CLINICAL VIGNETTE

Neutropenia and Transient Transaminitis Associated with Olanzapine Use

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Case Report

A previously healthy 23-year-old male with history of depression and unspecified psychosis was hospitalized with concerns of suicidal ideation after refusing to eat for one week. Admission labs included white blood cell count (WBC) 5.7 x 10^9/L. Alanine transaminase (ALT) and aspartate aminotransferase (AST) were normal when measured on hospital day 3. He continued to decline all food and medications until hospital day 7, after he was started on Olanzapine 5 mg intramuscularly twice per day and started on partial parenteral nutrition. He began eating on hospital day 8, with very limited diet and continued to refuse all oral medications. On hospital day 11, the Olanzapine was consolidated to 10 mg nightly. The olanzapine was held from hospital days 17 through 19 pending legal appeal, but was restarted on hospital day 20. Elevated transaminases were noted when labs were rechecked on hospital day 18. He continued to be minimally engaged and withdrawn but increased Olanzapine was deferred due to the elevated liver labs. The transaminitis began to decline despite the continuation of Olanzapine and AST had normalized by hospital day 28 (Figure 1). On hospital day 24, the patient was found to have a low WBC count of 3.48 x 10^9/L with absolute neutrophil count (ANC) 1.82 x 10^9/L, which continued to decline on subsequent days, and he developed concurrent neutropenia with WBC count of 2.53 x 10^9/L and ANC of 1.28 x 10^9/L on day 26 (Figure 2). Due to the persistently decreased WBC count and neutropenia, the Olanzapine was discontinued and he transitioned to Haloperidol 5 mg intramuscularly on hospital day 29. WBC count and neutrophils then quickly normalized.

In evaluating the elevated transaminitis, we considered drug induced elevation, however, he and family denied alcohol or other drug use. Hepatitis labs were all negative, and right upper quadrant ultrasound was normal without evidence of nonalcoholic fatty liver disease. We had also considered starvation induced transaminitis, however, his transaminitis began and worsened after he resumed eating. In regards to the patient's neutropenia, there was no evidence that he had an infection at any point in the hospitalization. While vitamin deficiencies from starvation could have contributed to the leukopenia and neutropenia, the sharp decline is unusual for the prolonged starvation.

Discussion

Antipsychotics are commonly associated with hepatotoxicity, with chlorpromazine, clozapine, and olanzapine posing the greatest risk.[1] While olanzapine is generally well tolerated, multiple side effects have been reported. In the premarketing experience for olanzapine in adults, the incidence of ALT elevations >200 IU/L in patients with previously normal ALT was 2% (50/2381). Most had transient changes that tended to normalize while olanzapine treatment was continued. In placebo-controlled olanzapine monotherapy studies in adults, clinically significant ALT elevations (defined as change from <3 times the upper limit of normal [ULN] at baseline to ≥3 times ULN) were observed in 5% (77/1426) of patients exposed to olanzapine compared to 1% (10/1187) of patients exposed to placebo. No patient with elevated ALT values developed jaundice or liver failure.[2]

The mechanism by which olanzapine causes serum aminotransferase elevations is not known. It has been hypothesized that since olanzapine undergoes extensive hepatic metabolism, partially via the cytochrome P450 system - some cases of hepatotoxicity may be due to production of a toxic intermediate of metabolism.[3] While the premarketing data supports continuing olanzapine in the setting of mild transaminitis, a study in patients taking antipsychotics identified approximately 0.12% of patients given olanzapine develop drug induced liver injury.[4] A review of 28 patient case reports, reported olanzapine had not caused any fatalities secondary to liver injury. They noted one instance of re-elevation of LFTs after it had been discontinued and re-started.[5] Further case reports have shown that presence of underlying liver disease, such as Hepatitis C – may result in further worsening, with accelerated elevations in liver aminotransferases.[6] If there is no evidence for pre-existing drug induced liver injury and transaminitis is mild, patients can be continued on Olanzapine with careful monitoring.

Leukopenia and neutropenia have also been associated with antipsychotic use. While olanzapine was developed to reduce the hematological risk frequently reported with use of clozapine, it also is associated with neutropenia. It is the third most common antipsychotic medication associated with neutropenia with incidence of 0.05%.[7] The mechanism for granulocytopenia in both clozapine and olanzapine is hypothesized to be due to oxidative metabolism of the drug to produce nitrenium ion –

which at high concentrations is toxic to neutrophils.[8] A case report has found that plasma G-CSF was not detectable with olanzapine induced granulocytopenia.[9]

The FDA label for olanzapine states that patients with an absolute neutrophil count <1000/mm3 should discontinue olanzapine and monitor white blood cell count until recovery.[2] Case reports have associated leukopenia associated with olanzapine as dose-dependent. Reducing olanzapine dose resulted in normalization of the white blood count.[10] WBC counts quickly recover after olanzapine is discontinued,[11] which is consistent with our case. Patients with a history of drug induced hematologic abnormalities may be at greater risk of olanzapine induced leukopenia or neutropenia.[2,12] One patient developed neutropenia in 17 days after the initiation of olanzapine, and a second patient, 5 months after initiation.[13]

Our previously healthy patient developed transient transaminitis followed by neutropenia, in the setting of Olanzapine initiation. Our case was unique with minimal exposure to other medications due to refusal of oral medications. This isolated the effects of Olanzapine associated lab abnormalities. Transaminitis began 11 days after the initiation of Olanzapine, leukopenia after 17 days, and Neutropenia after 19. Although rarely reported, monitoring for lab abnormalities after the initiation of Olanzapine may need to promptly recognize adverse reactions and minimize sequelae.

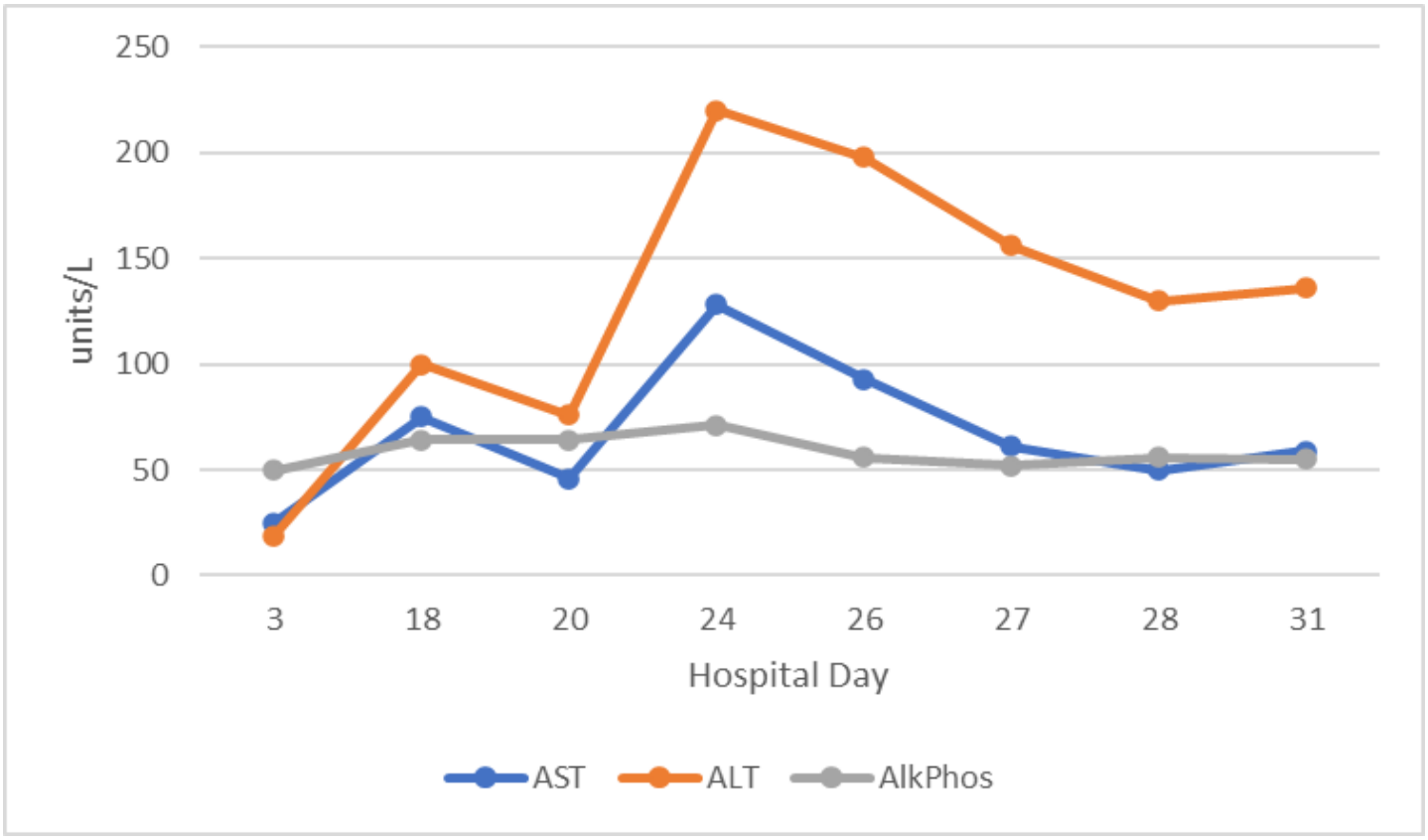

Figure 1. Liver Function Test Trends Over Hospital Course

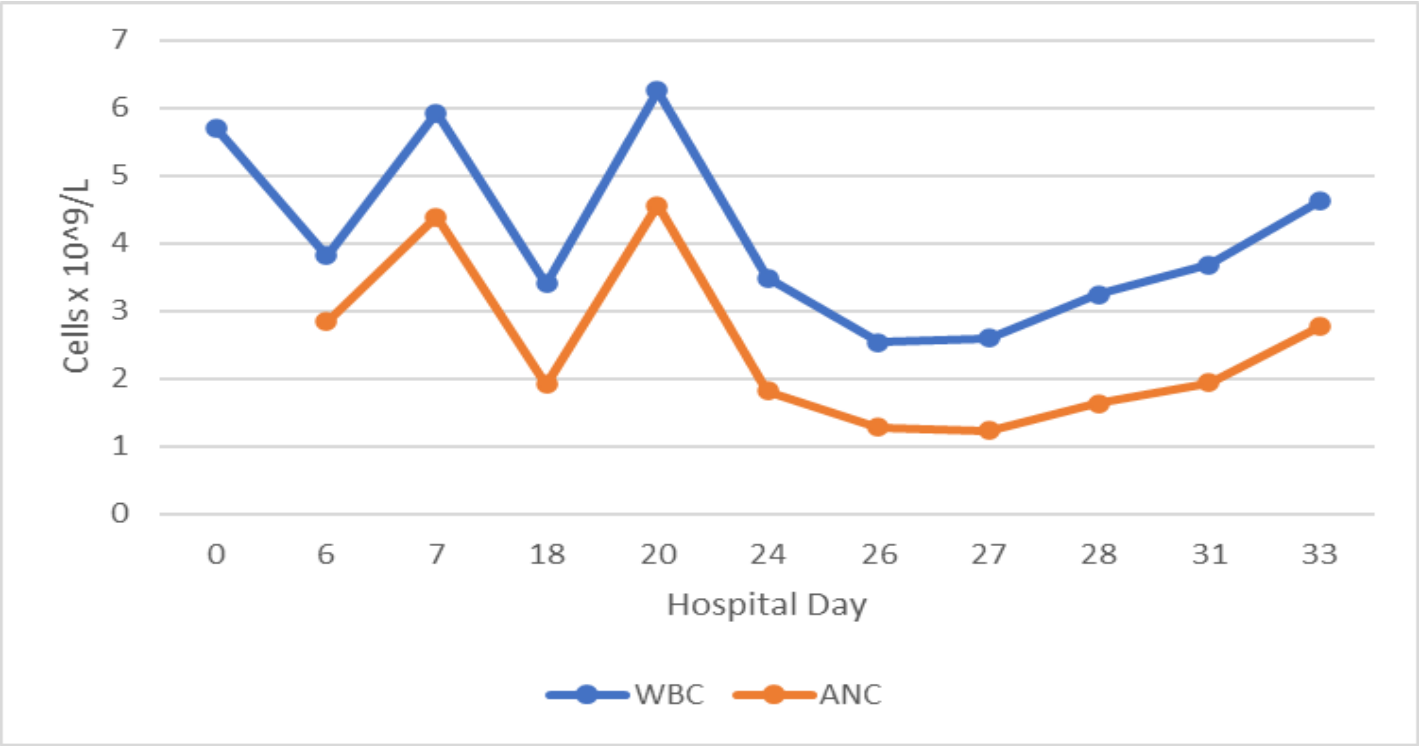

Figure 2. White Blood Cell (WBC) and Absolute Neutrophil Count (ANC) Trends Over Hospital Course

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