Life threatening torsades de pointes due to abiraterone-induced hypokaelemia in a patient with metastatic prostate cancer

Afrasyab Khan, Barry Kneale

ABSTRACT

We present a case of a 77 year-old gentleman with previous coronary artery bypass grafting, admitted to hospital with recurrent torsades de pointes (TdP) due to abiraterone-induced hypokalaemia and prolonged QTc. The patient was on abiraterone and prednisone for metastatic prostate cancer. He required multiple defibrillations for recurrent TdP. Abiraterone is a relatively novel drug used in metastatic prostate cancer and we discuss this potential adverse effect and its management in this unusual presentation.

Abiraterone acetate is an inhibitor of CYP17 and is used in metastatic prostate cancer with mineralocorticoid excess and resultant hypokalaemia as a known side effect. We present a case of recurrent torsades de pointes due to abiraterone-induced hypokalaemia. This is a relatively novel drug and we discuss this potential adverse effect and its management in this unusual presentation.

Case report

A 77 year-old gentleman with ischaemic heart disease (IHD), previous coronary artery bypass grafting (CABG) and atrial fibrillation was brought to the emergency department (ED) after a syncopal event. He had metastatic castrate-resistant prostate cancer treated with prednisone and abiraterone. At the scene he was noted to have runs of ventricular tachycardia—subsequently diagnosed as TdP. Intravenous (IV) amiodarone (300mg) was administered before transport to the emergency department (ED). On arrival in ED his heart rate was 70 beats/min and BP was 150/85mmHg. Physical examination revealed minimal crackles at lung bases but was otherwise unremarkable. An electrocardiogram (ECG) showed a prolonged corrected QT interval (QTc) of 650ms which was new compared to a previous ECG (Figure 1). Chest x-ray showed a left lower lobe infiltrate suggestive of atelectasis or infection.

He had three episodes of TdP in ED, resulting in syncope and requiring defibrillation (200 joules biphasic). His regular medications were abiraterone (started six months ago) 250mg four times a day, prednisone 10mg once a day, goserelin injections 10.8mg three-monthly (last dose three months ago) and warfarin 4mg once a day. He had been compliant with his medications. Serum electrolyte levels were as follows (normal ranges in brackets): sodium 135mmol/L (135–145), potassium 2.7mmol/L (3.5–5.2), magnesium 0.84 mmol/L (0.7–1.0) and calcium 2.17 mmol/L (2.10–2.55). IV replacement of potassium and magnesium were started. Liver and renal function tests were normal. He had four further episodes of TdP requiring defibrillation as well as multiple episodes of non-sustained TdP (Figure 2 and 3). He was commenced on isoprenaline by IV infusion to increase the heart rate and thus trying to decrease his QT interval. This was weaned off during hospital day 2.

Over the first 24 hours he received a total of 160mmol of potassium. His QTc interval improved significantly after potassium replacement.
replacement. A transthoracic echocardiogram showed mild left ventricular impairment with previously known inferior wall motion abnormalities (WMA). He was discharged home after remaining stable off abiraterone without any further arrhythmias. His QTc on discharge and at clinic follow-up one month later was 460ms (Figure 1). His electrolytes remained normal at clinic follow-up. Our discharge diagnosis was abiraterone-induced hypokalaemia initiating TdP in a patient with known IHD.

**Discussion**

Abiraterone acetate is an inhibitor of CYP17, which is an important enzyme in testosterone and oestrogen synthesis and is currently used for metastatic castration-resistant prostate cancer.\(^1\) Its effectiveness was studied in a trial but patients with clinically significant heart disease were excluded.\(^2\) In the abiraterone arm of the study, cardiac disorders as adverse events were reported in 126 (23.2%) versus 96 (17.7%) patients

![Figure 1: ECG from old records (a); on arrival in the emergency department showing prolonged QTc (b); and after discharge from the hospital (c).](image_url)

![Figure 2: Episode of non-sustained TdP with R-on-T phenomenon.](image_url)
taking placebo without any mention of statistical significance. QTc interval was not measured in this study. Abiraterone is not known to cause a prolonged QTc and certainly did not result in any QTc prolongation in one study with 33 participants.\(^5\)

The patient was not on any medications known to cause QTc prolongation. There is no causal relationship between goserelin and QTc prolongation.\(^4\)

The cytochrome P450 enzyme involved in the metabolism of abiraterone is CYP3A4.\(^5\) The patient was not on any medications known to affect the metabolism of abiraterone. Mineralocorticoid excess and hypokalaemia are known side effects of abiraterone due to CYP17 inhibition.\(^2\)

Inhibition of CYP17 by abiraterone results in reduction of cortisol. This in turn leads to an increase in adrenocorticotropic hormone (ACTH). ACTH drives the biosynthesis pathway of steroids and hence results in increased levels of corticosterone (by a median 40-fold) and deoxycorticosterone (by a median 10-fold) as a result of CYP17 inhibition.\(^6\) Prednisone is added with abiraterone to enhance its anti-tumour activity by lowering ACTH and suppress steroids upstream of CYP17 as well as to prevent mineralocorticoid excess associated with CYP17 inhibition.\(^7\) This reduces hypokalaemia in patients on abiraterone. Mineralocorticoid excess can also manifest as hypertension and oedema. Potassium levels are frequently monitored during treatment with abiraterone. In a phase III study, potassium levels were checked at initiation of abiraterone, then every two weeks for three months and then monthly as long as the treatment was continued.\(^8\) We recommend similar frequency of monitoring as long as potassium levels are satisfactory.

Hypokalaemia occurred in 17 percent of patients treated with abiraterone even while being on prednisone.\(^9\) Hypokalaemia is well known to cause prolongation of the QTc interval and this can lead to torsades de pointes.\(^10\) There is limited or no data regarding abiraterone treatment in patient with known structural heart disease or prior cardiac surgery. By calculating the Naranjo probability score, the likelihood of an adverse effect due to a drug can be scored as definite, probable, possible or doubtful.\(^11\)

The score for abiraterone causing hypokalaemia in this case was 7 deriving from hypokalaemia being a known side effect of abiraterone, occurring after drug administration, potassium level remained normal at follow-up after withdrawal of suspected drug, no alternative cause was evident and it was confirmed with objective evidence of a low potassium level. The score of 7 indicates a probable adverse drug reaction.

### Conclusion

This report describes a potentially fatal adverse consequence of a relatively novel agent having predictable metabolic side effects. To our knowledge there is one other reported case of TdP and hypokalaemia in the setting of abiraterone treatment.\(^12\) The hypokalaemia is easily treated and QTc prolongation can be prevented. We recommend that clinicians be alerted to this serious adverse event both as a possible emergency presentation and when prescribing this therapy.

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**Figure 3:** Torsades de pointes resulting in syncope requiring defibrillation.
Competing interests:
Nil.

Author information:
Afrasyab Khan, Advanced Trainee, Department of Medicine, Bay of Plenty District Health Board, Tauranga; Barry Kneale, Consultant Cardiologist, Bay of Plenty District Health Board, Tauranga.

Corresponding author:
Afrasyab Khan, Advanced Trainee, Department of Medicine, Bay of Plenty District Health Board, Cameron Road, Tauranga. afrasyabkhan@gmail.com

URL:

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