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• Forum •

Forum: Is clozapine over-used or under-used?

Proper use of clozapine: experiences in China

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According to surveys conducted in ten provinces and independent municipalities in China, clozapine is the most commonly used antipsychotic medication in the country. These surveys reported that it was administered to 39.0% of all patients taking antipsychotic medication in 2002 and to 31.7% of all patients taking antipsychotics in 2006.[1,2] With the advent and marketing of newer antipsychotic medications there has been as steady decline in the use of clozapine over the last two decades, a decline that is particularly noticeable in major cities and in other economically developed areas. However, clozapine remains the drug of choice for patients with schizophrenia in remote and economically less developed areas.

The efficacy of clozapine in the treatment of schizophrenia—especially in the treatment of refractory schizophrenia—and in lowering the risk of suicide among patients with schizophrenia is superior to that of other currently available antipsychotics. But the safety and tolerance of clozapine remain a concern. As a poly-receptor antagonist, clozapine has fewer extrapyramidal side effects than most antipsychotics but it can trigger many other types of adverse reactions such as sinus tachycardia, orthostatic hypotension, excessive sedation, excessive salivation, weight gain, and abnormalities in the metabolism of glucose and lipids. Potentially fatal adverse effects including agranulocytosis, myocarditis, and epilepsy limit its clinical use. Determining the best strategies for balancing the risks and benefits of using clozapine in the treatment of schizophrenia will require further, more detailed follow-up studies.

In 1990, the Food and Drug Administration of the United States approved the application of clozapine for inpatients with refractory schizophrenia and for those who could not tolerate the adverse reactions of conventional antipsychotics. Conley and Kelly (2001)[3] recommended that patients be tested at two dosage ranges: 200 to 400 mg/day and 500 to 600 mg/day; only patients with few adverse reactions should be considered for doses beyond 600 mg/d. Myoclonus during clozapine treatment may be predictive of future epilepsy so patients who experience myoclonus should not be treated with high doses. The current Chinese *Guidelines for the Management of Schizophrenia*[4] propose that clozapine be 'used cautiously' in the dosage range of 200 to 600 mg/d. Interestingly, the guidelines do not state that clozapine should be limited to use as a second-line drug. Routine blood tests are highly recommended because this is an effective way to prevent clozapine-induced agranulocytosis. Scientists are actively searching for genes that are related to the risk of clozapine-induced agranulocytosis. In the future genetic profiling may be able to identify individuals susceptible to this adverse outcome before initiating treatment.

In China, the mean (sd) dosage of clozapine administered to patients with schizophrenia (216 [133] mg/d)[5] is much lower than that reported in foreign literature (431 [522] mg/d).[6] One reason for the lower dose may be that clozapine is much more commonly used as a secondary adjunctive antipsychotic in China than elsewhere (41.2 v. 16.6%).[5,6] This inappropriate use of clozapine as an auxillary medication at sub-therapeutic doses is an ongoing problem in China; in some cases this has occurred because it proved impossible to completely wean patients off clozapine when trying to convert them from clozapine to a newer antipsychotic. We believe that if a patient can tolerate clozapine then it should probably be used as monotherapy at therapeutic dosages.

Therapeutic drug monitoring (TDM) for clozapine has been conducted in many psychiatric hospitals and psychiatric departments of general hospitals in China. Foreign studies report a 45-fold range in the steady-

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state plasma concentrations of clozapine;[7] similar studies from China find a 10-fold range in plasma concentrations.[8] To be effective, steady state plasma concentrations of clozapine in acute schizophrenia must be at least 350 to 420 ng/ml;[9,10] the lowest effective plasma concentration during maintenance treatment is 200 ng/ml.[11] Plasma clozapine concentration is correlated with adverse reactions; when plasma clozapine concentrations exceed 600 ng/ml EEG abnormalities increase markedly.[12]

In the future treatment with clozapine will be individualized. Administration of clozapine according to the manufacturer's guidelines or based on blood monitoring requires a long time to arrive at an appropriate dosage. Population pharmacokinetics and pharmacogenomics are promising approaches to individualizing treatment. By establishing models that reflect both population pharmacokinetics and efficacy, we can calculate the pharmacokinetic indicators of a specific patient and predict the impact of various factors (e.g. gender, age, smoking, status of enzymes that metabolize drugs, and target gene type) on the outcome of treatment. These models would allow clinicians to predict the dose needed to reach the target plasma clozapine concentration and, thus, individualize treatments. To promote this trend towards individualized treatments, our group is currently conducting population pharmacokinetic and pharmacogenomic studies with clozapine.

Conflict of interest

The authors report no conflict of interest related to this manuscript.

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