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Metyrapone To Reset The Nocturnal Cortisol Rhythm In Mild Autonomous Cortisol Secretion (MACS) - Safety And Impact On Cardiometabolic Risk Factors

Simon Berry, MBChB (Hons)[1], Ahmed Iqbal, PhD[2], John D. C. Newell-Price, MD, PhD, FRCP[2], and Miguel Debono, MD,FRCP, PhD[1]

[1]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom; [2]University of Sheffield, Sheffield, United Kingdom

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Background: MACS is associated with increased cardiometabolic risk including hypertension, type 2 diabetes and dyslipidemia. In MACS, serum and salivary cortisol and cortisone levels are significantly higher in the nocturnal period but follow the usual daytime pattern. Combined early and late evening dosing with the short-acting 11-beta hydroxylase inhibitor, metyrapone, has previously been shown to acutely 'reset' this abnormal part of the cortisol curve to normal. We have now assessed the impact of long-term evening metyrapone on cardiometabolic dysfunction in MACS. **Method:** A retrospective, controlled, longitudinal study evaluated the safety and tolerability of nocturnal metyrapone and its impact on cardiometabolic risk factors. We included all patients (n=15) who were initiated on metyrapone treatment, 250mg-500mg at 6pm and 250mg at 10pm, for MACS at a tertiary endocrinology center between 2015 and 2022. Age and sex-matched controls were selected from patients with adrenal incidentalomas and non-suppressed serum cortisol following 1mg overnight dexamethasone suppression testing. Systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, HbA1c and non-HDL cholesterol were assessed at baseline and after 6 months. Morning serum cortisol values were evaluated to check for adrenal axis over-suppression. Wilcoxon signed-rank test was used to compare pre/post-treatment, and Mann-Whitney U test was used to compare metyrapone group to controls. **Results:** Metyrapone was tolerated by 12/15 patients - two stopped due to diarrhea and one due to high androgens in a female. There were no occurrences of adrenal crises. The morning cortisol after metyrapone was 365 nmol/L (IQR 254-431nmol/L, n=13). ACTH increased from 4.5 pg/ml to 7.5 pg/ml (SE±2.15, n=12) after treatment. In the metyrapone group compared to controls, there were significant decreases in SBP (-26.4 SE±8.1mmHg, p=0.008, n=9) and DBP (-12.9 SE±5.5mmHg, p=0.024). Four patients in the control group had up-titration of antihypertensive medication between measurements compared to only one in the metyrapone group. The differences between groups in HbA1c, weight and non-HDL cholesterol were not statistically significant. However, the increase in HbA1c was less in the metyrapone group compared to the control group by 3.0 SE ±4.5mmol/mol, as was the non-HDL cholesterol by 0.4 SE ±0.33mmol/L (n=10). **Conclusion:** Evening metyrapone is associated with significant reductions in SBP and DBP in patients with MACS, without causing adrenal insufficiency and with preservation of normal morning serum cortisol. Monitoring 9am cortisol is important to avoid over-treatment. A larger, powered, prospective study is needed to definitively investigate the broader metabolic outcomes and assess the clinical utility of metyrapone in MACS.

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