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Long-term treatment of persistent hyperinsulinaemic hypoglycaemia of infancy with diazoxide: a retrospective review of 77 cases and analysis of efficacy-predicting criteria

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Abstract Primary persistent hyperinsulinaemic hypoglycaemia of infancy is rare. Diazoxide treatment remains the mainstay of medical therapy in long-term management. We reviewed 77 cases of primary persistent hyperinsulinism in neonates and infants who were treated with diazoxide and studied criteria predictive of therapeutic efficacy. The only criterion identified was age at manifestation. All but 1 of the 31 neonatal cases were unresponsive to diazoxide. Responsiveness increased with age: 12 of 39 early-infantile cases, and all seven late-infantile cases were diazoxide-responsive. In responders, a diazoxide dose of 10–15 mg/kg per day was always effective, suggesting an "all or none" response. Diazoxide-resistant hyperinsulinism is characterized by its severity with higher plasma insulin levels. The analysis of 46 surgically treated patients showed that the efficacy of diazoxide is not related to the aetiology of the pancreatic lesions. In six cases, after many years of management, diazoxide treatment was stopped without recurrence of hypoglycaemia.

Conclusion Diazoxide is an efficient treatment in the long-term management of most persistent hyperinsulinaemic hypoglycaemia of infancy revealed in infants and children but is usually ineffective in neonatal forms. Drug efficacy does not correlate with anatomical lesions. Medical treatment can sometimes be stopped after many years of management without recurrence of disease manifestations.

Key words Hyperinsulinism · Hypoglycaemia · Diazoxide · Sulphonylureas · Management

Abbreviations *PHHI* primary hyperinsulinaemic hypoglycaemia of infancy · *DZX* diazoxide

Introduction

Primary persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) is a rare disorder which is currently difficult to treat [22, 27]. Treatment is important because of the high risk of neurological damage. Although many regimens and drugs have been proposed to control glycaemia, diazoxide (DZX) remains the main orally available medication for long-term management which

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may prevent the need for pancreatectomy [7]. We reviewed 77 cases of PHHI in neonates and infants who were treated with DZX and studied criteria predictive of therapeutic efficacy. Due to the progress in imaging localisation of hypersecreting pancreatic regions by pancreatic venous catheterisation [6, 16, 27], an increasing number of our DZX sensitive patients have been treated by limited surgery in recent years, allowing us to study correlations between histopathological findings and DZX effectiveness.

Patients and methods

All patients showed inappropriately high levels of insulin (> 8 mU/l) at times of hypoglycaemia (blood glucose < 2.4 mmol/l in neonates and < 2.8 mmol/l in infants and children). The diagnosis of PHHI was also based on sharp response of hypoglycaemia to 0.5 mg in glucagon (increase in blood glucose by more than 50%) [8] and on glucose requirements of more than 14 mg/kg per min (far above the hepatic glucose production) to maintain normoglycaemia.

Our therapeutic approach was as follows. Patients were initially treated with symptomatic measures including iv glucose, mostly delivered to neonates via a central venous line, and/or high oral intake by nasogastric drip, in order to maintain blood glucose ≥3 mmol/l. Various diets and sequential medical treatment such as glucagon, somatostatin and hydrocortisone, were used in some cases.

DZX treatment was assessed in all recipients. We used 15 mg/kg per day in three divided doses initially for at least 5 days. Because of frequent asymptomatic hypoglycaemia, DZX efficacy was defined as the normalization of blood glucose levels (≥3.0 mmol/l) measured before and after each meal in patients fed normally, after stopping iv glucose and any other medications for at least 5 consecutive days. Two confirmed episodes of hypoglycaemia in such a 24 h glucose cycle led us to consider the patient as DZX-unresponsive and to restart continuous drip feeding and/or other measures to regain permanent normoglycaemia. When DZX treatment at 15 mg/kg per day was effective, the dose was reduced to the effective minimum.

The following clinical criteria were assimilated: age at clinical manifestation, birth weight, and time between onset and diagnosis (a potential indicator of the severity and frequency of hypoglycaemia). We also reviewed plasma values of insulin and glucose when measurements were done with the same method. We found 392 joint glycaemia-insulin assays in which glucose levels were less than 2.8 mmol/l. To assess only inter-individual variations, we also analysed the first sample when measurements were done without theraphy which could alter the glycaemia level, and 51 assays in 51 patients were then assessed.

Blood glucose was measured by a glucose oxidase method and serum circulating insulin levels by radioimmunoassay (Phadeseph Insulin RIA, Kabi Pharmacia Diagnostics, Uppsala, Sweden).

Statistical analysis used the non parametric Mann-Whitney U test.

Patients

During the last 10 years, we have treated 77 patients (68 French cases, 9 referred from other countries: Italy, Tunisia, Morocco) with PHHI, aged from birth to 14 years. Two patients, with late infantile onset of PHHI, were sisters. The others were sporadic. The age distribution of the patients at the onset of symptoms is shown in Fig. 1. Thirty-one patients had their first symptoms before 48 h of life, 46 after 1 month. None of our patients had initial symptoms beginning between 48 h and 1 month of life.

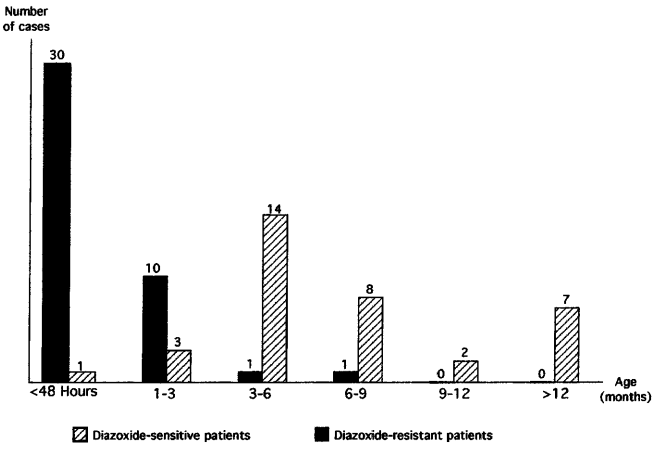

Fig. 1 Diazoxide response according to age at onset of symptoms in 77 patients affected with persistent hyperinsulinaemic hypoglycaemia of infancy

Of our patients, 40% (31/77) had severe neonatal hyperinsulinism, with initial hypoglycaemia occurring before 48 h of life (< 24 h in 21). The initial manifestations in these neonatal-onset forms were seizures in 51% (16/31), non specific signs (cyanosis, pallor, hypotonia, hæmodynamic disorders etc) in 29% (9/31), and routine glycaemia tests in asymptomatic neonates in 19% (6/31).

The 46 patients in whom the symptoms began after the 1st month of life were classified as having "late-onset" forms. Of these, 39 (85%) had first symptoms before 1 year (early infantile forms), and only seven patients (15%) developed symptoms after 1 year (late infantile forms). The main presenting symptoms in this "late-onset" group were seizures in 32/46 (70%) or seizure-equivalent symptoms (absence, loss of consciousness, twitching etc) in 9/46 (20%). Only 5/46 (10%) were diagnosed without convulsive disorders because of non-specific signs (limpness, tremor, irritability, pallor or behaviour disorders).

Most patients (62/77) underwent radiological examination with pancreatic venous catheterisation [6, 16]. Because of ineffectiveness of medical treatment and/or signs of local hypersecretion on radiological examination, surgical treatment became necessary in 46 cases (27 of 31 neonatal forms, 16 of 39 early infantile forms, three of seven late infantile forms). When infants were treated surgically, the pancreas was analysed histologically and classified according to published criteria [11, 17, 19] which distinguish between diffuse hyperplasias, focal hyperplasias and adenoma-like lesions. The latter include classical adenomas and focal adenomatous hyperplasias. In our patients, we identified diffuse hyperplasias in 22 of 46 (48%) patients (16 neonates, 6 early infantile forms), focal hyperplasias in 13 of 46 (28%) patients (6 neonates, 6 early infantile forms, 1 late infantile form), and adenoma-like lesions in 7 of 46 (15%) patients (4 neonates, 1 early infantile form, 2 late infantile forms). In four cases (9%), histological examination was not done or was inconclusive.

Of neonates, 62% (16/26) displayed diffuse hyperplasia. Among infants and children, the frequency of focal lesions (7/13 before 1 year, 4/4 after 1 year) may be overestimated as surgery was mainly offered to patients with radiological findings in favour of focal hypersecretion.

Results

Of the 77 patients, 35 responded to DZX. Effectiveness was highly age-dependent. Only 1 of 31 patients with a neonatal form was clearly responsive to DZX. Among the 39 early infantile forms, 12 were unresponsive and 27

were responsive. All seven late infantile forms were responsive. Figure 1 shows the age distribution of the DZX-sensitive and -resistant infants. DZX sensitivity clearly increased with age, and most patients over 3 months at the onset of hypoglycaemia were responsive.

Table 1 summarizes clinical parameters related to DZX responsiveness. Age at onset of PHHI was significantly different between these two groups. A shorter time between onset and diagnosis in the unresponsive patients may reflect more frequent and more severe hypoglycaemia. Birth weight was analysed since neonatal hyperinsulinism is classically associated with macrosomy. Nine of the 31 neonatal forms, and 6 of the 46 late-onset forms, had a birth weight >4.000 g, and mean birth weight was in the upper normal range for gestational age. No significant difference was found between neonatal-onset and late-onset forms, or between DZX-responsive and -unresponsive patients.

Table 1 Clinical characteristics and response to diazoxide treatment in 77 hyperinsulinaemic infants and children. Median and range values are given. Correlation analysis using Mann Whitney U test

	Responsive $n = 35$	Unresponsive $n = 42$	P
Age at first signs (months)	6.0 1 m–13 y	0.1 0–9 m	0.0001
Birth weight (g)	3410 2010–4350	3380 2250–4900	0.38
Time to diagnosis (months)	2.0 0–30	0.1 0–26	0.014

Table 2 Plasma levels of glucose, insulin, and the insulin/glucose ratio during acute hypoglycaemia (<2.8 mm/l) in infants and children affected with PHHI. Comparison of diazoxide-sensitive and resistant patients. Mean ± standard error are given. Correlation analysis using Mann Whitney U test

	Responsive $n = 21$	Unresponsive $n = 30$	P
Glycaemia (mmol/l)	1.90 ± 0.70	1.94 ± 0.57	0.98
Insulinaemia (μU/ml)	15.8 ± 11.6	40.5 ± 88.3	0.037
Insulin/glucose	11.0 ± 13.4	20.0 ± 32.3	0.06

Table 2 compares biochemical findings related to DZX efficacy. Blood glucose and insulin levels, and the insulinaemia/glycaemia ratio were studied on 51 samples collected when blood glucose was <2.8 mmol/l. During these episodes of hypoglycaemia, a similar level of glycaemia but a higher level of insulinaemia was found in DZX-unresponsive patients. We also studied 392 samples collected during the survey from the 77 patients when blood glucose was <2.8 mmol/l. In this larger number of measurements, mostly under medical treatment, DZX-unresponsive patients had significantly higher blood insulin levels ($P<0.01$) and insulin/glucose ratios ($P<0.001$). Insulinaemia was also higher in DZX-unresponsive than in DZX-sensitive patients with only the non neonatal form (19.8 ± 1.8 μU/ml vs 15.8 ± 0.8 μU/ml, $P<0.05$).

Figure 2 shows the outcome of the 77 PHHI patients. Only 34 of the 42 DZX-unresponsive hyperinsulinaemic patients were surgically treated because of persistent severe hypoglycaemia despite other medical treatment. Eight DZX-unresponsive patients were medically treated (frequent meals, uncooked cornstarch, glucocorticoids). Twelve DZX-sensitive patients also underwent surgery of whom 10 were treated surgically because venous catheterisation showed radiological evidence of focal lesions. In one case, effective DZX therapy had to be stopped because of immuno-allergic haematological manifestations. In another case, the parents could not accept the marked DZX-induced hirsutism.

In these 46 surgically-treated patients, histological findings showed no clear link to DZX responsiveness. Table 3 compares pathological anatomy with DZX

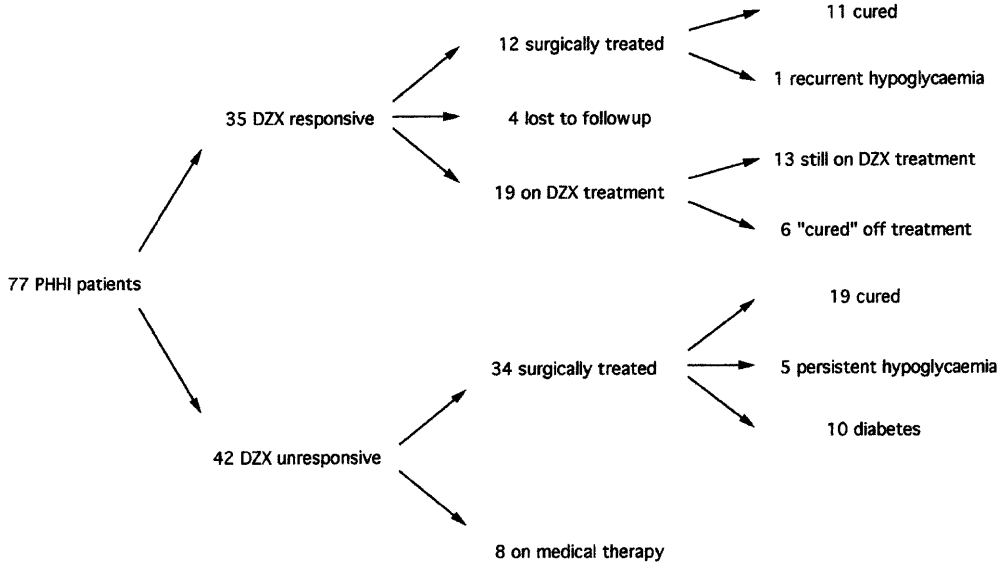

Fig. 2 Outcome of 77 patients affected with persistent hyperinsulinaemic hypoglycaemia of infancy. (*DZX* Diazoxide)

Table 3 Pathological lesions in 46 surgically treated patients related to pre-operative sensitivity to diazoxide. [*DZX* Diazoxide, *S* sensitivity *R* resistance, *ND* not determined (anatomical examination not done or inconclusive)]. Adenomas-like = focal adenomatous hyperplasia [5] in 4 neonatal and 1 early-infantile cases, and classical adenomas in the 2 children with late-onset PHHI

	DZX	Diffuse hyperplasia	Focal hyperplasia	Adenoma-like	ND
Neonates ($n = 31$)	S	0	0	0	0
	R	16	6	4	1
Early infancy ($n = 39$)	S	4	3	0	2
	R	2	3	1	1
Late infancy ($n = 7$)	S	0	1	2	0
	R	0	0	0	0

effectiveness in the 46 patients. Among the 34 DZX-resistant patients, 14 had focal lesions: 9 focal hyperplasias, 5 focal adenomatous hyperplasia [17]. Of the 12 DZX-sensitive patients, 6 had focal lesions (4 focal hyperplasias, 2 adenomas).

Among the DZX-responsive patients, the effective dose was always lower than 15 mg/kg per day. When treatment was ineffective at this dosage, resistance always persisted despite higher doses. The maximal prescribed dose was 10.8 ± 2.7 mg/kg per day in DZX-sensitive patients, and 14.0 ± 4.9 mg/kg per day in DZX-resistant patients. The tolerability of DZX was usually excellent. The main adverse effect was hirsutism in almost every case, but this was the reason for withdrawal treatment in only one case. Haematological side-effects (immuno-allergic neutropenia) occurred in two patients and caused the therapy to be stopped in one.

Most of the DZX-sensitive patients were treated for long periods. None of them has became secondary refractory to DZX therapy. As many patients were referred from other countries, 4 have been lost to followup. Of the other 15, 9 are still on DZX. The weight-adjusted dose has usually been slowly reduced with age (never less than 5 mg/kg per day).

Six patients have been able to discontinue treatment without recurrence of hypoglycaemia. All were in the late-onset group (age at first symptoms: 3.5 to 12 months). Age at the withdrawal of treatment ranged from 5 years 2 months to 10 years. The time off treatment without recurrence of hypoglycaemia is now more than 2 years in these six patients. None of the analysed criteria could differentiate these six patients from others at the onset of PHHI.

Discussion

PHHI may be divided into two clinical forms:

1. An early neonatal form, which is usually severe and manifests with recurrent, profound and refractory hypoglycaemia. Diagnosis is easy. DZX is usually ineffective, and must be tried with other aggressive methods to prevent hypoglycaemia. Therapies such as glucagon [3] or somatostatin analogues [10, 24] may temporarily be of help. Surgery may be required rapidly, after transient hyperinsulinism has been ruled out.
2. The second clinical subtype which always begins after the neonatal period, is usually less severe. Hypoglycaemia may be less frequent and diagnosis can be difficult. DZX is usually the treatment of choice.

DZX inhibitory action is mediated through a receptor that acts by modulating the activity of ATP-sensitive K^+ channels, suggesting that the drug interacts with the final stages of insulin exocytosis in beta cells [9]. Insulin secretion also involves calcium channels and treatment using calcium channel blocking agents has also been suggested to modify insulin exocytosis in beta cells [15]. Efficacy is not yet established.

DZX has a long half-life (18 to 24 h, more in neonates), and 5–8 days of treatment are required before judging its effect. Because hypoglycaemia is frequently asymptomatic in infants, effectiveness has to be checked by repeat blood glucose measurements. When effective, glycaemia usually normalizes within 2–4 days after beginning treatment. We found that doses higher than 15 mg/kg per day are not helpful. The usually effective dose is around 10 mg/kg per day.

Age at diagnosis is the only clinical factor predictive of sensitivity to this drug. The shorter diagnosis delay and the higher plasma insulin levels in DZX-unresponsive patients may point to more severe hyperinsulinism. The age range and DZX sensitivity of our patients may not be typical of all PHHI patients however, because neonates and infants with severe intractable PHHI are more often referred to specialized units such as ours. This probably leads to an underestimation of the frequency of late onset DZX-sensitive forms.

In our series, only one infant with neonatal-onset PHHI responded to DZX. High frequency of DZX-resistant PHHI in neonates has been suggested [2, 4, 12, 21] and confirmed by our study.

We found no correlation between the response to DZX and morphological findings using the criteria described by Rahier et al. [11, 17, 19]. Histological features were similar in DZX-sensitive and -resistant patients, with 41% of focal lesions in the resistant group and 50% in the sensitive group.

The reason for DZX resistance in neonates is unknown. We found that the nature of anatomical lesions was not the cause. We also found that DZX-

resistant forms were clinically and biologically more severe, suggesting that the severity of hyperinsulinism might be involved. However, when patients underwent surgery, we observed no case in which a surgical reduction in insulin secretion restored DZX sensitivity. A pharmacological reason, such as progressive maturation of cytochrome P450 which is involved in the metabolism of the drug, could be advocated, but this seems unlikely given the fact that resistance usually persists for many years, i.e. long after cytochrome P450 is mature.

Rotenstein et al. [18] have advocated combination of cyproheptamide with DZX. We tried this treatment in six infants with DZX-resistant hyperinsulinism, but without success.

Tolerance of DZX is usually excellent. The most frequent adverse effect is hirsutism, which can be sometimes marked and distressing in young children. Haematological side-effects like immuno-allergic neutropenia occurred in two of our patients and may disrupt the treatment. DZX has been reported to cause troublesome fluid retention [1], essentially in neonates after iv infusion of the drug at a high dose (> 15 mg/kg per day). This effect usually regresses when the dose is reduced and, if necessary, thiazide diuretics are added. We never observed this adverse effect, probably because we used the oral form of DZX at a dose of less than 15 mg/kg per day in three divided doses. Other reported side-effects, such as neurological symptoms (extra-pyramidal syndrome) and cardiomyopathy have not been observed in our patients.

When medical treatment is ineffective, most authors [20, 25, 28] recommend near-total pancreatectomy to avoid recurrent intractable hypoglycaemia and prevent brain damage. It is often a blind procedure with a high risk of persistent, albeit often attenuated, hypoglycaemia if inadequately complete, and a high risk of long-term complications like diabetes mellitus and pancreatic exocrine insufficiency if excessive.

There are few reports on long-term DZX therapy. Most authors have reported recurrence of hypoglycaemia when DZX is withdrawn [13]. In contrast, treatment may be discontinued after some years [12, 14, 23]. Grant et al. [12] were able to stop treatment in seven of nine patients (onset of hypoglycaemia: 2–8 months) between the ages of 2.7 and 14 years. This underlines the possibility that some patients can enter spontaneous remission. We do not know the nature of the anatomical lesions in these patients but this calls for care before deciding on extensive pancreatectomy in hyperinasulinaemic infants. In DZX-responsive PHHI we stop treatment every 2 years and check blood glucose and insulin levels from 3 to 7 days after arrest. In our experience, most hypoglycaemic recurrences are observed within 7 days after withdrawal of the drug. This attitude, however, would need to be assessed in a future prospective and systematic study.

PHHI is a heterogeneous group of diseases [22]. The recent elucidation of molecular defects in diffuse and focal forms of PHHI [5, 19, 26] will probably highlight in the future the molecular basis of DZX response. At present the only factor predictive of responsiveness to DZX treatment is age at the onset of hypoglycaemia. Because of their severity, most neonatal forms are operated on at an early age, and we do not know if they might become sensitive with age. This, and the possibility of spontaneous remission after many years of medical therapy, raises questions as to the indications for extensive surgery.

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