Apparent excess of mineral corticoids and a point of view of an alternative statistical evaluation: A case report and mini-review of the literature

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Abstract. The present study describes the case of a 71-year-old male patient with hypocalcemia, hypomagnesemia and hypokalemia. Following infusion therapy, the serum calcium and serum magnesium levels were normalized. Conversely, serum potassium did not respond to the infusion therapy, with the progressive reduction of the serum concentration, in spite of the high dose of potassium infusion. Although unusual, the present study analyzed how infusion treatment affects kalemia. The present study used, over time, the measurements of variables on a single patient as 'cases' and the set of measurements of the patient himself (single patient) as a 'cohort'. One patient can be considered as one single cluster; thus, the independence assumption is not violated. The present study quantitatively analyzed the effect of one or more treatments and in finding unknown causes that may influence the therapeutic response, particularly in situations with a paradoxical response. Thus, it was found that only potassium canreonate was related to an increase in kalemia (β=0.03, P<0.01). Based on this finding, together with the low aldosterone concentration in hypokalemia, an apparent excess of mineral corticoids was assumed.

Introduction

Rare diseases, identified as an incidence of <5 out of 100,000 individuals, are difficult to diagnose and treat. An unknown response to treatment can often manifest in such cases. The analysis of the responsiveness to therapy could aid in the understanding of these uncommon diseases. Etiological studies allow us to associate some risk factors to a specific outcome, including the differential response to treatment, and regression analysis computes the slope of this association. Linear regression is subjected to the assumption of independence, where each case should be not related to a cluster, such as repeated measures (1). This assumption does not exclude the analysis of repeated measures when all the analyzed measures refer to one patient, as in this case, the patients represents the cohort and the measures represent the cases. Repeated measures are analyzed through mixed models, which relax the independence assumption and take into account more complex grouped or clustered data. Similar to a single center study, where a single center represents one cluster and this analysis does not need to be analyzed for repeated measures, a single patient represents a cluster in which all the measures do not depend from the independence assumption. Indeed, adding the patient as a random variable in the mixed model, would not change the results due to this being a constant. Each patient has a different response to one therapy and sometimes, mostly in uncommon diseases, this response is not clear. For this reason, the present study describes the case of a patient with hypocalcemia, hypomagnesemia and hypokalemia. It also presents a statistical approach using a single patient which may help solve the not understandable physio-pathological pathways.

Case report

A 71-year-old male patient presented with paresthesia and motor deficits in all four limbs, at the University Hospital 'G. Martino' of Messina. The results tests for hemato-chemical parameters revealed metabolic alkalosis and severe hypokalemia-hypocalcemia-hypomagnesemia, for which infusion therapy with calcium gluconate (2 g/die i.v.) and magnesium sulfate (2 g/die i.v.) was necessary, in order to achieve the normalization of serum magnesium and calcium levels. However, the severe hypokalemia persisted, despite the progressive increase in potassium chloride (KCl) supplementation up to 120 mEq/day. Each administration was performed with a speed between 40 and 200 ml/h. Potassium, calcium and magnesium were administered in different periods of the

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day. Serum potassium levels were measured at the central laboratory of the aforementioned hospital, in the morning with a sample obtained via the peripheral vein. The urinary potassium/creatinine ratio >1.5 mmol/mmol excluded extra-renal loss, for which the hypothesis of hyperaldosteronism was posed. This hypothesis was rejected based on a serum concentration of aldosterone <15 pg/ml, repeated several times during the week, without alterations in renin, cortisol, adrenocorticotropic hormone (ACTH) and dehydroepiandrosterone-sulfate (DHEA-S). Upon the suspicion of an apparent mineralcorticoid excess (AME), as described in the study by Monnens and Levtchenko (2), potassium canreonate was added in increasing doses up to 400 mg/day, with the gradual normalization of kalemia observed.

The lack of response to the intravenous potassium supplement led the authors to perform a statistical analysis to evaluate the impact of the therapy on kalemia, in an attempt to identify possible confounders that could explain the lack of a therapeutic response. The serum potassium concentration was considered as an outcome and the dose of potassium canreonate administered in the previous 48 h (according to the mechanism of action of the canreonate), the amount of daily KCl administered in the 24 h preceding the kalemia dosage, and, similarly to the latter, the quantity of NaCL0.9% physiological solution, as independent variables.

To perform the statistical analysis, the distribution of each variable was evaluated using the Kolmogorov Smirnov test and graphical evaluation of the distributions. Thus, linear regression models were performed using kalemia as dependent variables, and NaCl 0.9% (l/die), KCl infusion (mmol/die) and potassium canreonate (mg/die) as independent variables, in univariate and multivariate models. The analysis revealed a statistically significant positive association between serum potassium and potassium canreonate ($\beta=4.3x10^{-3}$, $P<0.05$) (Fig. 1), contrary to the association between kalemia and KCl infusion (mmol/day) and NaCl0.9% (l/day), which exhibited a negative association ($\beta=-1x10^{-2}$, $P<0.05$ and $\beta=-4.98x10^{-4}$, $P<0.05$, respectively) (Figs. 2 and 3). All these three were added in a multivariate model, and only potassium canreonate was found to have a significant impact ($\beta=0.03$, $P<0.01$), whereas no significant associations were found with potassium infusion ($\beta=-0.004$, $P=0.28$) and NaCl infusion ($\beta=1.2x10^{-4}$, $P=0.38$). The adjusted impact of potassium canreonate is presented in Fig. 4. Thus, only potassium carneonate significantly affected kalemia. This may be explained by the highest association between NaCl infusion and K infusion, related with a Pearson's coefficient of 0.68 ($P<0.01$). These results demonstrated that neither NaCl infusion nor KCl infusion affected kalemia in this patient, conversely to potassium canreonate.

The literature reports association between AME and some glomerulonephritis, such as IgA nephropathy (IgAN) and focal and segmental glomerulosclerosis (3).

Discussion

Aldosterone-related diseases. Aldosterone is a steroid hormone synthesized in the glomerular part of the adrenal gland that acts on the mineralocorticoid receptor (MR) by increasing the reabsorption of sodium and the excretion of potassium at the level of the collecting tubule. It also activates Na/K pumps in myocardial cells (PKC), probably without interaction with MR and, through Na/H pumps, activates MAPKs and modulates intracellular Ca^{2+}. Its dysregulation causes two pathological features: Hypoaldosteronism and hyperaldosteronism (4).

Hypoaldosteronism is a condition caused by a serum aldosterone concentration <15 pg/ml. It may occur due to the impaired surrealist gland function, with a high ACTH level to compensate this gap, or a reduced central ACTH secretion, which does not stimulate hormone secretion (5). The clinical manifestations often include arterial hypotension, hyponatremia and hyperkalemia. It may be related to a low renin production, causing hyporeninemic hypoaldosteronism (6). Conversely, the excess serum concentration of aldosterone causes hypernatremia with hypokalemia and hypertension (5). However, a similar clinical manifestation may be due to a defective receptor function, which impairs or improves aldosterone function.

Cortisol is a glucocorticoid hormone with an affinity for MRs, such as aldosterone; however, its concentration in plasma is 100-fold greater than aldosterone. The enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) is expressed in the distal nephron and collecting duct, and metabolizes cortisol to cortisone, which does not affect MR. HSD2 deficiency results in the reduced inactivation of cortisol, with a high ratio of urinary tetrahydrocortisol to tetrahydrocortisone (7,8). Other enzymes, including HSD1, 20β-oxidoreductase, 6β-hydroxylase, 5β-reductase, 5α6-reductase and 3α-HSD affect the metabolism of cortisol (9).

Hyperaldosteronism, but with low or normal serum concentrations of aldosterone, is observed in pseudo-hyperaldosteronism (Liddle's syndrome or other receptor genetic mutations) and the syndrome of an apparent excess of mineralocorticoids (11β-HSD2 defect).

AME. In AME, the enzyme, 11β-HSD2, co-expressed in the kidneys with the MR, plays a critical role: Cortisone is converted from cortisol, as its inactive metabolite. In the case of AME, mutations in the 11β-HSD2 gene result in a lack of the enzyme with consequent failure to metabolize the cortisol that binds to MRI and causes sodium, hypokalemia, the suppression of Plasmatic renin activity (PRA) and hypertension. AME is a genetic disease, but several exogenous factors can determine the function of the 11β-HSD2 enzyme.

The inhibition of the 11β-HSD2 gene can also be caused by the ingestion of bioflavonoids, licorice and carbenoxolone; thus, a correct medical history is critical for a good differential diagnosis. Furthermore, some studies have documented an association between the reduction of 11β-HSD2 activity with preeclampsia in renal disease and liver cirrhosis (due to increased sodium retention) and with Cushing's syndrome, due to enzyme saturation, excess of corticoid minerals and ectopic ACTH production (3). In the latter case, it is the excess substrate that overwhelms the conversion capacity of 11β-HSD2. Furthermore, the reduced expression of 11β-HSD2 can already manifest itself at the placental level with the reduction of birth weight and hypertension in adults (10).

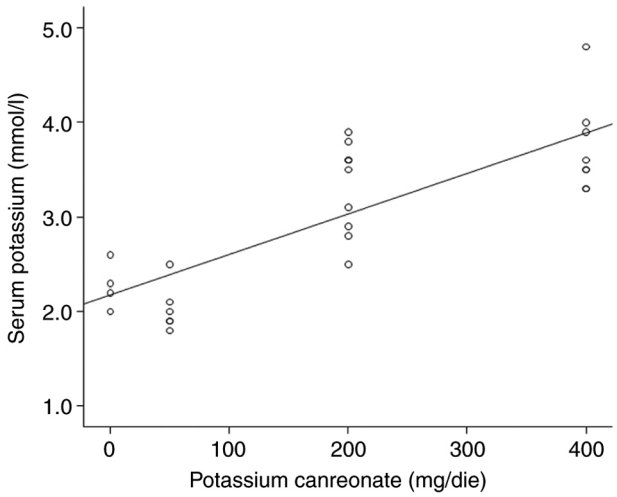

Figure 1. Impact of the administration of potassium canreonate on serum potassium.

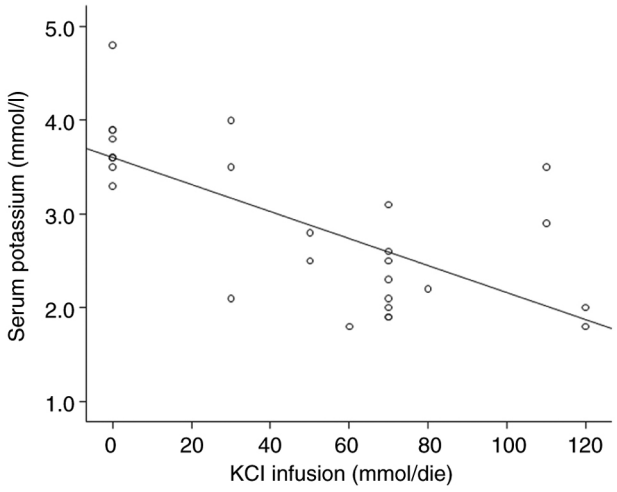

Figure 2. Impact of the administration of intavenous KCl on serum potassium.

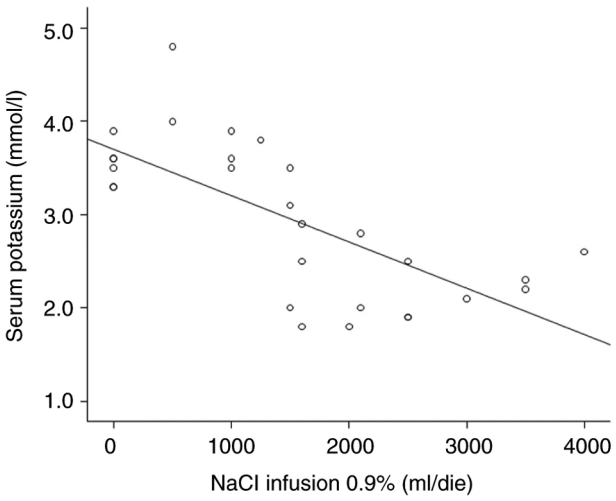

Figure 3. Impact of the administration of intavenous NaCl 0.9% on serum potassium.

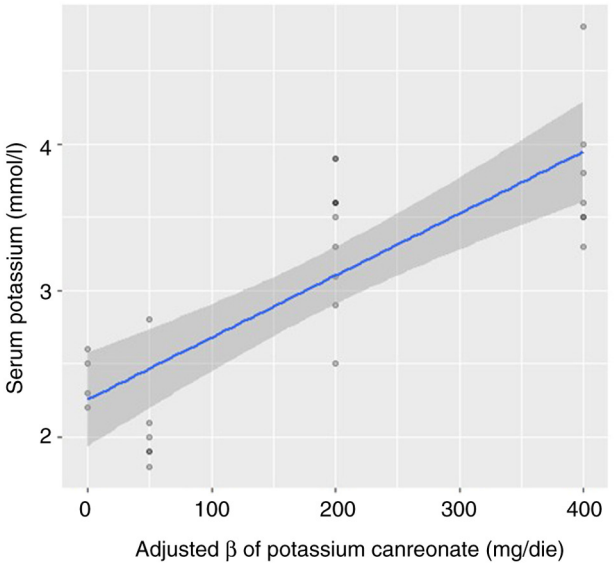

Figure 4. Adjusted impact of the administration of potassium canreonate on serum potassium.

In 2006, the study by Sechi *et al* found a more rapid progression of chronic kidney disease and a higher albumin/creatinine ratio in urine in patients with primary aldosteronism (11). Similar result were shown in the systematic review of 2020 (12).

It is not yet clear whether the cause of this worsening is due to the concentration of aldosterone itself or the activation of its receptor. In this regard, the research published by Bantis *et al* (3,13) in 2011 revealed an association between the aldosterone receptor C-344T polymorphism and the progression of renal disease in patients with IgAN and focal and segmental glomerulosclerosis, probably due to the interaction with the MAPK system.

In the present study, statistics was only a tool for providing an answer, and a clinical explanation is warranted. The analysis revealed a negative association between kalemia and KCl infusion, as well as between kalemia and NaCl infusion. KCl doses could be considered both as a confounding factor by indication, on account of the higher prescribed doses in lower kalemia. The positive association between KCl and NaCl infusions may be explained by the administration of KCl with NaCl. Thus, the KCl doses were strongly related to the NaCl doses, that could affect the negative association revealed at the univariate regression. Indeed, at the multivariate model, their association lost the significance. Thus, the negative association between KCl and kalemia may be explained by these two mechanisms.

As regards the association between NaCL and kalemia, the reduction in serum potassium levels related to higher doses of NaCl may be due to the probable effect of the increase in the tubular flow of sodium on the kir1.1 channels, which increases potassium excretion, in accordance with the findings of Palmer and Clegg (14). This mechanism is known as the aldosterone paradox, and allows for the compensation of light hormonal variation, ensuring potassium homeostasis.

The effect of potassium canreonate on the augmentation of kalemia was confirmed by multivariate analysis in our analysis as the only variable related to the kalemia, highlighting the hyperstimulation of the MR.

The main limitations of the present study are represented by the possible unknown diseases, due to the worse compliance of the patient, and by the 'observational design' of the study. However, this may allow us to improve the diagnosis of AME and its consequent possible association with the diagnosis of IgAN.

In conclusion, as demonstrated in the present study, although unusual, conceiving over time the measurements of variables on a single patient as 'cases' and the set of measurements of the patient himself (single patient) as a 'cohort' may be an aid in quantitatively analyzing the impact of one or more treatments and in identifying unknown causes that may influence the therapeutic response, particularly in cases with a paradoxical response.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FZ and VC conceptualized the study. FZ and RS examined the patient. AL, FZ and FGV were involved in the search for relevant literature. RS, FZ and VC were involved in the writing and preparation of the original draft of the manuscript. VC and DS were involved in data analysis. AL and RS were involved in the writing, reviewing and editing of the manuscript. RS was involved in the processing of images. DS and VC confirm the authenticity of all the raw data. DS supervised the study. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from the participant included in the study. 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 Declaration of Helsinki and its later amendments or comparable ethical standards.

Patient consent for publication

Written informed consent was obtained from the participant included in the study for the publication of his data.

Competing interests

The authors declare that they have no competing interests.

References

1. Tripepi G, Jager KJ, Dekker FW and Zoccali C: Linear and logistic regression analysis. Kidney Int 73: 806-810, 2008.
2. Monnens L and Levtchenko E: Distinction between Liddle syndrome and apparent mineralocorticoid excess. Pediatr Nephrol 19: 118-119, 2004.
3. Bantis C, Heering PJ, Stangou M, Kouri NM, Schwandt C, Memmos D, Rump LC and Ivens K: Influence of aldosterone synthase gene C-344T polymorphism on focal segmental glomerulosclerosis. Nephrology (Carlton) 16: 730-735, 2011.
4. White PC: 11beta-hydroxysteroid dehydrogenase and its role in the syndrome of apparent mineralocorticoid excess. Am J Med Sci 322: 308-315, 2001.
5. Rajkumar V and Waseem M: Hypoaldosteronism. In: StatPearls. StatPearls Publishing, Treasure Island, FL, 2023.
6. Arai K, Papadopoulou-Marketou N and Chrousos GP: Aldosterone Deficiency and Resistance. In: Endotext. Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, *et al* (eds): MDText.com, Inc. South Dartmouth, MA, 2000.
7. Dammann C, Stapelfeld C and Maser E: Expression and activity of the cortisol-activating enzyme 11β-hydroxysteroid dehydrogenase type 1 is tissue and species-specific. Chem Biol Interact 303: 57-61, 2019.
8. Morineau G, Sulmont V, Salomon R, Fiquet-Kempf B, Jeunemaître X, Nicod J and Ferrari P: Apparent mineralocorticoid excess: Report of six new cases and extensive personal experience. J Am Soc Nephrol 17: 3176-3184, 2006.
9. Gathercole LL, Lavery GG, Morgan SA, Cooper MS, Sinclair AJ, Tomlinson JW and Stewart PM: 11β-Hydroxysteroid dehydrogenase 1: Translational and therapeutic aspects. Endocr Rev 34: 525-555, 2013.
10. Palermo M, Quinkler M and Stewart PM: Apparent mineralocorticoid excess syndrome: An overview. Arq Bras Endocrinol Metabol 48: 687-696, 2004.
11. Sechi LA, Novello M, Lapenna R, Baroselli S, Nadalini E, Colussi GL and Catena C: Long-term renal outcomes in patients with primary aldosteronism. JAMA 295: 2638-2645, 2006.
12. Monticone S, Sconfienza E, D'Ascenzo F, Buffolo F, Satoh F, Sechi LA, Veglio F and Mulatero P: Renal damage in primary aldosteronism: A systematic review and meta-analysis. J Hypertens 38: 3-12, 2020.
13. Bantis C, Heering PJ, Siekierka-Harreis M, Kouri NM, Schwandt C, Rump LC and Ivens K: Impact of aldosterone synthase gene C-344T polymorphism on IgA nephropathy. Ren Fail 33: 393-397, 2011.
14. Palmer BF and Clegg DJ: Physiology and pathophysiology of potassium homeostasis: Core curriculum 2019. Am J Kidney Dis 74: 682-695, 2019.