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Cystic Fibrosis Research News

Title:
Ivacaftor Withdrawal Syndrome: A potentially life-threatening consequence from a life-saving medication

Lay Title:
Ivacaftor withdrawal syndrome: A rare but potentially life-threatening consequence from a life-saving medication

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What was your research question?
A child with cystic fibrosis (CF) presented to the emergency room with severe difficulty breathing, fever, and fatigue after suddenly stopping ivacaftor treatment. Ivacaftor withdrawal syndrome (IWS) may occur when ivacaftor therapy is altered. In 2018, four adults with CF suffered IWS after changes in ivacaftor treatment. Was this child's case consistent with IWS?

Why is this important?
Ivacaftor, the first highly effective modulator therapy, changed the outlook for patients suffering from CF. It was the first targeted treatment for abnormal CF protein with certain mutations. This allowed about 5% of CF patients to enjoy easier breathing and better quality of life. However, for some patients that have a lapse in taking the medication, they seem to quickly develop severe pulmonary issues for unclear reasons. Approval of combined elexacaftor/tezacaftor/ivacaftor treatment now allows more than 90% of patients with CF to enjoy the benefits of highly effective modulator therapy; however, this also may increase the number of patients susceptible to IWS.

What did you do?
The child mentioned above was admitted to the hospital for antibiotics, supplemental oxygen, and CF respiratory care. Their family informed the medical team that they had run out of

medication at home about two weeks earlier. The child's sweat chloride at time of admission was abnormally high, demonstrating medication non-compliance, as reported by the family. Pulmonary function test at that time showed all-time low results for this patient. Ivacaftor was restarted on the second day in the hospital. Other laboratory results and a chest x-ray did not demonstrate any other obvious reason for the patient's severe decompensation.

What did you find?

One day after resuming ivacaftor treatment, the child's fever resolved, and rapid breathing and low oxygen levels normalized. After five days, repeat sweat chloride was within normal range, demonstrating medication effectiveness for this patient. With time, the patient's pulmonary function tests improved back to levels achieved prior to discontinuation of ivacaftor. The patient was eventually transitioned to elexacaftor/tezacaftor/ivacaftor combination therapy with further improvement in pulmonary function.

What does this mean and reasons for caution?

The inciting event for this patient's decompensation is thought to be a lapse in ivacaftor treatment. What remains unclear is why some patients may be susceptible to IWS and others may not be affected. Beyond the cause for IWS, the clinical picture of this entity is important to recognize, given that more patients will be treated with ivacaftor in the form of elexacaftor/tezacaftor/ivacaftor combination therapy. Although IWS is a rare complication of withdrawal from these medications, caution must be exercised as patients move into this next phase of highly effective CF treatment.

What's next?

Open communication about CF medication effectiveness, compliance, and side effects between patients and clinicians is even more important in the era of highly effective modulator therapy than previously. Ivacaftor and combined elexacaftor/tezacaftor/ivacaftor therapies should be celebrated. However, clinicians, patients, and families must be vigilant in recognizing this uncommon entity, IWS.

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