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Research Paper

Treating Pharmacoresistant Schizophrenia in Elderly With Clozapine – Safety Profile Experience from Mental Hospital Kromeriz, Czech Republic

Public Health

KEYWORDS : Pharmacoresistant schizophrenia - Positive and Negative Symptoms of Schizophrenia scale (PANSS) - Clinical Global Impression

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ABSTRACT

Background: Pharmacoresistant schizophrenia is not a rarity. It is defined as un successfull 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. Clozapine is used as a „rescue"antipsychotic when previous treatment of schizophrenia fails. The objective is to evaluate effectiveness, safety and side effects of clozapine used for treatment senior patients with pharmacoresistant schizophrenia hospitalized in inpatient psychogeriatric ward in Mental hospital in Kromeriz (2010-2011).

Subjects and methods: psychiatric scales Positive and Negative Symptoms of Schizophrenia (PANSS) and Clinical Global Impression (CGI) were used initially before starting with clozapine treatment, then after 4. and 8. weeks and finally after 12 weeks of using clozapine. White blood cells and agranulocytes count was monitored initially before starting with clozapine treatment, t 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 using clozapine.

Results: clozapine decreased the main symptomatology of pharmacoresistant schizophrenia in old age patients, with no 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.

Introduction

Pharmacoresistance in treating schizophrenia is defined as un successfull 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 by two 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 [3], nonadherence of a patient, underdosing the therapy, evaluation of time when patient got the antipsychotics [2]. Clozapine is recommended in treating pharmacoresistant schizophrenia [4] with respect to side effects of clozapine and when benefit to risk ratio is considered [5, 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].

Subjects 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. 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.

Methods: psychiatric scales Positive and Negative Symptoms of Schizophrenia (PANSS) and Clinical Global Impression (CGI) were used initially before starting with clozapine treatment, then after 4. and 8. weeks and finally after 12 weeks of using clozapine. White blood cells and agranulocytes count was monitored initially before starting with clozapine treatment, t then after 4. and 8. weeks and finally after 12 weeks of using clozapine. 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).

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Tab. 1 Descriptive data.

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

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 Impression scale (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).

Table 2. Changes in Psychopathology

Patient	Dosage-	PANSS*	PANSS**	PANSS***	PANSS****	CGI*	CGI**	CGI***	CGI****
1.	350	122	100	87	65	15	12	9	7
2.	450	100	89	75	58	13	10	7	4
3.	400	96	80	67	44	13	11	8	5
4.	250	103	85	62	40	13	11	7	5
5.	350	90	77	52	34	11	8	7	4
Average	360	102.2	86.2	56.6	48.2	13.0	10.4	7.6	5.0
SD	52	8.2	6.6	14.2	10.6	0.8	1.1	1.4	0.8
Significance	-	-	0.0023	0.0012	0.0011	-	0.0031	0.0024	0.0022

- daily dosage of clozapine in miligrammes

*initially **after 4 weeks *** after 8 weeks ****after 12 weeks
SD standard deviation

PANSS - Positive and Negative Symptoms of Schizophrenia (total score)

CGI - Clinical Global Impression (total score)

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 [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) during treatment with clozapine were not detected (table 3).

Table 3. White blood cells changes

Patient	leu*	leu**	leu***	leu****	gran*	gran**	gran***	gran****
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
Significance	-	0.0855	0.1224	0.1204	-	0.2251	0.2225	0.2232

*initially **after 4 weeks *** after 8 weeks ****after 12 weeks
SD standard deviation
leu – leukocytes(total white blood cells count) in [10 9/l]
gran – granulocytes in [10 9/l]

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).

Table 4. Side effects monitoring

P.	Sedation	Hypotension	Salivation	Dysrytmia	↑Weight	Delirium	Agitation	↑Glu	↑Lip
1	+	0	0	0	+	0	0	0	0
2	+	0	0	0	+	0	0	0	0

3	0	+	0	0	0	0	0	+	+
4	0	0	0	0	0	0	+	0	0
5	0	0	0	0	0	0	0	+	+
n	2	1	0	0	2	0	1	2	2
%	40	20	0	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

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 [1, 2], 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 [4, 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 fiction [5, 6] or even severe and potentialy lethal paralytic ileus [14].

The results of this restrospective 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]. 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. 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.

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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