CURRENT PROBLEMS OF PSYCHIATRY 2010, 11, 1, 20-23

Cases of patients with treatment-resistant schizophrenia treated with clozapine and sertindole

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Summary

Treatment-resistance to clozapine in schizophrenia is defined as the failure in achieving the appropriate therapeutic effect by the only use of adequately high dose of clozapine of (600-800 mg per day) over at least 6 weeks.
Materials/Patients: We report the cases of 3 patients (2 men and 1 woman) with the medical history suggesting the drug-resistant schizophrenia, in whom all neuroleptics available in Poland were used without any effect. Patients were treated in the Department of Psychiatry of Medical University of Lublin between 2008 and 2010. The applied combined therapy consisted of sertindole of 16 - 20 mg per day and clozapine of 100-600 mg per day doses.

Results: The significant improvement of the mental state was achieved during the first two months of gradually introduced treatment. The scores in CGI scale decreased from 5 to 3 points. According to the GAF scale the evaluation of the functioning improved from 30 to 70 points. With regard to positive symptoms measured by the use of BPRS-4 the significant lowering of productive symptoms from 18 to 9 points was observed. The intensity of negative symptoms measured using the BNS scale decreased meanly from 20 to 15 points. The heart function was monitored strictly according to the recommendations of the physician. Neither the QT segment nor the QTc was remarkably prolonged. No arrhythmias were observed.

Conclusion: The used combined treatment of sertindole and clozapine was found to be effective and safe for patients with treatment-resistant schizophrenia.

Key words: schizophrenia, neuroleptics

Introduction

Clozapine is a neuroleptic recognized as a drug of the third choice in treatment of schizophrenia. However a part of patients do not react positively on treatment with clozapine despite of taking this medicine for appropriate period of time and in high doses. According to the literature, about 30% of patients with schizophrenia are resistant to treatment with any neuroleptic. In 36-67% patients treated with clozapine there is lack of therapeutic response (total or partly). Treatment-resistant schizophrenia to clozapine is defined as lack in achievement of appropriate therapeutic response after taking clozapine alone in the appropriately high doses (600-800 mg per day) for at least 6 weeks. Reason of failure in the treatment with clozapine also may be intolerance of this drug, defined as a lack of possibility in treatment with clozapine in high doses due to adverse events (low blood pressure, salivation, somnolence, lack of activity). There is also possibility to occur some complications caused by clozapine, for example intolerance of glucose and diabetes, significant weight gain, epileptic attacks and worsening of EEG record. In such situations we look for possibilities of augmentation clozapine with other drugs, for example with neuroleptics of second generation as amisulpride, aripiprazole, ziprasidone, olanzapine, risperidone [1]. Papers describing combined treatment with clozapine and sertindole were not found in the databases EBSCO and Medline. Sertindol is a atypical antipsychotic drug that has high affinity to D2, 5HT2A, 5HT2C and alpha 1 adrenergic receptors. Preclinical investigations found that it acts selectively on dopaminergic neurons in mesolimbic and mesocortical systems and is effective with low occupancy of D2 receptors [2].

Three cases of patients with drug-resistant schizophrenia treated with clozapine augmented by sertindole were described.

Cases

Patient 1, K.I.

Man, aged 31, unmarried, second level of education, currently he lives with his parents, on social pension. Patient's brother has been suffered from schizophrenia since 16 years old. His parents conduct specialistic stock-farm (poultry-farming). Patient fell ill in 1999. After his coming from the USA, delusions of "being poisoned" and hypochondriac ones appeared. For this reason he was hospitalized first in 2000 and next two times in 2002. He was systematically treated in the outpatient settings; he sometimes decreased doses of drugs on his own or overused benzodiazepines. Earlier he has been treated with classic neuroleptics. Negative symptoms has been increasing for last three years. The clinical picture comprised: 1) disorganization of thinking up to catathymic level, disturbances in the abstract and casual thinking; 2) asociality – he spent

most of the time alone in his room, he left it very seldom, he had minimal contacts with his ill brother, he had no emotional bonds with his close relatives; 3) apathy – sometimes he helped in farming during the summer; he ate a lot – he gained up to 140 kg weight; he left his house only with parents; he had not been cleaning his room; 4) autism – he has been thinking out unrealistic plans about professional activities, about earning "much money"; he has not been watching TV or surfing internet. During the worsening periods he had suicidal ideations, deeply depressive mood, anxiety. Periodically delusions of "being poisoned" has been recurring – he used oxygen therapy, took Cocarboxylase, drunk alcohol, had obsessive thoughts about using sharp devices, he became referenced, had thought about harming anybody, did not care about hygiene. Some rehabilitation programs has been trying to conduct in 2008. He left the Psychiatric Rehabilitation Department after one week, did not agree to participate in daily occupational therapy. Some attempts in changing treatment from classic neuroleptic to atypical ones or combined therapy were made. The treatment with olanzapine was conducted (20 mg daily), patient gained weight then. Next risperidone was taken in dose to 6 mg daily, it caused increasing of suicidal ideations and depressive thoughts and acathisia. Aripiprasole in dose of 15 mg daily caused aggression and agitation. After 800 mg daily of amisulpride – impotence appeared caused by hyperprolactynemia. Patient demanded change of drug. Amisulpride was decreased to 400 mg daily and from July 2008 sertindole was added. In December 2008 therapy was changed into clozapine (up to 100 mg daily) with sertindole (16 mg daily). Gradual withdrawal of depression and obsessive thoughts was achieved. Patient became more active, he meets his friend, takes care of hygiene, started to drive a car, to help with farming. ECG was taken regularly, last QTc was 290 ms, pulse rate to 86/min. Gain weight has been stopped. Cognitive functions has been improved significantly, patient has begun writing a book about methods of quitting smoking.

Patient 2, J.A.

Woman, aged 43, teacher, breeds adolescent daughter alone. The beginning of illness was pseudoneurotic with undetermined functional complaints like headaches, insomnia. Next suddenly acute psychotic symptoms appeared, she was admitted to psychiatric hospital without her agreement. She has still resided in the psychiatric hospitals since this time (about one year). Nihilistic delusions and cenesthetic hallucinations (she felt lack of the heart and organs in abdominal cavity) dominated; delusions of punishment, guilty, sinfulness were also present. She refused to eat, drink, she was negativistic, agitated. States of catatonia (in type of oneiric agitation) intermittently occurred (especially at nights) or catatonic stupor appeared. It was necessity to use protective means in the form of immobilization with safety belts due to auto-aggressive behaviors. She has been treated with classic neuroleptics (haloperidol, perazine, levomepromazine) which caused retention of urine. Next she has been treated with atypical neuroleptics as amisulpride, sulpiride, risperidone. Then symptoms of EPS and hyperprolactynemia appeared. Injections with aripiprazole were used (3 vials daily) – agitation appeared then. Treatment with olanzapine (to 15 mg daily) and quetiapine (to 800 mg daily) did not cause the improvement. Quetiapine caused significant decreases of blood pressure. Significant agitation appeared during the treatment with ziprasidone (160 mg daily). As a procedure of the third choice – 11 electroconvulsive treatments were conducted (transcript of the higher necessity was made because the patient did not agree to this procedure) – catatonic stupor stopped but delusions were still present. Valproic acid was added that caused leucocytopenia (2900 leucocytes) so this medicine was removed. Sertindole in the dose of 20 mg daily was gradually introduced and some betterment appeared, regression of positive symptoms. Nocturnal consciousness disturbances (of oneiric type) were still present, so clozapine was gradually added (600 mg at night) and it caused normalization of night sleep. Patient could take part in the occupational therapy, walks, she took after her hygiene by herself. Leucopenia subsided, appetite came back, level of prolactin normalized and menstruations came back, there is no trouble with retention of urine, mood improved. Due to low blood pressure (about 90/60 mmHg) – 2,5 mg midodrine was added and improvement was achieved. ECG was systematically taken, QTc on average was 225 ms.

Patient 3 M.J.

Man, aged 24, unmarried, second level of education, suffering without any remission for three years. He has been treated – with short pauses – in psychiatric hospitals. Predominant symptoms comprised delusions being overwhelmed by devil, auditory hallucinations ordering to commit suicide or self-injuries, persecutory delusions. Many times it was necessity to use protective means due to danger to his or other people life. Being under the influence of hallucinatory orders he behaved aggressively to other patients or hospital staff. Patient was moved from another hospital, where he was treated with clozapine in dose of 700 mg daily and lamotrygine in dose of 200 mg daily and next valproic acid in dose of 2500 mg daily (this medicine level in serum

was 87 mg/dl). Earlier he had been treated with almost all accessible neuroleptics in monotherapy or combined therapy, but without any betterment. Decision was made to lower dose of clozapine (minimally to 400 mg/d) trying to add another neuroleptic. Among a few neuroleptics which patient has never taken – trifluoroperazine was used in the higher doses up to 24 mg/d and next zuclopenthixol. Symptoms of EPS appeared. In the next step quetiapine in dose of 400 mg daily was added and it caused significant sedation and somnolence and decrease of blood pressure. Gradually sertindole in dose of 20 mg daily was added to earlier dose 400 mg daily of clozapine. Significant decrease of psychotic symptoms was achieved and normalization of blood pressure, lack of sedation, better activity and improvement of cognitive functioning appeared. ECG was systematically taken, an average length of QTc was 357 ms.

For assessment of psychopathological symptoms severity the following scales were used:

- Clinical Global Impression CGI
- Global Assessment of Functioning according to DSM-III-R (GAF)
- Calgary Depression in Schizophrenia Scale (CDSS)
- The scale for assessment of negative symptoms BNS
- Subscales of positive symptoms from BPRS

Results for each patient were shown in the table 1.

Tab. 1. Severity of psychopathological symptoms in the discussed patients before and after combined treatment with sertindole and clozapine

Scale	Patient 1		Patient 2		Patient 3	
	Before	After	Before	After	Before	After
CGI	5	3	7	4	4	5
GAF	40	70	30	50	40	60
CDSS	12	6	20	10	5	3
BNS total	17	8	20	12	16	10
Alogia	3	2	5	3	4	3
Flat affect	4	2	5	3	4	3
Asociality	5	2	5	3	4	2
amotivation	5	2	5	3	4	2
BPRS total	21	6	23	8	16	7
Suspiciousness	4	2	6	3	3	2
Delusions	5	1	6	3	3	2
Hallucinations	4	1	6	1	6	2
Formal thinking disorders	4	2	5	1	3	1

Parameters of blood cell count, electrolytes and the heart functions were systematically measured (by measuring of blood pressure and assessing length of QT and QTc).

Discussion

Patients met criteria for drug-resistant schizophrenia according to 4D: diagnosis was correct, organic brain disorders and substance overuse were excluded. Patients were treated at least with two neuroleptics (drugs) in the appropriately high doses (dose) and for appropriate time (duration) [3]. In the literature there are some data about combined therapy with clozapine and other neuroleptics. Ciprani et al. [4] conducted meta-analysis of data from randomized researches in Cochrane Schizophrenia Group Trials Register and Medline. On the basis of three studies with small patient groups (28-60 patients) there were found no better strategies than combined therapy with clozapine and other neuroleptics [4]. Adding another neuroleptic to clozapine we always must consider possible overlapping adverse events and think of pharmacokinetic interactions. Clozapine is metabolized in the liver mainly by cytochrome CYP1A2 and sertindole by system of cytochromes CYP2D6 and CYP3A4. Combination of these drugs seems to be safe on the pharmacokinetic level, because its do not change concentrations of drugs in blood [5].

Some symptoms appearing as adverse events during treatment with clozapine may improve after adding sertindole – what is observed in the discussed patients. There was improvement in negative symptoms severity and better cognitive functioning what may be due to the fact that sertindole does not cause sedation (lack of influence on muscarinic receptors M1). Extrapyramidal symptoms were not observed. Symptoms caused by antycholinergic action were not more severe. There was no weight gain; metabolic parameters (including level of glucose in blood) did not worsen and prolactine level

was normal. Sertindole does not affect hematopoietic system, so there was no troubles in blood cell count. Sertindole is contraindicated in people who have prolongation of QT, disorders in heart conduction, circulatory disorders with dysrhythmias. Before introducing combined therapy, anamnesis concerning heart diseases (especially dysrhythmias) was conducted, electrolytes level were measured (K, Na, Ca, Mg), ECG was taken before therapy and next every week during first month of therapy [6]. Sertindole – like clozapine – binds to alpha 1 adrenergic symptoms, influencing circulatory system. ECG was systematically taken and no worsening was observed (as far as heart rate and length of QT and QTc are concerned). Only morning blood pressure decreases were observed, well corrected after adding 2.5 mg midodrine. These decreases were probably caused by accumulation of total dose of clozapine at night. Taking sertindole in one morning dose did not cause changes in the blood pressure.

Conclusion

Therapy of drug-resistant schizophrenia force to necessity of using different combinations of pharmacological treatment. Receptor profiles, pharmacokinetic interactions and overlapping of drugs adverse events must be considered. In the discussed cases – combined therapy with sertindole and clozapine was effective and safe for patients, reducing the disorder symptoms and improving patients functioning in the all dimensions.

References

1. Jaracz J. Dodanie leku przeciwpsychotycznego II generacji lub leku przeciwpadaczkowego jako metoda postępowania u chorych na schizofrenię ze słabą odpowiedzią na klozapinę. Farmakoter. Psychiatr. Neurol., 2008; 24(3): 167-176.
2. Żebrowska A., Jarema M. Zastosowanie kliniczne sertindolu w leczeniu schizofrenii. Farmakoter. Psychiatr. Neurol., 2008; 24(2): 75-93.
3. Jarema M. Oporność na leki w schizofrenii; rozpoznawanie i postępowanie. Medipress Psychiatr.-Neurol., 2001; 5(1).3-6 8: 10-11.
4. Cipriani A., Boso M., Barbui C. Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia. Cochrane Database Syst. Rev., 2009; 8: 3.
5. Spina E., de Leon J. Metabolic drug interactions with newer antipsychotics: a comparative review. Basic. Clin. Pharmacol. Toxicol., 2007; 100(1): 4-22.
6. Jarema M., Rybakowski J. Zalecenia w sprawie stosowania leków przeciwpsychotycznych II generacji. Zalecenia dotyczące stosowania preparatów klozapiny. Psychiatr. Pol., 2008; 42(1): 135-145.
7. Stahl M.S. Podstawy psychofarmakologii. 2008. Gdańsk; VM Medica: 254-260.

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