

## Acute Exenatide Overdose

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### Abstract

Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, was quite recently approved as adjunctive therapy to improve glycemia control in type 2 diabetes patients. There is very limited information on overdose consequences. We report 3 cases of exenatide overdose involving 2 suicidal self-injections associated with psychotropic intake and one medication error. Two patients rapidly experienced gastro-intestinal symptoms and none of them presented severe hypoglycemia, which is in accordance with the known biological activity of GLP-1 that acts in a glucose-dependent manner and does not inhibit glucagon release in case of hypoglycemia. Interestingly one patient, who ingested large amounts of psychotropic drugs together with self-injection of a large dose (600 µg) of exenatide, presented unexpected delayed onset of central nervous system (CNS) symptoms whereas no hypoglycemia was experienced and no neurological feature is anticipated from exenatide exposure. Physicians should be aware of exenatide property to inhibit gastric emptying which can delay symptoms of acute poisoning due to co-ingested drugs.

**Keywords:** Exenatide; Acute overdose; Delayed co-ingestions toxicity

### Introduction

Exenatide (Byetta<sup>®</sup> commercialized by AstraZeneca), a glucagon-like peptide-1 (GLP-1) receptor agonist, was approved in 2005 as adjunctive therapy to improve glycemia control in patients with type 2 diabetes. It belongs to the incretin-based therapies and exhibits many effects of endogenous GLP-1, a gut hormone, which plays a major role in glucose homeostasis by stimulating insulin secretion, suppressing glucagon secretion, and inhibiting gastric emptying. GLP-1 does not impair hypoglycemia counterregulation as glucagon release returns to normal when hypoglycemia occurs. Since exenatide acts in a glucose-dependent manner and does not inhibit glucagon release in case of hypoglycemia, severe hypoglycemia is not expected during monotherapy [1]. Exenatide maximal blood concentration is obtained 2.1 hours after administration; its half-life is 2.4 hours and it is predominantly eliminated by glomerular filtration. Usual dose regimen starts with 5 µg subcutaneous injections twice daily, but it can be increased to 10 µg. Exenatide is available in disposal, pre-filled, multi-dose self-injectable pen devices containing either 300 µg or 600 µg of exenatide in the entire disposal for Byetta<sup>®</sup> 5 µg and Byetta<sup>®</sup> 10 µg, respectively.

As data on the consequences of exenatide overdose are still limited, our aim was to describe the only three cases of overdose collected by Lyon Poison Center since marketing of the drug.

### Case Reports

**Patient n°1:** A 58-year-old female patient with a history of depression and type 2 diabetes mellitus was treated with levomepromazine, clonazepam, zopiclone, mianserine, metformin, glibenclamide and exenatide 10 µg twice daily. On April 4th, 2011, at 10 h 00 min a.m., she voluntary ingested 120 tablets of

levomepromazine 100 mg and 84 tablets of clonazepam 2 mg combined with the subcutaneous injection of the entire content (600 µg) of an exenatide pen (Byetta<sup>®</sup> 10µg). Initial findings were unremarkable, except for nausea and one episode of vomiting with several tablets found in the vomit. During medical transfer (H+4), finger stick glucose levels decreased from 1 g/L to 0.7 g/L, and quickly rose to 2 g/L after a single 10% dextrose administration. No hypoglycemia recurred thereafter. At the time of hospitalization (H +4.75), the patient was drowsy and complained of moderate abdominal pain only. Medical examination evidenced tachycardia (heart rate between 120 and 140 bpm) with moderately elevated blood pressure (159/100) and normal QTc and QRS on ECG recording. Blood glucose was 0.89 g/L and other laboratory data were unremarkable (sodium: 137 mmol/L; potassium: 3.9 mmol/L; chloride: 96 mmol/L; bicarbonate: 31 mmol/L; creatinine: 48 µmol/L; calcium: 2.63 mmol/L; aspartate transaminase level: 21 U/L; alanine transaminase level: 15 UI; hemoglobin: 125 g/L). Toxicological screening (high-performance liquid chromatography/diode) performed on the early blood sampling (H+4) revealed elevated serum level of clonazepam at 90 ng/L (therapeutic range: 10-50 ng/L), upper therapeutic limits of mianserine level at 0.16 mg/L (therapeutic range: 0.05-0.14 mg/L) and trace amount of levomepromazine. Exenatide plasma level was not measured as this assay was not routinely available. The patient remained under intensive care during 8 hours and no clinical or biological changes were noticed except for persisting tachycardia. Despite of recommendation provided by Poison Center to be aware for clinical deterioration since exenatide can slow down gastrointestinal absorption of co-ingested drugs by inhibiting gastric emptying, she was transferred to a non-intensive care unit where she was given food in the evening. She became abruptly comatose (H+14) and was admitted back to the intensive care unit where she required intubation and ventilation (H+16). Unfortunately blood levels of co-ingested drugs were not controlled at that time. Her consciousness subsequently improved and she was discharged 2 days later.

**Patient n°2:** A 67-year-old female patient with a history of depression, alcoholism, hypertension and type 2 diabetes mellitus was treated with paroxetine, bromazepam, valsartan, hydrochlorothiazide, metformin, repaglinide and exenatide, 5 µg twice daily. On February 14<sup>th</sup>, 2009 at 9 p.m., she drank a large amount of alcohol and then voluntarily ingested 2 tablets of repaglinide 1 mg combined with the intentional subcutaneous administration of 6 doses (60 µg) of exenatide pen (Byetta® 10 µg). At hospital admission 3 hours later, she had only moderate clinical symptoms of drunkenness with blood alcohol level at 1.5 g/L and blood glucose level at 0.65 g/L. Other laboratory data were unremarkable (including normal liver enzymes). She received 10% dextrose infusion for a few hours, and her blood glucose level remained higher than 1 g/L even after dextrose infusion withdrawal. She was discharged after 2 days of clinical monitoring.

**Patient n°3:** A 52 year male patient with a history of type 2 diabetes mellitus and peripheral arterial occlusive disease was treated with antiplatelet drug and exenatide 5 µg twice daily. On March 2014, he was admitted for lower limb revascularization, and mistakenly received 300 µg of exenatide (the whole 1.2 ml disposal of Byetta® 5 µg) administered by a non-trained nurse unaware of exenatide use. One and a half hour later, he experienced severe nausea that quickly subsided after ondansetron infusion. No hypoglycemia occurred during the whole period of clinical monitoring.

## Discussion

Based on exenatide mechanism of action and the few available published data, limited consequences of exenatide overdose are anticipated. During clinical trials, three cases of inadvertent delivery of a dose 10-fold the recommended dose were reported [2]. All patients experienced nausea and vomiting, but only one required glucose administration (blood glucose levels not provided). Vomiting without hypoglycemia were reported in two cases of voluntary acute poisoning involving 90 µg of exenatide in one, and a massive subcutaneous injection of 1800 µg in the other one [3-4]. Our case reports confirm that severe hypoglycemia is unlikely to occur following exenatide overdose. However, due to exenatide-related inhibition of gastric emptying, attention should be paid to clinical consequences from delayed intestinal absorption of co-ingested drugs as indirectly confirmed here. Indeed, as most medications are absorbed rapidly and extensively in the small intestine, prolonged gastric emptying time can result in slower absorption with prolonged time to maximum concentration ( $T_{max}$ ) and decreased maximum concentration ( $C_{max}$ ). The effect of exenatide on the pharmacokinetics and pharmacodynamics of concurrent oral medications has been studied for several drugs [5]. Prolonged  $T_{max}$  and/or decreased  $C_{max}$  have

been evidenced for digoxin, lisinopril, warfarin, paracetamol, lovastatin, ethinyl oestradiol and levonorgestrel with no or only mild change in the area under the concentration–time curve (AUC). Whereas no or clinically irrelevant alterations in pharmacodynamic properties resulting from a drug-drug interaction are expected in the setting of exenatide therapeutic use, this has to be considered in case of voluntary intoxication. Voluntary intoxications with ingestion of large amounts of drugs available as solid tablets, particularly those inducing gastrointestinal hypomotility (e.g., anticholinergic drugs such as phenothiazines or some antidepressants) are a risk factor for drug aggregate formation [6]. Accordingly, exenatide should be considered to be an additional potential risk factor by delaying gastric emptying. Since drug aggregates reduce the available surface for dissolution, the onset of symptoms may be delayed. Furthermore, it can also be hypothesized that food intake may promote aggregate dissolution resulting in abrupt clinical deterioration. Whereas no neurological features were expected following single exenatide overdose and based on our case of non hypoglycemic delayed CNS deterioration following suicidal self-injection of 600 µg of exenatide associated with large ingestion of psychotropic drugs (case n° 1), we recommend that voluntary intoxication involving drug co-ingestion should be closely monitored within hours or the few days post-ingestion since it is not immediately obvious whether the patient is at risk. The blood level of co-ingested drug should be monitored, especially in case of clinical deterioration.

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