Proceedings Paper:
Ramezani-Pour, N., Esfahani, S.H.Z., Pradhananga, S. et al. (3 more authors) (2020) SAT-396 A non-surgical animal model of hypoparathyroidism for testing PTH analogues. In: Journal of the Endocrine Society. ENDO 2020 - Annual Meeting of the Endocrine Society, 28-31 Mar 2020, San Francisco, CA, USA (cancelled). Oxford University Press (for The Endocrine Society) .

https://doi.org/10.1210/jendso/bvaa046.505

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-I SDS data from the Phase 3 study showed that the previously-developed model, with adjustments to two parameters (baseline IGF-1, EC_{50}) 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 IFG-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 values 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 2% 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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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 8 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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Adrenal

ADRENAL - TUMORS

Evaluation of Life Style and Anthropometric Parameters in Patients with Nonfunctional Adrenal Incidentalomas

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EVALUATİON OF LIFE STYLE AND ANTHROPOMETRIC PARAMETERS IN
PATIENTS WITH NONFUNCTIONAL ADRENAL INCIDENTALOMAS