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CASE REPORT

Combination of ziprasidone and clozapine in treatment-resistant schizophrenia

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In cases of treatment-resistant schizophrenia the combined application of antipsychotic drugs often becomes necessary. Clozapine has been combined successfully with other atypical antipsychotic drugs such as risperidone or amisulpride in the past.

We report the difficult treatment of a 28-year-old schizophrenic woman. Psychotic symptoms were found resistant to monotherapy with clozapine or ziprasidone. In contrast, combined application led to a marked improvement in both positive and negative symptoms of schizophrenia along with a decrease of side effects.

The reported combination is a promising option in cases of treatment-resistant schizophrenia and should be further evaluated in prospective studies. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — clozapine; ziprasidone; schizophrenia; treatment resistance

INTRODUCTION

Clozapine, the first atypical antipsychotic agent (Buchanan, 1995), facilitates treatment of patients with psychotic symptoms resistant to typical neuroleptic drugs (Hellewell, 1999), but shows a number of potentially dangerous side effects (Miller, 2000). If antipsychotic monotherapy even with clozapine fails due to incomplete efficacy or to intolerable side effects, the combined application of antipsychotic drugs is a necessity (Freudenreich and Goff, 2002). Augmentation strategies of clozapine with risperidone (Henderson and Goff, 1996) or with amisulpride (Zink *et al*., 2004), for example, have been used successfully and provide a pharmacological rationale. The benzisoxazole ziprasidone (Caley and Cooper, 2002) exerts antipsychotic effects (Gunasekara *et al*., 2002) with the unique receptor binding profile of pronounced dopamine and 5-HT (serotonin) receptor antagonism (Seeger *et al*., 1995). Due to its main metabolism via aldehyde oxidation in liver cells (Prakash *et al*., 1997) this drug may be an ideal candidate for combinations with substances metabolized via the cytochrome p450 system. One recently published letter (Kaye, 2003) reports on clozapine augmentation with ziprasidone based on clinical evaluation. Detailed information on psychopathological states using psychometric scales, on serum levels of clozapine or on side effects is missing. On the basis of the desired detailed background information we report the success of a combined application of ziprasidone and clozapine.

CASE REPORT

A 28-year-old woman with a genetic burden of psychosis had suffered from schizophrenia following the criteria of DSM IV since 15 years of age. In the past she had been treated with typical antipsychotic drugs (benperidol, flupentixol) and clozapine, also in combination with flupentixol. However, side effects, lack of compliance and partial resistance of symptoms rendered the treatment difficult. Upon admission to the psychiatric day clinic she predominantly presented negative symptoms of schizophrenia such as blunted affect, lack of drive and social inactivity along with side effects of clozapine such as sedation, sialorrhea and increase of body weight. The positive and negative symptoms score (PANSS) assessed 10 (+), 29 (−) and 39 points of global psychopathology (see Figure 1). Pathological

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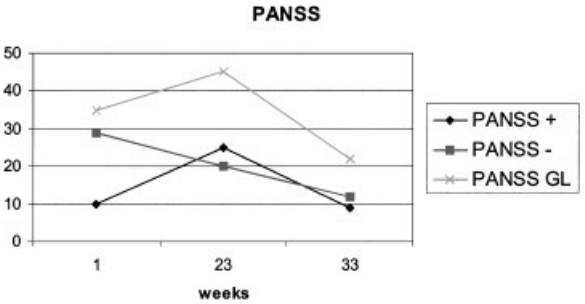

Figure 1. Changes of psychopathological state as depicted by the PANSS-rating scale. The selected time points represent the state at admission, during the psychotic exacerbation (week 23) and at discharge (week 33). PANSS, (positive (+) and negative (−) syndrome scale; GL, global psychopathology scale

scores in global assessment of functioning (GAF) and clinical global impression (CGI) (see Table 1) also reflect these deficits. She was medicated with clozapine (150 mg), citalopram (20 mg) and valproic acid (600 mg), which had been introduced after epileptic seizures during clozapine therapy. Over a period of 8 weeks treatment was changed to monotherapy with ziprasidone (120 mg). Importantly, clozapine was tapered off slowly to prevent a clozapine-withdrawal syndrome (Shiovitz *et al*., 1996). The patient experienced relief from clozapine-side effects (no sedation or sialorhea, reduction of body weight by 3 kg), affective improvement and reduced negative symptoms. She scored better on a day clinic instrument assessing behaviour during work, social skills, motivation and self-evaluation. Unfortunately, her state was unstable, and 12 weeks after clozapine-withdrawal she developed a psychotic syndrome with formal thought disorder and paranoid delusions (PANSS 25/20/45), which remitted after reintroduction of clozapine at a lower dose. With the combination of ziprasidone 120 mg and clozapine 75 mg over the following 10 weeks a marked psychopathological improvement was achieved. PANSS scored at discharge with 9/12/22, GAF, CGI and working abilities had improved. Body weight further decreased, blood pressure, pulse and the electrocardiogram remained normal. Antiepileptic therapy with valproic acid was successfully tapered off. The patient started a rehabilitation programme aimed at achieving a regular employment.

DISCUSSION

This is the first detailed case report on the combined application of ziprasidone and clozapine, which offers a promising therapeutic alternative in treatment-resistant schizophrenia.

In the past the schizophrenic psychosis of our patient had been partially resistant to monotherapies with typical as well as atypical antipsychotic drugs and a combination of clozapine with flupentixol. Though clozapine monotherapy was able to control sufficiently the symptoms of formal thought disorder and delusions, it was less effective with regard to negative symptoms and induced intolerable side effects such as sedation, sialorrhea, weight gain and liability to epileptic seizures. Ziprasidone, on the other hand, was well tolerated, improved mood and negative symptoms, but signs of a psychotic exacerbation occurred. Tapering off clozapine may lead to a withdrawal syndrome (Berecz *et al*., 2000; Shiovitz *et al*., 1996). Considering this danger we cross-tapered, reducing the clozapine dose slowly without noting typical somatic symptoms, extrapyramidal motoric dysfunction or psychotic symptoms within the critical time window. Thus, the exacerbation can be interpreted as a sign, in this case, of insufficient antipsychotic efficacy of ziprasidone. We therefore assumed a partial and in monotherapy insufficient response to both substances and thought a combination therapy was justified according to recently published criteria (Freudenreich and Goff, 2002).

Table 1. Summary of changes between time of admission, psychotic exacerbation and discharge including psychometric scales, a day clinic scale (working abilities) assessing behaviour during work, social skills, motivation and self-evaluation between 4 (optimal) and 24 (worst) points, actual antipsychotic medication, clozapine serum level, side effects and body weight. CGI-assessment (severity of illness/ change of state/therapeutic effect/ side effects)

	Admission	Psychotic exacerbation (week 23)	Discharge (week 33)
GAF	40	35	80
CGI	6/-/-/3	6/5/4/0	3/1/1/2
Working abilities	14	16	8
Antipsychotic medication (mg/day)	Clozapine 150	Ziprasidone 120	Clozapine 75, Ziprasidone 120
Clozapine serum level (mg/l)	0.5	< 0.05	0.14
Unfavourable drug effects	Sedation sialorrhea, increase of body weight	Formal thought disorder, paranoid delusions	Slight sedation
Body weight (BMI)	77.6 kg (31.9)	74.6 kg (30.6)	72.8 kg (29.9)

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While clozapine is well tolerated in combination with risperidone (Henderson and Goff, 1996) and amisulpride (Zink *et al*., 2004), ziprasidone seems an additional candidate for antipsychotic augmentation of clozapine: its metabolism does not interfere with the cytochrome p450 system, and it is able to counteract clozapine side effects such as sedation or should at least not worsen others such as weight gain. Therefore, an additive antipsychotic effect may be combined with a reduction of side effects, as documented in the improvement of PANSS-rating (see Figure 1) and a decrease of side effects (see Table 1). This is particularly notable in the fact that an antiepileptic therapy was no longer necessary.

In a recent report on the ziprasidone augmentation of clozapine (Kaye, 2003) the author described improvement of affectivity and reductions of both daily clozapine doses and side effects. In contrast to this work, we first describe this new approach in detail including the treatment rationale, psychometric data, serum clozapine levels and monitoring of side effects. We therefore consider our finding as significantly relevant to psychiatric practice and plan a randomized, prospective study to further evaluate the potential and risks of the proposed combination.

REFERENCES

Berecz R, Glaub T, Kellermann M, de la Rubia A, Llerena A, Degrell I. 2000. Clozapine withdrawal symptoms after change to sertindole in a schizophrenic patient. *Pharmacopsychiatry* **33**: 42–44.

Buchanan RW. 1995. Clozapine: efficacy and safety. *Schizophr Bull* **21**: 579–591.

Caley CF, Cooper CK. 2002. Ziprasidone: the fifth atypical antipsychotic. *Ann Pharmacother* **36**: 839–851.

Freudenreich O, Goff DC. 2002. Antipsychotic combination therapy in schizophrenia. A review of efficacy and risks of current combinations. *Acta Psychiatr Scand* **106**: 323–330.

Gunasekara NS, Spencer CM, Keating GM. 2002. Ziprasidone: a review of its use in schizophrenia and schizoaffective disorder. *Drugs* **62**: 1217–1251.

Hellewell JS. 1999. Treatment-resistant schizophrenia: reviewing the options and identifying the way forward. *J Clin Psychiatry* **60**(Suppl. 23): 14–19.

Henderson DC, Goff DC. 1996. Risperidone as an adjunct to clozapine therapy in chronic schizophrenics. *J Clin Psychiatry* **57**: 395–397.

Kaye NS. 2003. Ziprasidone augmentation of clozapine in 11 patients. *J Clin Psychiatry* **64**: 215–216.

Miller DD. 2000. Review and management of clozapine side effects. *J Clin Psychiatry* **61**(Suppl. 8): 14–17; discussion 18–19.

Prakash C, Kamel A, Anderson W, Howard H. 1997. Metabolism and excretion of the novel antipsychotic drug ziprasidone in rats after oral administration of a mixture of 14C-and 3H-labeled ziprasidone. *Drug Metabol Disp* **25**: 206–218.

Seeger TF, Seymour PA, Schmidt AW, *et al*. 1995. Ziprasidone (CP-88, 059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. *J Pharmacol Exp Ther* **275**: 101–113.

Shiovitz TM, Welke TL, Tigel PD, *et al*. 1996. Cholinergic rebound and rapid onset psychosis following abrupt clozapine withdrawal. *Schizophr Bull* **22**: 591–595.

Zink M, Knopf U, Henn FA, Thome J. 2004. Combination of clozapine and amisulpride in treatment-resistant schizophrenia—case reports and review of the literature. *Pharmacopsychiatry* **37**: 26–31.

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