Previous studies revealed that aldosterone-producing adenoma(APA) had a potential for excess co-secretion of cortisol. APA was considered to be composed of heterozygous cell types, including cortisol producing cells(expression of CYP11B1) and aldosterone-producing cells(expression of CYP11B2). The proportion of two cell types and the expression of two steroid synthases showed great heterogeneity in APAs, which may lead to differences in cortisol secretion. However, the hypothesis has not been tested. Therefore, we examined the correlation between tumor size and the ability to autonomously secrete cortisol of APA from the perspective of steroid hormones and immunohistochemistry. 165 patients with surgically proven APA were retrospectively studied. Patients with apparent excess cortisol co-secretion were excluded, which was confirmed by an overnight 1 mg dexamethasone suppression test(1mg-DST). Immunohistochemical staining was performed in 88 tumor specimens and CYP11B2-negative APAs were excluded. The expression of the steroidogenic enzymes was immunohistochemically analyzed, and semi-quantified according to the McCarty H-score system. All APA cases were classified into 2 groups according to the median(15mm) of maximum diameter detected by histological examination: the smaller(n=102) and larger group(n=63). 24am cortisol[78.7(47.7–121.5) VS. 54.6(33.6–81.4) nmol/l, p =0.002] and cortisol after 1mg-DST[28.8(19.1–40.9) VS. 24.1(16.8–30.7) nmol/l, p =0.024] were significantly higher in the larger APA group. The larger APA group had a higher H score of CYP11B1 (p=0.028) and a lower H score of CYP11B2 (p=0.036). Both 24pm cortisol (r =0.2424, p =0.0058)and cortisol after 1mg-DST(r =0.2476, p =0.042) were positively correlated with tumor diameter. The tumor diameter was positively correlated with the H score of CYP11B1 (p=0.0328) and inversely with the H score of CYP11B2(p=0.0285). We tentatively used a new ratio B1 index, calculated by H score of CYP11B1 divided by the sum of H score of CYP11B2 and CYP11B1, to represent the relative expression intensity of CYP11B1 in tumor specimens. B1 index had a stronger correlation with tumor diameter (r =0.3134,p=0.0041). Cortisol after 1mg-DST increased linearly with the tertiles of tumor diameter(p for trend<0.0001). These results suggested that APA without clinically overt cortisol secretion might have a higher proportion of cells expressing CYP11B1 to produce more cortisol with the increasing of tumor size, even developing to overt Cushing syndrome.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Assessment of Chronic Supraphysiological Glucocorticoid Dosing Needs of Patients With Adrenal Insufficiency

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Background: Patients who require higher than replacement glucocorticoid doses to avoid symptoms of adrenal insufficiency (AI) may have inadequate adherence or abnormal drug absorption or metabolism. The goal of this study was to identify why excessive glucocorticoid doses were needed in patients with ongoing AI symptoms. **Methods:** We performed pharmacokinetic (PK) analysis of glucocorticoid plasma concentrations (prednisone, prednisolone and dexamethasone measured by tandem mass spectrometry, Mayo Laboratories, and cortisol by immunoassay, Clinical Center) in 8 AI patients after weight-based oral hydrocortisone (HC) dose (1), IV HC 20 mg and /or prednisone 5 mg PO. The time (Tmax) to maximal plasma concentrations (Cmax), time to a 50% decrease in concentration (T1/2), elimination rate (ER) and area under the concentration curve (AUC) were determined using MATLAB and SimBiology, and compared to literature reference ranges (RR) (1,2). **Results:** Patients included one man; six had secondary AI due to previous supraphysiologic hydrocortisone or prednisone treatment and two had primary autoimmune AI. One of the latter was appropriately replaced with thyroid hormone. No patient was taking any medication known to be a strong inhibitor or inducer of CYP3A4 and none were taking oral estrogens. To study the potential contribution of intestinal absorption to abnormal pharmacokinetics, serum cortisol values were compared to expected values at 3.5 or 4 hours after a weight-based oral dose of HC in eight patients (1); 7 patients had values at the 50 - 80th centile of expected values. The eighth patient's cortisol level at 4 hours after 5 mg HC was 30.3 nmol/L, below the 10th centile. She then underwent the same sampling with a 15 mg dose, with values also at the 10th centile. To uncover any discrepancy between PK oral and IV HC administration, four patients, including the patient with a low 4 hour value (LowHC4h) underwent sampling after 20 mg hydrocortisone, IV (2). Tmax and Cmax were within the RR in all four patients, while one patient had a faster T1/2 but an AUC similar to others. The LowHC4h patient had a dexamethasone level 8 hours after a 1 mg dose that was also within the RR and was maintained on dexamethasone. All others were eventually able to be weaned to a conventional glucocorticoid replacement dose. **Conclusions:** Evaluation of oral and IV HC PK may be useful in patients suspected of having abnormal absorption of oral glucocorticoids. **Ref:** 1. Mah PM et al. Clin Endo 61:367,20042. Thomson AH et al. Clin Endo 66:789,2007

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Audit on Steroid Replacement in Confirmed or Suspected COVID-19 Patients With Adrenal Insufficiency or Adrenal Suppression in a District General Hospital

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Aim: In response to new updated guidance from Society For Endocrinology April 2020, this Audit was conduct to assess the adequacy of steroid replacement in confirmed or suspected COVID-19 patients with adrenal insufficiency or adrenal suppression admitted to Bedford District General Hospital. In steroid dependent patients (Addison's disease, adrenal insufficiency, pituitary steroid insufficiency, use of long term steroids for other conditions - 5mg or more

of prednisolone (or equivalent doses) daily for longer than 4 weeks) admitted to hospital very unwell with confirmed or suspected COVID recommendations is to start on Hydrocortisone 100 mg per IV injection followed by continuous IV infusion of 200 mg hydrocortisone/24h (alternatively 50 mg every 6 h per intravenous or IM bolus injection). **Method:** Retrospect data collection on Patients admitted in May 2020 to Bedford Hospital with suspected or confirmed COVID 19 disease with adrenal insufficiency or on long term steroid use. Those patients should be started on Hydrocortisone 100 mg per IV injection followed by continuous IV infusion of 200 mg hydrocortisone/24h (alternatively 50 mg every 6 h per intravenous or IM bolus injection).
Results: In May 2020, 295 patients admitted under the medical team in Bedford Hospital with confirmed or suspected COVID-19. Only 12 patients met the inclusion criteria, one patient with a diagnosis of Addison disease and the remaining 11 patients on long term steroids. None of these patients were managed as per updated guidelines. 6 patients had less than the adequate dose, they were started on prednisolone 30-40mg. 4 patients dose of oral steroids was only doubled, 1 patient received the same dose of oral steroid and the only confirmed Addison had higher dose of hydrocortisone. Moreover, In June 2020, The RECOVERY Outcome trial results showed that Dexamethasone 6mg for 10 days reduces the death by one third in hospitalised patient with severe respiratory complications of COVID-19. Dexamethasone 6mg is 12 times the physiological required steroid dose, this is equivalent to 240mg hydrocortisone, which is adequate for steroid replacement in patients with adrenal insufficiency or suppression.
Conclusion: In view of these results and the outcome of the RECOVERY Trial, Local trust guidelines updated, indicated that any patient with Adrenal insufficiency or suppression including those on long term steroids very unwell admitted to the hospital should receive Dexamethasone if requiring oxygen or Hydrocortisone if not requiring oxygen. Recommendation of changes included teaching sessions delivered to doctors, posters on updated guidelines distributed in major areas in hospital and trust guidelines updated on the intranet.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Changes in Adrenal and Gonadal Androgens After 14-Day Treatment With CRF1 Receptor Antagonist, Crinecerfont (NBI-74788), in Men With Classic 21-Hydroxylase Deficiency

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Background: Congenital adrenal hyperplasia due to classic 21-hydroxylase deficiency (21OHD) causes cortisol insufficiency and androgen excess. A phase 2 trial of crinecerfont, a CRF1 receptor antagonist, in 18 adults with 21OHD showed prominent decreases in ACTH, 17-hydroxyprogesterone, and androstenedione (A4), and in women, testosterone (T), after 14 days of treatment. In men with 21OHD, T derives from both adrenals and testes; in poor disease control, A4/T ratio is elevated due to disproportionately increased adrenal A4 production and decreased testicular T production. We sought to determine the impact of crinecerfont on both adrenal and gonadal androgen production in men with 21OHD in this phase 2 trial.
Methods: A4 and T data were analyzed for 7 men who completed 1 or more of 4 oral dosing regimens: Cohort 1, 50 mg QHS, n=4; Cohort 2, 100 mg QHS, n=2; Cohort 3, 100 mg QPM, n=5; and Cohort 4, 100 mg BID, n=3 (14 total treatment periods). Mean 0600-1000 4-hour morning window (M4hMW) and mean 24-hour (M24h) A4, T, and A4/T ratios were analyzed from serial serum samples at baseline and on day 15.
Results: Dose-dependent reductions in M4hMW A4 were observed [median (range)] in men, consistent with previously presented data in all subjects:Cohort 1: -21% (-84 to -12%);Cohort 2: -37% (-51% to -23%);Cohort 3: -43% (-85% to +140%);Cohort 4: -62% (-90% to -33%).
In contrast, M4hMW T showed inconsistent changes [median (range)]: Cohort 1: +18% (-40% to +82%);Cohort 2: -4% (-4.3% to -3.8%);Cohort 3: +9% (-11 to +24%);Cohort 4: +9% (-3% to +27%).
Thus, M4hMW A4/T ratios decreased with dose. Values at baseline, on day 15, and percent changes [median (range)] were, respectively:Cohort 1: 0.9 (0.3–2.6), 0.6 (0.1–2.1), -26% (-91% to +23%);Cohort 2: 5.0 (4.8–5.2), 3.3 (2.5–4.2), -35% (-49% to -20%);Cohort 3: 0.6 (0.1–6.9), 0.3 (0.1–2.7), -54% (-85% to +178%);Cohort 4: 3.9 (0.6–5.9), 0.4 (0.3–2.1), -65% (-92% to -31%).
M24h A4/T ratios similarly declined in all cohorts. Values at baseline, on day 15, and percent changes [median (range)] were, respectively:Cohort 1: 1.0 (0.3–2.3), 0.4 (0.1–1.9), -33% (-92% to +2%);Cohort 2: 4.3 (3.8–4.9), 2.7 (2.4–3.0), -36% (-51% to -22%);Cohort 3: 0.5 (0.1–4.7), 0.4 (0.1–2.4), -59% (-78% to +310%);Cohort 4: 3.2 (0.4–4.1), 0.4 (0.3–1.7), -58% (-89% to -31%).
Conclusions: Following crinecerfont therapy, A4 and A4/T decreased in a dose-dependent manner in men with 21OHD. In contrast to reductions in T observed in women with 21OHD, T did not change consistently and rose in some men. Preserved T values despite marked A4 reductions suggests testicular T production increased during crinecerfont therapy, perhaps due to release of gonadotropin suppression from adrenal-derived androgens. Long term studies are needed to determine if crinecerfont treatment improves additional measures of testicular function in men with 21OHD.
Reference: RJ Auchus, et al. *J Endocr Soc* 2020;4(Suppl 1):OR25-03.

Adrenal

ADRENAL – CLINICAL RESEARCH STUDIES

Changes in Clinical Presentation and Perioperative Management of Pheochromocytomas and