Dutasteride and 5α-reductase type 1 activity: for androgens only?

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Background and Aim

• Three 5α-reductase (5α-R) isoenzymes are described (5α-R1-3)
• The role of 5α-R1 in physiological or pathological states is not clear
• 5α-R2 deficiency causes XY pseudohermaphroditism
• 5α-R3 deficiency causes neurological problems
• Urine steroid profiling (USP) by Gas-Chromatography Mass-Spectrometry (GC-MS) is effective in demonstrating 5α-R activity
• In the context of diagnosis of 5α-R2 deficiency significantly reduced excretion of 5α- compared with 5β-reduced steroid metabolites are seen
• These 5α-/5β-ratios are split into four: two androgen metabolite ratios, androsterone (A) to aetiocholanolone (Ae) and 11β-hydropxyandrosterone (11OHA) to 11β-hydroyxyaetiocholanolone (11OHAe)

Method

• Retrospective case-control study using USP data compiled from samples submitted to our departmental database
• Three study groups formed: genetically confirmed 5α-R2 deficient patients (n=28), finasteride use (n=6) and dutasteride use (n=2) – compared with matched controls (n=36)
• Data analysed for significance with Mann-Whitney U test

Results

• Results summarised in box-and-whisker plots (figures 3-5)
• Controls showed higher 5α-/5β-ratios for androgen and corticosteroid metabolites – some overlap seen between controls and 5α-R2 deficiency in 11OHA:11OHAe ratio, all differences significant
• 5α-R2 deficiency and finasteride had range overlap in all four ratios, differences were not statistically significant
• Dutasteride and 5α-R2 deficiency had no range overlap in androgen metabolite ratios that was statistically significant, but gross overlap in corticosteroid ratios

Conclusions

• We confirm that 5α-R2 deficiency and finasteride produce similar USP, with corticosteroid metabolites (aTHB:THB and aTHF:THF) being the main ratios affected, supporting the expectation that 5α-reduction of corticosteroids is more dependent on 5α-R2 activity
• We show there is a statistically significant reduction in androgen 5α-/5β-metabolite ratios (A:Ae and 11OHA:11OHAe) in dutasteride compared to 5α-R2 deficiency where 5α-R1 is inhibited in addition to 5α-R2, with the implication that 5α-R1 has a significant role in androgen catabolism
• This may include 5α-reduction of testosterone and dihydrotestosterone which may explain why the measuring the ratio of these androgens in the serum of patients with 5α-R2 deficiency can have a low diagnostic sensitivity
• There is evidence from animal studies that supports 5α-R1 having an involvement in androgen metabolism, including knockout studies that demonstrate derangement of sex steroids – there may be potential for similar pathological states in humans exhibiting similar USP to those seen in dutasteride