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RESEARCH LETTER

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Abiraterone and prednisone therapy may cause severe hypoglycemia when administered to prostate cancer patients with type 2 diabetes receiving glucose-lowering agents

Marcello Tucci[1] · Elisa Roca[2] · Laura Ferrari[2] · Anna Pia[3] · Alberto Dalla Volta[2] · Francesca Bedussi[4] · Consuelo Buttigliero[5] · Giorgio Vittorio Scagliotti[5] · Sandra Sigala[4] · Alfredo Berruti[2]

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Abiraterone acetate (abiraterone) is a prodrug of the CYP17A1 inhibitor abiraterone, that blocks androgens biosynthesis. The drug is approved for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC), in combination with 10 mg/die prednisone (or prednisolone) [1]. Prednisone is administered as glucocorticoid replacement therapy, to compensate the abiraterone-induced reduction in serum cortisol and the consequent rise in adrenocorticotropic hormone levels, leading to an increased synthesis in mineralcorticoid hormones [2, 3]. Prednisone supplementation, however, could potentially worsen blood glucose levels in patients with type 2 diabetes. No data on the tolerability of abiraterone plus prednisone are available in diabetic patients, since this co-morbidity was always an exclusion criterion in randomized prospective registration clinical trials. Oral glucose lowering agents are the drugs most frequently administered in the management of type 2 diabetes. Noteworthy, in pivotal trials testing these drugs, subjects with malignancies were excluded, so their use in cancer patients is not supported by a literature evidence.

In vitro studies demonstrated that abiraterone is a strong inhibitor of CYP1A2, CYP2C8, and CYP2D6 and a moderate inhibitor of CYP2C9, CYP2C19, and CYP3A4/5 [4, 5]. Since several glucose-lowering agents, such as sulphonylurea (SU), usually administered in type 2 diabetes, are metabolized by the CYP pathways, drug–drug interactions may occur when abiraterone is concomitantly administered with these drugs. Moreover, diabetic patients usually present several additionl co-morbidities, dyslipidaemia being the most frequent. This implies that glucose-lowering drugs are frequently administered in association with lipid-lowering agents such as statins, a class of drugs that includes many active substances metabolized by the CYP system, CYP3A4 and CYP2C9 in particular [6]. Therefore, their use is endowed with an increased risk of CYP-mediated pharmaco-metabolic interactions. Indeed, competition among drugs at the enzymatic level is common in a multiple drug therapeutic plan and this may induce changes of drug bioavailability, leading to increased/decreased plasma levels and greater risk of adverse events or inefficacy.

Here we report two cases of severe hypoglycemia in mCRPC patients with type 2 diabetes mellitus in whom abiraterone was administered in association with glucose lowering agents and statins. To our knowledge, these are the first two cases of hypoglycemia associated with abiraterone and prednisone treatment ever described.

Case presentation

Case 1: abiraterone plus prednisone were administered to a 69-year-old man with castrate resistant prostate cancer

These authors contributed equally: Marcello Tucci, Elisa Roca

✉ Alfredo Berruti
alfredo.berruti@gmail.com

[1] Medical Oncology, Cardinal Massaia Hospital, Corso Dante Alighieri, 202, 14100 Asti, Italy

[2] Medical Oncology, ASST-Spedali Civili, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Piazzale Spedali Civili 1, 25123 Brescia, Italy

[3] Endocrinology Unit, San Luigi Gonzaga Hospital, Regione Gonzole 10, 10043 Orbassano, Turin, Italy

[4] Section of Pharmacology, Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy

[5] Medical Oncology, Department of Oncology, University of Turin at San Luigi Ginzaga Hospital, Regione Gonzole 10, 10043 Orbassano, Italy

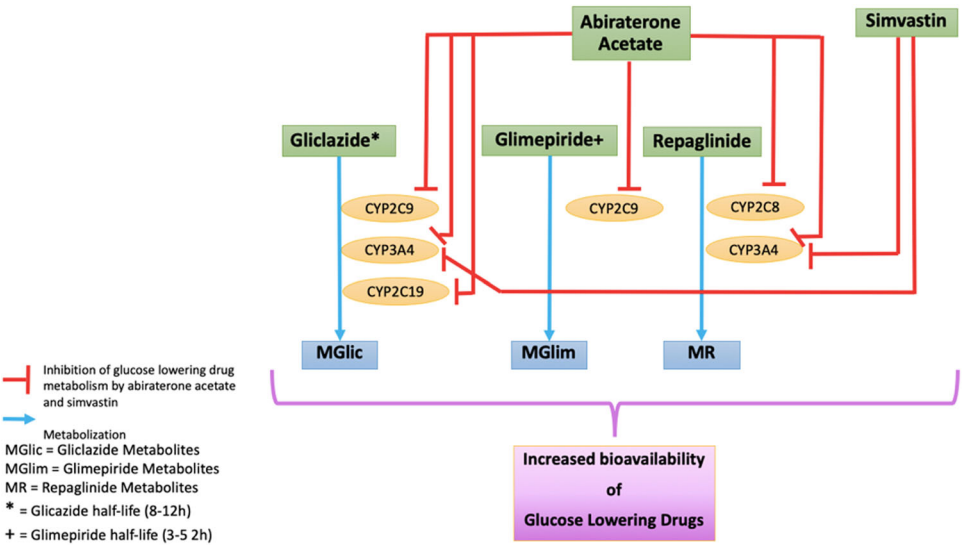

Fig. 1 Abiraterone inhibits several CYP related enzymes and increases the bioavailability of glucose-lowering drugs. This effect can be potentiated by statins. Due to its shorter plasma half life glimepiride administration may be associated with a lower risk of hypoglycemic episodes than other sulphonylureas

(CRPC) and type 2 diabetes treated with 200 mg/die gliclazide. After 2 weeks of treatment, he reported symptomatic hypoglycemia episodes, up to a minimum blood glucose level of 40 mg/dl in the morning fasting state. Gliclazide was firstly reduced at 160 mg/die and, due to the persistence of hypoglycemic episodes, it was replaced with 2 mg/die glimepride. No further hypoglycemic episodes were recorded and the patient is still on abiraterone therapy.

Case 2: a 79-year-old CRPC patient and concomitant type 2 diabetes on repaglinide therapy (4 mg/die) received abiraterone plus prednisone as third line treatment. After 5 days, a severe hypoglycemia (< 30 mg/dl) occurred, that required hospitalization. Abiraterone was interrupted for 7 days and a glucose-insulin curve was performed during repaglinide administration without abiraterone. Since neither reactive hypoglycemia nor hyperinsulinism were observed, abiraterone was reintroduced in association with repaglinide at 50% of previous dose. Despite the dose reduction, severe Hypoglycemic episodes reappeared, so repaglinide was definitely interrupted and substituted by insulin.

Discussion

The two case reported here indicate that, in a complex multidrug therapeutic plan in diabetic patients with prostate cancer, including glucose lowering agents in association with abiraterone and prednisone, the potential risk of hypoglycemia instead of the expected hyperglycemia may occur.

In the case report 1, the suspected drug/drug interaction responsible for the hypoglycemic adverse event was the association of abiraterone with the sulphonylurea (SU) gliclazide. Gliclazide is a second generation SU, cleared by hepatic metabolism, mainly by CYP2C9 and to a lesser extent by CYP3A4 and CYP2C19 [7] (Fig. 1).

Indeed, in this patient, gliclazide dose reduction was inadequate to completely prevent hypoglycemic episodes and a long-term glycemic control was reached when the drug was replaced with glimepiride. The concomitant administration of simvastatin, a CYP3A4 inhibitor [8], could also have contributed to increased gliclazide bioavailability (Fig. 1). Noteworthy, also glimepiride is mostly metabolized by CYP2C9 [9, 10]. We hypothesize that the short half-life of glimepiride serum levels (3–5 h) as compared to gliclazide (8–12 h) prevented drug accumulation as a consequence of reduced metabolism. Due to its pharmacokinetics properties, Glimepride could be a SU less susceptible to a pharmaco-metabolic interaction in a multiple therapy plan.

The second patient received repaglinide as glucose lowering agent that is mainly metabolized by CYP2C8 and CYP3A4 enzymes [11]. In this case, the pharmaco-metabolic interaction with abiraterone led to the occurrence of severe hypoglycemic episodes that occurred early (after few days). Similarly to the case 1, symptomatic hypoglycemia still occurred after a 50% reduction of repaglinide and the concomitant administration of simvastatin could have contributed to increase repaglinide availability (Fig. 1). The effect on repaglinide plasma concentration by concomitant use of CYP2C8 inhibitor was already reported [1]. In a study of healthy volunteers, the concomitant use of repaglinide and the CYP2C8 inhibitor deferasirox resulted in an increased repaglinide AUC and Cmax of 2.3-fold [12]. This case description suggests that drug–drug interaction of abiraterone and repaglinide is strong and occur rapidly. On these bases repaglinide is contraindicated in association with abiraterone.

In conclusion, glucose-lowering SUs are in principle not the best choice of treatment in cancer patients with type 2 diabetes, particularly if a cardiovascular disease co-exists. However, the short life expectancy of advanced prostate cancer patients with castration resistant disease, may justify the use of these drugs. Noteworthy, when a SU is administered together with abiraterone/prednisone to prostate cancer patients with type 2 diabetes, the risk of hypoglycemia should be carefully considered, due to a pharmaco-metabolic interaction, leading to increased SU bioavailability.

Hence SUs are not the drugs of choice in this setting, also considering the availability of new glucose-lowering drugs with low risk of hypoglycemia, such as glucagon-like peptide-1 receptor agonists (GLP-1 RA) and selective sodium glucose transporter 2 (SGLT2) inhibitors [..].

Type 2 diabetes therapy often includes treatment of concurrent dyslipidaemia and other co-morbidities, therefore drugs that present a low risk of pharmaco-metabolic interactions should be preferred in a poly-therapy that included abiraterone/prednisone administration.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent One patient signed the consent to publish and the other patient who died, had been enrolled in the italian Abiraterone expanded access (EAP) study. He therefore signed a informed consent in which he authorized the publication of his clinical data and treatment toxicity.

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