Drospirenone (DRSP) is a compound with mingled identities having been viewed as a diuretic, a progestational agent, and/or an antimineralocorticoid agent with an ability to reduce blood pressure (BP). The multiple personalities of this compound can be seen by examining the position adopted by the United States Anti-Doping Agency on its use as a diuretic in athletes. Until January 2005, athletes were prohibited from using the fixed-dose combination contraceptive product (3-mg DRSP/0.03-mg ethinylestradiol [EE]) in or out of competition specifically because it contained the diuretic DRSP, albeit a compound with very weak diuretic properties. This restriction on DRSP use in athletes has been lifted, although the use of spironolactone is still outlawed. More recently, DRSP has gained some momentum as an antihypertensive agent. All along, DRSP has been a progestational agent used in combination with estrogen for birth control or treatment of vasomotor symptoms relating to menopause.

DRSP, formerly called dihydrospirorenone, is chemically related to 17α-spiroloactone. It is a synthetic progestogen, which more closely resembles natural progesterone than conventional synthetic progestogens. As such, it possesses clinically recognizable antimineralocorticoid activity and is estimated to be 8 times more potent than spironolactone (3 mg of DRSP = 25 mg of spironolactone). DRSP pharmacokinetics are such that it has an oral bioavailability of ~80%, a half-life of 30 to 35 hours, and is without active metabolites, a characteristic that distinguishes it from spironolactone.

In early studies, administration of 2 mg of DRSP daily for 6 days to young women resulted in a negative sodium (Na+) balance of 85 mmol compared with placebo. Subsequently, in 1995, it was observed that a combination of EE plus 3 mg of DRSP reduced body weight and BP, suggesting that DRSP may have counterbalanced both the Na+ and water retaining and aldosterone-stimulating effects of the coadministered EE. These initial observations served as the basis for studies that set out to examine the BP-lowering ability of DRSP in hypertensive patients. Preston et al showed that 3 mg of DRSP/1 mg 17β-estradiol (E2) reduced BP by 9/5 mm Hg from a baseline of 139/80 mm Hg when given to nonsmoking postmenopausal women already receiving 10 mg of enalapril twice daily. In another study by Preston et al, 3-mg DRSP/1-mg E2 was administered to hypertensive postmenopausal women with and without diabetes mellitus and receiving either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. Three-milligram DRSP/1-mg E2 reduced BP values by −8.6/−5.8 mm Hg (placebo, −3.7/−2.9 mm Hg) from a baseline of 133/81 mm Hg. Finally, in a study in >200 postmenopausal women with stage I hypertension, White et al demonstrated that 3-mg DRSP/1-mg E2 reduced 24-hour ambulatory BP by −8.5/−4.2 mm Hg versus −1.6/−1.6 mm Hg for those on placebo.

What was lacking from the research portfolio for DRSP was a true dose-ranging study as to its BP lowering effect. The studies by White et al in this issue of Hypertension undertook to resolve this question and did so in a rather rigorous manner. These studies relied on the gold standard for ascertainment of antihypertensive medication effect, 24-hour ambulatory BP monitoring. In so doing, they carefully characterized the extent and duration of DRSP effect and found a clear dose–response relationship for DRSP relative to BP reduction. The no-effect dose was 1 mg, and there was an incremental BP-lowering benefit in moving from a 2- to a 3-mg dose. Because doses >3 mg of DRSP were not studied, the top end of the dose-response curve for BP reduction could not be established. It is likely that doses >3 mg of DRSP were not studied because of the risk of hyperkalemia. Of equal importance, these studies showed that at the doses studied, there was an inconsequential change in serum potassium values with DRSP, a finding of some importance in that regulatory bodies, such as the Food and Drug Administration, have adopted a position of extreme caution when DRSP is being used for fear of hyperkalemia developing.

What does the future hold for DRSP? Although this is a compound with some promise relative to BP reduction, it is doubtful that it will ever be formally put to this use in the United States. DRSP is currently marketed for oral contraception and is used for the treatment of moderate-to-severe vasomotor symptoms in association with menopause. When used as an oral contraceptive, 3 mg of DRSP is given in combination with EE. This amount of DRSP is sufficient to significantly reduce BP; however, the target population for contraceptive therapy is not one that typically has a high rate of hypertension. In the United States, when DRSP is used for the treatment of vasomotor symptoms in association with menopause, it is given at a 0.5-mg dose together with E2. At this dose level, there is no BP-lowering effect; therefore, in a population more prone to hypertension, a dose of DRSP...
capable of reducing BP is currently not going to be marketed in the United States. Of note, a 2-mg DRSP dose with E2 is available in >50 countries outside of the United States, and a similar strength is being proposed for approval in the United States.

Two additional considerations arise relative to DRSP and how its potential to lower BP might find use (or not) in clinical practice. First, whether given as a fixed-dose combination product for contraception (3.0-mg DRSP/0.03-mg EE) or as treatment for vasomotor symptoms (0.5-mg DRSP/1.0-mg E2) as per its labeling, it is contraindicated in patients with renal insufficiency because of the possibility of hyperkalemia developing. Although this may be relevant to the former dose (3.0-mg DRSP/0.03-mg EE) it is not to the latter low-dose combination (0.5-mg DRSP/1.0-mg E2). The quandary that eplerenone found itself in seems to have been repeated with DRSP.10 The issue with a contraindication to the use of DRSP in renal insufficiency should be the pretherapy level of serum potassium and not simply the presence of renal failure. It is unlikely that the Food and Drug Administration will unilaterally change their position on this issue, although it is not unreasonable to presume that provision of additional safety data might lead to a reassessment of their stance.

Second, it would require a deft marketing touch to appropriately market DRSP-containing products for hypertension therapy with their primary use being for gynecological matters. In whatever dose that DRSP becomes available as a combination product, it is hard to imagine that it would gain any sort of a foothold such that it could substitute for usual antihypertensive therapies. However, in the postmenopausal female with vasomotor symptoms and stage I hypertension, it might be given a try, and if it fails to bring BP to goal, other agents can be added. Unfortunately, DRSP is currently only indicated for short-term use and should not be used if vasomotor symptoms are no longer present. As such, DRSP/E2 would be stopped and the patient converted to more traditional antihypertensive therapies. If the postmenopausal female with hypertension responds to DRSP/E2 with a fall in BP, it is not unreasonable to presume that aldosterone may have been playing a role in the hypertension and that spironolactone might be a suitable replacement.

Disclosures

The author has participated in an advisory board for Berlex Laboratories for which he received an honorarium. He has never been on a Speaker’s Bureau or received research funding from Berlex Laboratories.

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