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Hypoglycaemia with Oral Antidiabetic Drugs

Results from Prescription-Event Monitoring Cohorts of Rosiglitazone, Pioglitazone, Nateglinide and Repaglinide

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Abstract

Background: Hypoglycaemia is an acute complication associated with intensive treatment of patients with diabetes mellitus. This complication poses a major challenge in diabetes management. Furthermore, severe hypoglycaemia may be life threatening. Although hypoglycaemia is more often associated with insulin treatment, oral hypoglycaemic agents have the potential to trigger hypoglycaemia.

Aim: The aim of this study was to quantify the incidence of hypoglycaemic events and to describe the pattern of these incident events during the first 9 months of treatment with four oral antidiabetic drugs, rosiglitazone, pioglitazone, nateglinide and repaglinide, prescribed in general practice in England.

Methods: We used data collected for prescription-event monitoring (PEM) studies of rosiglitazone, pioglitazone, nateglinide and repaglinide. PEM is an observational, non-interventional, incept cohort study. Observation time for each patient and incidence rate (IR) per 1000 patient-years of treatment for hypoglycaemia was calculated for each drug cohort. Smoothed hazard estimates were plotted over time. Case/non-case analysis was performed to describe and compare patients who had at least one hypoglycaemic event in the first 9 months of treatment with those who did not.

Results: The total number of patients included in the analysis was 14 373, 12 768, 4549 and 5727 in rosiglitazone, pioglitazone, nateglinide and repaglinide cohorts, respectively. From these, 276 patients experienced at least one episode of hypoglycaemia. The IR was between 50% and 100% higher in patients receiving treatment with meglitinides compared with those treated with the thiazolidinediones (TZDs) [IR = 9.94, 9.64, 15.71 and 20.32 per 1000 patient-years for rosiglitazone, pioglitazone, nateglinide and repaglinide, respectively]. The plot of the hazard function and the estimated shape

parameter from the Weibull regression model showed that pioglitazone, nateglinide and repaglinide had non-constant (decreasing) hazards over time, whereas the hazard for rosiglitazone-treated patients was approximately constant over time. Nateglinide and repaglinide had similar shape hazard function, indicating a significantly higher number of hypoglycaemic episodes shortly after starting treatment. For women treated with TZDs, hypoglycaemia was reported more frequently than for men.

Conclusion: This analysis shows that the frequency of reported hypoglycaemia within the study cohorts was relatively low. The rates of hypoglycaemia were not equal between drug classes. Treatment with nateglinide or repaglinide was characterized by a higher incidence of hypoglycaemia at the beginning of treatment. Further investigation is necessary to assess whether women treated with TZDs are more prone to hypoglycaemia than men. Findings from this study should be taken into account with other clinical and pharmacoepidemiological studies.

Introduction

Type 2 diabetes mellitus is a very common progressive disease, characterized by chronic hyperglycaemia and metabolic disturbances resulting from reduced pancreatic insulin secretion and impaired insulin sensitivity.[1] The global burden of diabetes is estimated to approximately double between 2000 and 2030.[2] Therefore, the safety of antidiabetic drugs is an important issue.

The main risk factor for type 2 diabetes is obesity. Increased physical activity, weight reduction and appropriate diet are among the cornerstones of the treatment. The main oral glucose-lowering drugs currently available are sulfonylureas, biguanides, thiazolidinediones (TZDs), meglitinides, α-glucosidase inhibitors and, most recently, dipeptidyl peptidase-4 inhibitors. These antidiabetic drugs have different mechanisms of action; however, none of these agents target all causes of the disease.[3] Furthermore, progressive β-cell dysfunction leads to progressive loss of glycaemic control.[4] Therefore, many patients with longstanding diabetes are likely to require multiple therapies or insulin for achievement of recommended target glucose levels.[5]

Hypoglycaemia is an acute complication of intensive diabetic therapy and is thus common in patients with type 1 and insulin-treated type 2 diabetes.[6] The goal of therapy is to achieve and maintain near-normal glucose level; however, maintaining tight glycaemic control may increase incidence of hypoglycaemia. The fear of hypoglycaemia poses a major challenge for diabetes management.[7] Although hypoglycaemia is more often associated with insulin treatment, oral hypoglycaemic agents have the potential to cause hypoglycaemia especially when they are used in combination.[8]

The Drug Safety Research Unit (DSRU) has previously monitored the safety of four oral antidiabetic drugs, rosiglitazone, pioglitazone,[9] nateglinide[10] and repaglinide,[11] which are used for the treatment of type 2 diabetes.

Rosiglitazone and pioglitazone are members of the TZD drug class and are insulin-sensitizing agents. Hypoglycaemia is not listed among the frequently reported undesirable effects of treatment with TZD monotherapy.[12,13] When rosiglitazone or pioglitazone were used as monotherapy in clinical trials, the rate of hypoglycaemia was similar[14] or slightly higher[15] than that observed in the placebo group. However, in some studies when TZDs were used in combination with other oral antidiabetic drugs or insulin, an increased incidence of hypoglycaemia compared with placebo groups was reported.[4,16-18]

Nateglinide and repaglinide belong to the group of rapid-onset insulin secretagogues called meglitinides. Both agents have less potential to induce hypoglycaemia because of their short metabolic half-lives.[19] Nevertheless, hypoglycaemia is one of the most frequently reported adverse events with these drugs.[20,21]

The aim of this study was to quantify the incidence of hypoglycaemic events and to describe the pattern of these incident events over time, in the incept cohorts of diabetic patients who were prescribed these four oral antidiabetic drugs in general practice in England.

Methods

Study Design

This study quantifies the incidence of hypoglycaemia in the patients included in the prescription-event monitoring (PEM) studies of four oral antidiabetic drugs, rosiglitazone, pioglitazone, nateglinide and repaglinide. PEM is an observational, non-interventional, incept cohort technique, described in more detail previously.[22]

Patients were identified from dispensed National Health Service prescriptions issued by general practitioners (GPs) in England supplied in confidence to the DSRU by the Prescription Pricing Division of the National Health Service Business Services Authority. Collection periods for the prescriptions are given in table I. Outcome data were obtained by sending a simple questionnaire ('green form') to the prescribing GP of each patient at least 6 months after the initial prescription was issued for individual patients.

The GPs were asked for demographic details, indication for prescription, start and stop dates, reason for stopping (if the drug had been discontinued), causes of death (if applicable), events[1] occurring during and after treatment and concomitant antidiabetic therapy (except for repaglinide). All events recorded on the green forms were coded onto the DSRU database using the DSRU dictionary, which is arranged in a hierarchical system.

Hypoglycaemia was defined as an event recorded by GPs on the green forms. A patient was defined to be a case if the event 'hypoglycaemia' occurred during treatment. The higher level term (HLT) 'hypoglycaemia' in the DSRU dictionary includes the terms, hypoglycaemia, hypoglycaemic attack, hypoglycaemic episode, low blood glucose or low blood sugar.

GPs completed these questionnaires on a voluntary basis. Green forms returned with no clinical or demographic information were classified as 'void' and excluded from the study.

The PEM studies were conducted within ethical guidelines for records-based research.[9-11]

Analysis

For the purpose of this study, we excluded patients whose first prescription was >2 months prior to launch date of the study drugs. The observation time for each patient was calculated from the date of first prescription to the date of the hypoglycaemic event, the date of stopping the treatment stated on the green form or 270 days, whichever was the earliest. If the GP stated that the patient had stopped the drug but did not provide a stop date then 30 days was added to the last prescription date, and if no last prescription date was supplied, the patient was assumed to have the median treatment duration for those who stopped the drug. The incidence rate (IR) per 1000 patient-years of treatment for hypoglycaemia was calculated for each drug cohort. Smoothed hazard estimates were plotted over time using an epanechnikov kernel with a half width of 30 days (Stata version 10 [Stata Corp., TX, USA]). A parametric survival model (Weibull) was fitted to each cohort. The Weibull model has a baseline hazard (h) of the form (equation 1):

$$h(t) = pt^{p-1} \exp(\beta_0) \qquad \text{(Eq. 1)}$$

1 The term 'event', as used in prescription-event monitoring, is defined as, "any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter in the patient's notes".

Table I. Patients' characteristics in the original prescription-event monitoring cohorts

Drug	Cohort size	Response rate (%)	Age [mean (SD)]; n[a]	Sex [n (%)]			Period during which the first prescriptions were dispensed
				male	female	sex data missing	
Rosiglitazone	14 418	53.0	61.6 (12.1); 5859	7314 (50.7)	6860 (47.6)	244	July 2000–June 2001
Pioglitazone	12 772	54.7	60.9 (12.6); 9869	6777 (53.0)	5833 (45.7)	162	November 2000–June 2001
Nateglinide	4 557	50.2	59.4 (12.4); 3879	2439 (53.5)	2093 (45.9)	25	October 2001–June 2004
Repaglinide	5 731	43.8	59.1 (12.4); 3108	2860 (50.0)	2846 (49.7)	25	December 1998–January 2001

a Number of patients for whom age data was available.

where t = time, β_0 is a constant and p is a shape parameter. When p is <1 the hazard is estimated to monotonically decrease over time, when $p = 1$ the baseline hazard is estimated to be constant across time. The shape parameter p and 95% confidence interval were estimated for each cohort to determine if the rate of hypoglycaemic events was constant.

A case/non-case analysis was performed to characterize the patients who had at least one hypoglycaemic event in the first 9 months of treatment. Summary statistics for age and sex in each cohort were calculated. Differences between cases and non-cases were tested by Pearson Chi-squared test for sex and by unpaired t-test for age. Because of a high proportion of missing ages in the original PEM studies, the age of cases with a missing value was followed up by telephoning individual GPs.

Results

Baseline demographic characteristics of the original PEM cohorts are summarized in table I. The mean age and proportion of men and women (for those with complete data) were found to be similar between the cohorts.

Patients who started treatment >2 months before the drug launch date were excluded from this analysis; therefore, total number of patients in each cohort included in the analysis was 14 373, 12 768, 4549 and 5727 in rosiglitazone, pioglitazone, nateglinide and repaglinide cohorts, respectively. In these four cohorts, 276 patients experienced at least one episode of hypoglycaemia during the 9 months from the initial prescription. Hypoglycaemia was most frequently reported for patients treated with repaglinide. The IR was approximately 50% and 100% higher in the nateglinide and repaglinide cohorts, respectively, compared with the rosiglitazone and pioglitazone cohorts (table II).

The smoothed hazard plot depicted in figure 1 shows that the incidence of hypoglycaemia in patients treated with rosiglitazone was approximately constant over time. A slight decrease in hazard over time is observed in patients receiving pioglitazone. Patients treated with repaglinide experienced more hypoglycaemic episodes at the beginning of their treatment. Similarly, patients treated with nateglinide tended to have more hypoglycaemic episodes after starting the treatment but the difference was not as pronounced as it was for repaglinide. These findings are confirmed

Table II. Incidence rates of hypoglycaemia per 1000 patient-years of treatment for each of the antidiabetic drugs

Drug	Person-time in days[a]	Hypoglycaemic events	Incidence rate (95% CI)
Rosiglitazone	3 121 108	85	9.94 (8.03, 12.30)
Pioglitazone	2 914 911	77	9.64 (7.70, 12.04)
Nateglinide	999 060	43	15.71 (11.64, 21.17)
Repaglinide	1 275 333	71	20.32 (16.10, 25.66)

a Stop date missing [n (%)]: rosiglitazone 214 (1.5); pioglitazone 235 (1.8); nateglinide 127 (2.9); repaglinide 151 (2.6).

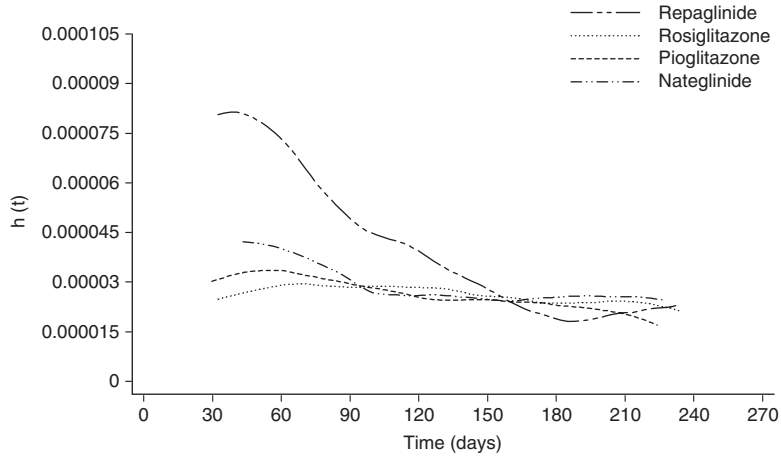

Fig. 1. Smoothed hazard estimate of hypoglycaemia over time by drug cohort. **h (t)** = hazard over time.

by results from the Weibull model, which can be seen in table III. The shape parameter was less than one for all cohorts; however, the parameter was not found to be statistically significantly different from one at the 5% level for rosiglitazone ($p = 0.438$), indicating that the hazard was approximately constant over time and suggesting no relationship between hypoglycaemic events and initiation of the treatment. Pioglitazone was estimated to have a significant shape parameter of 0.80, which would suggest that the hazard decreased slowly over time. Nateglinide and repaglinide had similar estimated shape parameters of 0.56 and 0.58, respectively, indicating a high hazard initially, which decreased over time. Such a relationship between hazard and time could indicate an association with starting of the treatment.

The comparison of baseline characteristics between cases and non-cases is described in table IV. Differences between mean age of cases and non-cases were not statistically significant in any of the four cohorts. The percentage of males and females was similar when comparing cases and non-cases for nateglinide and repaglinide cohorts. However, the proportion of women treated with TZDs who experienced hypoglycaemia was higher, 66.7% and 66.2% of cases were females compared with 48.4% and 46.1% of non-cases in the rosiglitazone and pioglitazone cohorts, respectively.

The proportions of patients who had stopped treatment are shown in table V. Unlike the rosiglitazone and pioglitazone cohorts,[9] hypoglycaemia appeared among the most frequently reported reasons for stopping in the nateglinide and repaglinide cohorts.[10,11] Approximately twice the proportion of patients had stopped as a result of hypoglycaemia in these cohorts compared with the rosiglitazone and pioglitazone cohorts (table V). There were no cases reported of hypoglycaemic coma. In the pioglitazone cohort, the causes of death reported for a very elderly woman were septicaemia and hypoglycaemia; however, no other information was provided.

Table III. Results from the Weibull regression model

Drug	Exp (β_0) [95% CI]	*p* (95% CI)	p-Value
Rosiglitazone	4.15^{-5} [1.46^{-5}, 1.17^{-4}]	0.92 (0.75, 1.13)	0.438
Pioglitazone	7.76^{-5} [2.95^{-5}, 2.08^{-4}]	0.80 (0.65, 0.99)	0.046
Nateglinide	4.39^{-4} [1.65^{-4}, 1.15^{-3}]	0.56 (0.42, 0.76)	<0.001
Repaglinide	5.31^{-4} [2.46^{-4}, 1.14^{-3}]	0.58 (0.46, 0.73)	<0.001

β_0 = constant; **Exp** = exponential; ***p*** = shape parameter.

Table IV. Baseline characteristics of cases vs non-cases of hypoglycaemia in four prescription-event monitoring cohorts

Drug	Number [n (%)]	Age (y) [mean (SD)]	T-test			Sex [n (%)][a]		χ^2 test	
			n	difference (95% CI)	p-value	male	female	χ^2 value	p-value
Rosiglitazone									
cases	85 (0.6)	64.3 (11.8)	61	–2.73 (–5.78, 0.31)	0.079	28 (33.3)	56 (66.7)	11.20	0.001
non-cases	14 288 (99.4)	61.6 (12.1)	5803			7253 (51.6)	6793 (48.4)		
Pioglitazone									
cases	77 (0.6)	63.1 (13.8)	65	–2.21 (–5.28, 0.86)	0.158	26 (33.8)	51 (66.2)	12.43	<0.001
non-cases	12 691 (99.4)	60.8 (12.6)	9809			6748 (53.9)	5781 (46.1)		
Nateglinide									
cases	43 (0.9)	60.0 (12.3)	42	–0.53 (–4.31, 3.25)	0.782	22 (51.2)	21 (48.8)	0.12	0.725
non-cases	4 506 (99.1)	59.5 (12.4)	3831			2413 (53.9)	2068 (46.2)		
Repaglinide									
cases	71 (1.2)	61.3 (12.5)	49	–2.20 (–5.70, 1.30)	0.217	35 (49.3)	36 (50.7)	0.02	0.888
non-cases	5 656 (98.8)	59.1 (12.4)	3071			2823 (50.1)	2808 (49.9)		

a Percentage was calculated for those for whom sex was specified.

There were no other cases of death as a result of hypoglycaemia.

Discussion

This study analysed the incidence of reported hypoglycaemia using data from four PEM studies. As patients were identified from dispensed prescriptions, all patients with a completed green form and start date of no more than 2 months before the drug-launch date were included. Therefore, there were no exclusion criteria, on the basis of age, concomitant medication or concomitant disease. Thus, unlike pre- and post-marketing clinical trials, the PEM studies provide the opportunity to study the drugs in a 'real life' setting.

The average response rate for the four PEM studies was 50.4%, which is lower than the mean response rate for 98 PEM studies (56.3%) that have been completed to date. Thus, one limitation of these studies is non-response bias, which would only affect the results if the probability of the GP responding is associated with the probability of a patient having a hypoglycaemic adverse event. Another limitation is the missing data. Both these limitations could be associated with the fact that GPs complete the green forms on a voluntary basis and are not paid for completing these questionnaires. A high number of missing ages in the repaglinide and rosiglitazone cohorts is explained by the change in policy at the DSRU for data collection: from January 2001, GPs were requested to give the patient's age on the green form rather than their date of birth. Another issue that should be considered is that PEM does not collect data directly from hospitals; however, GPs in the UK do receive summaries of hospital care to include in the patient's medical record.

For the purpose of our analyses, we identified patients as cases when an event coded to the HLT 'hypoglycaemia' was recorded on the green form during treatment with the study drugs. We did not include events that might be signs and symptoms of hypoglycaemia (such as dizziness, faintness, palpitation, tremor, sweating, anxiety, etc.) as cases because information was not available to ascertain whether these events were due to hypoglycaemia. Although there might have been under-reporting of hypoglycaemic events we do not have reason to believe that this under-reporting was differential across the four PEM studies.

The primary aim of the PEM studies was to monitor the overall safety of the four oral anti-diabetic drugs by collecting information on any

event (for the definition of an 'event' see footnote 1 in the Study Design section) reported since treatment started. The green form was not designed to collect data specifically on the past medical history of a patient. Therefore, we were unable to stratify the cohort by the high-hypoglycaemic risk patients or identify whether such patients had been prescribed particular antidiabetic drugs preferentially (i.e. channelling bias).

The present study shows a low incidence of hypoglycaemia reported by patients treated with TZDs in primary care in England (0.6% in both rosiglitazone and pioglitazone cohorts). Some previous studies have also reported a low risk of hypoglycaemia in patients treated with TZDs as monotherapy.[15,23] However, in a 52-week clinical trial carried out in a Mexican population, 15.7% of the patients treated with pioglitazone as monotherapy reported hypoglycaemia.[24] A long-term clinical trial evaluating time to failure of monotherapy with rosiglitazone has also revealed higher incidence of hypoglycaemic events in the rosiglitazone group (9.8%).[25] Increased incidence of hypoglycaemia was also reported when TZDs were administrated in combination with metformin,[17,26] a sulphonylurea[18,27,28] or insulin.[16,29]

The proportion of patients who experienced hypoglycaemia during the first 9 months of treatment with nateglinide was approximately 50% higher (0.9) and 100% higher (1.2%) with repaglinide compared with those treated with TZDs. This comparison does not take into account any underlying differences in the patients' characteristics because of the quantity of missing data across these four cohorts. In addition, the proportions of patients taking dual and triple therapy may vary between the four cohorts. However, we were unable to adjust for these confounding variables because we did not have information on concomitant medication for all study drugs. Nevertheless, our observations are consistent with those reported by Jovanovic et al.[30] and Raskin et al.,[31] where the incidence of hypoglycaemia was approximately 3-fold higher in the repaglinide group compared with the pioglitazone and rosiglitazone groups.

In this analysis of data from PEM studies, the incidence of hypoglycaemia reported by patients treated with nateglinide is lower than in the repaglinide cohort. This finding correlates with the results of clinical trials comparing repaglinide and nateglinide.[32,33] Nateglinide and repaglinide belong to the short-acting non-sulphonylurea secretagogues; however, compared with nateglinide, repaglinide is characterized by slower onset and longer duration of its effect on insulin secretion.[34] Hence, the higher incidence of hypoglycaemia with repaglinide could be associated with its pharmacodynamic profile.

The definition of hypoglycaemia varies across published studies; therefore, it is difficult to compare our findings with the results of other studies. Some studies have reported a higher frequency of symptomatic hypoglycaemia during treatment with repaglinide or nateglinide than in our study;[20,21,35] other studies have shown a very low frequency of confirmed hypoglycaemia in patients treated with nateglinide.[33,36] Our results suggest that the incidence of hypoglycaemia as recorded by the GPs was relatively low. One explanation could be under-reporting of these events. The questionnaire did not specifically ask for hypoglycaemia. In addition, patients were not requested to provide self-monitoring of blood glucose that characterizes some clinical

Table V. Numbers of patients who stopped treatment overall and who stopped because of hypoglycaemia

Drug	Patients who stopped treatment [n (% total cohort)]	Patients who stopped because of hypoglycaemia [n (%)][a]
Rosiglitazone	4555 (31.6)	41 (0.9)
Pioglitazone	3690 (28.9)	25 (0.7)
Nateglinide	1631 (35.8)	27 (1.7)
Repaglinide	1772 (30.9)	45 (2.5)

a Percentage was calculated for those patients who had stopped treatment.

trials, which would have revealed asymptomatic hypoglycaemic episodes.

The pattern of incident hypoglycaemic events over time was described by a graph of the hazard function and quantified by the Weibull model shape parameter estimate. The significantly higher occurrence of incident hypoglycaemic episodes at the beginning of the treatment for repaglinide and nateglinide could be explained by pharmacodynamic and pharmacokinetic characteristics of this class of drugs.

The hazard of hypoglycaemia over time in the nateglinide group is not as marked as that for repaglinide. Repaglinide was launched on the UK market in August 1998 as the first member of the meglitinide class of oral antidiabetics. Three years later (May 2001), another agent of this class, nateglinide, was marketed in the UK. Therefore, the clinical experiences with repaglinide may have helped in the usage of nateglinide.

Cases/non-case analysis has revealed a statistically significant higher proportion of women treated with TZDs who experienced hypoglycaemia (compared with non-cases, $p = 0.001$ and $p < 0.001$ for rosiglitazone and pioglitazone, respectively). Patel et al.[37] found that women responded better to treatment with TZD than did men. Thus, the effectiveness of these drugs might be related to sex because of pharmacokinetic and pharmacodynamic factors. It is possible that another explanation for a higher proportion of females experiencing hypoglycaemia in the present analysis was better compliance with the treatment. However, two recent studies have shown no statistically significant difference between males and females in adherence with oral antidiabetic therapy.[38,39]

Conclusion

This study reflects that frequency of reported hypoglycaemia with rosiglitazone, pioglitazone, repaglinide and nateglinide in day-to-day clinical practice was low. The proportion of patients who experienced hypoglycaemia during treatment with repaglinide and nateglinide was 50–100% higher compared with those treated with rosiglitazone or pioglitazone. For nateglinide and repaglinide, the highest hazard appeared shortly after starting treatment and decreased over time. Further investigation is necessary to assess whether women treated with TZDs are more prone to hypoglycaemia than men. Findings from this study should be taken into account with other clinical and pharmacoepidemiological studies.

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