BRIEF COMMUNICATION

Laboratory Diagnosis of Primary Aldosteronism, and Drospirenone-Ethinylestradiol Therapy

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Background: Primary aldosteronism is recognized as the most frequent cause of secondary hypertension. Screening for primary aldosteronism by determination of the aldosterone-to-renin ratio (ARR) is much more frequently performed in current practice. However, most antihypertensive medications interfere with ARR determination, and although verapamil and α-adrenergic blockers are considered sufficiently neutral, the specific drugs which should be discontinued before ARR screening are a matter of debate. Our objective was to evaluate the possible interference of a new progestin with antimineralocorticoid activity (drospirenone) on the determination of ARR and the diagnosis of primary aldosteronism.

Methods and Results: We describe an instance of a false-positive laboratory diagnosis of primary aldosteronism (by both screening and confirmatory test) in a normotensive 34-year-old healthy woman taking Yasmin (drospirenone + ethinylestradiol) (Shering S.p.A., Milan, Italy). Subsequent ARR values during Yasmin therapy changed during the menstrual cycle (days 7, 14, 21, and 28 were tested), reaching values above the screening ARR threshold that led to a suspicion of primary aldosteronism just before menses. In contrast, during a drug-free menstrual cycle, the ARR remained constantly below the screening ARR threshold.

Conclusions: We report for the first time that drospirenone may interfere with laboratory screening and confirmatory testing for the diagnosis of primary aldosteronism. As a consequence, this drug should be withdrawn in hypertensive women investigated for secondary hypertension. Although drospirenone was demonstrated to possess antihypertensive properties when taken as postmenopausal hormonal replacement therapy, its use for contraceptive purposes needs to be more carefully investigated. Am J Hypertens 2007;20:1334–1337 © 2007 American Journal of Hypertension, Ltd.

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Compelling evidence indicates that primary aldosteronism is the most frequent cause of secondary hypertension, with an estimated prevalence of 10% to 15% among hypertensive patients.1,2 As a consequence of such elevated prevalence, screening for primary aldosteronism, ie, determination of the aldosterone-to-renin ratio (ARR), is much more frequently performed in current practice. In the presence of clinically demonstrated hypertension, ARR is an early marker of an “inappropriately high” aldosterone secretion for the degree of renin-angiotensin system activation, and is often the only index capable of distinguishing patients with normokalemic primary aldosteronism from those with essential hypertension.1,2 Despite wider acceptance, some technical aspects of the determination of ARR are not universally accepted and are still a matter of debate.

One important issue involves the medications that should be discontinued before the determination of ARR.

Because most antihypertensive drugs influence the renin-angiotensin system and aldosterone levels, some authors recommend their withdrawal before ARR screening.3 For example, β-adrenoreceptor blocking agents, clonidine, and α-methyl-dopa increase the ARR value by suppressing renin levels more than aldosterone levels, thus giving false-positive results,4,5 whereas angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, and, to a lesser extent, dihydropyridine-type calcium channel blockers may give false-negative results,4–6 whereas angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, and, to a lesser extent, dihydropyridine-type calcium channel blockers may give false-negative results by increasing the renin value.4–6 A prolonged effect on an ARR with abnormally low values is also recognized in patients using mineralocorticoid receptor (MR) receptor antagonists, in whom renin levels may remain elevated for several weeks after the cessation of treatment.7 Neutral agents, such as slow-release verapamil and α-adrenergic blockers, can be safely used to control hypertension before screening.4,7

On the other hand, useful information can be obtained...
even when patients are still taking drugs known to interfere with the renin-angiotensin-aldosterone system (RAAS) (perhaps with the exception of MR receptor antagonists). For example, a raised ARR in a patient taking a diuretic or an angiotensin-converting enzyme inhibitor would be even more strongly suggestive of a condition of relative aldosterone excess. Furthermore, in this way, screening can be safely performed without risk of the hypertensive rebound associated with pharmacologic washout.

Subsequent confirmation of the diagnosis involves a demonstration of “autonomous” aldosterone production, ie, independent of angiotensin II. The most widely used tests are the oral or intravenous saline load and the fludrocortisone-suppression test. Although fludrocortisone suppression is considered the most reliable test, intravenous saline-loading (SL) was recently demonstrated to be an equivalent, reasonable, and less expensive alternative. It consists of the determination of plasma aldosterone after infusion of 2 L of 0.9% sodium chloride solution over 4 h; primary aldosteronism is diagnosed when nonsuppressed levels (usually between 50 and 60 pg/mL) are found.

Here, we describe a false-positive laboratory diagnosis of primary aldosteronism in a normotensive healthy woman on drospirenone (DRSP) therapy, providing the first evidence of pharmacologic interference in both screening and confirmatory primary aldosteronism testing by this agent.

Methods and Results

In recent research on possible urinary markers of mineralocorticoid activity, a group of healthy, normotensive volunteers was selected and underwent the intravenous SL test. The criteria for participation in the study included an absence of signs or symptoms of diseases or current drug therapy, with the exception of the contraceptive pill.

Among the participants, a 34-year-old woman began to feel unwell during saline infusion. She complained of nausea and headache, and the symptoms became more severe at the end of hour 4 of infusion. Her blood pressure (BP) was normal (120 to 130/75 to 80 mm Hg). Unlike the other similarly infused volunteers, this subject did not urinate for the duration of the test, and in the following 18 h, her urinary output was very low. One day later, because of the persistence of her headache, she was given 25 mg hydrochlorothiazide, with a subsequent increase of urine output and complete relief from headache within a few hours.

The results of her hormone assessment indicated a biochemical diagnosis of primary aldosteronism. Basal concentrations of serum aldosterone were 626 pg/mL, and basal concentrations of active renin were 14.7 pg/mL, with a calculated ARR of 42.6 (diagnostic cutoff level at our institution, 32). In addition, after 2 L of saline infusion, serum aldosterone was incompletely inhibited (72.3 pg/mL).

Because the subject exhibited consistently normal BP values and was taking nothing but the contraceptive pill Yasmin (Shering S.p.A., Milan, Italy) (3 mg DRSP + 30 μg ethinylestradiol [EE]/day, with 1 week per month off the pill), we considered possible interference by this drug on the results. The patient’s history indicated that an inhibitory test had been performed on day 28 of her menstrual cycle; ie, 1 day before the expected onset of menses, with the last pill taken 2 days before testing.

The subject was therefore asked to undergo repeated hormone determinations on different days of her menstrual cycle, both during therapy with Yasmin and again after 2 months of spontaneous menses after withdrawal of the pill.

Results of the hormonal determinations are shown in Fig. 1. While taking Yasmin, the patient’s aldosterone levels gradually increased from day 7 to day 28 (as expected, because of MR blockade), and active renin increased until day 21 but then declined (see values for day 28). As a result, ARR values progressively increased throughout the menstrual cycle, with the lowest value (18.8) on day 7, and the highest value (60.6) on day 28.

During the Yasmin-free control cycle, aldosterone levels measured in the first 2 weeks were on average lower than those obtained in the second half of cycle, whereas the active renin concentration gradually increased through the cycle (ranging from a value of 7.6 pg/mL on day 7 to 23.6 pg/mL on day 28). At variance with the pattern observed while the patient was taking Yasmin, ARR values tended to decrease over time, with the lowest ratio on day 28. At no time during the pill-free control cycle was the ARR above the cutoff for further diagnostic workup at our institution (Fig. 1).

Discussion

We describe a healthy, normotensive woman in whom both screening and confirmatory laboratory testing, as used in the diagnostic workup of primary aldosteronism,
were affected by concomitant treatment with DRSP + EE (Yasmin) for contraceptive purposes.

This observation has implications with both practical and theoretical importance. First, it is necessary to include Yasmin among the drugs that can interfere with the laboratory evaluation of the renin/angiotensin/aldosterone system (RAAS). In particular, the ARR could produce false-positive screening results during treatment with, or after withdrawal of, the drug. In the present case, a raised ARR was confirmed twice after a few days of drug withdrawal, whereas sequential determinations of ARR were normal during the early weeks of treatment with Yasmin and during all of the Yasmin-free menstrual cycle. To our knowledge, no previous study specifically evaluated ARR, or the effect of DRSP on ARR, during the different phases of the menstrual cycle, including the monthly week of pill withdrawal. Considering the widespread use of ARR determination among hypertensive patients as a screening tool, and given that the standardization of ARR (ie, the cutoff values for screening) has not been firmly established because of low reproducibility in different conditions, specific studies on variation of ARR in females are warranted.

Our findings also suggest considerations regarding possible interactions between natural sexual hormones, synthetic progestogens such as DRSP, and RAAS. It is known that estrogens increase plasma angiotensinogen by stimulation of the transcription of the angiotensinogen gene in the liver. The midcycle increase of estrogen in healthy women, however, is not sufficient to increase plasma angiotensinogen, whereas the ingestion of oral ethinylestradiol (EE) as a constituent of combined oral contraceptives (OCs) significantly raises plasma angiotensinogen, sometimes with hypertensive effects. At the same time, renin secretion is chronically suppressed in women taking a dose of estrogen that stimulates plasma angiotensinogen, because of a feedback inhibition of renin secretion by the raised angiotensin II levels.

In contrast, progesterone has natriuretic and BP-lowering effects, because of its competition with aldosterone for MR. As a consequence, plasma renin activity, plasma angiotensin II, and aldosterone increase as a compensatory mechanism, while angiotensinogen remains unchanged. Therefore, in the luteal phase of the menstrual cycle, progesterone causes an increase in plasma renin activity, angiotensin II, and aldosterone, whereas the suppression of ovulation by MR-inert synthetic progestogen abolishes the activation of RAAS.

Drospirenone is a relatively novel progestogen, derived from 17α-spiroloactone, and developed for oral contraception and postmenopausal hormone replacement therapy in combination with 17β-estradiol. Among progestogens, it is the only compound similar to progesterone with regard to its antialdosterone activity. Both progesterone and DRSP bind to MR as antagonists, with an affinity at about 100% and 230% of aldosterone, respectively. The lack of antimineralocorticoid activity of older synthetic progestogen components of OCs, and the activation of RAAS induced by estrogens, are thought to be the cause of the increase in BP associated with OC therapy.

Because of its antimineralocorticoid properties, it is probable that in the future, DRSP will be prescribed more frequently in hypertensive women for both contraception and hormone replacement postmenopause. Recent clinical trials demonstrated that DRSP reduces BP in hypertensive postmenopausal women, and DRSP has been defined as “an antihypertensive in waiting” because the extent of ambulatory BP reduction observed in clinical trials is comparable to that observed for many other antihypertensive agents, including the selective MR antagonist eplerenone. Although to date it is not possible to extend these findings to women of gestational age (because the major studies were conducted in postmenopausal women), it is easy to anticipate a similar use for DRSP in younger populations.

In our patient, we observed a different pattern of RAAS activation in the drug-free cycle and in the DRSP + EE modulated cycle. In the first case, as expected, higher values of aldosterone and renin were detected in the luteal phase of the cycle without relevant variations of ARR values. Thus, the spontaneous pattern of cyclic variations of the different RAAS components was preserved.

When the patient took DRSP + EE, two important differences were observed: (1) a fall in renin, and (2) an even larger increase of aldosterone on day 28, with a factitious elevation of ARR values. All these changes are consistent with a possible diagnosis of primary aldosteronism, apparently confirmed by incomplete suppression of aldosterone on SL challenge.

Of note, these abnormalities in hormonal pattern were recorded during the monthly week of pill withdrawal, ie, when the postulated natriuretic effects induced by DRSP were no longer present. It is possible that, during this relatively brief time, aldosterone levels were no longer balanced by DRSP antagonism, and activated MR to produce sodium and water retention. This interpretation is consistent with the estimated DRSP half-life of 30.8 to 32.5 h, and the clinical picture displayed by our subject during SL.

The effects of DRSP on RAAS and sodium excretion were summarized by Oelkers in 2004. Generally, plasma renin activity and plasma aldosterone rose significantly in patients taking DRSP as a progestogen. However, these hormonal changes were recorded during long-term therapy, whereas no information was given on hormone concentrations after pill withdrawal. Our findings suggest that, after the offset of DRSP antagonism, mineralocorticoid excess may spontaneously occur.

In conclusion, DRSP may interfere with laboratory screening and confirmatory testing for the diagnosis of primary aldosteronism. As a consequence, this drug should be withdrawn in hypertensive women under investigation for secondary hypertension.
References


