Genotropin allowed further evaluation of the IGF-1 SDS analysis paradigm. Enrolled subjects were randomized to receive treatment with either once weekly Somatrogon (0.66 mg/kg; N=109) or once daily Genotropin (0.034 mg/kg; N=115). IGF1 was sampled ~ five times during 52 weeks of treatment with Somatrogon, providing a total of 557 samples obtained after the first dose of Somatrogon. IGF-1 SDS values were calculated using Bidlingmaier’s equations [2]. Analysis of IGF-1 SDS data from the Phase 3 study showed that the previously-developed model, with adjustments to two parameters (baseline IGF-1, EC₅₀) and adapted to fit IGF-1 values in the absence of Somatrogon concentration data, fit the IGF-1 data for Somatrogon with minimal bias. This allowed prediction of IGF-1 SDS values at timepoints throughout the dosing interval as well as calculation of the mean value during a dosing interval. Of the samples obtained between 48–72 hours post-dose (representing peak IGF-1 SDS), approximately 17% had an IGF1 SDS > +2. At 96 hours (corresponding to mean IGF-1 SDS), fewer than 2% of modeled values were > +2. Mean IGF-1 SDS over the dosing interval was between -1 and +1 for all subjects. These findings indicate that IGF-1 SDS values need to be interpreted in the context of when the sample was obtained relative to the last dose of Somatrogon. Our results indicate that samples obtained 96 hours post-dose best represent mean IGF-1 levels and that values obtained between 48–72 hours post-dose represent closer to peak IGF-1 concentrations. In our Phase 3 study, of the 557 samples collected from 114 patients during the 12-month Somatrogon treatment period, fewer than 1% of the corresponding values at 96 hours postdose (estimated from a pharmacokinetic/pharmacodynamic model) had IGF-1 SDS levels > +2.

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Bone and Mineral Metabolism
PARATHYROID HORMONE TRANSLATIONAL AND CLINICAL ASPECTS
A Non-Surgical Animal Model of Hypoparathyroidism for Testing PTH Analogues
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SAT-396
Background:
In vivo animal models for testing the pharmacokinetics and bioactivity of PTH and its analogues require parathyroidectomy by surgery (1, 2). As the parathyroid glands of rodents are very small the surgery often includes thyroidectomy, making this animal model time-limited, single use, complex, and expensive. We have developed a non-surgical rodent model of hypoparathyroidism using the Type II calcimimetic compound, Cinacalcet-HCl, to suppress PTH and thereby serum calcium levels.

Methods:
Normal male Wistar rats were gavaged with 30 mg/kg Cinacalcet-HCl (or vehicle only). To test the effect of PTH 1–34, animals were dosed immediately after Cinacalcet-HCl gavage with either a single subcutaneous injection of PTH at 20 nmol/kg or given as same dose repeated every hour for 6 hrs or vehicle only. Serum samples were analysed for ionised calcium (iCa) using an EasyLyte, fully automated electrolyte analyser (Medica Corporation) and phosphate using a Phosphorus Detection Assay Kit (Pars Azmun, IRAN) and an Hitachi 917 Clinical Chemistry Analyser.

Results:
Rats gavaged with 30 mg/kg Cinacalcet-HCl produced a significant reduction in iCa levels between 2-24hrs returning to baseline at 48–72hrs post dose with the nadir at 8 hours (ANOVA P<0.0001). This equated to a 25% reduction in iCa at 5 hrs: mean±SD, iCa 1.19 ± 0.09 mmol/L at predose and 0.891 ± 0.04 mmol/L at 8 hours (t-test P<0.0001). For phosphate there was an initial lowering within the first 2 hrs in all test groups but then a rise such that phosphate was at higher levels than control from 8–24 hrs (ANOVA, ns), returning to baseline at 48 hrs. PTH at 20 nmol/kg given as a single sc dose abrogated the Cinacalcet-HCl induced fall in iCa for up to 2 hrs (AUC±SD (mmol/L).hr, 0.076 ±0.047 versus 0.168±0.0874, t-test P=0.0289).

Conclusions:
We have shown that the administration of Cinacalcet-HCl provides a robust and reproducible lowering of calcium which is line with current published data (3). These studies demonstrate that the use of Cinacalcet-HCl in normal rats produces a hypocalcemic state that can be abrogated by the addition of PTH. This non-surgical animal model of hypoparathyroidism will be of value in testing the pharmacodynamics of PTH analogues.

References
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Introduction

Adrenal lesions that are found incidentally during routine imaging of people who do not have any complaints or physical findings related to adrenal gland are called adrenal incidentaloma (1,2). Incidentalomas appear more frequently with the increasing use of imaging techniques and increasing age. It is unclear why most of these masses emerged. It is controversial whether nonfunctional adrenal incidentalomas (NFAI) increase the risk of cardiovascular disease or metabolic syndrome or are more common in people with these diseases. In this study, we aimed to investigate whether lifestyle and body fat have an impact on the occurrence of NFAI.

Materials and Methods

100 patients with NFAI were included in the study. Control group consisted of 50 healthy and similar age groups. Physical activities of these groups (with the International Physical Activity Questionnaire Short Form), smoking were questioned and anthropometric measurements were made (Height, body weight, body mass index (BMI), neck, hip, waist circumference and body fat mass, fat percentage, total body water, fat free mass with bioimpedance method). Laboratory tests were examined from the patient file.

Results

Female dominance was observed in patients with NFAI. BMI, waist circumference, hip circumference, neck circumference, total body fat percentage and mass and smoking were found to be higher in the patient group compared to the healthy group and a statistically significant difference was found. When a subgroup of patients with similar age and BMI among the patients and the control group were constituted (25-29.99 kg/m²) waist circumference and total fat mass were again significantly higher in the patient group compared to controls. In addition, there was a significant positive correlation between mass size and waist circumference, BMI, neck circumference, cortisol after 1 mg dexamethasone suppression test and a significant negative correlation with ACTH.

Conclusion

The data obtained showed that body adiposity and smoking were higher in patients with NFAI. Also, it was shown that although the patients were regarded as nonfunctional, suppressibility of the cortisol decreases as the mass size of the incidentaloma increase.

Resources

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Reproductive Endocrinology

FEMALE REPRODUCTION: BASIC MECHANISMS

Effects of Delta-9-Tetrahydrocannabinol (THC) on Oocyte Competence and Early Embryonic Development

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Cannabis is the highest used recreational drug amongst individuals of reproductive age. Fertility clinics advise against cannabis use when undergoing fertility treatments, but the literature backing this statement is weak. This rise in cannabis use has occurred simultaneously with the increase in the percentage of the main psychoactive component of cannabis, delta-9 tetrahydrocannabinol (THC) (1). Current literature suggests that THC mimics the effects of endogenous cannabinoids, binding to cannabinoid receptor 1 (CB1), which has been identified in reproductive tissues (2).

Our research aims to study the impact of THC on oocyte maturation and pre-implantation embryonic development. An in vitro bovine system was used as it is the most appropriate translational model to humans for in vitro reproductive toxicity studies. Bovine oocytes were collected and matured under five treatment groups: control, vehicle (1:1:18 ethanol: TWEEN: saline), low THC (0.032uM), mid THC (0.32uM) and high THC (3.2uM). These doses mimic plasma concentrations reached after therapeutic (0.032uM) or low/high recreational (0.32uM and 3.2uM) cannabis use (3). We hypothesise that THC affects oocyte competence and proper early embryonic development in vitro.

A negative THC dose-dependent response in cleavage rate was observed, with the highest THC group cleaving at 70.2% rate compared to 86.8% and 85.5% of control and vehicle groups, respectively (p<0.0001, n=7). There was no significant difference in blastocyst rate, suggesting that oocyte THC exposure affects the numbers of oocytes capable of development, but those able to cleave will properly reach blastocyst stage. We analyzed changes in gene expression, i) by a full RNA transcriptome analysis (24,128 transcripts screened) and ii) by quantification of Connexin 37 (CX37) and 43 (CX43) mRNA levels. Connexin expression is correlated to oocyte competence (4). RNA transcriptome analysis showed 62 genes that were significantly downregulated only in the low THC group. CX mRNA levels were measured via droplet digital PCR in both cumulus-oocyte complexes (COCs) and blastocysts. No significant differences were detected in blastocysts, however, a significant decrease in both CX37 and CX43 levels was measured in the low THC group in COCs (p<0.05, n=9). Differences seen exclusively at the low THC dose suggest a role of THC as partial agonist of CB1.

This research aims to understand the effects of cannabis on fertility, as current knowledge during pre-implantation development is limited, making it difficult for physicians to properly advise patients undergoing IVF.

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