Access to emergency room for hypoglycaemia in people with diabetes

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Abstract

Background Hypoglycaemia is a major burden of the pharmacological therapy of diabetes and is associated with increased morbidity, mortality and treatment costs.

Methods We screened all admissions to the emergency room of the Pisa University Hospital from 1 January 2009 to 31 December 2013, selecting individuals with a discharge diagnosis of hypoglycaemia. We retrieved 500 admissions involving adult diabetic patients: age 71 ± 16 years; M/F 50.2/49.8%; 70.2% type 2 diabetes (T2DM).

Results Among T2DM, 42.2% were on insulin, 10.8% on insulin plus oral anti-diabetes drugs and 38.2% on oral anti-diabetes drugs alone (92% sulphonylureas/glinides ± insulin-sensitizers). Glibenclamide was the most frequently used sulphonylurea (69%). Individuals treated with oral anti-diabetes drugs were older than those on insulin (79 ± 11 versus 74 ± 12 years; p < 0.0001). Among patients taking sulphonylurea, 47% had estimated glomerular filtration rate <60 mL/min/1.73 m² and 13.5% had <30 mL/min/1.73 m². In-hospital admission occurred in 20% of cases. Hospitalized patients with T2DM were older than those discharged (80 ± 10 versus 76 ± 12 years, p < 0.01) and were on oral antidiabetic drugs in 54.8% of the cases, whereas 35.7% were on insulin (χ², p < 0.0001) and 8.3% on combined therapy. Notably, 93.5% of those on oral anti-diabetic drugs were taking a secretagogue. Insulin-treated subjects were younger than those treated with oral anti-diabetic drugs alone (77 ± 12 versus 82 ± 7 years; p < 0.02). The mean in-hospital annual mortality rate was 85 deaths per 1000 patients-year.

Conclusions Our results support the recommendation that the risk associated with insulin and insulin-secretagogues should be carefully assessed, particularly when prescribed in vulnerable patients with T2DM. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords hypoglycaemia; emergency room; type 2 diabetes; sulphonylurea

Introduction

Achieving good glycaemic control to minimize the risk of diabetic microvascular and macro-vascular complications in type 1 (T1DM) [1,2] and type 2 diabetes (T2DM) [3,4] is considered cost effective because the cost of...
treatment is offset by reduced expense of treating complications and because of better quality of life [5,6]. Nonetheless, multiple hurdles hamper the achievement and maintenance of long-standing glycaemic control. Hypoglycaemia is one of the main obstacles [7,8] and a major burden of pharmacologic therapy of diabetes [9] exposing individuals to excess risk of morbidity [10] and mortality [11] and aggravating the cost of treatment [12]. In a large survey including 2046 diabetic patients, Alvarez Guisasola et al. [13] found that approximately 38% reported symptoms of hypoglycaemia, an event more likely to occur in those with macro-vascular complications and limited physical activity. These persons had significantly lower treatment satisfaction scores and were more likely to report barriers to treatment adherence.

In spite of this, hypoglycaemia remains an under-appreciated condition in T2DM patients who are commonly considered at lower risk as compared to T1DM subjects. Yet the literature data show that there is no such a striking difference in the rate of hypoglycaemia between insulin-treated T2DM and T1DM individuals [14].

Even more underestimated remains the frequency and the consequences of hypoglycaemia associated with the use of oral anti-diabetic drugs (OADs) in spite of the fact that even mild hypoglycaemic events may represent a potential risk in vulnerable persons, a cause of loss in quality of life, and a source of increased direct and indirect costs of diabetes.

One reason for diabetes-related expense is the need to refer to the emergency room (ER) because of severe hypoglycaemia. With respect to this, we have performed a retrospective analysis to determine the characteristics of hypoglycaemic events requiring admission to the ER of our community hospital.

**Materials and methods**

We have screened all admissions to the ER of the ‘Nuovo Ospedale Santa Chiara’ in Pisa from 1 January 2009 through 31 December 2013 of subjects with a diagnosis of hypoglycaemia (ICD9-CM 251.0, 251.2, 250.8). Age, gender, lab tests, any available diagnosis for known pathologic conditions, pharmacologic treatments and triage assignment [15] were collected, and diabetes was identified using the ER electronic database.

All individuals taking OADs (sulphonylureas/glinides alone or in combination with an insulin-sensitizer and/or insulin) have been classified as T2DM. Insulin-treated patients for whom type of diabetes was not specified have been classified as ‘unknown diabetes type’. When no information on therapy was available, the electronic database of the local diabetes outpatient clinic was interrogated, and, if the person was identified, the last recorded therapy was annotated. Glomerular filtration rate (eGFR) was evaluated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [16]. The study received the approval from the local Ethics Committee.

All statistical analyses were performed using the **STATVIEW** software (SAS Institute; Cary, NC) and referred to recorded episodes of hypoglycaemia. Continuous measures are expressed as mean ± SD, except for variables with non-normal distribution that are expressed as median (range). Discrete variables are reported as count and/or percentage. Statistical significance was tested by unpaired Student’s t-test or χ² test as appropriate. Logistic regression analysis was used to estimate the association between the risk of hospitalization (dependent variable) and the risk factors (independent variables). In the model, age and eGFR were included as nominal variables (age ≥75 years and eGFR < 60 mL/min/1.73 m²), while other variable, like insulin or secretagogue use, was dichotomized as present or absent. Results from this analysis are presented as odds ratio with 95% confidence intervals. p values < 0.05 were considered statistically significant.

**Results**

During the survey period, out of a total of 417,280 admissions to the ER, 553 were recorded as severe hypoglycaemia (defined as an event requiring assistance of another person to actively administer carbohydrates and glucagon or take other corrective actions) occurring in a total of 443 individuals (Figure 1). The vast majority of the events (n = 500, 90.4%) occurred in people with diabetes (n = 401; mean age 71 ± 16 years, range 18–103 years; M/F 50.2/49.8%). Table 1 shows baseline characteristics of the diabetic population. Repeated admission to ER for hypoglycaemia occurred in 59 diabetic subjects (158 events) and in three individuals without diabetes (14 events). Of 48 events (8.7%) occurring in non-diabetic subjects, two were related to alcohol intake with or without concomitant use of cocaine, 15 were classified as reactive hypoglycaemia, two due to dumping syndrome, six occurred in highly compromised patients with renal and heart failure, seven had no known reasons and three were due to assumption of wrong medication or use of insulin as an anabolic agent. Two events were related to exercise or scare food intake and 11 to current or prior cancer including a case of insulin-secreting adenoma, one neuro-endocrine tumour of the pancreas and one neuroendocrine tumour of the stomach. These events were not included in subsequent analysis.
Among diabetic patients, 70.2% had T2DM, 13.2% T1DM, 5.2% had secondary diabetes and in 11.4% type of diabetes was unknown (Table 1). T2DM patients were older than T1DM (77 ± 11 versus 44 ± 15 years; \( p < 0.0001 \)) with 62% of the former being ≥75 years old. One or more co-morbidities were present in 365 events (73%), including cardiovascular (36%), renal (35%), respiratory disease (18%), cancer (4%) and psychiatric disorders (22%). Cognitive impairment (cognitive decline, vascular encephalopathy and Alzheimer’s disease) was confirmed in 88 events (17.6%).

The vast majority of diabetic patients (86.5%) arrived to the ER by ambulance, whereas the remaining 13.5% used other forms of transportation (personal vehicle, helicopter in two cases and police car in another one). By triage, 66% of diabetic subjects were classified as having an emergent condition. In particular, 6% were defined critical, that is, with life-threatening condition requiring immediate access to care (red code) and 60% as moderately critical patient with risk of evolution and potential life-threatening condition (yellow code). In 42 cases, people were unresponsive at the time of admission, and in 37 cases, individuals reported loss of consciousness at home although they were responsive at the time of arrival at the ER. A history of recurrent hypoglycaemia was identified in 34% of the subjects. Symptoms associated with hypoglycaemia are reported in Table 2. Association with trauma was present in 12 cases (2.4%) and with road accidents in two cases (0.4%).

Mean capillary blood glucose (\( n = 196 \)) before transportation to ER was 2.2 ± 1.6 mmol/L (40 ± 29 mg/dL), while at the time of ER, admission average plasma glucose level was 4.6 ± 2.9 (83 ± 52 mg/dL; \( n = 478 \)). Capillary blood glucose readings at ER admission were ≤3.9 mmol/L (70 mg/dL) in 51% of the cases and ≤2.8 mmol/L (50 mg/dL) in 31%. Hypoglycaemia was initially treated at home (with or without external help) by oral carbohydrates or intramuscular glucagon injection in 79 cases (16%), while 190 cases (38%) received treatment, both at home and during transportation to the ER, either with oral carbohydrates, intravenous glucose or intramuscular glucagon injections. Additional intravenous glucose treatment upon admission to ER was required in 377 cases (75%).

Among T2DM patients, 42.2% were on insulin monotherapy, while 10.8% were on insulin plus OADs (18% glibenclamide or repaglinide; 58% metformin, or DPP-4 inhibitor or acarbose; 24% sulphonylurea/glinide and metformin). Among individuals on OADs, 31% were on insulin secretagogues mono-therapy (sulphonylurea 19%, repaglinide 12%), while 61% of the events occurred in people using a secretagogue together with insulin-sensitizers. Metformin mono-therapy, or metformin plus DPP-4 inhibitor or pioglitazone was used by 8% of the subjects (Figure 2). Type of sulphonylurea was recorded in 107 out of 111 cases with glibenclamide being most commonly used (69%), followed by glimepiride (20%), gliclazide (8%) and others (3%). No information on anti-diabetes therapy was available in 8.8% of cases.

Table 1. Clinical characteristics of people with diabetes requiring ER admission for hypoglycaemic events

| Male/female | 251 (50.2)/249 (49.8) |
| Age (M ± SD) | 71 ± 16 |
| Type of diabetes | |
| Type 1 DM | 66 (13.2) |
| Type 2 DM | 351 (70.2) |
| Secondary diabetes | 26 (5.2) |
| Non-specified type of diabetes | 57 (11.4) |
| Type of treatment | |
| Insulin alone | 277 (55.4) |
| Oral anti-diabetic drug alone | 134 (26.8) |
| Insulin + oral anti-diabetic drug | 50 (10.0) |
| No treatment/non-specified | 39 (7.8) |
| Glomerular filtration rate (M ± SD) | 64 ± 32 |
| >60 mL/min/1.73 m² | 213 (54.8) |
| 60–30 mL/min/1.73 m² | 108 (27.8) |
| 29–15 mL/min/1.73 m² | 34 (8.7) |
| <15 mL/min/1.73 m² (dialysis, %) | 34 (8.7) (5.7) |

Table 2. State of consciousness and symptoms in people with hypoglycaemia admitted to emergency room

| Symptoms reported in ER records (people with diabetes) | n (%) |
| Unresponsive patient | 42 (8.4) |
| At home loss of consciousness | 37 (7.4) |
| No loss of consciousness ever | 421 (84.2) |
| Altered mental status | 81 (16.2) |
| Neuro-vegetative symptoms | 60 (12) |
| Seizures | 44 (8.8) |
| Presyncope | 27 (5.4) |
| Other neurologic signs | 51 (10.2) |
| Falls | 17 (3.4) |

People on OADs were older than those on insulin (79 ± 11 versus 74 ± 12 years; p < 0.0001); among the former, those on sulphonylureas or repaglinide were older than those treated with other OADs (81 ± 9 versus 74 ± 16 years; p < 0.005).

Calculation of eGFR was possible in 285 T2DM patients. Normal renal function was found in 47.7% of cases, while 31.9%, 10.2% and 10.2% people had an eGFR between 60–30, 29–15 and <15 mL/min/1.73 m², respectively. Seven individuals were on dialysis while 20% (T1DM = 8; T2DM = 88, other type = 4) were in hospital due to renal failure. Hospitalization was more frequent in patients on OADs than in those on insulin (32 versus 21%, p = 0.05).

Median duration of hospitalization was 6 days (range: 1–46 days) with a mean in-hospital mortality rate of 85 deaths per 1000 patients per year (0–187.5 deaths per 1000 patients per year in different years). Hospitalized T2DM patients were older than those discharged from ER (80 ± 10 versus 76 ± 12 years, p < 0.01), were more frequently on OADs (54.8%) with 35.7% on insulin (p < 0.0001, \(X^2\) between groups) and 8.3% on combination therapy. In the remaining cases, therapy was unknown. Of those on OADs, 93.5% were taking sulphonylureas or glinides. Finally, insulin-treated subjects were younger than those treated with OADs alone (77 ± 12 versus 82 ± 7 years; p < 0.02) with no significant difference in the duration of the hospitalization (7 ± 5 versus 9 ± 9 days) and mortality rates (43 and 103 deaths per 1000 patients per year, respectively).

In a logistic regression model including treatment with insulin or secretagogues, the reduction of eGFR was independently associated with the risk of hospitalization (odds ratio 2.73 (confidence intervals 95% 1.36–5.48), p < 0.005).

**Discussion**

We have retrieved all admissions for hypoglycaemia at the ER of our community hospital from 2009 and 2013. Over this 5-year time, more than 550 episodes of hypoglycaemia were recorded with the majority of them (90.4%) occurring in adult T1DM or T2DM patients. This observation confirms that severe hypoglycaemia is a relatively frequent acute metabolic complication in diabetic subjects. Considering the total number of hypoglycaemic events per the time of observation, it can be estimated that hypoglycaemia is responsible for an average of two ER accesses per week. This, however, is likely to represent just the ‘tip of the iceberg’, as already pointed out decades ago [17]. Our results are in keeping with other reports of the literature [18,19] and stress the importance of appreciating the number of ER referral because these events remain associated with both short-term [20] and long-term risk of mortality [21].

Among T2DM patients, insulin treatment (as monotherapy or in combination with OADs) was only slightly more commonly associated with hypoglycaemia as compared to OAD treatment (53 versus 38.2%). Previous studies [14,22,23] have reported that the majority of the hypoglycaemic events occur in insulin-treated patients, suggesting that insulin treatment, rather than the type of diabetes, is a main risk factor for severe hypoglycaemia. Nonetheless, T2DM patients are commonly believed to have a lower absolute risk of severe hypoglycaemia, even when they are treated with insulin. Although this may be the case in younger people and in those with short diabetes duration, with duration of the disease getting longer and with individuals growing older, hypoglycaemia becomes more common and more severe [24]. This change in the rate of hypoglycaemia has been well described in the UK Hypoglycaemia Study [25]. The study showed how the rate of hypoglycaemia in T2DM patients on insulin therapy for more than 5 years and with progressive loss pancreatic β-cell function can be as high as the one seen in T1DM patients.

An increased risk of severe hypoglycaemia associated with the use of sulphonylureas and glinides is readily apparent in our survey. Among people treated with OADs, 92% of the cases of severe hypoglycaemia occurred in individuals taking a sulphonylurea or a glinide either as mono-therapy or combination therapy. A number of severe renal impairment (77 ± 12 versus 82 ± 7 years; p < 0.02) with no significant difference in the
studies [19,26,27] and meta-analyses [28,29] have emphasized the risk of hypoglycaemia associated with these secretagogues pointing out that the risk is greater in the elderly [30] and in those with impaired liver or renal function [31]. In keeping with this, the average age of people referred to the ER because of severe hypoglycaemia while on sulphonylurea therapy was 81 ± 9 years, with 47% of them having an eGFR <60 mL/min/1.73 m². This is well in keeping with the notion that risk for hypoglycaemia increases in the presence of either diabetes or chronic kidney disease, with the risk being most pronounced in the presence of both conditions [32]. Moreover, in people treated with sulphonylureas or glinides, hypoglycaemia is likely to be more severe and duration even longer than in insulin-treated T2DM patients [20]. Because of that, caution is usually suggested in the use of secretagogues in diabetic individuals with impaired kidney function, with the recommendation to consider dosage reduction for eGFR below 30–50 mL/min/1.73 m² according to the agent in use [33]. In spite of that, 35% of our T2DM population was still on sulphonylureas or glinides. With regard to this, not only our results are in keeping with others [34–36] but they also highlight a widespread use of glibenclamide in spite of this sulphonylurea has repeatedly being shown to be associated with a marked risk of hypoglycaemia [37]. It is therefore surprising that in spite of the availability of new generation sulfonylureas and novel molecules with much less associated risk, no reduction in the number of glibenclamide-related cases can be appreciated over a 5-year period. In our survey, the rate of hospitalization was more frequent in these individuals than in those on insulin, although a lower eGFR increased the risk of hospitalization in both groups. Fadini et al. [20] have reported that hypoglycaemia due to OADs is associated with greater prevalence of coma and with longer in-hospital stay as well as greater 2-year mortality. Altogether, these findings support the need for cautious prescription of sulphonylureas and glinides in elderly people with T2DM.

The occurrence of a severe episode of hypoglycaemia can be considered a marker of vulnerability and frailty as suggested by the analysis of the results of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR-Controlled Evaluation (ADVANCE) trial [11]. It is this increased vulnerability that may well explain the increased mortality recorded among people with diabetes incurring into severe hypoglycaemia [34]. In our survey, a 2.9-fold increased mean in-hospital annual mortality rate was observed among hospitalized patients requiring ER admission for hypoglycaemia versus admitted patients with medical diagnosis-related group (DRG) (mean annual mortality rate of 85 versus 29 deaths per patient-year, p < 0.02), a result consistent with the 3.4-fold raised risk of death in diabetic patients self-reporting severe hypoglycaemia pointed out by McCoy et al. [21]. Therefore, appreciation of a severe event such as the one requiring access to an ER may well improve risk stratification.

Our observations as well as those previously reported emphasize the economic burden of severe hypoglycaemia in T2DM, particularly when requiring access to an ER. Cost estimation is not simple, and it is generally limited to estimation of direct costs. In our survey, based on the Italian Ministry of Health cost estimate for the ER access and ambulance services [38], an economic burden of almost 121,000 Euro per year can be attributed to hypoglycaemia. This costs and includes the ER access based on different triage (26,000 Euro/year) and ambulance services (95,000 Euro/year) not adding in the cost of helicopter services and police interventions. Based on this estimate, the average cost per event can sum up to 1200 Euros, a figure in line with the one reported by Frier [39] calculating the cost for treatment of hypoglycaemia by secondary-care health professional ranging from 1269 Euro in UK, to 1370 in Spain and to 2924 in Germany.

Our study has some limitation. This is a retrospective survey that may led to underestimation of the events and loss of some data on the clinical history of people requiring ER admission for a hypoglycaemia. Moreover, it is a single centre survey making up a picture of a town counting about 100,000 inhabitants, although assessing a relative long period of time (5 years). In contrast, the nature of the database (i.e. ER registry, discharge documents and local diabetes registry) can offer the advantage of a better-standardized data collection and more accurate detection of the type of diabetes. The selection bias, moreover, may be limited by the universalistic healthcare system (Beveridge type) effective in our country, as already shown by Marchesini et al. [19].

In summary, the present survey confirms that severe hypoglycaemia is a relatively frequent cause of ER admission both for T1DM and T2DM patients. The event is more common in the elderly and in those with impaired kidney function. Insulin therapy and/or use of sulphonylureas and glinides are the most common cause of severe hypoglycaemia. This conclusion is well in keeping with the recent observations of Budnitz et al. [40] showing that nearly half of the hospitalizations for adverse drug events occurred in adults >80 years of age with an equal distribution between adverse events due to insulin (13.9%) and OADs (10.7%). In conclusion, our results support the recommendation that the risk associated with insulin and even more with sulphonylureas and glinides should be carefully assessed, particularly when prescribed in vulnerable T2DM individuals.

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Conflicts of interest

S. D. P. has served on the scientific board and received honoraria for consulting fees from Novartis Pharmaceuticals, Merck Sharp & Dohme, Roche Pharmaceuticals, Eli Lilly and Co., Boehringer Ingelheim, Bristol–Myers Squibb, Astra Zeneca, GlaxoSmithKline, Sanofi–Aventis, Takeda Pharmaceuticals, Novo Nordisk and Intarcia. S. D. P. also received research support from Merck Sharp & Dohme, Takeda Pharmaceuticals and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

References


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36. Ng JM, Mellor DD, Masson EA, Allan B. Sulphonylurea as a cause of severe hypoglycaemia in the community. Prim Care Diabetes 2010; 4: 61–3.