Cyclosporine-Olanzapine Drug-Drug Interaction

To the Editor: Aplastic anemia is a quantitative marrow failure caused by the decrease or disappearance of hematopoietic cells with no evidence of neoplastic infiltration or myeloproliferative syndrome. Aplastic anemia can affect the whole hematopoiesis or a single cell line. Because of pancytopenia, patients are at risk of infection, bleeding, and symptoms caused by anemia.[1]

In young patients, the treatment for this condition is allogeneic transplant-related donor hematopoietic progenitors. In older patients, immunosuppression is performed, for example, with cyclosporine A, which acts by inhibiting the first phase of T cell activation. Cyclosporine A decreases the cellular immune response, inhibiting the production of T-dependent antibodies. It also inhibits the production and release of lymphokines, including interleukin 2. With adequate treatment, the prognosis of aplastic anemia is favorable in 80% of cases.[2] However, studies[3] show that patients with acquired aplastic anemia can evolve into myelodysplastic syndrome or acute myeloid leukemia with abnormal karyotype and poor prognosis.

Schizophrenia is a serious mental disorder with an unknown etiopathogenesis. Several etiologic theories have been proposed for the disease.[4] There is no single etiologic factor in schizophrenia, and its appearance depends on factors affecting both the genotype and phenotype. Some preliminary studies[5] have suggested that the peripheral cytochemokine network is one of the systems involved in the pathophysiology of schizophrenia. Schizophrenia treatment is based on the use of antipsychotic drugs such as olanzapine, whose mechanism of action lies in moderate affinity for D_4, D_2, 5-HT, adrenergic, histaminergic, and muscarinic receptors. Olanzapine has an antagonistic effect on dopamine and serotonin receptors.

It is important to highlight the significance of pharmacodynamics and pharmacokinetics in drug interactions. These interactions affect drug plasma concentrations and must be considered when a patient is taking more than one medication. Although in most cases the mechanisms of these interactions can be explained, some cannot due to unknown metabolic pathways, the mechanism of action of particular drugs on the body, and idiosyncratic drug reactions. We present a clinical experience with the concomitant use of olanzapine and cyclosporine A.

Case report. A 19-year-old woman with a history of severe aplastic anemia diagnosed at the age of 7 years presented to the emergency department. She had been treated with rabbit thymoglobuline with partial response until age 15 years when she decided to discontinue treatment. During the examination, we observed preserved cellularity with severe dysplastic features affecting the 3 series and 5.5% blasts, indicating that the aplastic anemia had already evolved into a myelodysplastic syndrome.

The patient was diagnosed with paranoid schizophrenia at the age of 15 years when she experienced her first psychotic episode in the context of a drug overdose. Since that time, she had 7 admissions to the psychiatric unit because of psychopathological relapse with psychotic symptoms, which significantly impacted her both emotionally and behaviorally. Psychopharmacologic treatment with haloperidol (30 mg/d), paliperidone palmitate (150 mg/30 days), and olanzapine (40 mg/d) had produced acceptable clinical response but no complete recovery in any of the acute psychotic episodes. The patient was hospitalized in a mental health therapeutic community and began treatment with cyclosporine A 600 mg/d and olanzapine 40 mg/d. Due to a clinical response and unwillingness to maintain high doses of psychotropic drugs, the antipsychotic treatment was gradually reduced. Olanzapine 5 mg/d was maintained in combination with cyclosporine A 600 mg/d, with tested olanzapine blood plasma levels of 30 ng/mL. During 8 months of treatment with this low-dose medication combination, she exhibited no psychotic symptoms.

Our patient was maintained on treatment with 2 drugs: cyclosporine A 600 mg/d and olanzapine 5 mg/d. It would be expected that blood plasma levels of olanzapine at 5 mg/d would be much lower than 30 ng/mL. This level of olanzapine could not be explained by an overdose, as the patient had no access to the medication. Thus, a metabolic interference between both drugs was suspected. However, cyclosporine A is metabolized in the liver by cytochrome P450 (CYP) 3A4, while olanzapine is metabolized by glucuronidation or CYP1A2 and CYP2D6. If both drugs have different metabolic pathways, then other mechanisms might be influencing their interactions, for instance, an interference at the level of P-glycoprotein, which has been shown in previous studies.[6,7]

Although described previously,[5] to date, there is little information on the interaction of antipsychotic drugs with medications that affect the immutatory pathway. In general, very little attention is paid in the present literature to the pharmacokinetics of drugs and even less to their interaction in different pathways of action.

Olanzapine may have an effect on autoimmunity mediated by DNA methylation.[8] With regard to the interaction of olanzapine and cyclosporine, olanzapine acts in many pathways and adheres to multiple receptors in addition to D_2. For example, as reported by Melka et al,[8] olanzapine caused an increase or a decrease in the methylation of genes implicated in schizophrenia, thus olanzapine could alleviate psychiatric symptoms via mechanisms involving DNA methylation. Therefore, methylation could be another cause of interaction between both drugs. Olanzapine acts on several pathways, so it is difficult to determine the effects of simultaneous treatment with cyclosporine and even more difficult to reflect the level of clinical translation of these effects.

Therefore, due to their autoimmune effects, both drugs may produce a synergistic effect, although the current literature on this topic is scarce and controversial. More research is required to identify specific metabolic effects of these drugs.

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