SUMMARY

Title of thesis: Hypoglycaemia as acute complication of diabetes mellitus
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This thesis was focused on hypoglycaemia as adverse drug reaction of rosiglitazone, pioglitazone, nateglinide and repaglinide, which have been launched to the UK market and on severe hypoglycaemia (SH) requiring the assistance of Emergency medical service (EMS) in region of Hradec Králové. Observed factors were described in two separate sections.

Hypoglycaemia as adverse drug reaction of selected oral antidiabetics

Aim

The aim of this study was to quantify the incidence of hypoglycaemic events during the first nine months of treatment with newly launched oral antidiabetics, rosiglitazone, pioglitazone, nateglinide or repaglinide, prescribed by general practitioners in England, to observe pattern of these events over time, to look for patients‘ characteristics which could influence the incidence of hypoglycaemia and to analyse the relationship between use of concomitant anti-diabetic therapies and the incidence of hypoglycaemia in patients treated with pioglitazone.

Methods

We used data collected for prescription-event monitoring (PEM) studies of rosiglitazone, pioglitazone, nateglinide and repaglinide. PEM is an observational, non-interventional, cohort study. Incidence rate per 1000 patient-years of treatment was calculated for each drug cohort. Smoothed hazard estimate was plotted over time. The pattern of incident hypoglycaemic events was further analysed by Weibull model. „Case/non-case“ analysis was performed to compare patients who had at least one hypoglycaemic epizode in the first 9 months of treatment with those who did not. Cox proportional-hazards regression model was used to assess the relationship between patients‘ characteristics, use of concomitant anti-diabetic therapies and the incidence of hypoglycaemia in patients treated with pioglitazone.

Results

The total number of observed patients was 14 373, 12 768, 4 549 and 5 727 in rosiglitazone, pioglitazone, nateglinide and repaglinide cohorts, respectively. From these, 276 patients experienced at least one hypoglycaemic event. The IR of hypoglycaemia was 50%

higher (IR=15,71/1000 patient-years) and 2 times higher (20,32/1000 patient-years) in patients treated with nateglinide and repaglinide, respectively, compared to those receiving treatment with thiazolidinediones (TZDs) (IR=9,94 and 9,64/1000 patient-years for patients treated with rosiglitazone and pioglitazone, respectively). Graph describing the occurence of incident hypoglycaemic events over time and the results of Weibull model (especially the value of shape parameter „p“) have shown that repaglinide and nateglinide-treated patients experienced significantly higher number of hypoglycaemic epizodes shortly after starting treatment. The hazard for patients treated with rosiglitazone and pioglitazone was approximately constant over time. Women receiving treatment with TZDs had 2 times the hazard of having hypoglycaemia than men did.

Results of Cox proportional-hazards regression model have shown that patients taking pioglitazone and sulphonylurea combination therapy and pioglitazone and insulin combination therapy had 3 and 4 times the hazard of having hypoglycaemia compared to those who were not taking these adjunctive therapies [HR=3,11 (CI 1,64, 5,88); HR=4,15 (CI 1,74, 9,91), respectively]. Patients taking the adjunctive metformin were 25% less likely to experince hypoglycaemia compared with those who did not take adjunctive metformin (HR=0,75; CI 0,44, 1,27).

Conclusion

Results of this study have shown that the incidence of hypoglycaemia in observed cohorts is relatively low. Patients treated with nateglinide or repaglinide are in higher risk of having hypoglycaemia compared to those who are taking TZDs. Furthermore patients receiving the combination therapy of pioglitazone and sulphonylurea or insulin have also higher hazard of having hypoglycaemia compared to those who are not taking these adjunctive therapies. The beginning of treatment with nateglinide or repaglinide was associated with higher incidence of hypoglycaemia signalizing the necessity of patient adaptation on new therapy to assure the optimal blood glucose control concurrently with minimalization of hypoglycaemia occurence. Further investigation is necessary to assess whether women receiving TZDs are more prone to hypoglycaemia than men.

Severe hypoglycaemia requiring the assistance of Emergency medical service in the region of Hradec Králové

Aim

The aim of this study was to quantify the incidence of SH requiring the assistance of EMS in the region of Hradec Králové, to describe the occurence of these epizodes during the day, to look for symptoms and causes which have statistically significant relationship with blood glucose level and to observe therapy of hypoglycaemia, termination of EMS action because of hypoglycaemia and other parameters.

Methods

Data for analysis were obtained by filling the patients' documentary lists by medical staff of EMS. Incidence of SH per 100 patient-years was calculated based on number of patients with type 1 and type 2 diabetes mellitus (DM) in region of Hradec Králové. Distribution of hypoglycaemic epizodes over the day was presented by graph and was analysed using contingency tables. General linear model and Regression trees technique were used to assess the relationship between blood glucose level and presence/absence of causes or symptoms of hypoglycaemia.

Results

During year 2007 there were 338 hypoglycaemic epizodes requiring the assistance of EMS in the region of Hradec Králové (1,2% of all tours of EMS in this region) recorded in 262 patients. Nearly one half of these events (n=150) appeared in 125 type 2. diabetic patients and 83 episodes were recorded in 42 type 1 diabetic patients. Type of DM was not specified in 103 epizodes. Incidence of SH was 2,4 and 0,4/100 patient-years in patients with type 1 and type 2 DM, respectively. The most epizodes appeared in the afternoon, between 2 pm and 6 pm ($p<0,001$). Almost one third of observed patients had impaired consciousness and 27% were in coma. 68% of patients did not aware of developping hypoglycaemia. The lowest glycaemia was measured out in patients who experienced unconsciousness and severe perspiration together. Food deficiency, insulin and physical activity belonged among the most frequently identified causes of SH. Among causes which led to significantly lower blood glucose levels compared to those who did not record these causes belonged insulin and alcohol consumption. Almost 90% of patients were treated with glucose i.v., glucagon was applied in 9 cases. Only 14 patients from 262 had glucagon at home. Nearly one third of patients (n=95) was hospitalized.

Conclusion

Hypoglycaemia represents important percentage of all epizodes requirig the assistance of EMS. Severe hypoglycaemia is more frequent in type 1 diabetic patients. The most critical period of the day for hypoglycaemia is in the afternoon, between 2 pm and 6 pm. Patients with type 1 DM should also thoroughly follow recommendation about therapy regime with regard to higher risk of hypoglycaemia during the night, between 10 pm and 2 am. Diabetic patients should always be informed about the risk associated with alcohol consumption. To minimise the frequency of SH, the necessity of meal in accordance with anti-diabetic treatment and exercise should be emphasized all the time. More frequent usage of glucagon by patients' relatives could minimize the incidence of SH requiring the assistance of EMS.