nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Letter to the Editor

Acute renal failure due to rhabdomyolysis in relation to abiraterone and rosuvastatin

Fracaso renal agudo por rabdomiólisis en relación con abiraterona y rosuvastatina

Dear Editor,

Acute kidney injury (AKI) in association with rhabdomyolysis is quite common. Depending on the patient's comorbidity, an association of up to 30% has been reported between cases of rhabdomyolysis and AKI.[1,2] We distinguish between traumatic and non-traumatic causes of rhabdomyolysis and it is notable that an increasing percentage of cases are now due to non-traumatic causes associated with commonly used drugs. In addition, associated risk factors have been described, such as advanced age, chronic kidney disease, diabetes, hypothyroidism, inflammatory or metabolic myopathies and trauma. In a population that is becoming progressively older and with polypharmacy, there is an ever-greater risk of drug interactions. We report a representative case.

This was an 89-year-old male, former smoker with hypertension, moderate aortic stenosis, hypothyroidism, dyslipidaemia, stage G3bA1 chronic kidney disease (basal creatinine: 1.9 mg/dl; glomerular filtration rate [GFR] CKD-EPI: 32 ml/min/1.73 m^2) and sleep apnoea, who was admitted to hospital with severe rhabdomyolysis. He had suffered a lacunar stroke 10 years earlier with residual ataxia-hemiparesia and had grade IV bladder cancer in situ, treated by transurethral resection (TUR). Twelve years before he had been diagnosed with grade IV prostate adenocarcinoma, treated by radiotherapy combined with hormone therapy. Five years earlier he had received a second treatment with radiotherapy and twice-yearly triptorelin, due to biochemical progression with the development of bone metastases.

One year earlier, he had suffered an episode of severe rhabdomyolysis (creatine phosphokinase [CPK] 13,000 IU/l), secondary to an accidental fall with trauma, which was accompanied by non-oliguric AKI stage 3 and a good response to conservative treatment. At that time, he was being treated with levothyroxine, candesartan, hydrochlorothiazide, acetylsalicylic acid, rosuvastatin, triptorelin and omeprazole. One month earlier, due to the progression of the prostate disease (pulmonary nodules, retrocrural and retroperitoneal lymphadenopathy), a new line of treatment was started with oral abiraterone 1000 mg/24 h and prednisone. In addition to the treatment described, he was taking the following drugs: calcifediol, calcium carbonate, bisoprolol, cetirizine and denosumab.

A year later, he was admitted to hospital after an accidental fall with a low-back contusion. The patient was also found to have AKI and severe rhabdomyolysis (Table 1). Obstructive uropathy was ruled out by renal ultrasound. Support treatment was started, with little response and progressive development of congestive heart failure, requiring acute haemodialysis and ultrafiltration from day three of admission. His CPK returned to normal on day ten after admission. Despite clinical recovery, the patient remains dependent on haemodialysis.

Abiraterone is a CYP17A1 inhibitor approved by the Food and Drug Administration in 2011 for metastatic prostate cancer. It blocks the synthesis of androgens in the prostate, testicles and adrenal glands, causing an increase in the synthesis of ACTH and mineralocorticoids by inhibiting the enzyme 17α hydroxylase. This can induce hypokalaemia, diarrhoea, elevated blood pressure, oedema and impaired liver function. It does not interact directly with the metabolism of statins, but it does inhibit a transporter, hepatic organic anion transporting polypeptide 1B1 (OATP1B1), dependent on the SLCO1B1 gene, which is a substrate for rosuvastatin. This can reduce the uptake of abiraterone by the liver resulting an increase in its levels. In addition, we know that in certain polymorphic variants in which the transport activity is genetically reduced,[3,4] it can induce an increase in the concentration of rosuvastatin, with the risk of toxicity and rhabdomyolysis. It is rapidly absorbed orally and is metabolised almost

DOI of original article:
https://doi.org/10.1016/j.nefro.2021.04.014.

Table 1 – Changes over time in laboratory parameters.

	23 days prior to admission	On admission day	+ 1	+ 3	+ 8	+ 11	+ 14	+ 16	At discharge
Analyses									
Cr (mg/dl)/CKD-EPI GFR (ml/min/1.73 m^2)	1.9 (29)	9.5 (4.0)	10.3 (4.0)	9.8 (4.0)	7 (6.0)	5.3 (9.0)	4.6 (10.0)	4.3 (12)	4.6 (17)
CPK (IU/l)	32	91,012	>100,000	28,193	4530	415	–	96	–
AST (U/l)		592	550	422	229	81	48	35	18
ALT (U/l)	12	189	179	190	230	145	86	58	24
LDH (U/l)	198	–	1115	873					
Bicarbonate (mmol/l)	–	15.8	17.3	17.3	27	21.6	22.6	23.2	22.9
Hb (g/dl)	11	10.2	9.3	9.1	8.9	8.4	10.1	9	9.6
WBC (10^3/μl)	7.5	11.9	8.24	9.21	10.2	8.3	8.8	8.3	9.9
CRP (mg/l)	–	67.7	83.7	196	112	85	71	72	17
D-dimer (μg/l)	–	–	–	25,600	9320	22,060	–	20,450	–
Sodium (mmol/l)	139	123	126	132	139	139	137	140	142
Potassium (mmol/l)	4.4	5.1	4.9	4.3	4.6	3.6	3.2	3	3.4
Corrected calcium (mg/dl)	8.9	–	7.9	9	10.5	10.5	9.9	10.1	9.2
Phosphorus (mg/dl)	2.9	–	6.6	7.5	4.3	2.7	2.8	2.7	3.8
Simple urine sample									
pH		5.5	–	–	–	–	–	–	–
Density (g/l)		1020	–	–	–	–	–	–	–
Red blood cells (cells/μl)		200	–	–	–	–	–	–	–
Proteinuria by test strip (mg/dl)		>300	–	–	–	–	–	–	–
P/C (g)		6.2			13	–	–	–	1.75

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CPK: creatine phosphokinase; Cr: plasma creatinine; CRP: C-reactive protein; GFR: glomerular filtration rate; GFR CKD-EPI: glomerular filtration rate estimated by CKD-EPI; Hb: haemoglobin; LDH: lactate dehydrogenase; P/C: urine protein/creatine ratio; WBC: white blood cells.

exclusively in the liver, being 99% bound to plasma proteins and reaching a maximum plasma concentration at two hours. Its metabolism in the liver uses two enzymatic pathways: cytochrome p450 (CYP) 3A4; and sulfotransferase (SULT) 2A1. It is excreted mainly through the faeces, with less than 5% being excreted through the urine.[5] Marbury et al.[5] studied the metabolism of abiraterone in severe renal failure and concluded that there are no clinically appreciable pharmacokinetic differences between patients with preserved renal function and renal failure.

A few cases have been described in the literature in which abiraterone was used in patients with advanced AKI and on haemodialysis. However, although anecdotal, this would support its safety.[6,7]

Three cases of rhabdomyolysis induced by abiraterone in combination with rosuvastatin have been published to date.[1,2,8] In two of these cases, in addition to rosuvastatin, there was a third drug associated: denosumab. In our case, the patient scored seven points on the Horn Drug Interaction Probability Scale and six on the Naranjo Adverse Drug Reaction Probability Scale,[9,10] which meets criteria for significant probability.

The patient began with severe rhabdomyolysis which induced AKI, requiring haemodialysis. It could be hypothesised that the abiraterone triggered liver failure leading to increased concentrations of rosuvastatin and abiraterone itself. In an older adult patient with hypothyroidism, previous renal failure, treatment with angiotensin-converting enzyme inhibitors and diuretics, dehydration, prolonged immobility due to his neurological sequelae, and polypharmacy (13 drugs), the chance of interactions is very high.[11] This case illustrates the importance of close follow-up in patients with polypharmacy and high levels

Funding

The authors declare that they did not receive any type of funding for conducting the study.

Conflicts of interest

The authors have no conflicts of interest to declare.

REFERENCES

1. Neyra JA, Rocha NA, Bhargava R, Vaidya OU, Hendricks AR, Rodan AR. Rhabdomyolysis-induced acute kidney injury in a cancer patient exposed to denosumab and abiraterone: a case report. BMC Nephrol. 2015;16, http://dx.doi.org/10.1186/s12882-015-0113-6.
2. Dineen M, Hansen E, Guancial E, Sievert L, Sahasrabudhe D. Abiraterone-induced rhabdomyolysis resulting in acute kidney injury: a case report and review of the literature. J Oncol Pharm Pract. 2018;24:314–8.
3. Romaine SPR, Bailey KM, Hall AS, Balmforth AJ. The influence of SLCO1B1 (OATP1B1) gene polymorphisms on response to statin therapy. Pharmacogenomics J. 2010;10:1–11, http://dx.doi.org/10.1038/tpj.2009.54. Epub 2009 Nov 3.

4. Van de Steeg E, Greupink R, Schreurs M, Nooijen IH, Verhoeckx KC, Hanemaaijer R, et al. Drug-drug interactions between rosuvastatin and oral antidiabetic drugs occurring at the level of OATP1B1. Drug Metab Dispos. 2013;41:592–601.
5. Marbury T, Lawitz E, Stonerock R, Gonzalez M, Jiao J, Breeding J, et al. Single-dose pharmacokinetic studies of abiraterone acetate in men with hepatic or renal impairment. J Clin Pharmacol. 2014;54:732–41.
6. Karakurt Eryılmaz M, Karaağaç M. Abiraterone experience in a patient with metastatic castration-resistant prostate cancer on hemodialysis. J Oncol Pharm Pract. 2019;25:2031–4.
7. Francini E, Petrioli R, Fiaschi AI, Laera L, Roviello G. Effects of abiraterone acetate on chronic kidney disease in 2 patients with metastatic castration-resistant prostate cancer. Medicine (Baltimore). 2014;93:e163.
8. Moore DC, Moore A. Abiraterone-induced rhabdomyolysis: a case report. J Oncol Pharm Pract. 2017;23:148–51.
9. Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother. 2007;41:674–80.
10. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239–45.
11. Blower P, de Wit R, Goodin S, Aapro M. Drug–drug interactions in oncology: why are they important and can they be minimized? Crit Rev Oncol Hematol. 2005;55:117–42.

Melissa Cintra [a,*], Luis A. Pedraza Cezón [b], Juan A. Martín Navarro [a], Esther Torres Aguilera [a], Marta Albalate Ramón [a], Roberto Alcázar Arroyo [a], Fabio Procaccini [a], Marta Puerta Carretero [a], Mayra Ortega Díaz [a], Laura Medina Zahonero [a], María T. Jaldo Rodríguez [a], Patricia de Sequera [a]

[a] *Servicio de Nefrología, Hospital Infanta Leonor, Madrid, Spain*
[b] *Servicio de Farmacia, Hospital del Tajo, Aranjuez, Madrid, Spain*

[*] *Corresponding author.*
E-mail address: melissacc7@gmail.com (M. Cintra).

https://doi.org/10.1016/j.nefroe.2021.04.018

Hypouricemia in a patient with metabolic syndrome

Hipouricemia en paciente con síndrome metabólico

Dear Editor,

Metabolic syndrome is defined as the presence of three of the following five criteria: 1) waist circumference ≥102 cm (males) and ≥88 cm (females); 2) hypertriglyceridaemia (≥150 mg/dl); 3) HDL cholesterol <40 mg/dl (males) and <50 mg/dl (females); 4) blood pressure ≥130/85 mmHg or being on antihypertensives; and 5) fasting blood glucose ≥110 mg/dl or being on hypoglycaemic agents.[1,2] A large number of studies link hyperuricaemia with metabolic syndrome, specifically with arterial hypertension and insulin resistance.[3–6]

Uric acid is the end product of purine degradation. It is eliminated by the kidneys, a process that involves reabsorption in the first segments of the proximal convoluted tubule (presecretory reabsorption), posterior tubular secretion and a second reabsorption in the final segments of the proximal convoluted tubule (postsecretory reabsorption). The result is a 10% of the filtered uric acid is excreted in the urine.[1]

Several transporters involved in the renal management of uric acid have been identified thanks to the advances in molecular biology in recent years (Fig. 1). One of these is URAT1, encoded by the *SLC22A12* gene and located in the apical membrane of proximal convoluted tubule cells that urate in exchange for a secreted anion. A Na+-monocarboxylate cotransporter (encoded by the *SLC5A8* gene) acts synergistically, reabsorbing both anions and sodium at the same time. The hyperinsulinaemia which characterises the patient with metabolic syndrome increases sodium reabsorption through the above cotransporter, and this also increases urate reabsorption by promoting URAT1 activity and anion exchange with the filtered urate; this explains the association between hyperuricaemia, insulin resistance and hypertension. The reabsorption of urate into the peritubular space is carried out by another transporter, GLUT9, located in the basolateral membrane and also responsible of hexose transport. It also has an apical isoform (GLUT9S) along with URAT1, so urate reabsorption through this transporter happens twice. The hyperinsulinaemia, a characteristic of metabolic syndrome, promotes the activity of GLUT9, increasing the reabsorption of uric acid and glucose.[1,4–6]

With the increasing incidence of metabolic syndrome in recent years and its implication as a cardiovascular risk factor, clinicians have begun to focus more on the diagnosis of hyperuricaemia and its treatment. Although hypouricaemia (urate <2 mg/dl) is a rare finding in the population (0.2%), we have to be aware that it may occur and it is the expression of abnormality in the renal tubular transport of uric acid. The differential diagnosis (Table 1) is made based on fractional excretion of urate (FEUa), distinguishing between hypouricaemia with low FEUa (xanthinuria, liver disease, drugs) and

DOI of original article:
https://doi.org/10.1016/j.nefro.2021.06.008.