Case Study: Trikafta and severe symptomatic hypoglycemia: cause or coincidence?

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Abstract

Background: Trikafta (Ivacaftor / Elecaftor / Tezacaftor) is a new combined CFTR modulator and potentiator for the treatment of cystic fibrosis (CF), approved by Swissmedic since December 2020. It has shown to improve lung function in CF patients. Trikafta also influences pancreatic function and glucose homeostasis, whereby hypoglycemic episodes have been described. The underlying mechanisms are not yet fully understood.

Case Report: We present a 16-year-old adolescent with CF with a first tonic-clonic seizure while being hypoglycemic approximately two weeks after therapy-onset with Trikafta. Diagnostic work-up found no other underlying cause for the seizure episode.

Discussion: Literature shows a complex influence of pancreatic CFTR channels on glucose homeostasis. CFTR channels have an important role in the first phase of insulin secretion as well as regulation of glucagon release. Hence, some effect on glucose homeostasis is expected from the treatment with CFTR modulators. Due to the timely connection in our patient the hypoglycemic state could have been provoked by a combination of changing eating habits and the direct influence of Trikafta on the regulatory mechanism of the pancreatic CFTR channels.

Conclusion: Medical caregivers should be aware of potential hypoglycemia risk in CF-patients put on Trikafta. Based on the literature CF-pathophysiology and the pharmacologic effect of Trikafta we assume that the medication may have triggered this critical event. We thus conclude that before initiating therapy a) patients should be evaluated for prediabetic state; b) patients should be instructed regarding hypoglycemia-risk and c) the possibility of continuous-glucose-monitoring should be considered and discussed with the patients.

Introduction

Cystic Fibrosis (CF) is caused by mutation in the cystic fibrosis transmembrane conductance regulator protein (CFTR) gene which leads to defects in the eponymous called protein. Because of these defects, the chloride conductance in and out of the cell is impaired in many organs, most importantly in lung and pancreas, which leads to building of thick mucus in these organs. In the last years there is a new way to treat CF-patients, namely with CFTR-potentiators/-modulators, Trikafta as an example. They have shown to be very potent with major lung improvements and seem to be safe concerning the adversary effects.

Case Presentation

A 16-year old adolescent with cystic fibrosis, who was under Trikafta-therapy was admitted to the emergency department following a generalized tonic-clonic seizure.

The event happened during moderate physical activity one hour after lunch.

Examination on site showed hypoglycemia (3.0mmol/L), 20 minutes after seizure onset. 10 minutes after spontaneous seizure termination...
glucose infusion was immediately started. Upon arrival at the hospital the patient was somnolent with GCS 8 but hemodynamically stable. Blood glucose was 4.6 mmol/l. Electrolytes and inflammation parameters were normal, lactate was 2.9 mmol/L. Critical sampling wasn’t performed because of normal glucose.

Head-CT and – MRI excluded intracranial hemorrhage and relevant ischemia as potential etiologies. ECG was normal.

After extubation, the patient remained drowsy but oriented when stimulated, complained about headache for the next 24 hours. Follow-up EEG performed after 36 hours showed an overall decelerated pattern, which 5 days later had disappeared.

The patient had been diagnosed with CF - compound heterozygote type with F508deletion and 1717-1G>A. – 14 years ago. His lung function had considerably declined resulting in nocturnal oxygen for the last 7 months. His last FEV1 was 38% with the lowest value of 21% during the latest exacerbation several months ago. Consecutively he was started off-label on Trikafta (Ivacaftor / Elexacaftor / Tezacaftor) additionally to his regular CF-treatment 18 days prior to the event. He noted an immediate substantial subjective improvement of lung function. Pulmonary secretion decreased and physical performance improved. His FEV1 almost doubled to 64% two weeks after treatment onset.

The adolescent had previously been diagnosed with exocrine pancreas insufficiency with failure to thrive and reduced bone mineral density despite pancreatic enzymes substitution. An oral glucose tolerance-test (oGTT) was normal nine months before the event. On Trikafta the patient developed increased appetite and a weight gain of 5kg in 18 days.

**Discussion**

Trikafta is a novel combined CFTR modulator and potentiator. Enhancing the quantity of correctly processed CFTR proteins and increasing their open-probability once integrated in the cell membrane, this medication has recently improved lung function in CF-patients by increasing the conductance of chloride across the epithelial cells.1 Whereas the primary target is improvement of epithelial lung cell function, the modulator therapy additionally influences the CFTR dependent function in other organs i.e., the pancreas.

CFTR channels are present in pancreatic islet cells. Animal and human studies show that CFTR deficiency leads to islet-intrinsic defects in insulin secretion. Kayani et al give an excellent overview of the role of the CFTR in insulin secretion focusing on the first-phase insulin response, which is depolarization-dependent and therefore possibly related to the CFTR function, whereas the second phase release is not.2 In addition to insulin secretion, CFTR presumably regulates glucagon release from the pancreatic alpha cell. Glucagon secretion was enhanced in response to glucose and forskolin following CFTR inhibition in human islets. The exact impact of CFTR in pancreatic cells remain conflicting and further studies are needed. 3

Therefore, CF related diabetes (CFRD) could partially be explained by a reduction in early-phase insulin secretion, which is considered the initial marker of impaired insulin secretion.3

Hence, some effect on glucose homeostasis is expected from the treatment with CFTR modulators. Hypoglycemic events have been described with the administration of Ivacaftor in patients with a CFRD resulting in reduced insulin-requirements. Ivacaftor also improved the early phase insulin secretion in a relatively young CF-patient group with normal to mildly impaired glucose tolerance comparable to our patient. The extent to which this arises from b-cell-specific effects remains unclear; since CFTR protein expression has been identified also in pancreatic alpha-cells, Ivacaftor and with it Trikafta may have effect on both cell functions. 4; 5

The American FDA (Food and Drug Administration) reports a prevalence of 1% of hypoglycemic events with Trikafta as compared to placebo. The WHOpharmacovigilance database (www.vigylize.who-umc.org) has listed nine cases of hypoglycemia since 2019. According to the criteria of the Institute of Clinical Pharmacology and Toxicology of the University Hospital of Zurich, a correlation of the hypoglycemic event and administration of Trikafta is possible, given the timely connection.

Our patient reported a sudden change of eating habits with the start of Trikafta, with larger meals and a weight gain of 5kg in two weeks, which lead us to assume a change in glucose homeostasis. The aforementioned mechanisms in CFRD and documented reduction in early phase insulin secretion even in patients without CFRD, let us speculate on a prediabetic state in our patient. We suggested that the improved insulin secretion from beta cells after the start of Trikafta cumulating with the second phase release and simultaneously impaired glucagon release from alpha cells led to the hypoglycemic event. Christian et al. published a case with postprandial hypoglycemic events during the treatment with Ivacaftor hypothesizing a potentiation of the insulin-effect after meals.4 An additional potential risk factor is the changed eating habit in our patient with the
possibility of faster gastric emptying and reduced insulin secretion 3; 5

While limitations lie in the thoroughly evaluation of hypoglycemia (C-peptide, Insulin, fasting-glucose-test), medication-induced hypoglycemia was the most possible solution. Knowing that a glucose of 3mmol/l doesn’t typically lead to general seizures we supposed a lower value during at the initiation, with counter-regulatory mechanisms already working until the first measurement, which we can’t prove

Conclusion

To our knowledge, this is the first reported case with a symptomatic hypoglycemic seizure event in a patient with CF under Trikafta. After exclusion of other potential causes, we hypothesize a combined effect of improved first phase insulin release together with a modifying effect on pancreatic glucagon secretion. This would be in line with the current literature on Trikafta and with data of CFTR-modulator pilotstudies suggesting an increased hypoglycemia risk.

Based on our patient’s case we suggest evaluating patients carefully for pre-diabetic state before starting Trikafta, a good education regarding the potential for postprandial hypoglycemia and considering a continuous glucose monitoring in the first weeks of treatment.