species and thus preventing DNA damage. Although previous studies have found TBHQ to cause cancer cell death at high concentrations, they have also contrastingly found TBHQ, when studied in animal models, to enhance carcinogenic effects. However, the effect of TBHQ on breast cancer has not been thoroughly explored. With the prevalence of breast cancer and the wide use of TBHQ in processed food items, it is imperative that we explore their possible relationship. This study examined the effects of TBHQ, alone and in combination with hormones and anti-hormones, on ERα and p53 expression in both MCF-7 and T-47D breast cancer cell lines. To ensure treatment conditions without the presence of endogenous steroids or growth factors, the cells were cultured with a 5% charcoal-stripped fetal bovine serum (FBS) for six days. Western blot analysis revealed alterations in the expression of ERα and p53 protein levels after 24 hours of treatment with varying concentrations of TBHQ (0.005 to 1 mM). A concentration-dependent decrease of ERα protein levels was observed in both cell lines, with a 49% reduction occurring with 100 μM TBHQ as compared to the control. P53 levels portray a continued increase of expression through concentrations of TBHQ (0.005 to 1 mM), found similarly in both cell lines. To gain further insight into possible similarities between BPS and other known effectors of ERα, the optimal concentration of TBHQ (100 μM) was used in combination with hormones and anti-hormones. Down-regulation of ERα protein levels was observed after 24-hour co-treatment of T-47D & MCF-7 cells with a combination of TBHQ and E_2. Antiestrogen ICI with TBHQ showed a significant down-regulation as compared to TBHQ alone, and TBHQ with TAM portrayed no significant differences. A similar trend in the effects on p53 expression was depicted in T-47D and MCF-7 cells. Image cytometric analysis with propidium iodide staining was utilized to quantify cell values and viability changes to further portray the effects of TBHQ on T-47D and MCF-7 cellular growth. The viability assay shows a biphasic effect with increasing concentrations of TBHQ, with a maximum decrease in proliferation seen at a concentration of 100 uM TBHQ. TBHQ alone and in combination with E_2 and antiestrogens showed a decreased proliferation compared to the control in T-47D cells. However, cytolocalization of ERα upon treatment with estradiol and TBHQ remained unaltered. Our studies offer a unique perspective on the effects of TBHQ on two different breast cancer cell lines, and provide valuable insight for further exploration of the mechanism of action of TBHQ on tumor suppressor gene and steroid receptors.

Endocrine Disruption

ENDOCRINE DISRUPTING COMPOUNDS: MECHANISMS OF ACTION AND CLINICAL IMPLICATIONS

Thyroid Gland and Male Reproductive Anomalies Among Fuel Handlers in Gampaha District, Sri Lanka

Dulani Chathurika Kottahachchi, Consultant Endocrinologist MD(Col), MRCP(UK)[1], Tania Warnakularuriya, MPhil[1], Deepthi De silva, MRCP[1], Kushan Madagoda, MD[1], Dilesha Wadasinghe, MD[1], BKTPI Dayanath, MD[2], Sajith Siyambalapitiya, MD[2], Niranga Devanarayana, PhD[1].

[1]University of Kelaniya,Sri Lanka, Kelaniya, Sri Lanka, [2]Colombo North Teaching Hospital,Sri Lanka, Ragama, Sri Lanka.

Introduction: Fuel handlers at petrol stations are continuously exposed to organic solvents from fuel and vehicle emissions. Endocrine disrupting chemicals (EDC) are present in fuel, which are harmful to endocrine organs. Thyroiditis and hypogonadism are reported among fuel handlers. Thyroid gland and male reproductive function anomalies were investigated among fuel handlers in the Gampaha district of Sri Lanka. **Method:** 43 were recruited from 6 fuel stations in the Gampaha district for the study and 28 age matched male workers who were not exposed to fuel in an occupational setting were recruited as controls. Thyroid gland was examined clinically and TSH, free T4, FSH, LH and Testosterone were done on all the participants. TPO antibody and a thyroid scan was done on the fuel handlers. **Results:** Median (IQR) age was 38 years (27-46 years). The mean TSH value was 1.62 IU/mL (1.15-2.35) vs 1.33 IU/mL (0.83-1.79) respectively in study and control populations with significantly higher levels in the study population (p=0.023). The median (IQR) TSH value above the reference range was identified in 7% of fuel handlers and all controls were within the normal range, while 16.9% of fuel handlers had a derangement in the TPO levels. On examination, only one control had a small goiter but his T4 and TSH levels were normal. On ultrasound thyroid scans, benign nodules were seen in 2 fuel handlers. TPO levels did not correlate with the TSH levels among the fuel handlers (r=-0.078, p=0.652). Inability to sustain an erection was reported by 35.5% fuel handlers which was significantly higher than controls who reported 5.6% (p=0.019). Premature ejaculation was reported by 27.9% of fuel handlers which was significantly higher than controls (p=0.023). The testosterone levels were significantly higher among fuel handlers compared to controls (p=0.048). The FSH and LH levels positively correlated with each other as expected in each subgroup and the total population (p<0.005). The TSH levels significantly negatively correlated with the testosterone levels among the fuel handlers. (r=- 0.338, p=.0.023). When the fuel handlers with premature ejaculation was considered the FSH, LH, Testosterone levels were not significantly different between the two groups, however the duration of employment was significantly longer among those reporting premature ejaculation. (p=0.024). **Conclusion:** There are thyroid and reproductive abnormalities among those exposed to fuel in an occupational setting. Disturbances to sexual functions may also be related to alteration of autonomic functions. Limiting exposure to fuel vapor will eliminate these detrimental effects and we propose self-service fuel pumps to be the best alternative to avoid occupational health hazards among fuel handlers.

Endocrine Disruption

ENDOCRINE DISRUPTING COMPOUNDS: MECHANISMS OF ACTION AND CLINICAL IMPLICATIONS

Tildacerfont for the Treatment of Patients With Classic Congenital Adrenal Hyperplasia: Results From a 12-Week Phase 2 Clinical Trial in Adults With Classic CAH

Richard Joseph Auchus, MD, PhD[1], Deborah P. Merke, MD, MS[2], Ivy-Joan Madu, MD[3], Samer Nakhle, MD[4], Kyriakie Sarafoglou, MD[5], Michael Huang, MD[6], David Moriarty, PhD[7], Chris Barnes, PhD[7], Ron S. Newfield, MD[8].

[1]University of Michigan, Ann Arbor, MI, USA, [2]National Institutes of Health Clinical Center, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, USA, [3]Diabetes Associates Medical Group, Orange, CA, USA, [4]Palm Medical Group, Las Vegas, NV, USA, [5]University of Minnesota Medical School, Minneapolis, MN, USA, [6]former employee of Spruce Biosciences, Daly City, CA, USA, [7]Spruce Biosciences, Daly City, CA, USA, [8]University of California San Diego, San Diego, CA, USA.

Background: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is an autosomal recessive disorder characterized by insufficient cortisol production resulting in excess adrenocorticotropic hormone (ACTH) and adrenal androgen production. Standard-of-care therapy with glucocorticoids (GC) is suboptimal due to the difficulty of balancing control of the ACTH-driven androgen excess against the serious long-term side effects associated with chronic supraphysiologic GC exposure. Tildacerfont, a second-generation corticotropin-releasing factor type-1 (CRF_1) receptor antagonist, lowers excess ACTH, and thus has the potential to reduce adrenal androgen production and to allow for GC dosing closer to physiologic doses. A prior study demonstrated that tildacerfont was effective in reducing ACTH, 17-hydroxyprogesterone (17-OHP) and androstenedione (A4) after 2 weeks of therapy. Here we report results from an open-label 12-week extension study. **Methods:** Subjects met either of the following criteria: 1) completion of prior study or 2) treatment naïve to tildacerfont with 17-OHP >800 ng/dL while on a stable GC regimen (excluding dexamethasone). Subjects were treated with oral tildacerfont at 400 mg once daily for 12 weeks. Efficacy and safety parameters were assessed at baseline through Week 12. **Results:** Subject characteristics (n=8) are as follows: median (range) age was 44.5 years (26-67 years; 5 females), median (range) body mass index 30.8 kg/m^2 (22-41 kg/m^2). In month 3, in the participants with poor control of disease at baseline (elevations in all key biomarkers: ACTH, 17-OHP, and A4) (n=5), maximum mean percentage reductions for ACTH, 17-OHP and A4 were 84%, 82%, and 79%, respectively. In this subgroup, 60% of subjects achieved ACTH normalization and 40% achieved A4 normalization during treatment. Tildacerfont treatment maintained, and did not suppress, biomarkers in participants with good control of disease at baseline (A4 below upper limit of normal) (n=3). Overall, tildacerfont was well tolerated with no serious adverse events.
Conclusions: This is the first study of 12 weeks' duration for a novel, non-steroidal mechanism-of-action agent for the treatment of 21-OHD. Results of this study show that tildacerfont was generally well-tolerated and effective in achieving meaningful reductions in ACTH and A4 in poorly controlled patients over 12 weeks. In addition, this is the first, non-steroidal therapeutic to show evidence of ACTH and A4 normalization over 12 weeks of therapy. Longer term future studies will evaluate whether treatment with tildacerfont can achieve further clinical benefits and allow reduction of GC doses while controlling relevant disease biomarkers.

Endocrine Disruption

ENDOCRINE DISRUPTING COMPOUNDS: MECHANISMS OF ACTION AND CLINICAL IMPLICATIONS

TLANDO, a Novel Oral TRT, Improves Sexual and Mental Domain Outcomes in Hypogonadal Men

Benjamin J. Bruno, PhD[1], Kiran Vangara, PhD[1], Kilyoung Kim, PhD[1], Kongnara Papangkorn, PhD[1], Nachiappan Chidambaram, PhD[1], Mahesh V. Patel, PhD[1], Anthony DelConte, MD[2], Culley C. Carson III, MD[3], Irwin Goldstein, MD[4], Jed Kaminetsky, MD[5], Martin Miner, MD[6], Mohit Khera, MD[7].

[1]Lipocine Inc., Salt Lake City, UT, USA, [2]Saint Joseph's University, Philadelphia, PA, USA, [3]University OF N CAROLINA SCHL OF Medical, Chapel Hill, NC, USA, [4]University of California at San Diego, San Diego, CA, USA, [5]NYU Grossman School of Medicine, New York, NY, USA, [6]Men's Health Center The Miriam Hotel, Providence, RI, USA, [7]Baylor College of Medicine, Houston, TX, USA.

Male hypogonadism is characterized by symptoms and deficiency (<300 ng/dL) in levels of in total testosterone (TT), a critical hormone for sexual, cognitive, and body function and development. TLANDO, a testosterone undecanoate (TU) comprising lymphatically delivered oral testosterone replacement therapy (TRT) option not requiring dose titration, treatment has demonstrated effective restoration in hypogonadal men of TT levels to the eugonadal range in multiple clinical studies. TLANDO therapy resulted in decreased sex hormone binding globulin with increased free testosterone (FT). TLANDO's unique delivery system enables consistent restoration of TT regardless of meal fat content. Moreover, TLANDO has shown potential to improve liver health through resolution of fatty liver disease in hypogonadal men and is not known to have any adverse liver effects. However, it is unclear if fixed dose TLANDO therapy without dose adjustment improves symptoms of psychosexual functions. The objective is to assess key sexual and mental domain Patient Reported Outcomes (PRO) post 52 weeks of treatment using TLANDO on the to-be-marketed dosing regimen in comparison with a widely used topical TRT, Androgel 1.62%. Data analysis was performed in in hypogonadal males post TLANDO treatment without dose adjustment, and in patients on the active control from a randomized, multi-center, open label, active controlled 52-week trial (SOAR, NCT02081300). Sexual and mental domain function PROs were measured at baseline (BL) and end of study (EOS) using Psychosexual Daily Questionnaire (PDQ) and Short Form (SF)-36 surveys and compared between TLANDO and active control. Post treatment with TLANDO dosing regimen not requiring dose titration, key sexual domain function PROs at week 52 were significantly ($p<0.05$) improved from BL: positive mood (BL:4.5 vs EOS:5.1, $p<0.001$), negative mood (1.8 vs 1.4, $p<0.01$), overall sexual desire (2.5 vs 3.7, $p<0.001$), sexual activity (2.5 vs 4.0, $p<0.001$), highest pleasure with partner (2.0 vs 2.8, $p=0.06$), highest pleasure without partner (1.8 vs 2.4, $p<0.05$), weekly maintained erection (3.3 vs 4.5, $p<0.001$), and weekly full erection % (50.5% vs 68.9%, $p<0.001$). Most sexual and mental function PROs were comparable to Androgel 1.62. TLANDO therapy was well tolerated through 52 weeks of treatment exposure. In conclusion, TLANDO, a novel easy to use and prescribe