Abiraterone acetate-induced life-threatening torsade de pointes

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Abiraterone acetate (AA) was approved in 2011 for the treatment of metastatic castration-resistant prostate cancer (mCRPC). AA selectively inhibits the CYP17 enzyme, resulting in the suppression of testosterone production and an increase in ACTH levels, and hence in mineralocorticoid production. Prednisone coadministration is warranted to suppress the adrenocorticotropic feedback loop and reduce the most common adverse effects of AA, including hypokalemia, hypertension, and fluid retention. Hypokalemia still affects up to 28% of patients taking AA.

We report the first case of life-threatening torsade de pointes (TdP) associated with a prolonged QT interval in a patient taking AA.

Case Presentation

A 74-year-old patient, without any personal or family history of cardiac disease, but known for hypertension, diabetes, anxiety disorder, and mCRPC, was admitted for a cardiac arrest. First observed rhythm was TdP alternating with ventricular fibrillation (Figure 1). After resuscitation, the electrocardiogram showed a prolonged QTc interval (620 ms). Laboratory results showed severe hypokalemia (2.5 mEq/L) and mild hypocalcemia (4.1 mEq/L). Other blood electrolyte levels, including magnesium (1.32 mEq/L); liver enzymes (aspartate aminotransferase, 75 IU/L; alanine aminotransferase, 43 IU/L); renal function (serum creatinine 0.87 mg/dL); thyroid function (thyroid-stimulating hormone 2.5 mIU/L); and complete blood count (hemoglobin 100 g/L; platelet count 123 × 10^9/L; white blood cell count 7.8 × 10^9/L) were in the normal range. Myocardial infarction was excluded.

The only concomitant medications were enalapril 20 mg once a day, metformin 850 mg thrice a day, and zolpidem 10 mg once a day, which the patient had been taking for 10 years. He had begun AA, 250 mg 4 times a day, 6 months earlier, which was decreased to 250 mg thrice a day because of diarrhea, and prednisone 5 mg twice a day for a mCRPC. Adherence was good, except for prednisone because its usefulness was not clear for the patient.

AA was stopped. The other medications were continued. Serum potassium was corrected and was in the normal range on day 2. Calcium levels normalized within 48 hours without supplementation. The QTc interval gradually decreased and was 440 ms on day 6. The patient was confused and agitated because of postanoxic encephalopathy. He slowly recovered and was discharged home 2 weeks later.

Discussion

The imputability of AA in our patient’s life-threatening TdP is supported by chronology and the exclusion of other potential causes of long-QT syndrome, including no other drugs known to prolong the QT interval. Based on the Naranjo probability scale, the score for AA-induced TdP in this case was 5, indicating a probable causal relation between the reaction and AA. Poor adherence to prednisone treatment explains the severity of the hypokalemia and might be the direct link between AA and TdP. In phase 3 clinical trials, AA was not associated with cardiac arrhythmia or a prolongation of QT interval. Contrary to most drugs prolonging the QT interval, AA was not shown to significantly inhibit the human ether-à-go-go-related gene (hERG) potassium channel. However, recent studies have shown that the magnitude of hERG block does not necessarily predict QT prolongation and TdP and that a drug’s potential to block several ionic channels may be a better indicator of TdP risk.

Conclusion

Hypokalemia may explain the arrhythmia in the case reported, although further investigations are needed to determine the exact mechanism involved. The case illustrates how premarketing data only provide limited assurance about a drug’s safety. It represents a new instance of drug-associated TdP and underlines the necessity of prednisone coadministration with AA treatment.

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Figure 1. Torsade de pointes with fast degeneration into ventricular fibrillation.