Mineralocorticoid substitution and monitoring in primary adrenal insufficiency

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Patients with primary adrenal insufficiency usually show pronounced impairment of aldosterone secretion and, therefore, require also mineralocorticoid replacement for full recovery. Clinical signs of mineralocorticoid deficiency comprise hypotension, weakness, salt craving and electrolyte disturbances (hyperkalemia, hyponatremia). Mineralocorticoid deficiency is confirmed by demonstration of profoundly decreased aldosterone and highly elevated plasma renin activity (PRA). Standard replacement consists of 9α-fluorocortisol (fludrocortisone) given once daily as a single oral dose (0.05–0.2 mg). Monitoring of mineralocorticoid replacement consists of clinical assessment (well-being, physical examination, blood pressure, electrolyte measurements) and measurement of PRA aiming at a PRA level in the upper normal range. Current replacement regimens may often be associated with mild hypovolemia. Dose adjustments are frequently needed in pregnancy to compensate for the anti-mineralocorticoid activity of progesterone and in high ambient temperature to avoid sodium depletion. In arterial hypertension a dose reduction is usually recommended, but monitoring for hyperkalemia is required.

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Introduction

In secondary adrenal insufficiency (SAI), caused by ACTH deficiency, aldosterone secretion remains largely intact, as it is mainly under the control of the renin angiotensin system. In contrast, in primary adrenal insufficiency (PAI) aldosterone secretion is usually severely impaired due to destruction (e.g. by an autoimmune adrenitis) or removal (bilateral adrenalectomy) of the zona glomerulosa. Thus mineralocorticoid replacement is required to compensate for the loss of aldosterone secretion causing electrolyte imbalance, hypovolemia and hypotension. Intriguingly, optimal mineralocorticoid replacement has received little attention in the last two decades, certainly much less than glucocorticoid substitution. This may indicate that mineralocorticoid replacement in PAI poses no or little problems for these patients. However, it is also conceivable that neglecting optimal mineralocorticoid substitution contributes to the well-known failure to fully restore the quality of life [3,11,19] to normal in these patients.

Clinical presentation and diagnosis of mineralocorticoid deficiency

Fatigue and loss of energy are mentioned most often in patients with PAI, e.g. Addison’s disease, as well as unspecific symptoms like weight loss, a loss of appetite, diarrhea, vomiting and nausea [4]. These unspecific symptoms and complaints quite often lead to the false diagnosis of psychiatric or gastrointestinal diseases [1]. In a German cohort, the more specific PAI symptoms like hypotension (55%), hyperpigmentation of patient’s skin (41%) and salt craving (38%) were less frequently present [4]. Other studies, however, showed higher percentages of hypotension (80%) and hyperpigmentation (90%) [31,41]. Aldosterone deficit leads to natriuresis and initially isosmotic dehydration resulting in arterial hypotension, in particular orthostatic hypotension [28]. Furthermore, volume deficit stimulates ADH secretion which may be further enhanced by glucocorticoid deficiency leading to a more pronounced loss of sodium than water and worsening hyponatremia. However, the classical combination of hyponatremia and hyperkalemia, resulting from impaired potassium excretion, is not always reliable, because hyponatremia is often only mild and also hyperkalemia is found in only in 50% of PAI patients. The latter is not only caused by aldosterone deficiency, but also by reduced glomerular filtration rate. Salt craving is also related to aldosterone deficiency, but is reported in only 15% [2,45]. However, it is our experience that salt craving is not reported spontaneously, but only after specific questioning.

A universally used diagnostic test to confirm PAI, is the rapid ACTH-test with 1–24 ACTH (250 µg synacthen intravenously) demonstrating a failure of the adrenal to adequately respond to exogenous ACTH in the presence of clearly elevated baseline ACTH levels [33]. To evaluate the mineralocorticoid axis in PAI patients combined measurement (8:00—0:00 h) of basal aldosterone and PRA should be performed and has high diagnostic accuracy typically demonstrating strongly elevated PRA together with a decreased aldosterone concentration. For example, in a series of patients with zona glomerulosa insufficiency plasma renin activity (PRA) showed levels higher than 3.08 ng/L’s (11.1 ng/mL*h), and aldosterone levels below 216 pmol/l [33]. The PRA/aldosterone ratio clearly differentiates between PAI patients (range 18.9—1287.9) and healthy subjects (range 0.19—2.79). As measurement of PRA is time consuming and demanding, it has largely been replaced in clinical practice by determination of PRC. While elevated levels of PRC have been demonstrated in Addison’s disease and have also been used for monitoring of replacement therapy [8], a formal comparison of the respective clinical utility of PRA and PRC in PAI remains lacking.

Mineralocorticoid substitution

Desoxycorticosterone (DOC), a mineralocorticoid precursor in aldosterone synthesis, was identified in 1937 [29] and used since 1939 in oil and pellets in the treatment of Addison’s disease [44]. Aldosterone itself is not suitable for replacement therapy because of its short half-life and rapid hepatic inactivation after oral ingestion. In 1954 9α-fluor-11β,17α,21-trihydroxy-pregnen-(4)-dion-(3,20), called 9α-fluorohydrocortison or 9α-fluorocortisol or fluadrocortisone, was discovered and patented in
1958 [13,14]. It exhibits 200 to 400-fold higher mineralocorticoid potency than hydrocortisone. However, it binds with similar affinity to the isolated human mineralocorticoid receptor (hMR). The mineralocorticoid potency is mainly due to the fact that the fluor atom on carbon 9 of the steroid molecule protects from rapid conversion by 11β-hydroxysteroid dehydrogenase type 2, the gatekeeper of the hMR, and guarantees the steroid free access to the hMR [32]. Transactivation studies with hMR in CV-1 cells revealed that the mineralocorticoid potency of 9α-fluorocortisol is 10-times higher than that of aldosterone [17]. Binding of 9α-fluorocortisol to the hMR leads to full mineralocorticoid action including sodium retention, potassium elimination, and water reabsorption. Since the availability of 9α-fluorocortisol, DOC is not used any more for mineralocorticoid therapy in PAI.

The absorption of 9α-fluorocortisol is rapid and virtually complete [46]. It occurs in blood 20 min after oral ingestion and peaks 90 min—120 min after intake. Newer studies showed that a patient in septic shock treated with one 50 µg dose of 9α-fluorocortisol acetate reached a maximal plasma concentration of 0.36 ng/mL after 2 h as measured with liquid chromatography—mass spectrometry (LC-MS) [40]. 9α-fluorocortisol acetate is hydrolyzed in human serum rapidly to 9α-fluorocortisol, the active molecule. Elimination from plasma has been reported to occur in two or three phases with half-lives of 2—3 h, 4.5 and 10.2 h respectively [46,47]. However, newer studies with LC-MS measurements revealed that there are only two different phases of elimination, the first 2—4 h, and the second 4—6 h after 9α-fluorocortisol acetate administration [40]. The mean half-time was 4.9 h resulting in 9α-fluorocortisol levels below 20% 16 h after administration. When dosing 9α-fluorocortisol every 12 h the limit maximum is reached after 25 h, amounting to the 1.3-fold of the maximum obtained after a single oral application [46]. Nearly 80% of 9α-fluorocortisol is eliminated via the urine [46].

Oelkers et al. described the titration of 9α-fluorocortisol in 15 Addison’s patients [33]. To avoid overtreatment they aimed at a PRA level between 3 and 10 ng/mL/h. In combination with hydrocortisone doses between 15 and 25 mg/day, this goal was obtained with 0.075 mg in 3 patients, 0.1 mg in 7 patients, 0.15 mg in 2 and 0.2 mg in 3 patients. Based on this data, 9α-fluorocortisol is usually recommended for mineralocorticoid replacement as a single morning dose of 0.05—0.20 mg upon awakening. Children and younger adults may require higher doses [22]. The currently available forms of 9α-fluorocortisol preparation include 0.1 and 0.05 mg tablets.

The new formulation instructions (e.g. for Florinef™) require patients to keep the medication refrigerated. The actual decay rate is, however, only 0.1% in the first 6 months at room temperature [21].

Patients should be advised to take salt and salty foods without restrictions. However, it should be sodium chloride salt and not potassium chloride salt to avoid hyperkalemia.

The dose of mineralocorticoid may be as critical as the dose of glucocorticoid in the management of congenital adrenal hyperplasia (CAH), and regular determination of PRA should be made, particularly if clinical control is difficult [16]. The inclusion of 9α-fluorocortisol in the therapy of patients with salt-wasting CAH resulted in a significant lowering of PRA [27]. Interestingly this was seen also in part of CAH patients with the simple-virilizing form. These findings resulted in recognition that treatment with mineralocorticoid should be continued indefinitely in salt-wasting CAH. Although stopping 9α-fluorocortisol may not always produce a salt losing crisis, it may be more difficult to achieve adequate androgen suppression even with larger doses of glucocorticoids [15,20]. This might be due to the fact that high 17-hydroxy-progesterone levels in poorly controlled CAH patients might have a direct impact on PRA and natriuresis, because 17-hydroxy-progesterone possesses an anti-mineralocorticoid potency [37—39]. Therefore it might be reasonable to increase 9α-fluorocortisol dose in salt-wasting CAH patients with high 17-hydroxy-progesterone levels and to avoid too high hydrocortisone dosages [27]. Secondly, it was shown that administration of 9α-fluorocortisol at doses of 0.5 mg, significantly reduced hormonal levels during the nocturnal nadir of HPA axis [6]. However, such a dose is clearly above the replacement needs in patients with mineralocorticoid deficiency. Yet another study showed that systemic administration of 9α-fluorocortisol in doses between 0.1 and 0.3 mg significantly inhibited the HPA response to the hypophysial stimulus CRH [23]. One explanation might be that 9α-fluorocortisol, which possesses a 10-times higher mineralocorticoid activity than cortisol, displays its potency at the glucocorticoid receptor [17].

On the other hand it is important to note that hydrocortisone, the most frequently used glucocorticoid for substitution therapy, possesses significant mineralocorticoid activity. It has been
estimated that the mineralocorticoid potency of hydrocortisone, given by the oral route, is about 1/400th that of 9α-fluorocortisol. If the mineralocorticoid potency of 1 μg 9α-fluorocortisol is defined as 1 mineralocorticoid unit (MCU), 0.4 mg hydrocortisone may also be regarded as 1 MCU. If this is correct, the standard dose of 20 mg hydrocortisone for glucocorticoid replacement equals in its mineralocorticoid activity 0.05 μg of 9α-fluorocortisol [33]. Although the relationship between hydrocortisone dose and mineralocorticoid activity may not be fully linear, this concept is highly useful and gives a good explanation, why high intravenous doses of hydrocortisone in adrenal crisis cover the mineralocorticoid needs making additional administration of 9α-fluorocortisol unnecessary.

Accordingly, patients with adrenal insufficiency on dexamethasone (e.g. in CAH), which has no mineralocorticoid activity, show higher PRA values than patients on hydrocortisone [35]. Therefore those patients require higher 9α-fluorocortisol doses. Prednisolone has an approximately 4-times lower MR-potency than hydrocortisone in vitro (but a still 10-times higher MR-potency than dexamethasone) [17]. This is the reason, why it is recommended in PAI patients on prednisolone therapy to slightly increase 9α-fluorocortisol doses.

**Monitoring of mineralocorticoid replacement**

Mineralocorticoid replacement is evaluated clinically by asking the patient about salt craving or lightheadedness, measuring blood pressure in the supine and standing positions to assess orthostatic dysregulation, and by identifying the presence of peripheral edema [21]. General well-being, electrolytes within the normal range and normal blood pressure without evidence of postural hypotension indicate adequate mineralocorticoid replacement. Furthermore, a PRA in the upper normal range has been found to be a useful marker for a correct mineralocorticoid dose [12,33] (Fig. 1). However, such a PRA in the upper normal range has not been uniformly accepted as proof of a correct replacement dose. Accordingly, it has been suggested that the dose titration should not necessarily attempt to normalize PRA levels because this might result in a higher incidence of arterial hypertension [22]. In addition, some patients may develop mild signs of over-replacement (e.g. edema) with a PRA in the upper normal range. On the other hand, it has been suggested that many patients with mineralocorticoid deficiency are under-replaced and higher doses were recommended [42] leading to PRA levels clearly below the upper normal range. However, in this study the initial increase from 0.1 to 0.3 mg 9α-fluorocortisol had later to be reduced to 0.2 mg, as six of the ten patients had developed ankle edema and five had low potassium. The initially slightly subnormal plasma volume (89%) in patients on 0.1 mg 9α-fluorocortisol increased to 105% at the end of the study and the blood pressure was significantly higher raising questions on the long term safety of this strategy. However, eight out of ten patients felt better on the higher final dose than on their initial dose prior

![Flow-chart for dose adjustment of 9α-fluorocortisol in primary adrenal insufficiency. * Look for alternative explanations of abnormalities prior to dose change.](image-url)
the dose adjustment and were reluctant to reduce their dose. Significantly increased fatigue has been reported in patients interrupting their mineralocorticoid replacement while their glucocorticoid therapy remained unchanged [22].

The time of day of blood sampling for PRA is not critical in the evaluation of mineralocorticoid replacement therapy [12]. Importantly, PRA and angiotensin II measurements reflected better the mineralocorticoid dose being more sensitive than serum sodium or potassium, total plasma proteins, heart rate, or orthostatic blood pressure [35]. However, in female PAI patients who are taking oral contraceptives, a higher PRA level should be taken into account due to stimulation of plasma renin substrate [35]. In PAI patients PRA correlates negatively with plasma volume [42]. However in PAI patients who have not yet received glucocorticoid replacement therapy, PRA levels underestimate volume deficiency due to the fact that concentration of plasma renin substrate are low due to glucocorticoid deficiency [43]. PRA was tested for usefulness in the assessment of mineralocorticoid replacement on 14 patients with Addison’s disease and showed to correctly determine mineralocorticoid under-replacement [8], although the authors suggested that atrial natriuretic peptide (ANP) is a more sensitive parameter of 9α-fluorocortisol over-replacement. However, in this study both PRA and ANP showed high variability indicating that the clinical utility of both measurements for the individual patient should not be overestimated.

The feedback of 9α-fluorocortisol on PRA is mediated via changes in extracellular fluid volume and blood pressure. This is the reason why changes in the PRA occur only days or even weeks after changing the 9α-fluorocortisol dose [25]. It is, therefore, recommended that PRA should be monitored not earlier than two weeks after changing the dose of 9α-fluorocortisol [33,35] and an even longer interval of 4 weeks has been suggested [42].

Studies assessing the volume status of patients with PAI consistently found some hypovolemia with standard replacement therapy [22,42]. In fact, under-replacement with 9α-fluorocortisol seems to be quite common, and is sometimes compensated for by over-replacement of glucocorticoids [21].

This may predispose to adrenal crisis, which occurs more frequently in PAI than in SAI [18]. Adrenal crisis could be triggered by further volume reduction, if salt depletion occurs either due to dietary restriction or by enhanced loss (e.g. via sweating) or if vomiting and diarrhea further lead to acute volume loss [18].

Slight puffiness of the face and hands and a PRA in the lower normal range are possible early signs for over-substitution with 9α-fluorocortisol [35]. Rapid weight gain, high blood pressure and hypokalemia clearly indicate a too high dose of 9α-fluorocortisol.

**Special therapeutic conditions**

**Pregnancy**

Progesterone has anti-mineralocorticoid potency in vitro [38] and in vivo [39], and is competing with aldosterone or 9α-fluorocortisol for binding to the hMR. During pregnancy progesterone levels steadily increase and the 9α-fluorocortisol dose may need to be increased depending on blood pressure and potassium levels. PRA concentrations are not informative during pregnancy due to the pregnancy induced increase in renin substrate [10]. Oelkers and other investigators reported increasing requirements of 9α-fluorocortisol substitution in Addisonian women during pregnancy [9,36] reaching doses of 0.3–0.6 mg (up to six-fold increase) to maintain normal potassium levels. After delivery the dosage has to be lowered to the pre-pregnancy level without delay, as progesterone rapidly declines after removal of the placenta [36]. Intriguingly, the need to increase 9α-fluorocortisol substitution in pregnancy seems to be not generally accepted [7,26] and more well documented pregnancies in patients with PAI are probably needed to settle this issue. However, we strongly recommend to closely monitor blood pressure and potassium levels during pregnancy and to early consider the need of increasing doses of 9α-fluorocortisol in the care of these women with PAI.

At delivery, hydrocortisone 100–150 mg/day intravenously during the first 24–48 h is recommended followed by rapid tapering and oral administration.
Concomitant hypertension

In hypertensive patients, the 9α-fluorocortisol dose may be reduced as a first therapeutic measure under monitoring of serum potassium levels to avoid hyperkalemia. However, it should not be entirely stopped, as this may facilitate the occurrence of hyperkalemia. As patients with PAI receiving standard replacement are often slightly hypovolemic (see above), diuretics are less useful and should be avoided. Obviously, also other medications such as carbenoxolone, liquorice, and NSAID are interacting and should not be given [30]. A direct vasodilator, e.g. calcium antagonist, is probably the best choice of anti-hypertensive treatment in patients with PAI. Again, more data on hypertensive patients with PAI are needed to better guide treatment.

Interfering drugs

Phenytoin has been reported to have adverse effects (hyponatremia, hyperkalemia and hypotension) on mineralocorticoid replacement with 9α-fluorocortisol in two patients with Addison disease [24]. Their 9α-fluorocortisol doses needed to be increased up to 0.4 mg daily. Phenytoin induces hepatic 6-hydroxylation, one of the major 9α-fluorocortisol metabolic pathways. Compared to cortisol itself, 9α-fluorocortisol has a strongly reduced Ring A metabolic clearance rate due to its fluor at position 9 [5]. Therefore, drugs which induce 6-hydroxylation, such as phenobarbital and rifampicin, might also enhance the metabolism of 9α-fluorocortisol.

Salt deficiency

Many patients note problems during hot weather, as it often leads to increased salt loss by sweating. In case of hot climate or strong perspiration it is, therefore, useful to transiently increase the 9α-fluorocortisol dose (by 0.1–0.2 mg/d) and/or the salt intake.

Adrenal crisis

PAI patients with acute adrenal crisis who receive 100 mg or more hydrocortisone per day do not need 9α-fluorocortisol medication on those days, because the increased dosage of hydrocortisone covers not only the glucocorticoid requirements but also provides sufficient mineralocorticoid activity [34], as has been outlined above. Administration of 0.9% NaCl is generally recommended in adrenal crisis to provide sufficient sodium and to correct hypovolemia.

Practice points

- Clinical signs of aldosterone deficiency are hypotension, salt craving, weakness, often combined with hyponatremia and hyperkalemia.
- The diagnosis is based on the demonstration of decreased basal serum aldosterone and elevated PRA.
- 9α-fluorocortisol is the standard therapy with doses of 0.05–0.2 mg once daily.
- Patients should take sodium salt without restrictions.
- Signs for adequate replacement therapy are general well-being, electrolytes within the normal range, normal blood pressure, and a PRA in the upper normal range.
- Doses often need to be increased during pregnancy (in case of hyperkalemia, hypotension), and in hot weather with increased sweating, and should be reduced in patients developing hypertension.
Research agenda

- More data including meaningful endpoints (well-being, blood pressure) is needed to establish improved monitoring strategies in mineralocorticoid deficiency.
- The role of mild volume deficit with current mineralocorticoid replacement regimens for fatigue should be investigated.
- More pregnant patients with primary adrenal insufficiency need to be analyzed to establish correct dose adjustments during pregnancy.
- Once versus twice daily dosing of 9α-fluorocortisol has not been investigated.
- PRC has not been evaluated and compared to PRA in patients with primary adrenal insufficiency, but is probably as good as PRA measurement.

Conflict of interest

None.

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References

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