A Rationale for Mineralocorticoid Supplementation in Classic Congenital Adrenal Hyperplasia

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The study by Mooij et al. [1] in this issue underscores the interrelatedness of adrenal cortical steroids in achieving balance in the treatment of patients with congenital adrenal hyperplasia (CAH). In this set of in vitro experiments, the investigators delineate the nature of 17-hydroxyprogesterone and progesterone interference with the ability of aldosterone to transactivate the mineralocorticoid receptor (MR). This occurs at the level of receptor transactivation, rather than nuclear translocation. It is reasonable to infer from these data that a similar in vivo phenomenon occurs at the high 17-hydroxyprogesterone levels and low physiologic aldosterone levels measured in inadequately controlled classic CAH patients. It has long been recognized that elevated plasma renin levels reflecting low aldosterone production and/or activity are found among CAH patients with elevated steroid 21-hydroxylase precursors [2, 3]. Previous in vitro studies have confirmed the hypothesis that progesterone and its analogs are the culprits inhibiting MR [4]. An obvious corollary of these findings is exacerbation of sodium wasting in CAH patients, potentially impeding normal growth and even triggering adrenal crisis.

In contrast to the ability of progesterones to interfere with aldosterone-induced MR activity, cortisol may bind to and activate the MR causing hypertension [5]. The

most common example of this phenomenon is Cushing syndrome due to high endogenous or exogenous cortisol exposure. Iatrogenic Cushing syndrome, characterized by inhibition of statural growth in children, excess weight gain, metabolic syndrome, and hypertension, may be observed in CAH patients receiving excessive glucocorticoid treatment [6]. This is why it is important to balance the need for suppression of adrenal androgen precursors with the opposing practical dictum of minimizing glucocorticoid exposure, particularly in growing children.

One way to achieve the desired balance is to treat classic CAH patients from infancy with a combination of moderate doses of both glucocorticoid and mineralocorticoid supplements. A systematic review and meta-analysis of treatment outcomes in CAH patients revealed that those children who received long-term treatment with mineralocorticoids achieved significantly better adult heights compared with those who were prescribed glucocorticoids alone [7]. On the other hand, investigators have observed elevated 24-hour ambulatory blood pressure in children [8] and adults [9] with CAH. However, it has not been demonstrated that young adults with CAH suffer clinically significant cardiac morbidities or mortality [10]. Taken together, the implication of the available data is that clinicians should prudently prescribe miner-

alocorticoid supplements to classic CAH patients to counterbalance the intermittent elevations in progesterones and thereby avoid overtreatment with glucocorticoids. At the same time, suppressed renin, a marker for elevated blood pressure, should be avoided [11]. This has been the position of the Endocrine Society Task Force in establishing clinical practice guidelines for CAH [12].

Among the other novel contributions of the present report is that testosterone and androstenedione do not interfere with MR ligand binding or transactivation. Moreover, introducing a common MR single nucleotide polymorphism associated with hypertension, Ile180Val, did not alter aldosterone-induced MR activation.

References

- 1 Mooij CF, Parajes S, Pijnenburg-Kleizen KJ, Arlt W, Krone N, Claahsen-van der Grinten HL: Influence of 17-hydroxyprogesterone, progesterone and sex steroids on mineralocorticoid receptor transactivation in congenital adrenal hyperplasia. *Horm Res Paediatr* DOI: 10.1159/000374112.
- 2 Rosler A, Levine LS, Schneider B, Novogroder M, New MI: The interrelationship of sodium balance, plasma renin activity and ACTH in congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 1977;45:500–512.
- 3 Kuhnle U, Land M, Ulick S: Evidence for the secretion of an antimineralocorticoid in congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 1986;62:934–940.
- 4 Quinkler M, Meyer B, Bumke-Vogt C, Grossmann C, Gruber U, Oelkers W, et al: Agonistic and antagonistic properties of progesterone metabolites at the human mineralocorticoid receptor. *Eur J Endocrinol* 2002;146:789–799.
- 5 Whitworth JA, Brown MA, Kelly JJ, Williamson PM: Mechanisms of cortisol-induced hypertension in humans. *Steroids* 1995;60:76–80.
- 6 Sarafoglou K, Addo OY, Turcotte L, Otten N, Wickremasinghe A, Pittock S, et al: Impact of hydrocortisone on adult height in congenital adrenal hyperplasia – the Minnesota cohort. *J Pediatr* 2014;164:1141–1146.e1.
- 7 Muthusamy K, Elamin MB, Smushkin G, Murad MH, Lampropoulos JF, Elamin KB, et al: Clinical review: Adult height in patients with congenital adrenal hyperplasia: a systematic review and metaanalysis. *J Clin Endocrinol Metab* 2010;95:4161–4172.
- 8 Roche EF, Charmandari E, Dattani MT, Hindmarsh PC: Blood pressure in children and adolescents with congenital adrenal hyperplasia (21-hydroxylase deficiency): a preliminary report. *Clin Endocrinol (Oxf)* 2003;58:589–596.
- 9 Mooij CF, Kroese JM, Sweep FC, Hermus AR, Tack CJ: Adult patients with congenital adrenal hyperplasia have elevated blood pressure but otherwise a normal cardiovascular risk profile. *PLoS One* 2011;6:e24204.
- 10 Han TS, Conway GS, Willis DS, Krone N, Rees DA, Stimson RH, et al: Relationship between final height and health outcomes in adults with congenital adrenal hyperplasia: United Kingdom congenital adrenal hyperplasia adult study executive (CaHASE). *J Clin Endocrinol Metab* 2014;99:E1547–E1555.
- 11 Bonfig W, Schwarz HP: Blood pressure, fludrocortisone dose and plasma renin activity in children with classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency followed from birth to 4 years of age. *Clin Endocrinol (Oxf)* 2014;81:871–875.
- 12 Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, et al: Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010;95:4133–4160.