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Case Report

Internal Medicine Section

# A Case of Janumet Poisoning

ARUN BAHULIKAR[1], VIHITA KULKARNI[2], DEEPAK PHALGUNE[3]

## ABSTRACT

Janumet, an anti-diabetic drug is being increasingly used. Each tablet contains 50 mg of sitagliptin + 500/1000 mg of metformin. Metformin works by decreasing glucose production in the liver and decreasing absorption of glucose by the intestines. Sitagliptin works by regulating the levels of insulin the body produces after eating (sugar dependant insulin release). A previously healthy 17-year-old female was found to be unconscious and had an alleged history of consumption of eight to nine tablets of Janumet. Patient had seizures on admission and evidence of hypoglycaemia. Patient remained drowsy for two days. Gradually her clinical condition improved and she was diagnosed with an adjustment disorder with disturbance of emotion and conduct. She was discharged from the hospital on the seventh day with normal clinical parameters.

**Keywords:** Hypoglycaemia, Metformin, Sitagliptin

## CASE REPORT

A previously healthy 17-year-old female was found to be unconscious in the morning by her parents. She was having jerky movements of all the four limbs with tongue bite. Her parents gave an alleged history of consumption of eight to nine tablets of Janumet (50/500mg) at around midnight; i.e., she had consumed around 450 mg of Sitagliptin and 4500 mg of Metformin. Her father was suffering from diabetes mellitus and was taking Janumet tablets which gave her access to these tablets. She was taken to a nearby hospital where her Blood Sugar Level (BSL) was found to be 19 mg%. She was given intravenous glucose in that hospital and was shifted for further management to Poona Hospital and Research Centre, Pune, Maharashtra, India (Higher centre) as per her parent's wish.

On examination, her pulse rate was 120 minute, Blood Pressure (BP) 110/70 mmHg, Respiratory rate 28/minute. Cardiovascular and respiratory systems were normal except tachycardia. She was having continuous seizures. There was tonic posturing of neck to the right side with conjugate deviation of eyes to right side. Pupils were reacting, 3 mm in size. Plantar reflexes were bilateral extensors. She was treated with intravenous (IV) Calmase 2 mg and dextrose containing fluids were administered. She required intubation for airway protection. She developed fever; temperature was 100-101°F. Rapid malaria test was conducted to rule out malaria (fever was probably due to seizure activity). Her BSL was 55 mg%. The investigations conducted at the time of admission are depicted in [Table/Fig-1]. CT brain was normal.

Ryles tube was inserted and aspirate sample was collected and sent for analysis. She was given 5% dextrose continuously and her BSL was monitored every two hours.

On day two, venous blood gas (VBG) showed pH 7.38, $pCO_2$ 44.5, $pO_2$ 21.3 and $HCO_3$ 26.1. Serum insulin was 32.2 uU/mL (normal range 5-25), Serum C-Peptide (fasting) -7.10 ng/mL (normal range 0.8-4.0), Ultrasound (USG) Abdomen – pancreas could not be well visualized due to distended bowel, electrocardiogram (ECG): Sinus tachycardia, QTc interval was normal, echocardiography showed normal chamber dimensions, Left Ventricular Ejection Fraction (LVEF)- 60%. no clot, vegetation, or effusion was found.

Patient had seizures on admission and evidence of hypoglycaemia. Patient remained drowsy for two days. Gradually her clinical condition improved.

| S. No. | Investigation | Actual values | Normal range |
|---|---|---|---|
| 1 | Arterial blood pH | 7.42 | 7.35-7.45 |
| 2 | Arterial blood $pCO_2$ | 31 mmHg | 35-45 mmHg |
| 3 | Arterial blood $pO_2$ | 50 mmHg | 80-100 mmHg |
| 4 | Arterial blood $HCO_3$ | 19.7 mmol/L | 20-26 mmol/L |
| 5 | Haemoglobin (Hb) | 11.2 gm/dL | 12.3-15.3 gm/dL |
| 6 | White blood count (WBC) count | 15,100 cumm | 4000-11,000/ cumm |
| 7 | Platelet count | 3, 72,000 cumm | 1.5-4.5 L/cumm |
| 8 | Urine Glucose | Two plus positive | Absent |
| 9 | Urine ketones | Absent | Absent |
| 10 | Blood urea | 17 mg/dL | 15-40 mg/dL |
| 11 | Serum creatinine | 1.0 mg/dL | 0.55-1.02 mg/dL |
| 12 | Serum sodium | 130 mmol/L | 136-145 mmol/L |
| 13 | Serum potassium | 4.0 mmol/L | 3.5-5.1 mmol/L |
| 14 | Serum chloride | 93 mmol/L | 98-107 mmol/L |
| 15 | Serum cholinesterase | 7.85 U/mL | 7-19 U/mL |
| 16 | Serum lipase | 157 U/L | 73-393 U/L |
| 17 | Serum bilirubin | 0.38 mg/dL | 0.00-1.00 mg/dL |
| 18 | Serum glutamic oxaloacetic transaminase (SGOT) | 22 U/L | 15-37 U/L |
| 19 | Serum glutamic-pyruvic transaminase (SGPT) | 30 U/L | 14-59 U/L |
| 20 | Serum alkaline phosphatase | 98 U/L | 46-116 U/L |
| 21 | Serum insulin levels | 44 mIU/L | 5-25 mIU/L |

**[Table/Fig-1]:** Report of the investigations.

On day three, ABG showed pH 7.49, $pCO_2$ 40, $pO_2$ 241, and $HCO_3$ 29.9. She was extubated on third day and became completely alert, was obeying commands by fourth day. She gave a history of consumption of Janumet tablets. The psychiatrist's opinion was taken. She was diagnosed with an adjustment disorder with disturbance of emotions and conduct. She was discharged from hospital on seventh day with normal clinical parameters.

## DISCUSSION

Darracq MA et al., retrospectively reviewed a state poison system database of Sitagliptin [1]. Out of the 62 cases reviewed by them, not a single patient had experienced hypoglycaemia. Out of the 19

children, less than nine years of age who were exposed to sitagliptin, one child had experienced symptoms but they were managed at home after one episode of vomiting. Three adolescent patients between 10 and 18 years of age who had unintentionally ingested sitagliptin did not develop any symptoms. One adult patient out of 40 had abdominal discomfort after ingesting 700 mg of sitagliptin but could be discharged from the emergency department itself after proper treatment. The authors concluded that majority of the patients were managed at home and no patient required hospitalization [1]. In the present case report the patient had severe hypoglycaemia (BSL 19 mgm%) and needed hospitalisation.

Russell JL et al., included 650 cases to review National Poison Database System of sitagliptin [2]. Five hundred sixty two developed no clinical side effects. They reported that two non-diabetic persons, who had accidental exposures, developed clinically significant hypoglycaemia that required treatment. One diabetic patient on sitagliptin developed prolonged hypoglycaemia and required admission and continuous intravenous dextrose. Of the 650 cases exposed to sitagliptin, 639 (98.3%) had no or only minor clinical effects. Three patients had clinically significant hypoglycaemia which required intervention. They concluded that exposure to sitagliptin rarely caused significant hypoglycaemia, but symptomatic patients should be evaluated and managed accordingly [2]. The present study substantiated the findings of the case report.

Toyoda-Akui M et al., reported a rare case in which sitagliptin was responsible for acute hepatic damage [3]. In the present case report liver function tests were within normal limits.

Nguyen HL and Concepcion L reported 12 cases requiring dialytic intervention of Metformin intoxication. They found that metformin toxicity is very serious clinical condition. It can cause severe lactic acidosis and even death. Management of metformin intoxication and correction of the metabolic abnormalities can be effectively done by haemodialysis [4]. In the present case report renal functions were normal.

Dell'Aglio DM et al., systematically reviewed 10 articles of metformin intoxication. They reported that there was not a single case of acute metformin overdose meeting the study's inclusion criteria wherein no patient with serum pH greater than 6.9, peak serum lactate concentrations less than 25 mmol/L, or peak serum metformin concentrations less than 50 µg/mL died. The authors concluded that patients who died of acute metformin overdose had lower serum pH, higher peak serum lactate and metformin concentrations than those who survived [5]. In the present case report pH was 7.42 at the time of admission.

Furukawa S et al., presented a case report of suicidal attempt by overdose of sitagliptin. In that case a 86-year-old female patient had consumed 1700 mg of sitagliptin (17 times the maximum approved dose). Four hours after ingestion, when she was seen in the emergency department, she was fully conscious, her blood sugar was 124 mg/dL and insulin level was 5.81 µU/mL. Patient was monitored and her plasma sitagliptin level rose 4.5 times higher than maximum therapeutic range, but patient did not suffer from hypoglycaemia. This case actually suggested that a single oral overdose of sitagliptin is unlikely to cause hypoglycaemia [6]. However, hypoglycaemia did occur in our patient with just about 450 mg of sitagliptin, thus, showing the rarity of our case.

Jeffrey R Suchard and Thomas A Grotsky reported a case of metformin toxicity (>60 gm) as a suicide attempt who on admission in an emergency department had acute renal insufficiency, severe lactic acidosis, and severe hyperglycaemia (BSL 707 mg/dL). This 29 year old male succumbed 25 hours after the ingestion in spite of sodium bicarbonate infusion and haemodialysis treatment [7]. In the present case report consumption of metformin was around 4.5 gm and patient did not have acidosis and survived after hospitalisation.

The incidence of hypoglycaemia following single overdose exposure of Janumet (Sitagliptin+Metformin) is not very common. Glucose dependent insulin release is a feature of gliptins. Although, the consumption in this case exceeded the maximum dose, the serum insulin levels were not in accordance to the blood sugar levels. Also, metformin is not known to cause rise in serum insulin levels, nor does it cause significant hypoglycaemia by itself. In our case there was no renal dysfunction, nor was there any evidence of acidosis (as secondary causes of hypoglycaemia).

## CONCLUSION

Overdose of Janumet (metformin+sitagliptin) rarely ever causes severe hypoglycaemia and convulsions. Early diagnosis and proper treatment can save the life of the patient.

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**PARTICULARS OF CONTRIBUTORS:**
1. Consultant, Department of Medicine, Poona Hospital and Research Centre, Pune, Maharashtra, India.
2. Consultant, Department of Medicine, Poona Hospital and Research Centre, Pune, Maharashtra, India.
3. Consultant, Department of Research, Poona Hospital and Research Centre, Pune, Maharashtra, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**
Dr. Deepak Phalgune,
18/27, Bharat Kunj-1, Erandawane, Pune-411038, Maharashtra, India.
E-mail: dphalgune@gmail.com

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