

Consensus of the French Endocrine Society

## Treatment: Symptomatic treatment of hypoglycaemia<sup>☆</sup>

*Traitement symptomatique d'une hypoglycémie*<sup>◇</sup>

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### 1. Medical treatment of insulinoma-related hypoglycaemia

The treatment of choice for insulinoma is surgical resection, which, when complete, abolishes hypoglycaemia. Medical treatment may nevertheless be indicated awaiting surgery or when surgery is impossible or incomplete (metastatic insulinoma). We will not discuss here the management of acute hypoglycaemic episodes (glucose administration) but only review medical treatments to control hypoglycaemia. Antitumoural treatments for metastatic malignant insulinoma are discussed in another article.

#### 1.1. Diazoxide

##### 1.1.1. Rationale of diazoxide treatment

Diazoxide, a non-diuretic benzothiadiazine derivative, is a non-specific ATP-dependent potassium channel agonist; it inhibits insulin secretion, which mainly accounts for its hyperglycaemic effect [1]. It also has a strong, notably venous, vasodilatory action, which accounts for its initial indication in the management of high blood pressure [1].

##### 1.1.2. Diazoxide in glycaemia control of insulinoma

In insulinoma and adults, published data are limited to case reports or very small series. However, diazoxide is

frequently used preoperatively when glucose administration fails to prevent hypoglycaemia, or to allow discharge home awaiting surgery. Dosage usually begins at 5 mg/kg per day and is then adapted to the glycaemic response. The effect is almost immediate (< 60 min) and observed for several hours [1]. Diazoxide binds strongly to plasma proteins and is eliminated by the kidney, mainly non-metabolised; elimination half-life is between 24 and 36 hours in adults. Diazoxide is marketed in France as Proglycem<sup>®</sup>, in two presentations: 25 and 100 mg. Two or three doses per day, initially low and then adapted to efficacy, are usually prescribed. It is restricted to hospital prescription.

Diazoxide is foetotoxic in animals and therefore contraindicated during pregnancy, unless maternal hypoglycaemia is life-threatening to the foetus. There is no evidence of transmission to breast milk.

The main side-effects (sodium and water retention and hirsutism) are dose-dependent and may appear after a few days' treatment. Thiazidic diuretics have a variable and moderate hyperglycaemic effect to increase the diazoxide effect while combating sodium and water retention.

Data for long-course use of diazoxide in hypoglycaemia mainly come from paediatric series of hyperinsulinism of varying aetiology. Data for long-term use in adults are sparse, based mainly on one single-centre series [2] and a British survey published in 1997 [3]. Diazoxide seemed to achieve control in most cases, but sometimes at the cost of high dosage with unacceptable side-effects. Goode reported results in 18 patients treated with diazoxide at doses of 40 to 1,500 mg per day for periods of between 3 weeks and 11 years [2]; in such a heterogeneous series, efficacy is difficult to judge but the authors reported that glycaemia control was "good" in 44% of cases, "moderate" in 33% and "poor" in 22%. Side-effects were frequent (15/18 patients): basically hirsutism, sodium and water retention (oedema and weight gain), and more rarely digestive disorder (nausea and abdominal pain); there was one case of Stevens-Johnson syndrome. Certain side-effects seem to be specific to young children: notably pulmonary arterial hypertension

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<sup>☆</sup> Hypoglycemia in non-diabetic patient.

<sup>◇</sup> L'hypoglycémie chez le patient non diabétique.

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[2]. A postal survey conducted in 1996 in the UK, where diazoxide prescription is under nationwide monitoring, described 40 patients treated for insulinoma, more than half of whom were over 70 years of age [3]; mean treatment duration was 7 years, ranging from 1 to 22 years; the main reason for prescription was failure to locate the insulinoma and failure of first-line surgery. Side-effects were as above, but considered minor and not requiring interruption or modification of dosage, although in almost half the cases a thiazidic diuretic was associated to the diazoxide. Long-course diazoxide prescription in case of failure or impossibility of surgery is thus feasible and apparently effective, although quantitative data are lacking for efficacy to be determined with precision or predictive factors of success or failure to be identified.

## 1.2. Somatostatin analogues

### 1.2.1. Rationale of treatment by somatostatin analogues (octreotide, lanreotide)

The theoretical rationale for using somatostatin analogues for glycaemia control in insulinoma is:

- various subtypes of somatostatin receptors are expressed by insulinoma cells: it has been studied in vitro in surgical human insulinoma specimens using various techniques: RT-PCR, radiolabelled agonist binding, and immunohistochemical revelation by specific antibodies. However, only a small number of insulinomas have been studied so far; the largest series [4–6] showed expression of subtype 2 (SSTR2), which is the main target of the presently available agonists, in 40% to 60% of insulinomas, although often less intensely than in most other digestive endocrine tumours. Of the other types of somatostatinergic receptors; subtype 5 seems to be the most frequently expressed, which may provide a rationale for using specific agonists that are in development but not yet available in this indication, such as pasireotide [4,5,7];
- in vivo studies using OctreoScan, which has an affinity for SSTR2 similar to that of octreotide, have been variable, with 24 to 60% positive results. Some, however, may have underestimated the prevalence of positive OctreoScans because of their methodology (planar slices, without SPECT) [4,6,8–11].

### 1.2.2. Octreotide in glycaemia control of insulinoma

Most published findings are case reports. Long-term glycaemia control has been reported in both benign and malignant insulinoma, usually by multiple daily subcutaneous octreotide injections [12–20]. These case reports demonstrate the feasibility of controlling inappropriate secretion of insulin, but publication bias in favour of positive results makes it impossible to estimate the real frequency of insulinoma responding to the available somatostatin analogues. Only two reports from one group have reported short- and long-term (> 6 months) analogue treatment, in a cohort of 21 patients [6,11]. In most cases, treatment was multiple daily octreotide by subcutaneous route or

more rarely continuous subcutaneous infusion or in long-acting form. The results may be summed up as follows:

- 60% of patients showed short-term control of hypoglycaemia, which persisted at lower frequency in others (partial responders);
- requisite dosage varied greatly between patients, from 50 to 2,000  $\mu\text{g}/\text{day}$ . Case-by-case adaptation is therefore indispensable;
- in short-term responders, there was no real tachyphylaxis during long-term treatment, although dose adjustment may be required;
- glycaemia control did not correlate with insulinoma size, contrarily to somatotrophic adenoma;
- octreoScan results were poor predictors of glycaemic response, with discordance in 50% of cases. Scintigraphy did not select patients for treatment response;
- glycaemic response to 6-hour acute octreotide test was more predictive of medium-term response, although the number of patients studied was too small for the test to be recommended for clinical practice (concordance in six out of eight cases);
- side-effects were minimal and tolerance was generally good, as in other indications for somatostatin analogues (digestive intolerance with diarrhoea).

The available somatostatin analogues thus provide a solution, efficiently controlling symptoms in about one half of patients. It is, however, important to note the rarely described fact that hypoglycaemia may actually be worsened by treatment, via a physiopathologic mechanism which remains unclear but may involve inhibition of glucagon secretion [21]. Over resolution of severe symptomatic hypoglycaemia, which is the prime objective, medium to long-term nycthemeral and ambulatory glycaemic control is hard to judge. Continuous glucose monitoring (CGMS) could improve assessment of treatment effects, especially at night-time and in case of loss of sensitivity to hypoglycaemia [22].

## 1.3. mTOR signalling pathway inhibition

### 1.3.1. Rationale of treatment by mTOR inhibitors

mTOR cell protein is a metabolic sensor which acts as a regulator, triggering or stopping cell growth and proliferation according to cellular nutritional status [23,24]. mTOR inhibitor molecules have recently been developed as anti-neoplasia agents. The rationale behind their application in insulinoma is antitumoural, mTOR overexpression being frequent in digestive endocrine tumours [25], and metabolic effects: physiologically, mTOR activation increases insulin production and, in human pathology, mTOR inhibitors often induce hyperglycaemia via a variety of physiopathologic mechanisms that are not fully understood but involve peripheral muscular and hepatic insulin resistance and reduced insulin secretion [26,27].

### 1.3.2. Glycaemic control in insulinoma by mTOR pathway inhibitors

Ten reports of mTOR inhibitors such as everolimus or rapamycin 2 in malignant insulinoma causing severe hypoglycaemia have recently been published [21,25,28–30]. The main common points are:

- pharmacologic inhibition of mTOR by everolimus dosed at 5 to 10 mg/day was remarkably effective in abolishing or significantly improving hypoglycaemia, where frequently associated agents such as diazoxide, somatostatin analogues, thiazide diuretics, etc. were systematically ineffective;
- the kinetics of this hyperglycaemic effect is unclear, but in some reports began within a few days of treatment [25,30];
- the hyperglycaemic effect appeared to be chronic, without tachyphylaxis, in follow-up extending to 1 year;
- resolution of hypoglycaemia may not be accompanied by any noticeable decrease in tumour size.

Several mechanisms may underlie the hyperglycaemic action of mTOR inhibitors in patients with insulinoma. The study that tried to analyse them, by frequent measurement of glycaemia, C peptide, insulin and pro-insulin with 18FDG-PET assessment of muscle glucose uptake, pointed on the one hand to direct inhibition of insulin secretion by the tumour tissue and on the other hand to reduced peripheral glucose uptake, notably in muscle [25].

Published data, however, are very sparse, counselling caution. Nevertheless, mTOR inhibition appears to be a promising indication in difficult situations where resecting the insulin-secreting tissue and controlling hypoglycaemia by classic pharmacologic agents is not possible.

### Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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