	16	9	-
2.	66	31	10	9	+
3.	66	36	13	12	+
4.	69	19	9	8	+
5.	70	50	12	13	-
Average	67.8	35.2	12	10.2	3 (+) 2(-)
SD	1.4	8.2	2.0	1.8	40% nonadherent

* years with schizophrenia since the diagnosis has been settled.
** number of hospitalizations – sequence of actual hospitalization.
*** number of different sorts of antipsychotics which have been used in patients history.
**** (+) patient was adherent, (-) patient was nonadherent in history.

Table 1: Descriptive data.

Patient	Dose of clozapine (mg)	PANSS – initial score	PANSS – 4 week score	PANSS - 8 week score	PANSS - 12 week score	CGI-S initial score	CGI-S 4 week score	CGI-S 8 week score	CGI-S 12 week score
1.	350	122	100	87	65	7	7	6	4
2.	450	100	89	75	58	6	5	4	3
3.	400	96	80	67	44	6	5	4	4
4.	250	103	85	62	40	7	7	5	4
5.	350	90	77	52	34	5	4	4	3
Average	**360**	**102.2**	**86.2**	**56.6**	**48.2**	**6,2**	**5,6**	**4,6**	**3,6**
SD	52	8.2	6.6	14.2	10.6	0.6	0.5	0.6	0.5
Significance	**-**	**-**	**0.0023**	**0.0012**	**0.0011**	**-**	**0.0031**	**0.0024**	**0.0022**

PANSS - Positive and Negative Symptoms of Schizophrenia (total score).
CGI-S - Clinical Global Impression- Severity of illness (total score).

Table 2: Results.

[10^9/l], the average leukocytes count after 12 weeks of treatment with clozapine was 5.7 [10^9/l].

The initial average granulocytes count was 2.608 [10^9/l], the average granulocytes count after 4 weeks of treatment with clozapine was 2.710 [10^9/l], the average granulocytes count after 8 weeks of treatment with clozapine was 2.536 [10^9/l], the average granulocytes count after 12 weeks of treatment with clozapine was 2.596 [10^9/l]. Significant changes in white blood count (leukocytes, agranulocytes) during treatment with clozapine were not observed (Table 3).

Potential side effects caused by clozapine in patients treated with pharmacoresistant schizophrenia were evaluated after 12 weeks of therapy. Sedation was detected in 40% of patients, hypotension (blood pressure bellow 100/60 Torr) was observed in 20% of patients, weight gain (more than 5 kg in last12 weeks) was detected in 40% of patients. Agitation was observed in 20% of patients, increase in venous blood glucose level (fasting glucose level from venous blood above 5.2 mmol/l - when initially normal level) was detected in 40% of patients, as well as increase in level of blood lipids (cholesterol above 5.0 mmol/l or triglycerids above 1.7 mmol/l - when initially normal levels) which was detected in 40% of patients (Table 4).

Discussion

Clozapine is used as a "rescue" antipsychotic for patients with pharmacoresistant schizophrenia when former treatment by two different antipsychotics in adequate dosage and lenght of treatment fails. This is the general recommendation for adult patients with pharmacoresistant schizophrenia,however, guidelines for treating pharmacoresistant schizophrenia in elderly are missing. Thus, therapy of pharmacoresistant schizophrenia in elderly very oftenly remains either empirical or"palliative"– this therapy usually covers just some of the main symptoms such as aggression, behavior or sleep disturbances, although treating pharmacoresistant schizophrenia in elderly by clozapine is not a contraindication [1-5].

Clozapine has many potential side effects which may impede in routine use of clozapine for treating pharmacoresistant schizophrenia in psychogeriatry – anticholinergic side effects and potentially severe myelotoxicity are the most important.

Anticholinergic side effects of clozapine used in psychogeriatry may lead to cognitive deterioration, delirious states, constipation, weight gain, increase of intraocular pressure in angular glaucoma, xerostomia, xerophtalmia, difficulties with miction or even severe and potentialy lethal paralytic ileus [5,6,14].

The results ofthis observatory study show the potential of clozapine to clinical improvement of symptoms in senior patients with pharmacoresistant schizophrenia, this result is in accordance with other authors [9,11]. Average CGI-S 12 week score was 3,6 with range from 3 to 4. It means mild residual psychotic symptoms (CGI-S=3) or moderate residual psychotic symptoms (CGI-S=4). Such improvement of psychotic symptoms thanks to clozapine was observed in different studies [15-18]. No clinically evident changes in white blood cells count in treated seniors were observed, this result can´t be compared to similar finding in literature (research for myelotoxicity of clozapine in elderly hasn´t been done). Other side effects, such as sedation, hypotension, weight gain, agitation, increase of blood glucose and lipid level, were detected in this research. This finding is in accordance with other researchers in this field [11-13]. Watchful monitoring of side effects of clozapine used in elderly is unevitable [12,13].

Limits of this research can be seen in limited size of the studied group of patients (five) which makes interpretation of results difficult.

Patient	Leu-initially	Leu–4 weeks	Leu-8 weeks	Leu-12 weeks	Gran- initially	Gran- 4weeks	Gran-8 weeks	Gran–12 weeks
1.	6.3	6.2	6.4	6.1	2.505	2.800	2.350	2.600
2.	5.8	6.1	5.7	5.9	2.600	2.750	2.500	2.580
3.	6.1	6.0	5.8	6.4	3.050	3.000	3.125	3.115
4.	5.2	5.5	5.8	5.1	2.550	2.650	2.405	2.400
5.	4.9	5.0	4.8	4.8	2.335	2.350	2.300	2.285
Average	**5.7**	**5.8**	**5.7**	**5.7**	**2.608**	**2.710**	**2.536**	**2.596**
SD	0.5	0.4	0.4	0.6	0.179	0.168	0.236	0.209
	No patient showed critical decrease in WBC (lower than 2,2 [109/l]).							

leu – leukocytes(total white blood cells count) in [10^9/l].
gran – granulocytes in [10^9/l].

Table 3: White blood cells changes.

P.	Sedation	Hypotension	Dysrytmia	↑Weight	Delirium	Agitation	↑Glu	↑Lip
1	+	0	0	+	0	0	0	0
2	+	0	0	+	0	0	0	0
3	0	+	0	0	0	0	+	+
4	0	0	0	0	0	+	0	0
5	0	0	0	0	0	0	+	+
n	**2**	**1**	**0**	**2**	**0**	**1**	**2**	**2**
%	40	20	0	40	0	20	40	40

P.- patient
n - absolutely % - relatively.
hypotension – blood pressure bellow 100/60 Torr.
dysrytmia – any of arytmia detected on ECG, behind physiological norms.
↑weight – weight gain more than 5 kg / 12 weeks.
↑glu – fasting glucose level from venous blood above 5.2 mmol/l (when initially normal level) after 12 weeks.
↑lip – cholesterol above 5.0 mmol/l or triglycerids above 1.7 mmol/l (when initially normal levels) after 12 weeks.

Table 4: Side effects monitoring.

On the other hand, pharmacoresistant schizophrenia in elderly treated with clozapine for the patients first time at the old age is a clinical rarity, this extraordinary phenomenon is a barrier to size of studied group of patients. Another limit comes from design of the study, which was designed as open and unblinded study.

Conclusion

Clozapine can be used as "rescue"antipsychotic for treating the pharmacoresistant schizophrenia in elderly. Clozapine has proved clinical efficiency in pharmacoresistant schizophrenia in old age patients together with relative safety and relatively good tolerance by a patient. However,monitoring of side effects of clozapine used in elderly is unevitable and this monitoring should respect profile of side effects of clozapine as it is well known in adult psychiatry.

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