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Safety Results from OCAPI: A European Observational Cohort Study of Insulin Glulisine-treated Children Aged 6–12 Years with Type 1 Diabetes

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Key words
- diabetes mellitus
- type 1
- children
- insulin glulisine
- safety
- hypoglycaemia

Abstract

Objective: Data on the safety of insulin glulisine for type 1 diabetes are limited in paediatric populations. The European post-marketing Observational prospective Cohort study of children with type 1 diabetes treated with APIDRA® (OCAPI) study evaluated the safety of insulin glulisine in children aged 6–12 years in real-life clinical practice, with a particular focus on the 6–8 years age group.

Research design and methods: OCAPI was an international, multicentre, observational, non-interventional, prospective cohort study, in which 94 participants with type 1 diabetes (6–8 years age group: n=31; 9–12 years age group: n=63) received insulin glulisine for 6 months under normal, local conditions. The primary objective was the incidence of severe hypoglycaemia in all participants.

Results: Overall incidence of severe hypoglycaemia was 6.6 events per 100 persons/year (7.2 and 6.3 events per 100 persons/year in the 6–8 and 9–12 years age groups, respectively). 12 participants (all aged 9–12 years) experienced transient injection-site reactions. No systematic hypersensitivity reactions were reported. Only 1 participant (9–12 years age group) experienced a serious class-effect risk possibly related to insulin glulisine (severe hypoglycaemia requiring an Emergency Department visit). Glycated haemoglobin levels did not change markedly throughout the study, and were inversely proportional to the risk of hypoglycaemia.

Conclusions: Insulin glulisine has a good safety profile in children with type 1 diabetes aged 6–12 years, with generally low rates of severe hypoglycaemia and few adverse reactions. These results are encouraging for its use in paediatric populations.

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Introduction

Intensive insulin therapy is recommended in people with type 1 diabetes (T1DM) to reduce the risk of long-term microvascular complications, but strict glycaemic control may increase the risk of experiencing a hypoglycaemic event [1]. In addition, intensively treated children with T1DM experience an increased risk of hypoglycaemia compared with intensively treated adults, which could be linked to irregularities in diet and exercise [2], and possibly a reduced ability to recognise or relay symptoms. The incidence of severe hypoglycaemia in paediatric populations with T1DM treated with a variety of insulins has been reported as 4.8 to 84 events per 100 persons/year [3–12].

Insulin glulisine (APIDRA®, Sanofi) is a rapid-acting, mealtime insulin analogue for adults with type 2 diabetes (T2DM) or adults and children ≥6 years old with T1DM, and its efficacy and safety profiles have been well characterised in adults [13–16]. Danne et al. [17] previously investigated the basic science (pharmacokinetics and postprandial blood glucose excursions) of insulin glulisine in a small paediatric population, concluding that the rapid-acting properties and safety of insulin glulisine demonstrated in adults was also observed in children. However, data regarding the safety of insulin glulisine in paediatric populations are currently limited and larger studies are needed to further investigate the safety of this insulin in children.

The European post-marketing Observational prospective Cohort study of children with type 1 diabetes treated with APIDRA® (OCAPI) study addresses the need to increase understanding of the safety of insulin glulisine in children in real-life practice. The objective of the OCAPI study was to evaluate the safety profile of insulin glulisine in children with T1DM aged 6–12 years, with a particular focus on the 6–8 years age group.

Materials and Methods

OCAPI study design and population

OCAPI was an international, multicentre, observational, non-interventional, prospective cohort study with a 6-month follow-up. Determination of sample size was based on a conservative expectation that the severe hypoglycaemia rate would be 25–45 events per 100 persons/year, with a standard deviation (SD) of 94–170. For an event rate of 25 or 45 severe hypoglycaemia events per 100 persons/year, a total of 120 participants aged 6–12 years would be required to achieve a 95% confidence interval (CI) with a precision of ± 17 (i.e. 8;42) or ± 30 (i. e. 15;75), respectively; the corresponding precision rates for the 6–8 years age group (n = 60) would be ± 24 and ± 43, respectively. The sample size also took into consideration the European Medicines Agency (EMA) requirement to follow an average of 100 participants for 6 months. Therefore, it was estimated that 120 participants, treated with insulin glulisine for at least 6 months, would be required. To achieve these final numbers, a total of 132 people with T1DM were to be enrolled in the OCAPI study, to account for potential dropouts.

The study was initially implemented in 30 centres in 9 countries (Bulgaria, Denmark, France, Germany, Ireland, the Netherlands, Poland, Spain and the United Kingdom). Due to low recruitment rates, it was decided to extend recruitment to 4 additional countries (Austria, Hungary, Portugal and Switzerland). Recruitment difficulties, especially in the 6–8 years age group, led to the study being stopped early, with a total of 94 participants recruited instead of the planned 132 initially estimated to be needed to achieve the required 120 participants with 6 months' follow-up. This protocol change was authorised by the EMA and the Committee for Medicinal Products for Human Use (CHMP).

This study was conducted in accordance with the principles expressed by the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments. Each participating country ensured that all necessary regulatory submissions (including permission from Institutional Review Boards and Independent Ethics Committees) were performed in accordance with local regulations, including those regarding data protection.

Inclusion criteria were as follows: children aged 6–12 years at inclusion; diagnosed with T1DM, and on stable insulin regimen at study entry for at least 3 months; naïve for insulin glulisine and prescribed insulin glulisine at study entry, as decided by the treating physician; and signed written informed consent obtained from parent(s)/guardian(s) and, if applicable, from children. Exclusion criteria were: T2DM; treatment with oral anti-diabetic drugs at any time from diagnosis, or with premixed insulins in the last 3 months; insulin pump treatment in the last 3 months; history of pancreatectomy, pancreas and/or islet cell transplants; treatment with any investigational drug in the last month; parent(s)/guardian(s) unable to understand the nature and scope of the cohort study, unable to read and write, or unlikely to comply with the protocol, e. g. displaying inability or unwillingness to complete the participant diaries; children or relatives of the physicians, research assistants, study coordinator or other staff directly involved in the conduct of the protocol; and an employee of the Sponsor or of the Sponsor's representatives.

Demographic and clinical data were recorded for each participant, including age, gender, glycated haemoglobin (HbA_{1c}), medical history, diabetes history, insulin regimen and class-effect risks. HbA_{1c} values were assessed at local laboratories and information regarding the method of measurement was not available. Participant's data were recorded at inclusion (the study visit, at which insulin glulisine was prescribed), and after 3 (update 1) and 6 (update 2) months of treatment with insulin glulisine. The following class-effect risks occurring during the on-treatment period were considered as adverse events: severe hypoglycaemia (symptomatic hypoglycaemia with at least one of the following characteristics were considered as severe: hypoglycaemia associated with loss of consciousness, hypoglycaemia associated with seizure, hypoglycaemia requiring visit to the Emergency Department or admission to hospital for treatment); symptomatic documented hypoglycaemia (all symptomatic hypoglycaemia with a plasma glucose value ≤ 3.9 mmol/L [70 mg/dL], generally measured from capillary samples using a plasma-calibrated glucose meter, were considered); injection-site reactions; systemic hypersensitivity reactions; and medication error.

Study outcomes

The primary outcome of interest was the incidence of severe hypoglycaemia in all participants. Secondary outcomes included the incidence of severe hypoglycaemia in the 6–8 years age group and the incidence of symptomatic documented hypoglycaemia, injection-site/systemic hypersensitivity reactions, and the change in HbA_{1c} in the total study population and in the 6–8 years age group.

Statistical and descriptive analyses

Demographic and clinical data are described overall and by age class. During data validation, missing values were followed-up to retrieve all possible relevant information, thus minimising missing data. The remaining missing data were handled in the following ways: hypoglycaemia with a missing onset date was considered as occurring during the on-treatment period; severe hypoglycaemia with a missing plasma glucose value was considered as symptomatic documented hypoglycaemia; and missing upper limit values of HbA_{1c} were replaced by '6%' in the calculation of normalised HbA_{1c}. No imputation of missing data was performed for other parameters.

Hypoglycaemia incidence in the current study was calculated as the number of documented hypoglycaemic events × 100/the sum of on-treatment duration for all participants in years. In published studies, the incidence of hypoglycaemia is often provided as events per person/month. Such estimates were converted to an incidence in events per 100 persons/year by using a multiplication factor of 1 200. CIs for hypoglycaemia incidence estimates were calculated using an exact method, assuming that the number of hypoglycaemic events had a Poisson distribution. In addition, as a *post-hoc* analysis, the relationship between the number of symptomatic documented hypoglycaemic events and the last measurement of HbA_{1c} by age group was characterised by a Poisson regression curve with a log-link function and the logarithm of the period duration as offset.

Results

A total of 94 participants (31 participants in the 6–8 years age group and 63 participants in the 9–12 years age group) were recruited into the study. All participants except one were naïve for insulin glulisine at the start of the study; this individual was prescribed insulin glulisine 5 months before study entry, but was included in the analyses because retrospective data were available. Baseline characteristics are summarised in **Table 1**.

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Table 1 Baseline, demographic, anthropometric and metabolic characteristics.

	6–8 years (n = 31)	9–12 years (n = 63)	Total (6–12 years) (n = 94)
age (years) [a]	7.3 (0.9)	10.5 (1.0)	9.4 (1.8)
male, n (%)	12 (38.7)	26 (41.3)	38 (40.4)
weight (kg) [a]	28.6 (4.8)	40.1 (9.1)	36.3 (9.6)
age-specific BMI z-score (kg/m^2) [a,b]	0.57 (0.98)	0.46 (0.94)	0.49 (0.95)
diabetes duration (years) [c]	1.0 (1.0; 3.0)	2.0 (1.0; 4.0)	2.0 (1.0; 3.0)
HbA_{1c} [a] (%) (mmol/mol)	8.05 (1.21) 64 (13.2)	8.37 (1.52) 68 (16.6)	8.26 (1.42) 67 (15.5)

[a] Mean (standard deviation [SD]); [b] LMS (Lambda-Mu-Sigma) adjusted; [c] Median (Q1; Q3)

Table 2 Current total insulin regimen at inclusion and update 2.

	6–8 years (n = 31) n (%)	9–12 years (n = 63) n (%)	Total (6–12 years) (n = 94) n (%)
Current at inclusion [a]			
injections per day			
2	2/31 (6.5)	7/63 (11.1)	9/94 (9.6)
3	1/31 (3.2)	2/63 (3.2)	3/94 (3.2)
4	21/31 (67.7)	32/63 (50.8)	53/94 (56.4)
5	7/31 (22.6)	12/63 (19.0)	19/94 (20.2)
6	0/31	9/63 (14.3)	9/94 (9.6)
7	0/31	1/63 (1.6)	1/94 (1.1)
insulin dose per day (U/kg)			
n	30	61	91
mean (SD)	0.83 (0.28)	0.82 (0.27)	0.82 (0.28)
Current at update 2			
injections per day [b]			
3	2/26 (7.7)	11/54 (20.4)	13/80 (16.3)
4	18/26 (69.2)	22/54 (40.7)	40/80 (50.0)
5	6/26 (23.1)	13/54 (24.1)	19/80 (23.8)
6	0/26	7/54 (13.0)	7/80 (8.8)
7	0/26	1/54 (1.9)	1/80 (1.3)
Insulin dose per day (U/kg)			
n	24	53	77
Mean (SD)	0.87 (0.25)	0.94 (0.27)	0.92 (0.26)

[a] The study visit, at which insulin glulisine was prescribed; [b] The number of injections is missing for participants for whom 'insulin regimen' is not completed: 13 participants who withdrew before or on the day of the update, and 1 participant for whom the update was performed but the 'insulin regimen' was not completed; SD, standard deviation

Insulin treatment regimen: 29 participants (11 in the 6–8 years age group and 18 in the 9–12 years age group) had a duration of diabetes of less than 1 year. The insulin regimen at inclusion and at update 2 is summarised in **Table 2**. No obvious change in the number of insulin injections was observed over the study period, whereas the mean (SD) total daily insulin dose increased from 0.82 (0.28) U/kg at inclusion to 0.92 (0.26) U/kg at update 2.

Severe hypoglycaemia incidence: The overall incidence of severe hypoglycaemia in the study was 6.6 events per 100 persons/year (**Table 3**), corresponding to 3 participants experiencing a severe hypoglycaemic event during the study period. The incidence of severe hypoglycaemia in children aged 6–8 years and 9–12 years was 7.2 and 6.3 events per 100 persons/year, respectively (**Table 3**).

Table 3 Incidence rate of severe and symptomatic documented hypoglycaemia.

	6–8 years (n = 31) [c]	9–12 years (n = 63)	Total (6–12 years) (n = 94)
Severe hypoglycaemia			
at least one event, n (%)	1 (3.3)	2 (3.2)	3 (3.2)
incidence rate [a] (95% CI) [b]	7.2 (0.2; 40.4)	6.3 (0.8; 22.9)	6.6 (1.4; 19.4)
Symptomatic documented hypoglycaemia			
at least one event, n (%)	25 (83.3)	47 (74.6)	72 (77.4)
incidence rate [a] (95% CI) [b]	7007.2 (6572.5; 7463.2)	5717.5 (5456.4; 5987.8)	6110.4 (5884.8; 6342.3)

[a] Per 100 persons/year; [b] Exact method using Poisson distribution; [c] 1 participant with information missing in the 6–8 years age group (no follow-up available)

Symptomatic documented hypoglycaemia incidence: The overall incidence of symptomatic documented hypoglycaemia was 6110.4 events per 100 persons/year (**Table 3**). In children aged 6–8 years and 9–12 years, the incidence of symptomatic documented hypoglycaemia was 7007.2 and 5717.5 events per 100 persons/year, respectively (**Table 3**).

Class-effect risks: Few class-effect risks other than symptomatic documented hypoglycaemia were observed in the study population. Only 12 participants (all aged 9–12 years) experienced injection-site reactions, and these were generally transient. No participants presented with systematic hypersensitivity reactions. **Table 4** summarises class-effect risks. Only 1 participant (in the 9–12 years age group) experienced a serious class-effect risk (severe hypoglycaemia requiring a visit to an Emergency Department) that was deemed to be possibly related to insulin glulisine. Class-effect risks led to discontinuation of insulin glulisine for only 3 participants (once due to symptomatic documented hypoglycaemia and twice due to injection-site reactions), all aged 9–12 years.

Change in HbA_{1c}: Mean (SD) HbA_{1c} in the total population at last recorded measurement was 8.25 (1.50) % (67 [16.4] mmol/mol). In children aged 6–8 years and 9–12 years, mean HbA_{1c} at last recorded measurement was 8.06 (1.36) % (65 [14.9] mmol/mol) and 8.34 (1.57) % (68 [17.2] mmol/mol), respectively. The change in HbA_{1c} between inclusion and last recorded measurement in the 6–8 years and 9–12 years age groups was −0.05 (1.34) % (0.5 [14.6] mmol/mol) and −0.08 (1.46) % (−0.9 [16.0] mmol/mol), respectively. The relationship between the last measurement of HbA_{1c} (%) and symptomatic documented hypoglycaemia per 100 persons/year during the OCAPI study is shown in **Fig. 1**.

Discussion

The results of the OCAPI study demonstrate that rates of severe hypoglycaemia in children with T1DM treated with insulin glulisine are generally low, and that treatment results in few adverse reactions. The OCAPI study was an observational study, aiming to enhance knowledge of insulin glulisine use in real-life practice – the study was non-interventional, so did not aim to affect treatment in any way. This may be one explanation for why

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Table 4 Incidence of class-effect risks.

	6–8 years (n = 31)[b]	9–12 years (n = 63)	Total (6–12 years) (n = 94)
Any class-effect risk, n (%)	25 (83.3)	49 (77.8)	74 (79.6)
Any class-effect risk leading to discontinuation of insulin glulisine, n (%)	0 (0)	3 (4.8)	3 (3.2)
Any serious class-effect risk[a], n (%)	1 (3.3)	2 (3.2)	3 (3.2)
Any serious class-effect risk[a] possibly related to insulin glulisine, n (%)	0 (0)	1 (1.6)	1 (1.1)

[a] Serious class-effect risk – any injection-site reaction, hypersensitivity reaction or hypoglycaemic event achieving seriousness criteria; [b] 1 participant with information missing in the 6–8 years age group (no follow-up available)

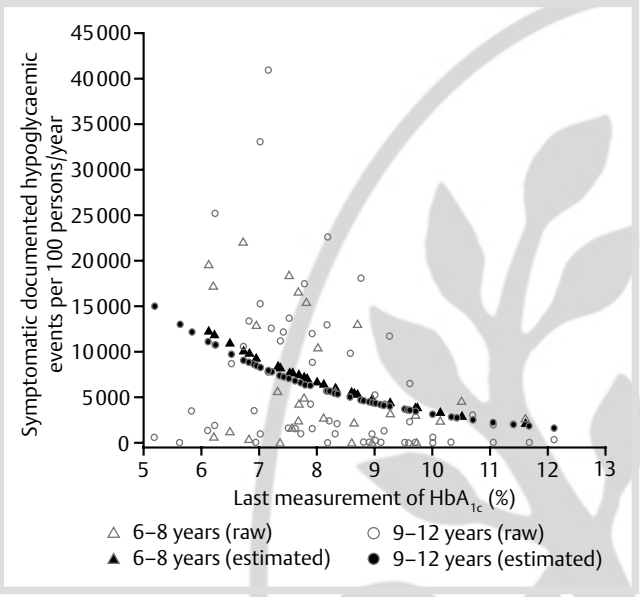

Fig. 1 Raw and estimated number of symptomatic documented hypoglycaemic events per 100 persons/year vs. last measurement of HbA_{1c} (%) in the OCAPI study, by age group (6–8 years [n = 29] and 9–12 years [n = 61]). Data estimated using a Poisson regression model.

HbA_{1c} levels did not change markedly throughout the study period. Another explanation could be linked to the fact that insulin glulisine is a relatively new drug, and a lack of familiarity with it may have caused clinicians to be less aggressive in the doses of insulin prescribed, compared with a more established treatment. It is likely that the relatively short period of time that insulin glulisine has been available for prescription has contributed to the large proportion of participants in this study who had a very short duration of diabetes, which may again have affected how aggressively their diabetes was treated.

The incidence of severe hypoglycaemia in the OCAPI study was in the lower range of estimates that have been previously reported in paediatric populations (4.8–84 events per 100 persons/year) [3–12], although it should be noted that this estimate is based upon only 3 severe hypoglycaemic events. A small change in the number of events could therefore have a relatively large impact upon the event rate reported. When making comparisons between different studies, it is also important to consider changes in glycaemia management over time. Although strict glycaemic control can be associated with an increased risk of hypoglycaemic events ([1] and **Fig. 1**), rates of severe hypoglycaemia in children and adolescents with T1DM have shown a decreasing trend over the last decade despite relatively stable HbA_{1c} levels, which may be attributable to improved and more intensive clinical practice [8]. The fact that different paediatric centres are used in different studies must also be taken into account when comparing data between published reports. As demonstrated by the Hvidoere study [18], HbA_{1c} and the frequency of severe hypoglycaemia can differ significantly between treatment centres, even in children less than 11 years of age. Even considering these potentially confounding factors, however, the incidence of severe hypoglycaemia observed in the OCAPI study is likely comparable to that seen in earlier studies.

The overall incidence of symptomatic hypoglycaemia in OCAPI was marginally greater than estimates of 3504 to 5880 events per 100 persons/year reported in 3 previous studies [9, 19, 20]. These figures, however, should be interpreted with caution, as estimates of symptomatic hypoglycaemia are typically prone to self-reporting bias. This problem is further enhanced in paediatric populations, as young children may struggle with awareness and reporting of hypoglycaemia, so it is possible that the figures reported are underestimates. The use of continuous glucose monitoring, as implemented in the PRESCHOOL study [21], would provide more accurate symptomatic hypoglycaemia estimates.

Another limitation to the accuracy of the hypoglycaemia incidence estimates, both symptomatic and severe, reported in the OCAPI study, may be the relatively small sample size. For example, the estimates of symptomatic hypoglycaemia may have been inflated by 4 participants who each experienced over 100 events; removing these 4 participants from the analysis reduces the symptomatic hypoglycaemia incidence estimate to 5076 events per 100 persons/year.

The results of the OCAPI study demonstrate that the incidence of both severe and symptomatic hypoglycaemia appears higher in the 6–8 years age group compared with the 9–12 years age group – this trend of increasing hypoglycaemia risk with decreasing age was expected and is similar to that seen in previously published studies [2, 12]. Overall, the hypoglycaemia incidence estimates from the OCAPI study are representative of insulin use in children in general. In addition, the fact that the incidence estimates for hypoglycaemia in people with T1DM treated with insulin glulisine are similar to estimates in people treated with other types of insulin would suggest that hypoglycaemic events in children under tight glycaemic control are not necessarily related to the type of insulin used, but may be linked more closely to other factors, such as education.

In conclusion, the results of the OCAPI study confirm the preliminary findings of Danne et al. [17], showing that insulin glulisine has a good safety profile in children aged 6–12 years with T1DM. The incidence of severe hypoglycaemic events was in the lower range of estimates from previously published reports in paediatric populations, and treatment resulted in few adverse reactions. These results have implications for the intensive treat-

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ment of children with T1DM, and in particular are encouraging for the use of insulin glulisine in paediatric populations.

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