

INCONSISTENCIES IN LABORATORY INVESTIGATIONS OF HYPERTENSION IN A YOUNG WOMAN TAKING ETHINYLESTRADIOL/DROSPIRENONE ASSOCIATION

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Keywords:

Hypertension; hyperaldosteronism; high renin level; drospirenone; ethinylestradiol

Abstract

Case presentation: A 34-year-old woman presented to the emergency department for arterial hypertension. Blood analysis requested by the endocrinologist showed very high level of aldosterone (1805 ng/L, normal values: <264 ng/L) and high level of renin activity (2.8 ng/mL/h, normal values: 0.1-2.0 ng/mL/h). The patient reported the use of Yasmin[®] (ethinylestradiol 30 µg/drospirenone 3 mg) continuously (without hormone-free week between cycles) as oral contraception. Medical imaging examinations revealed no anomaly in the kidneys and the adrenal glands. On the endocrinologist advice, patient stopped the intake of Yasmin[®]. Aldosterone and renin levels were measured several times after the discontinuation of the oral contraception and a diminution of these levels was observed with a complete normalization of both levels 26 days after the synthetic hormones discontinuation.

Discussion: The literature shows that ethinylestradiol/drospirenone association can interfere with the renin-angiotensin-aldosterone system and increase the levels of aldosterone and/or renin. We reported here a clinical case illustrating the significant impact of this medication on the renin-angiotensin-aldosterone axis of a young woman. However, this association is not listed among the drugs interfering with the aldosterone and renin-level measurements.

Conclusion: Considering the data in the literature and our clinical case, we suggest adding drospirenone and the ethinylestradiol/drospirenone association in the list of drugs interfering with aldosterone and renin level determination.

1. Introduction

The renin-angiotensin-aldosterone (RAA) system plays a key role in the regulation of human blood pressure [1]. Formerly considered rare, it is now recognised that primary aldosteronism (PA), a group of disorders associated with an excessive and autonomous secretion of aldosterone from the adrenal

cortex, is a common cause of secondary hypertension. Indeed, PA is reported to be present in 5 to 13% of hypertensive patients [2,3] this percentage rise to more than 20% in patient with resistant hypertension [4,5]. The plasma aldosterone/renin ratio (ARR) is the recommended test for detecting possible PA. ARR has therefore become a common test performed in many patients with hypertension. Several factors influence the ARR and it is recommended to perform the test in well-controlled conditions. In particular, some medications (mainly antihypertensive and non-steroidal anti-inflammatory drugs) should be withdrawn before ARR test [2,3]. The most recent guidelines do not recommend withdrawing oral contraceptives [2,6]. Nevertheless, women of childbearing age are often on oral contraceptives. Among the available contraceptives there is the combination of ethinylestradiol/drospirenone (EE/DRSP). Several studies have shown elevation of aldosterone and renin in women taking the EE/DRSP combination as oral contraception [7–10]. The impact of EE/DRSP on the ARR is less well established and could be dependent on the method used to measure renin levels [7,9]. The case described here illustrates a significant impact of the association EE/DRSP on the RAA axis.

2. Case description

A non-smoker 34-year-old woman presented to the emergency department with arterial hypertension measured at home at 180 mmHg associated with headaches and dizziness. Blood pressure measured at the emergency dept. was 170/80 mmHg. A dose of 0.15 mg of clonidine was administered and the blood pressure dropped to 110/80 mmHg. During her stay, blood and urine samples were collected. No abnormal parameters were found, except for a low potassium/ (potassium+sodium) ratio in urine: 20 % (normal values: 30–60%), reflecting a lack of urinary potassium excretion. The patient reported the use of two medications: levothyroxine 62.5 µg once daily and oral contraception, Yasmin (EE 30 µg/DRSP 3 mg) taken continuously without a hormone-free week between cycles.

After a stay of a few hours in the emergency department, patient was sent home and advised to check her blood pressure twice a day. The follow-up of the patient was carried out in cardiology and nephrology. Twenty-four hours ambulatory blood pressure measurement was performed and revealed a daily mean blood pressure of 152/107 mmHg. Except for arterial hypertension, cardiac and renal examinations showed no abnormalities. Extended biological examination was required 2 days after the visit to the emergency department by the nephrologist. A blood sample was taken to measure, among other parameters, blood levels of potassium, cortisol, ACTH, aldosterone, renin activity and ARR. Twenty-four-hour urine was collected to measure daily cortisol and aldosterone excretion and 24 h acidified urine was also collected to determine the daily excretion of catecholamines, metanephrines and metabolites. The results of the different laboratory investigations and the days of sample collection are reported in **Table 1**. High levels of aldosterone urinary excretion (= 144.5 µg/24 h, normal values: < 22 µg/24 h), plasma aldosterone concentration (1805 ng/L, normal values: < 264 ng/L) and high plasma renin activity (= 2.8 ng/mL/h, normal values: 0.1–2.0 ng/mL/ h) were measured, the calculated ARR (= 64.7) was well above the normal values (< 20). All these parameters were determined with LC-MS methodologies [11]. The patient was therefore referred to an endocrinologist. Magnetic resonance imaging (MRI) of the adrenal glands and a Doppler ultrasound of the kidneys were

performed and revealed no abnormality. Measurements of plasma aldosterone and renin activity were repeated 7 days after the first test and both parameters were elevated (3144 ng/L and 5.5 ng/mL/h, respectively) with an ARR (= 57.2) remaining above the threshold of 20. The day after this sampling, the endocrinologist advised the patient to stop the Yasmin (a non-hormonal contraception has been started by the patient). Menstruation started 4 days after stopping the EE/DRSP and aldosterone and renin activity were controlled 6 days after the stop of the contraception, renin activity (= 0.9 ng/mL/h) fell into the normal range while aldosterone level decreased to 369 ng/L even though remained above the upper threshold and ARR (= 39.3) also remained above 20. Ten days later, again an increase in renin activity (1.8 ng/mL/h) and aldosterone (= 1298 ng/L) was observed and the ARR (= 72.1) remained above the limit. Nevertheless, 26 days after stopping oral contraception, both renin activity (= 0.7 ng/mL/h) and aldosterone concentration (= 121 ng/L) had returned to normal, a normalization of the ARR (17.5) was also observed. This normalization was confirmed in a new blood sample collected 4 days later: aldosterone = 46 ng/L, renin activity = 0.7 ng/ mL/h and ARR = 6.5. It was concluded that the elevation of aldosterone and renin activity was the consequence of EE/DRSL intake and that there was no endocrinological reason for the arterial hypertension. During the investigations, treatment with moxonidine and then lercanidipine was started but rapidly stopped because of adverse effects (somnolence and tachycardia respectively). Finally, treatment with nebivolol 5 mg was started 28 days after the first investigations and was maintained. Blood pressure was well controlled with nebivolol and essential hypertension associated with professional overwork was diagnosed.

Table 1. Laboratory results of the patient according to the matrix (blood or urine) and the day of sampling, day 1 corresponding to the day of admission to the emergency department. Oral contraception (EE/DRSP) was withdrawn on day 11 and nebivolol treatment was introduced on day 28. Pathological results are in bold.

Parameters	Reference values	Day 1	Day 3	Day 5	Day 6	Day 10	Day 11	Day 17	Day 27	Day 37	Day 41
Blood											
K ⁺	3.50–5.10 mmol/L	4.02	4.24			3.97		3.84		4.19	4.25
ACTH	3.8–60.5 ng/L		7.9							14.3	
DHEA	2.00–11.10 µmol/L		7.95								
Cortisol	102.1–535.2 nmol/L		525.9								
Renin (standing)	0.1–2.0 ng/mL/h		2.8			5.5		0.9	1.8	0.7	0.7
Aldosterone (standing)	<264 ng/L		1805			3144		369	1298	121	46
Aldosterone/renin ratio	<20		64.7			57.2		39.3	72.1	17.5	6.5
Noradrenaline	0–500 ng/L							344			
Adrenaline	0–100 ng/L							60			
Dopamine	0–145 ng/L							10			
Urine											
Na ⁺	22.3–200.1 mmol/L	111									
K ⁺	20.6–101.9 mmol/L	27.8									
Ratio K ⁺ /K ⁺ +Na ⁺	30–60%	20%									
Aldosterone	<22 µg/24 H				144.5						
Noradrenaline	3.0–30.0 µg/24 H			5.4			9.2	8		<5.2	
Adrenaline	5.0–60.0 µg/24 H			50			49.2	22.1		45.2	
Dopamine	0–600 µg/24 H			190			203	230		203	
Metanephrine	0.0–400.0 µg/24 H			87.2			94	96.4		105.5	
Normetanephrine	0.0–500.0 µg/24 H			356			256.5	238.4		326.5	
Methoxytyramine	0–450 µg/24 H			173			110	126		148	
Vanillylmandelic acid	0.0–7.0 mg/24 H			3			4	3.6		4	
5-Hydroxyindoleacetic acid	<7.0 mg/24 H			7.5			4	24.4		4.9	

3. Discussion

The levels of aldosterone measured in our patient were significantly elevated and the ARR was suggestive of a PA. Renin activity was simultaneously measured above the normal threshold which excludes a PA, since suppression of renin activity is a prerequisite for diagnosis of this pathology [12]. These results were therefore suggestive of secondary hyperaldosteronism. The main etiologies of secondary hyperaldosteronism are reduced renal blood flow, pheochromocytoma and drug interactions. The first two causes were excluded by Doppler ultrasound of the kidney and normal levels of urinary catecholamines, respectively. Nevertheless, such investigations could have been avoided if the impact of EE/ DRSP on the RAA system had been suspected earlier. The differences between PA and secondary hyperaldosteronism are shown in **Table 2**. Neither in the 2016 guidelines proposed by the Clinical Guidelines Subcommittee of the Endocrine Society [2] nor in the 2018 update of these recommendations [6], was EE/ DRSP mentioned as a medication interfering with the ARR determination. However, a significant impact of EE/ DRSP on aldosterone and renin levels has been reported in some studies [7–10]. For instance, Klipping et al. [8] reported a median increase in aldosterone level of 179.5% (max = 617%) in women after 6 cycles of treatment with EE/DRSP compared to the baseline. Klipping et al. also reported an important elevation of aldosterone concentration up to 6930 pmol/L (\approx 2500 ng/L) in a patient after 6 cycles of treatment. In addition, in another clinical case, a significant impact of EE/DRSP on aldosterone and renin measurements was reported [13]. In this case, the high aldosterone level (= 2150 ng/ L) was accompanied by an extremely high level of renin activity ($>$ 187 ng/mL/h). These levels fell into the normal range (250 ng/L and 1.9 ng/mL/h, respectively) 1 month after the discontinuation of the oral contraception. Our observation is therefore in addition to other reports of significant elevations of aldosterone and renin in patient taking EE/DRSP. Two mechanisms could explain these observations. On one hand, it has long been known that estrogens and consequently EE induce a slight increase in the renin activity [14,15]. On the other hand, DRSP, such as progesterone and spironolactone, has a high affinity for the mineralocorticoid receptor and shows significant anti-mineralocorticoid activity. Consequently, DRSP induces a rise in urinary sodium excretion, potassium sparing and a compensatory increase of the aldosterone [15]. Given the high specificity of LC-MS/MS methods used to determine aldosterone level and renin activity, it is not expected that the increases observed were due to analytical interference or cross reaction with synthetic hormones as it could be the case with immunoassays for instance.

In our patient, the very high elevation of aldosterone may have been caused by the continuous intake of EE/DRSP without free-hormone period. Nevertheless, we cannot exclude that the normalization of the aldosterone and renin levels observed in our patient was the consequence of the introduction of nebivolol treatment at day 28 after the beginning of the investigations and thus 17 days after EE/DRSP discontinuation. Indeed, in the days following the discontinuation of contraception, renin and aldosterone levels fell but aldosterone remained above the normal threshold, we observed a rise of both parameters a few days later and complete normalization was noted after the introduction of nebivolol (although the normalization of renin level was observed before the nebivolol introduction). However, it was not expected that nebivolol would have such an impact on the RAA axis.

Furthermore, DRSP has a half-life of 31 h [16]; consequently, some days are required to complete the wash out of this molecule. Finally, the rise of aldosterone and renin observed after discontinuation of

the contraceptive pill could be the consequence of the influence of the menstrual cycle. Indeed, aldosterone level and renin activity increase during the luteal phase of the menstrual cycle [17] and Pizzolo et al. [18] have shown that the impact of EE/DRSP on aldosterone and renin levels, and more specifically on the ARR varies along the cycle.

After this clinical case study, we explored the laboratory data (between 01/01/2021 and 01/06/ 2022) to list the women aged 18–45 years with plasma aldosterone concentration >500 ng/L, renin activity >2 ng/mL/h and ARR >20 and we checked the clinical data for potential DRSP treatment. During the study period, renin activity and plasma aldosterone concentration were measured in 250 women aged 18–45 years, among them, 7 women corresponded to the inclusion criteria, 3 of whom were taking oral contraception with DRSP (no information was available (n = 3) or another contraception (n = 1) was reported for the other patients). The results for patients meeting the inclusion criteria and taking DRSP are gathered in **Table 3**. Even though the aldosterone concentrations measured in our clinical case are very high, comparable results are seen in some other patients taking DRSP oral contraception.

Table 2. Comparison between primary and secondary hyperaldosteronism.

	Primary hyperaldosteronism	Secondary hyperaldosteronism
Aldosterone	Elevated	Elevated
Renin	Suppressed	Elevated
Aldosterone/renin ratio	Elevated (>20)	Normal or elevated
Main etiologies	Adrenal nodule Bilateral adrenal hyperplasia Familial hyperaldosteronism Adrenal cancer	Reduced renal blood flow Pheochromocytoma Drug interactions Renin secreting tumor

Table 3. Age, aldosterone concentration, renin activity and aldosterone-renin ratio (ARR) measured in some other patients taking drospirenone (DRSP) with or without ethinylestradiol (EE) as oral contraception.

Patient #	Age	Aldosterone concentration (ng/L)	Renin activity (ng/mL/h)	ARR	Contraception
1	43	1553.6	3	51.8	Yasmin (EE 30 µg/DRSP 3 mg)
2	30	747.7	2.9	25.8	Yaz (EE 20 µg/DRSP 3 mg)
3	23	595.5	2.8	21.5	Slinda (DRSP 4 mg)

4. Conclusion

Our clinical case and exploration of our laboratory data showed that DRSP and the EE/DRSP combination could increase the levels of renin, aldosterone and the ARR. These observations are in agreement with some data published in the literature. Therefore, we suggest adding DRSP and the EE/DRSP association to the list of medication interfering with the ARR test and to consider withdrawing these oral contraception drugs at least 3 weeks before ARR testing.

Acknowledgements

Authors would like to thanks Drs Castiglione and Grifnée for their careful reviewing of the paper.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Authors' contributions

PD wrote the main manuscript text. PD, CLG and EC assayed the biological samples of the patient. LV performed the clinical examination of the patient. All authors reviewed the manuscript.

Consent to participate

Patient gave her consent for publication.

Data availability statement

There is no supplemental data to share.

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