1–34 maintained iCa levels for 2 hours after administration above that of Cinacalcet-HCl (AUC±SD (mmol/L).hr from baseline, 0.076 ±0.047 and 0.168±0.0874, t-test P=0.0289) but then levels fell and recovered as for Cinacalcet-HCl alone. Subcutaneous doses of both fusions were able to abrogate the effects of Cinacalcet-HCl from 4hrs post dose onwards giving a prolonged response, with iCa levels quicker to return to baseline levels at 48hrs compared to Cinacalcet-HCl. The AUC±SD (mmol/L).hr from baseline for iCa over 72 hours was 3.93±1.4 for Fusion-1, 5.0±2.7 for Fusion-2 & 10±2.8 for Cinacaclet-HCl and were significantly reduced for both fusions compared to Cinacalcet-HCl alone (t-test P = 0.0028 & P = 0.019, respectively) and not significantly different from vehicle only.

Conclusions: Cinacalcet-HCl behaved as expected in terms of iCa lowering (2). PTH maintained iCa but only for 2 hours. Both PTH fusion molecules showed a delayed and prolonged response and reduced the impact of Cinacalcet-HCl induced low iCa levels from 4hrs to 24hrs. These data provide proof of concept for long acting biological activity of these novel PTH fusion proteins.

References:

1. Shimizu M, Joyashiki E, Noda H, Watanabe T, Okazaki M, Nagayasu M, et al. Pharmacodynamic Actions of a Long-Acting PTH Analog (LA-PTH) in Thyroparathyroidectomized (TPTX) Rats and Normal Monkeys. J Bone Miner Res. 2016;31(7):1405–12.

2. Nemeth EF, Heaton WH, Miller M, Fox J, Balandrin MF, Van Wagenen BC, et al. Pharmacodynamics of the type II calcimimetic compound cinacalcet HCl. The Journal of pharmacology and experimental therapeutics. 2004;308(2):627–35.

Pediatric Endocrinology

UNDERSTANDING AND TREATING PEDIATRIC GROWTH DISORDERS

Diagnosis of Severe GH Deficiency in Newborns: New Reference Range for the Preterm and Confirmation of the GH Cut-Off

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Introduction

Inborn severe GHD is caused by rare disorders of pituitary morphogenesis or function and frequently associated with additional pituitary hormone deficiencies. Affected newborns commonly present with recurrent hypoglycemia; therefore early diagnosis and therapy is warranted. The GH content of the newborn screening card is a reliable indicator of severe neonatal GHD. Here, we studied the GH content in screening cards and the history of 25 newborns with severe GHD. In addition, we determined the reference range of the GH content in screening cards from 282 healthy preterm newborns.

Patients and Methods

Since 2010, a total of 110 screening cards from hospitalized ill newborns were sent to our laboratory for measuring GH content. Using a questionnaire we obtained relevant clinical information from senders in 61 cases. Severe GHD was defined by the presence of recurrent neonatal hypoglycemia with either a significant cerebral MRI morphology or two additional pituitary hormone deficiencies. In addition, the GH content of screening cards from 282 healthy newborns born preterm with a gestational age at birth from 34.0 to 37.9 weeks was prospectively analyzed. The GH concentration of the eluate from the screening card was measured by a highly sensitive ELISA (Mediagnost, Germany); the GH serum concentration was calculated.

Results

In 25 patients, the definition of severe GHD of the newborn was fulfilled; based on recurrent hypoglycemia in combination with ectopia of the neurohypophysis in 17, septum pellucidum agenesis plus opticus hypoplasia in two, severely hypoplastic pituitary gland in two, and combined TSH and ACTH deficiency with no cMRI findings in four newborns. Five newborns with severe GHD were preterm. The median GH concentration of the term newborns with severe GHD (n=20) was 3.9 µg/l (range; 1.1 to 11.8). This was significantly below the previously reported reference data from healthy term newborns (n=269) (median 16.4 µg/l; 95% reference range 7.0 to 39.4) (p<0.001). Using ROC plot analysis a GH serum concentration of 7.0 µg/l was identified as cut-off with the highest accuracy (90.0% sensitivity and 98.7% specificity). The median GH concentration of the 5 preterm newborns with severe GHD was 7.7 µg/l (range; 2.1 to 9.9). The newly determined 95% reference range for healthy newborns born preterm with a gestational age from 34.0 to 37.9 weeks (n=282) spanned from 7.9 to 41.1 µg/l with a median of 20.3 µg/l.

Conclusions

A GH content below 7.0 ng/ml in the newborn screening card identified severe GHD with 90% sensitivity and 98.7% specificity. In preterm newborns, the lower limit of the 95% reference interval was by 0.9 µg/l higher than in term newborns. The newborn screening card is a valuable source for the diagnosis of GH deficiency in newborns and young infants.

Neuroendocrinology and Pituitary

HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

Osteocalcin and Exercise Improve Mood and Cognition in Female Mice with High-Fat Diet Induced Type 2 Diabetes.

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The skeleton has been characterized as an endocrine organ, demonstrating a capacity to modulate cognition, mood and energy homeostasis (1,2). These endocrine actions of the skeleton have been attributed to the osteoblast-derived peptide osteocalcin. In mice, uncarboxylated osteocalcin (ucOCN) decreased the acquisition of type 2 diabetes mellitus (T2DM) and ameliorated depressive- and anxiety-like behaviours (1,2). Clinically, T2DM patients present with reduced serum osteocalcin levels and approximately 1 in 4 also suffer from co-morbid depression (3,4). The cognitive and metabolic benefits of ucOCN are similar to the