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Serum concentrations of clozapine and norclozapine in the prediction of relapse of patients with schizophrenia

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Abstract

Schizophrenic outpatients ($n=102$) whose condition had stabilized with clozapine (CLZ) therapy and were being maintained on CLZ were followed for 1 year. Clinical status and concentrations of serum clozapine (CLZ) and its metabolite norclozapine (NCLZ) were evaluated periodically or when relapse occurred. Relapse was defined as a significant exacerbation of psychotic symptoms or hospitalization. Thirty-three patients relapsed and 69 did not. Relapse patients displayed significantly lower serum concentrations of CLZ and a sum of CLZ and NCLZ at endpoint than non-relapses (CLZ: 162 ng/ml vs. 237 ng/ml, $p<0.001$; CLZ+NCLZ: 225 ng/ml vs. 301 ng/ml, $p<0.001$). When all subjects were pooled together, a significant inverse correlation was observed between percent increase in the total score on the Brief Psychiatric Rating Scale (BPRS) from baseline and serum levels of CLZ alone ($r=0.404$, $p<0.001$) and the sum of CLZ and NCLZ ($r=0.364$, $p<0.001$). Relapses and non-relapses were well separated by a threshold CLZ serum concentration of 200 ng/ml with a sensitivity of 73% and a specificity of 80%. The threshold value represented about a 40% lower serum CLZ level than concentration achieved in acute treatment. Survival analysis showed a similarity of the relapse risk over time defined by the CLZ serum threshold and by symptomatic criteria. These results suggest that effective relapse prevention may require maintenance of patients at CLZ serum concentrations above 200 ng/ml and above 60% of the acute-phase level during long-term maintenance treatment of schizophrenia.

Keywords: Schizophrenia; Relapse; Clozapine; Norclozapine; Serum concentration

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1. Introduction

Despite the fact that use of clozapine (CLZ) is generally restricted to patients who do not respond to other neuroleptic treatments due to the potential risk of severe hematological complications (Gaszner et al., 2002; Honigfeld et al., 1998), it has been well documented that the clinical efficacy of CLZ is comparable to newer atypical antipsychotic agents (e.g., risperidone, olanzapine, and quetiapine) (Tuunainen et al., 2002; Serretti et al., 2004; Wahlbeck et al., 1999). CLZ is also the only drug that has an indication for decreasing the risk of suicide in patients with schizophrenia (Kane et al., 1988; Meltzer et al., 2003). Moreover, the cost-effective index of CLZ is much higher than newer atypical antipsychotic drugs (Wahlbeck et al., 2000). Based on these considerable advances, CLZ has been widely introduced into the maintenance treatment of psychotic disorders (Wahlbeck et al., 2000), particularly in undeveloped countries where a large proportion of patients cannot afford long-term use of newer medications (Chong et al., 2004; Hamann et al., 2003).

Many attempts have been made to establish the relationship of therapeutic response to blood concentrations of CLZ and its active metabolites (Llorca et al., 2002; Mauri et al., 2003; Perry et al., 1998; Spina et al., 2000). Although there is disagreement on the value of CLZ monitoring in predicting clinical response, it is generally accepted that the achievement of a moderate CLZ blood concentration of 300–600 ng/ml is required for satisfactory clinical outcomes with minimal adverse effects in a majority of patients (Llorca et al., 2002; Ulrich et al., 2003a). However, the determination of "optimum" CLZ concentrations was basically based on populations with an active psychotic episode and receiving CLZ short-term (6–12 weeks) therapy (Perry et al., 1998; Ulrich et al., 2003a,b). Little is known about blood CLZ concentrations in long-term maintenance treatments of stabilized patients, despite there have been some studies conducted in relapsed and treatment-resistant subjects with schizophrenia (Gaertner et al., 2001; Hasegawa et al., 1993; Ulrich et al., 2003a,b).

There is large interindividual variability in CLZ pharmacokinetics (Masellis et al., 2000). This is because the disposition of the drug is significantly affected by many factors, such as age, gender, cigarette smoking, diet, and comedications (Diaz et al., 2005; Haring et al., 1990). CLZ is metabolized by the hepatic cytochrome P450 system into several metabolites, the most important of which is *N*-desmethylclozapine or norclozapine (NCLZ). Although NCLZ possesses weak pharmacological activities (Guitton et al., 1998), it has been found that NCLZ may contribute to therapeutic effects of CLZ via a novel mechanism involving the modulation of muscarinic and 5-HT_2 receptors (Heiser et al., 2004; Odou et al., 1996; Spina et al., 2000; Weiner et al., 2004). Thus, active metabolites of CLZ are often included in therapeutic drug monitoring of CLZ.

In the present study, schizophrenic outpatients whose condition had stabilized in CLZ therapy and were being maintained on this drug were followed for 1 year. Clinical status, concentrations of serum CLZ and its metabolite NCLZ were measured periodically or when patients relapsed into psychosis. We sought to determine whether there exists a relationship between CLZ and NCLZ serum concentration and maintenance treatment outcomes. We also sought to determine threshold concentrations of CLZ and NCLZ that would predict psychotic relapse.

2. Methods

2.1. Subject

Outpatients who met the following criteria were eligible for participating in this prospective study: 1) aged 18 to 65 years; 2) had been diagnosed as schizophrenia according to criteria of International Classification of Diseases, 10th edition (World Health Organization, 1992); 3) had received CLZ therapy for at least 4 weeks and whose current condition was stable or in remission, as evidenced by the total Brief Psychiatric Rating Scale (BPRS) score of no more than 30; and 4) agreed to continue on CLZ maintenance treatment without other psychoactive comedication. All subjects were enrolled from outpatients who were just discharged from Anding Hospital of Beijing Capital University of Medical Sciences, Beijing, China.

The protocol was approved by Medical Ethical Committee of Anding Hospital and conducted in conformity with the Declaration of Helsinki. All