Effects and Limitations of Cinacalcet Therapy In Neonatal Severe Hyperparathyroidism

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Conclusion

Cinacalcet offers an option to treat neonatal severe hyperparathyroidism (NSHPT) resulting from inactivating mutations in the calcium-sensing receptor (CaSR) gene and postpone parathyroidectomy.

Laboratory parameters and ultrasound of the kidneys have to be closely monitored in order to prove the effect of the therapy and avoid side effects.
Additional factors affecting hypercalcemia and calcium sensing should be considered.

Background

NSHPT has been associated with inactivating mutations of the CaSR gene.
Impaired inhibition of PTH secretion by extracellular ionized calcium and decreased urinary excretion of calcium can lead to severe hypercalcemia in the first days of life.
Calcium responsiveness of the CaSR is amplified by type 2 calcimimetic agents like cinacalcet, which has been able to normalize PTH and calcium levels in cases of NSHPT and postpone parathyroidectomy[1,2].

Case Report

A full-term female newborn presented with severe respiratory distress due to thoracic and pulmonary hypoplasia at birth and hypotonia and failure to thrive in the following weeks.

On the sixth day of life the serum calcium level was elevated to 3.27 mmol/l (N: 2.10-2.65). Further evaluation showed hyperparathyroidism (iPTH 790 pg/ml, N: 15-65) in the presence of low urinary calcium excretion.

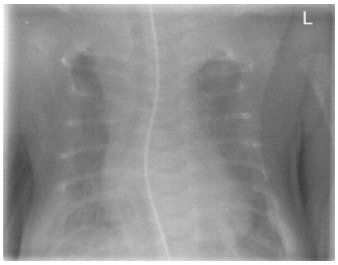


Figure 1: Thoracic hypoplasia

Sequence analysis of the CaSR gene revealed a heterozygous de novo mutation in exon 4 (c.554G>A; p.Arg185Gln).

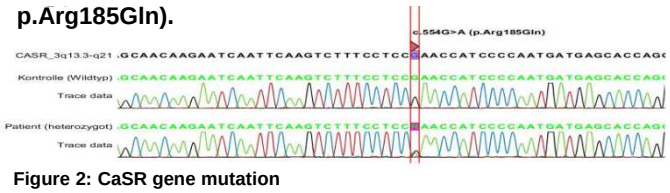
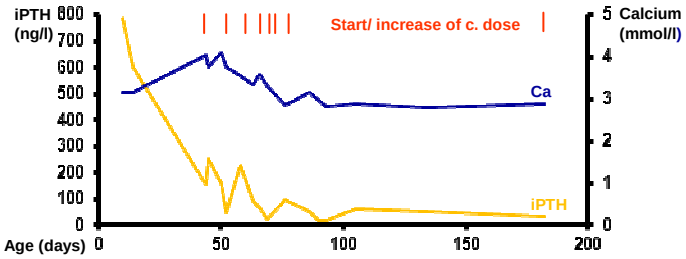


Figure 2: CaSR gene mutation

Intravenous hydration, diuretics and a single dose of pamidronate (0.5 mg/kg) did not show relevant effects on serum calcium levels.

While cinacalcet therapy was able to normalize PTH secretion and increase urinary excretion of calcium, serum calcium levels remained elevated and the patient developed nephrocalcinosis (stage 2a). After a gradual increase of cinacalcet from 10 to 80 mg/m² and cessation of vitamin D prophylaxis due to elevated 25-OH-vitamin D3 calcium levels were maintained below 2.90 mmol/l and nephrocalcinosis improved (stage 1).

Figure 3: Course of calcium and iPTH with cinacalcet therapy



Discussion

The mutation above has been associated with NSHPT that has successfully been treated with cinacalcet experimentally[1,2]. A dosage has not been established for this indication and long-term effects on kidneys and other organs are unknown.

In the presence of normal PTH levels and increased urinary calcium excretion other mutations have been discussed to additionally impair calcium sensing in patients who do not reach eucalcemia. Vitamin D prophylaxis might also influence calcium levels.

References

1: Reh CMS, Hendy GN, Cole DEC, Jeandro DD (2011): Neonatal Hyperparathyroidism with a Heterozygous Calcium-Sensing Receptor (CASR) R185Q Mutation: Clinical Benefit from Cinacalcet. J Endrocrinol Metab 96: 707-712.
2: Gannon AW, Monk HM, Levine MA (2014): Cinacalcet Monotherapy in Neonatal Severe Hyperparathyroidism: A Case Study and Review. J Clin Endocrinol Metab 99: 7-11.