

# Non-surgical treatment of diazoxide-resistant of early diffuse hyperinsulinism using long-acting (LA) octreotide, a somatostatin analog: follow-up of six cases

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## OBJECTIVES

Some cases of severe diffuse hyperinsulinism resist to diazoxide which inhibits insulin secretion by its action on the sulfonurea receptor (SUR). Subtotal ablation of the pancreas has been largely practiced but may induce serious complications (local complications, pancreatic exocrine insufficiency, diabetes mellitus). An alternative could be the administration of another drug inhibiting insulin secretion, such as octreotide, a long-acting analog of somatostatin. The aim of this study is to evaluate the efficacy and the tolerance of octreotide in this situation.

## METHODS

Hyperinsulinism is considered before the association of hypoglycaemia (glycaemia < 0.40 g/l) and a titrable insulin, and contingently C peptide. Its diffuse character is asserted according to a diffuse fixation <sup>18</sup>F-DOPA-PET/CT scan. Differential diagnostic work-up in the search of the cause of hyperinsulinism was done for every patient. Patients had been before treated by oral diazoxide, subcutaneous glucagon and glucose supplements. Diazoxide-resistance was defined by the persistence of hypoglycemia despite the administration of a dose of diazoxide equal or more than 15 mg/kg/d.

Octreotide was initially administered subcutaneously through a pump and then monthly through its a long-acting form. Subcutaneous octreotide administration was started not later than one month after the revelation of the illness. Its maximal dose ranged from 40 to 60 µg/kg/d and its minimal one from 30 to 40 µg/kg/d. Intramuscular long-acting octreotide relay was started from 2 months to 2 years and three months after the initiation of the subcutaneous form. Its maximal dose was 38 to 60 µg/kg/d. One patient is still under the subcutaneous form because she is still a baby of 4 months.

Continuous subcutaneous monitoring of glucose (CGMS) has been realized several times in every patient during cycles of seven days from year 2012.

## PATIENTS

Six patients, 3 females and 3 males have been recruited into the study, with hypoglycemia revealed by faintness or convulsions in the immediate neonatal period (3 cases) or later at 6-7 months of life (3 cases). At time of diagnosis, glycaemia ranged from undetectable to 0.33 g/l and insulinaemia from 4.4 to 94 mU/l. A mutation in pancreas potassium channels was found in all cases, one homozygous for ABCC8 gene, one composite heterozygous for this gene, three heterozygous for it and finally one heterozygous for KCNJ11. Follow-up of the patients ranged from the age of 4 months to 15 years and 1 month.

## RESULTS

**Efficacy:** Hypoglycemic episodes (glycemia less than 0.50 g/l, down to 0.24 g/l) could not completely be prevented by octreotide administration, but CGMS proved them to last concurrently less than 7% of the total time, inciting the medical staff to optimize the nutritional support and to adapt the octreotide posology.

As possible complications of hyperinsulinism, no obvious mental delay was noticed, cardiac ultrasound examination did not reveal any cardiomyopathy, 2 patients became obese (BMI: 3 and 3.4 DS) and abdominal ultrasound examination showed 2 cases of hepatomegaly suggesting steatosis.

**Follow up :** the oldest 15 years old patient developed a persistent hyperglycemia (>2.5 g/l), despite very low somatostatin doses attesting the spontaneous evolution towards diabetes.

**Adverse effects of octreotide:** One patient developed several gallstones, a known complication, needing surgery. Except for one patient, whose height was at - 1.7 SDS, growth was about the average values for age (this is paradoxical since octreotide has been used for treating tall stature, through the inhibition of growth hormone secretion).

## CONCLUSIONS

- 1) Administration of octreotide by an intramuscular monthly injection is an efficient and safe alternative to subtotal pancreatectomy in severe diazoxide-resistant diffuse hyperinsulinism, the present study being characterized by the longest follow-up ever described.
- 2) CGMS constitutes an important progress in the surveillance of the illness and allows to titrate octreotide doses and adapt nutritional support.
- 3) Abdominal ultrasound examination has to be regularly performed in the search of gallstones
- 4) The disease may at long term spontaneously, slowly progress towards diabetes

## REFERENCES

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