Clinical Effects of Exposure to DPP-4 Inhibitors as Reported to the National Poison Data System

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Abstract DPP-4 inhibitors (sitagliptin, saxagliptin, and linagliptin) are approved for the treatment of diabetes. They are considered safe due to their hyperglycemia dependent mechanism of action. We examined all isolated exposures to DPP-4 inhibitors reported to the National Poison Database System since 2006 to determine if significant toxicity occurs after exposure with attention to pediatric and intentional overdoses. NPDS data regarding DPP-4 ingestions in all age groups between January 2006 and March 2013 was collected. Cases were reviewed, and the following inclusion criteria applied: (1) reported ingestion of a DPP-4 inhibitor and (2) known clinical outcome. Exclusion criteria included the following: (1) exposure to more than a single substance, (2) no known outcome, and (3) clinical outcome judged to be unrelated to the exposure. One thousand four hundred seventy-six cases were reviewed while 826 were excluded. Of 650 included cases, 562 developed no clinical effects. Mild effects were noted in 77. There were no deaths. Moderate/major effect cases were investigated: two medication-naïve nondiabetic individuals with accidental exposures developed clinically significant hypoglycemia

requiring treatment. One diabetic patient on a DPP-4 inhibitor developed prolonged hypoglycemia requiring admission and continuous exogenous dextrose. Of 650 included exposures to DPP-4 inhibitors, 639 (98.3%) had either no or minor clinical effects. Three resulted in clinically significant hypoglycemia requiring intervention. None of the moderate or major clinical outcomes were the result of intentional overdoses for the purpose of self-injury. No exploratory ingestions resulted in moderate or major effects. Based on this data, exposure to DPP-4 inhibitors may rarely result in clinically significant hypoglycemia.

Keywords DPP-4 inhibitor · Sitagliptin · Linagliptin · Saxagliptin · Diabetes

Introduction

The first dipeptidyl peptidase-4 inhibitor (DPP-4) sitagliptin was approved by the US Food and Drug Administration for the management of type II diabetes in 2006. There are presently three available DPP-4 inhibitors in the US market: sitagliptin, linagliptin, and saxagliptin. We describe the experience of US poison centers with these toxicants.

The DPP-4 inhibitors lower serum glucose levels by preventing the degradation of the glucagon-like peptides gastric inhibitory peptide (GIP) and glucagon-like peptide 1 (GLP-1). These glucagon-like peptides are released by gut endocrine cells in response to nutrient ingestion and subsequently induce a glucose-dependent insulin secretion from the beta cells in the pancreas. Additional actions of the glucagon-like peptides may include inhibition of glucagon release, reduced hunger, and delayed gastric emptying. Glucagon-like peptides are inactivated by dipeptidyl peptidase-4. Inhibition of dipeptidyl peptidase-4 by DPP-4 inhibitors increases the plasma level of the active forms of the glucagon-like peptides and prolongs their function after release from the gut endocrine cells. There is

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no direct action of DPP-4 on release of insulin, insulin levels, or insulin activity. Asymptomatic hypoglycemia (BG <60 mg/dl) that resolved spontaneously without treatment has been reported with therapeutic dosing; however, there is limited information on overdose or supra-therapeutic dosing. A single case report of overdose with 1,700 mg of sitagliptin produced no clinical effects and no laboratory evidence of hypoglycemia [1].

Based on the mechanism of action, it would be expected that the DPP-4 inhibitors function via antihyperglycemic action rather than by inducing hypoglycemia. However, the limited acute toxicity data presents a difficult dilemma in regard to triage or management decisions when faced with a reported accidental or intentional exposure to DPP-4 inhibitors. Therefore, we performed a retrospective study of all DPP-4 exposures reported to US poison centers to describe the risks associated with and management of these cases. Subgroup analysis of intentional ingestions and pediatric exploratory exposures was performed to determine the impact on these at-risk groups.

Methods

Following study approval, the National Poison Data System (NPDS) was queried for data regarding ingestions of the three available DPP-4 medications in all age groups between January 2006 and March 2013. These cases were reviewed for substance involved, clinical effects and outcome. The inclusion criteria were (1) human patient, (2) reported exposure to a DPP-4 inhibitor, and (3) patient followed to a known clinical outcome. Exclusion criteria included (1) exposure to more than a single substance, (2) patient not followed to a known outcome, or (3) clinical outcome judged to be unrelated to the exposure. Medications that were a combination formulation (e.g., Janumet® with sitagliptin and metformin) were considered exposure to more than one substance and therefore excluded as polysubstance ingestions. Medical outcome definitions in NPDS use standard criteria that have been published in detail elsewhere [2]. Known outcomes include no effect, minor effect, moderate effect, major effect, death, and unrelated. The categories of patient not followed to a known outcome include cases (1) purposely not followed up by the poison center because during the initial contact, the ingestion was considered unlikely to produce an adverse event (e.g., trivial ingestion such as a double dose) or (2) the poison center was unable to follow up, but the history or dose was such that a potential for an adverse event existed. Of those excluded in the not followed to known outcome group, >90 % was ingestion that was considered unlikely to produce an adverse event. For patients that had a reported serious medical outcome (i.e., moderate, major, or death), the poison center that had reported the case was contacted and requested to provide the full chart, with any personal identifiers redacted, to allow for review by the authors.

Subgroup analysis was accomplished by assessing the outcome of reported exposures coded as “intentional” within NPDS. Cases were considered to be pediatric exploratory exposures if the patient was under the age of 10 years.

To compare the quantitative risk of serious outcome from DPP-4 inhibitor outcomes to pharmaceuticals from other classes, we calculated a hazard index, representing the number of cases with a major or fatal outcome, per 1,000 exposures followed to a known outcome [3].

Results

A total of 1,476 cases of reported DPP-4 exposure were reviewed. Of those cases, 806 were excluded for the following reasons: 741 cases were not followed to a known outcome, 11 cases were confirmed non-exposures, and 54 cases had clinical outcomes unrelated to the exposure.

Of the 670 cases that initially met the inclusion criteria, 36 recorded moderate or major effects. There were no deaths. Complete poison center charts were then requested on those 36 patients (33 moderate effects and 3 major effects) for further assessment of the effects as well as to determine if the cases did indeed meet inclusion criteria. Of 36 requested charts, 29 were returned. Twenty cases of the 29 reviewed charts were subsequently excluded after further analysis; 13 involved more than one substance and six clinical effects were felt to be unrelated to the exposure. One case involved a confirmed non-exposure. Three cases were included after re-coding: three documented no clinical effects, while two cases were re-coded as minor clinical effects. We did not exclude from further analysis the remaining seven cases, but assumed their coding had been correct.

After final application of criteria and re-coding, as above, 650 cases were included. No clinical effects were found in 562 (86 %) cases. Seventy-seven (12 %) patients experienced only minor effects. Nine cases (2 %) had moderate clinical effects, including the seven requested cases not returned for further analysis. After exclusion, only one major clinical outcome (0.002 %) was observed (Fig. 1). The hazard index for DPP-4 inhibitors in our sample was 1.54.

Average age of patients was 31.7 years [range 2 months to 97 years, standard deviation 30.7 years]. Females were over-represented in the sample (358 females to 293 males). Two hundred eighty-seven were 10 years of age or younger and likely represent exploratory ingestions. Only 29 cases were intentional ingestions either for purposes of misuse or self-injury.

Of the three included moderate/major effect cases available for analysis, two were coded as moderate effects. One case was a result of a pharmacy error—the patient was mistakenly dispensed sitagliptin 100 mg tablets by her pharmacy instead of an antibiotic. The patient had no history of diabetes and was

Fig. 1 DPP-4 exposures by outcome

650 Reported Exposures to DPP-4 Inhibitors by Clinical Outcome

naïve to sitagliptin. She had taken two doses when she developed nausea, vomiting, and abdominal pain. In the ED, she had a finger stick blood sugar of 56 mg/dl. After oral glucose load and overnight observation, she was released without further incident.

The second patient in whom a moderate effect was recorded was evaluated at an emergency department for multiple “low” blood sugars at home. His only reported diabetic medication was sitagliptin. His finger stick blood sugar dropped as low as 39 mg/dl. The only other reported symptom in this case was dehydration. He was given 50 g of IV dextrose in the emergency department and did not develop any recurrent hypoglycemia. The patient was admitted for observation and received exogenous intravenous glucose overnight. No further symptoms were recorded, and he was discharged the next day.

The only major clinical effect was recorded in a patient who accidentally took her spouse’s sitagliptin 25 mg tablet. She did not have a history of diabetes and was naïve to sitagliptin. She was taken to the ED and found to have a finger stick blood sugar of 34 mg/dl. Her blood glucose level initially responded to oral supplementation, but ultimately dropped again while in the ED. Despite aggressive intravenous dextrose administration, including a continuous infusion of D5 at 100 ml/h followed by D10 at an unknown rate, she had recurrent episodes of hypoglycemia (generally 65–68 mg/dl) for over 24 h. No other symptoms were noted. She required a 2-day hospitalization prior to stabilization of her blood sugar.

Subgroup analysis of 287 exploratory exposures revealed 266 (93 %) recorded no clinical effect. Twenty cases (7 %) reported only minor effects. One moderate effect was reported – a 22 month-old child who possibly ingested sitagliptin 100 mg. The child was referred in to the hospital for observation due to limited data available regarding exploratory ingestions of DPP-4 inhibitors. The patient had serial blood sugar measurements via finger stick—the lowest of which was 66 mg/dl. The patient was asymptomatic at the time. No exogenous glucose was required. The patient was observed

for 24 h without complications and discharged without incident. This case was re-coded as a minor effect as the patient did not have symptoms when her blood sugar was 66 mg/dl, and the reason for overnight admission was noted to be due to a lack of published data on pediatric exploratory exposures.

Twenty-nine intentional ingestions were included in the final analysis. Of these, 25 were suspected suicide attempts while four were intentional misuse. No clinical effects were reported in 24 (83 %) while five (17 %) were coded as minor effects. Though three of these cases were initially coded as moderate effects, after analysis two were re-coded as having no clinical effects while one was judged to be a minor effect. The minor effect was observed in a 49-year-old female who admitted ingesting four tablets of sitagliptin (unknown milligram strength). The patient had one episode of hypoglycemia with a finger stick blood sugar of 50 mg/dl. She had no symptoms at that time and was treated with food. She was observed overnight with no recurrent episodes of hypoglycemia. Ultimately, no moderate or major effects were seen in intentional ingestion patients.

Discussion

Because DPP-4 inhibitors do not directly affect insulin levels, the risk of significant hypoglycemia could be anticipated to be low [4]. However, while our data supports the assertion that hypoglycemia is a rare complication, we did find at least five cases of hypoglycemia requiring intervention among our sample of 650 exposures.

Of the 650 included exposures to DPP-4 inhibitors, 639 had either no or minor clinical effects. Of the three moderate/major cases we were able to examine more thoroughly, all resulted in hypoglycemia requiring intervention. In one of these cases, however, oral food intake was a sufficient intervention. This is similar to reported effects during clinical trials with therapeutic dosing in which asymptomatic hypoglycemia

(BG <60 mg/dl) resolved spontaneously without treatment. The single case of prolonged hypoglycemia presents some reason for caution. Sitagliptin has a half-life of 12 h [4]. A reported intentional overdose with 1,700 mg of sitagliptin produced no clinical effects and no laboratory evidence of hypoglycemia [1]. Unfortunately, the amount of information related to the single major effect is limited. Though no mention of any co-ingestants is made, specifically sulfonylureas, the authors cannot definitely exclude the possibility of additional substances. Given the severity of clinical effects compared to the remainder of the data, this case is certainly an outlier. None of the moderate or major clinical outcomes identified in this study were the result of intentional overdoses for the purpose of self-injury.

The hazard index was only 1.54. By way of comparison, a 2008 study of antidepressant exposures during attempted suicide showed tricyclic antidepressants' hazard indices in the range 56–292 and selective serotonin reuptake inhibitors' hazard indices in the range 4–27 [3]. Early published experience with DPP-4 inhibitors overdose without co-ingestants, including the present report, suggests that the risk of serious outcome is low [4].

The most significant limitation associated with this study is the dependence on retrospective Poison Center data. The American Association of Poison Control Centers (AAPCC) maintains the national database of information logged by the country's 57 poison centers (PCs). Case records in this database are from self-reported calls: they reflect only information provided when the public or health-care professionals report an actual or potential exposure to a substance (e.g., an ingestion, inhalation, or topical exposure, etc.) or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to verify the accuracy of every report made to member centers. Additional exposures may go unreported to PCs, and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance. Still, we found over-coding in 90 % of the charts originally coded as moderate or major which we were able to review; we did not review any charts coded as no effect or mild outcome to check for under-coding. We were unable to review charts of seven patients identified as having moderate outcomes. Of the patients with moderate or major outcomes, only one had clinical effects other than reported low blood sugar levels (abdominal pain and vomiting), and all of these levels were measured only by finger stick capillary blood testing, which can be inaccurate [5]. We know neither how many cases were excluded due to reported co-ingestants nor what happened to those cases which poison centers were unable to follow.

Unfortunately, over 50 % of reported exposures to DPP-4 inhibitor were not followed to a known outcome, significantly limiting analysis of the effects of exposure to the drug class.

Finally, due to the infrequent nature of significant effects as well as a lack of data, no dose/response curve could be generated. Drug dose in milligrams was reported in only 132 (20 %) of cases, with only 40 % of those cases having a recorded patient weight. None of the included major or moderate cases included both weight and milligram dose.

Conclusion

Single-agent exposure to DPP-4 inhibitors rarely results in clinically significant hypoglycemia. Pediatric exploratory ingestions, which composed 44 % of our sample, did not reveal any increased risk as compared to the study group in general. Intentional ingestion of DPP-4 inhibitors for the purpose of self-harm or intentional misuse similarly did not generate an increased risk. Our data suggests that while the incidence is very low, the potential for hypoglycemia exists, and symptomatic patients with exposures to DPP-4 inhibitors should be evaluated appropriately.

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Conflict of Interest None

References

1. Furukawa S, Kumagi T, Miyake T, Ueda T, Nijya T (2012) Suicide attempt by an overdose of sitagliptin, an oral hypoglycemic agent: a case report and a review of the literature. *Endocr J* 59(4):329–33
2. Bronstein AC, Spyker DA, Cantilena LR, Rumack BH, Dart RC (2012) 2011 Annual report of the American Association of Poison Control Centers' National Data System (NPDS) 29th annual report. *Clin Toxicol* 50:911–1164
3. White NC, Litovitz T, Clancy C (2008) Suicidal antidepressant overdoses: a comparative analysis by antidepressant type. *J Med Toxicol* 4: 238–250
4. Park H, Park C, Kim Y et al (2012) Efficacy and safety of dipeptidyl peptidase-4 inhibitors in type 2 diabetes: meta-analysis. *Ann Pharmacother* 46:1453–1469
5. Olansky L, Kennedy L (2010) Finger-stick glucose monitoring, issues of accuracy and specificity. *Diabetes Care* 33:948–9