

Treatment of Cushing's Syndrome with Mifepristone: Impact Over Time on Insulin Sensitivity

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Hypothesis: Our goal was to examine whether the improvement in insulin sensitivity seen with mifepristone (glucocorticoid receptor antagonist) is independent of changes in body weight (WT) and waist circumference (WC). **Methods:** Adults with Cushing's syndrome, who completed SEISMIC (a study examining the safety and efficacy of mifepristone) with hypertension alone (C-HT) (n=11) or with diabetes/impaired glucose tolerance (C-DM) (n=17) & who had evaluable data at all major study efficacy visits (wks 6, 10, 16, & 24) were included in these analyses. WT, WC, fasting insulin & glucose (GLU) were measured, & 75g 2 hr oral GLU tolerance tests (oGTT) with insulin levels were performed. Insulin sensitivity (Matsuda Index, MI) was calculated for all C-DM not on insulin (n=9) & C-HT (n=11). Statistical analysis included paired t-tests and linear mixed models for continuous variables. Data are shown as mean $\pm$ SEM. **Results:** From baseline to wk 6 in C-DM, there was a $-1.69 \pm 0.81\%$ (p=0.09) change in WT, a $-0.74 \pm 1.02\%$ (p=0.42) change in WC, & a marked change of $-19.49 \pm 4.59\%$ (p=0.001) in GLU Area Under the Curve (AUC) on oGTT. From wk 6 to 24, there were marked changes in WT ($-7.11 \pm 1.77\%$, p=0.014) and WC ($-8.01 \pm 1.20\%$, p=0.003) with a relatively smaller change in GLU-AUC ($-14.6\% \pm 6.01\%$, p=0.550). Regression analysis confirmed a nearly identical continuous linear best fit model for both changes in WT (r=-0.998, p=0.0001) & WC (r=-0.981, p=0.003); a two-phase model (0-6wks, & 6-24wks) was a much better fit than a linear model (p=0.005 for model difference) for change in GLU-AUC, suggesting a biphasic effect on AUC with the first phase being independent of changes in WT or WC. In C-HT & C-DM not on insulin, further evaluation of insulin sensitivity (MI) over time showed that more than 2/3 of the improvement in MI occurred between wk 0 & wk 6 ($64.92\% \pm 21.96$, p=0.018) as compared to a non-significant change from wk 6 to 24 ($31.33\% \pm 9.86$, p=0.15). Concurrently, at wk 6 there were minimal changes in WT ($-1.16\% \pm 0.69\%$, p=0.11) & WC ($-1.19\% \pm 0.74\%$, p=0.08) as compared to significant changes seen between wks 6 & 24 (WT $-6.69\% \pm 1.42\%$, p=0.002) (WC $-6.41\% \pm 1.27\%$, p=0.006). **Conclusion:** Mifepristone use was associated with an early improvement in insulin sensitivity prior to any significant change in WT or WC, likely due to direct glucocorticoid receptor blockade. Later in the course of treatment, the change in WT and WC had additional effects in increasing insulin sensitivity.