CASE SERIES

Hypoglycaemia after post-operative oral analgesics administration: A case series

Tashfeen Ahmad, Zehra Abdul Muhammad

Abstract

Analgesics-related hypoglycaemia is rare and is under exploration. The objective of this study is to illustrate the hypoglycaemia in at-risk fracture patients, concurrently treated with post-surgery oral analgesics and concomitant drugs. In a prospective cohort study, 288 adult proximal femoral, ankle, and hindfoot fracture patients, operated on between June 2022 to January 2024 were enrolled. Up to two-weeks post hospital discharge, prescribed analgesics, and adverse events were recorded. Out of these, five cases were observed who developed hypoglycaemia after administration of concomitant analgesic(s), anti-diabetics, and anti-hypertensives. Analgesics prescribed on discharge were Acetaminophen, Tramadol-Acetaminophen, Pregabalin, Celecoxib, etoricoxib, Diclofenac-Misoprostol, Tapentadol, and Ketorolac Tromethamine. With normal dietary intake, the elderly hypertensive and diabetic patients experienced hypoglycaemia (symptoms and/or <70mg/dL glucose level) after analgesics administration. Patients were treated with dextrose, sugar, etc., and after adjustment of analgesics dose were directed to an endocrinologist. It seems that certain analgesics increase the risk of hypoglycaemia in elderly hypertensive and diabetic fracture patients which might be a combinatory effect of analgesics, anti-hypertensive, and/or anti-diabetic agents.

Keywords: Hypoglycaemia; analgesics; bone fracture.

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Introduction

Usually, patients with diabetes mellitus have other co-morbid conditions which also require regular drug treatment along with anti-diabetic agents which increase the risk of drug-drug interaction. While managing fractures, most orthopaedic surgeons prescribe analgesic(s). This increases the risk of adverse consequences in diabetic patients by the interaction of anti-diabetic agents, other concomitant drugs, and analgesic(s), and thus, appropriate adjustment of anti-diabetic agents is essential to avoid hypoglycaemia/hyperglycaemia. Analgesic-related side effects could be serious. Depending on the patient or clinical factors, analgesics can cause some unexpected adverse events (AE) like hypoglycaemia (glucose level <70 mg/dL) which is still under exploration.[1,2] Hypoglycaemia is usually overlooked by physicians which is alarming as it might produce fatal consequences.

This case series illustrates the potential hypoglycaemia in elderly diabetic and hypertensive patients who were on anti-diabetic and anti-hypertensive medication and concurrently took oral analgesics for fracture pain post-operatively. This finding provides valuable insight regarding potentially analgesic-related hypoglycaemia in at-risk patients.

Case Series

After institutional and ethical approvals, the prospective cohort study was conducted at the Aga Khan Hospital, Karachi, between June 2022 to January 2024. As per the guidelines for Good Clinical Practise (GCP),[3] 288 proximal femoral, ankle, and/or hindfoot fracture patients, ≥18 years of age, who consented and voluntarily participated were included in the study, while patients unable to give consent or those who were treated with limb amputation were excluded. Oral analgesics were routinely prescribed at the time of hospital discharge and one-week follow-up, and their potential AE or serious adverse event (SAE) were recorded at one- and two-week follow-ups. A case series of five fracture patients who experienced hypoglycaemia after administration of oral analgesics and concomitant drugs was extracted from the study data. The normal blood glucose levels were fasting 65-100 mg/dl and random 80-160 mg/dl. Analgesic compliance was checked by daily drug records and verbal communication. Table presents the details of concomitant drugs, assessments, operations, blood glucose levels, and analgesics administered in-hospital, at the time of discharge from hospital, and at one-week follow-up.

The first case was that of a 69-year-old male patient with a left ankle trimalleolar fracture who was admitted to the Aga Khan University Hospital, Karachi on April 18, 2023. The patient had hypertension, diabetes mellitus, ischaemic heart disease, and dyslipidaemia. On discharge from

Department of Surgery, Aga Khan University, Karachi, Pakistan.
Correspondence: Zehra Abdul Muhammad. e-mail: zehra.abdul@aku.edu
ORCID ID: 0000-0002-6048-9042

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Table: Concomitant drugs, analgesics, and blood glucose levels recorded during hospitalisation, at hospital discharge, and one-week follow-up.

				At hospital discharge and one-week follow-up		
Case	**ASA**	**Vital signs**	**Surgery**	**Concomitant drugs**	**Location**	**Data collected**
1	IV	Heart rate 78/minute, respiratory rate 18/minute, temperature 36.7°C, blood pressure 125/70 mmHg	External fixator	Insulin, ondansetron, esomeprazole, ascorbic acid, atorvastatin, calcium, dapagliflozin, metformin, aluminium hydroxide-magnesium trisilicate, glyceryl trinitrate, apixaban, itopride HCL, nebivolol, and acetylsalicylic acid	Acetaminophen, nalbuphine, tramadol, ketorolac, tramadol, added acetaminophen, diclofenac, gabapentin, orphenadrine added acetaminophen	**Fasting:** 132, 133, 156, 223, 314, 174, 165, 222, 212, 163. **Random:** 278, 173, 331, 360, 275, 210, 234, 193, 142, 177, 236, 142, 324, 182, 190, 90, 165, 117, 149, 151, 121, 226, 225, 81, 133, 166, 171, 198, 256, 143, 191, 249
2	III	Heart rate 101/minute, respiratory rate 20/minute, temperature 36.6°C, blood pressure 144/98 mmHg	Closed reduction internal fixation (CRIF) and dynamic hip screw (DHS) fixation	Omeprazole, metoclopramide hydrochloride, insulin Humalog, Glargine, piperacillin/tazobactam, amlodipine, atorvastatin, cetirizine dihydrochloride, and acetylsalicylic acid	Tramadol, acetaminophen, ketorolac, morphine, nalbuphine, pregabalin	**Fasting:** 370, 261, 207, 222, 127, 265, 128, 217, 191. **Random:** 304, 209, 218, 88, 139, 172, 180, 159, and 150
3	III	Heart rate 83/minute, respiratory rate 18/minute, temperature 36°C, blood pressure 160/90 mmHg	DHS fixation	Clindamycin, ciprofloxacin, omeprazole, atenolol, Sinemet, glimepiride, amantadine, and acetylsalicylic acid	Tramadol, acetaminophen, ketorolac, morphine, Humalog 2 units	**Fasting:** 178, 260, 190, 154 **Random:** 142, 127, 216, 293
4	III	Heart rate was 74/minute, respiratory rate 20/minute, temperature 37°C, blood pressure 160/64 mmHg	Proximal femur nailing	Cephalexin monohydrate, thyroxine sodium, calcium, vitamin D3, vitamin K2, amlodipine/valsartan, metformin 750 mg, and acetylsalicylic acid.	Acetaminophen, tramadol, ketorolac, nalbuphine, fentanyl, gabapentin, pregabalin	**Fasting:** 168, 188, 181, 195, 127 **Random:** 207, 311, 215, 199, 152
5	III	Heart rate 95/minute, respiratory rate 16/minute, temperature 36.1°C, blood pressure 202/102 mmHg	Bipolar hemiarthroplasty	Glargine and Humulin insulin, alprazolam, furosemide bisoprolol, losartan potassium, sitagliptin, and amlodipine	Morphine sulfate, ketorolac, acetaminophen, tramadol	**Fasting:** 154, 108, 142, 192, 209, 408, 253 **Random:** 352, 207, 299, 316, 186, 119

	At hospital discharge and one-week follow-up			
Case	**Analgesics prescribed at hospital discharge**	**Glucose level *(mg/dL)* within one week of discharge *(symptoms)***	**Glucose level *(mg/dL)* after treatment**	**Analgesics adjusted at 1-week follow-up**
1	Pregabalin 75mg BID, tapentadol 75mg BID, celecoxib 200mg HS PRN, acetaminophen 1000mg QID (please remove analgesics adjusted at 1-week follow-up)	51, 57, 67 (chest pain)	100	Acetaminophen 1000 mg PRN, celecoxib 200 mg HS, Tapentadol 75 mg BID
2	Acetaminophen 1000mg QID, tramadol 37.5mg-acetaminophen 325mg BID	**Fasting:** 99. **Random:** Between 50-90 (sweating, drowsiness).	128, 167	Acetaminophen 1000 mg QID, tramadol 37.5mg-acetaminophen 325mg PRN
3	Tramadol 37.5 mg-acetaminophen 325 mg HS, etoricoxib 90 mg OD, acetaminophen 1000mg TID	35, 46, 50, 60 (drowsiness)	71	Etoricoxib 60 mg PRN, tramadol 37.5 mg-acetaminophen 325 mg PRN (self), acetaminophen 1000mg TID
4	Pregabalin 75 mg HS, tramadol 37.5 mg-acetaminophen 325 mg HS, acetaminophen 1000 mg TID, ketorolac tromethamine 30 mg HS (taken self)	46 (dizziness)	56 later 240	Tramadol 37.5 mg-acetaminophen 325 mg BID, pregabalin 75 mg HS
5	Acetaminophen 1000 mg QID, diclofenac 50 mg-misoprostol 200 µg BID	90 (sweating and confusion)	119	Acetaminophen 1000 mg PRN, diclofenac 50 mg-misoprostol 200 µg BID

The American Society of Anaesthesiologists physical status classification grade (ASA), Quater in die/four times daily (QID), Ter in die/three times daily (TID), Bis in die/twice daily (BID), Omne in die/once daily (OD). Pro re nata/As needed (PRN).
Note: Laboratory normal reference: Fasting blood glucose levels 65-100 mg/dL and random 80-160 mg/dL

hospital, he was prescribed routine oral analgesics. Because of his cardiac problems, he was taking a soft diet regularly. On the fifth post-discharge day (April 23, 2023), the patient arrived at the hospital with complaint of chest pain and constipation. There was no complaint about a decrease in appetite or anorexia. On investigation, his glucose level was 51mg/dL for which sweets were given and after 15-20 minutes the blood glucose level reached 100mg/dL. His analgesics were re-adjusted by the treating surgeon. The patient was admitted with unstable angina. Echocardiography showed grade I left ventricular diastolic dysfunction.

The second case was a 72-year-old diabetic and hypertensive female who was admitted to the Aga Khan University Hospital, Karachi on May 15, 2023, with a right femur intertrochanteric fracture. On discharge from the hospital routine oral analgesics were prescribed. After two days (May 20, 2023), in the morning, her fasting blood glucose level was 99mg/dl but after some time of taking breakfast and analgesics she had episodes of hypoglycaemia with symptoms of drowsiness and sweating (random blood glucose level 50 mg/dL). She also had complaints of weakness and fatigue. After the episode of hypoglycaemia, she took bananas and sweets and did not take Humalog insulin throughout the day. After 30 minutes, her glucose level was 167 mg/dL. Upon notification in the clinic (May 23, 2023), the surgeon gradually stopped Tramadol-Acetaminophen, and the endocrinologist adjusted her insulin doses.

The third case was a 64-year-old male who was admitted to the Aga Khan University Hospital, Karachi with a right intertrochanteric fracture on November 21, 2023. He had diabetes mellites hypertension, and Parkinson's disease. The patient was discharged on oral analgesics, and on the same day after taking analgesics, he became drowsy. With normal meal intake, his random blood glucose level was 50mg/dL. He initially took sweets and stopped Glimepiride. The patient experienced a few episodes of hypoglycaemia from November 23 to 27, 2023, even with a regular normal diet. He was compliant with all prescribed analgesics, but on the follow-up day, he skipped the morning dose. On November 27, 2023, his glucose level was 35mg/dL during the follow-up, which was managed by dextrose 25%, juices, and sugar. After 45 minutes the level reached 71mg/dl. His analgesics were re-adjusted and he was referred to an endocrinologist.

On December 11, 2023, the fourth case of a 64-year-old female, arrived at the Aga Khan University Hospital, Karachi with a right femur pertrochanteric fracture. The patient had hypertension, diabetes mellitus, and hypothyroidism. On discharge from the hospital, routine oral analgesics were prescribed. On the same day, she travelled for 7-8 hours, and her pain aggravated for which she took Tramadol-Acetaminophen and Pregabalin. At night, she self-treated with the injection Ketorolac Tromethamine and took night-time meal normally. In the morning (December 15, 2023), she took Acetaminophen with Cephalexin 500mg, Thyroxine sodium 50mg, Metformin 750mg, and Amlodipine/Valsartan 5/160mg before breakfast and suddenly became dizzy with a fasting glucose level of 46mg/dL. She ingested sapodilla and sugar and her blood glucose level reached 56mg/dL. Thereafter, she took juice, and the level reached 240 mg/dL. On notification in the clinic (December 21, 2023), the surgeon adjusted analgesic doses and referred her to an endocrinologist.

The fifth case was an 80-year-old female with diabetes mellites, hypertension, and valvular heart disease, who arrived at the Aga Khan University Hospital, Karachi on November 16, 2022, with a right femoral neck fracture. Routine oral analgesics were prescribed at discharge. Her husband reported that she was on normal dietary intake after discharge but after two days (November 23, 2022), she had excessive sweating, tachycardia, and confusion (glucose level 90mg/dL). She took some sugar and stopped Humalog insulin. While on concomitant drugs, she never had a blood glucose level of ≤90mg/dL. On notification in the clinic (November 26, 2022), the Acetaminophen dose was reduced and she was referred to an endocrinologist.

Discussion

This report presents the cases of five elderly diabetic and hypertensive patients who experienced hypoglycaemia after concurrently administering analgesics (Acetaminophen, Tramadol-Acetaminophen, Pregabalin, Diclofenac-Misoprostol, Tapentadol, Celecoxib, Etoricoxib, and Ketorolac Tromethamine) with regular concomitant drugs. Hypoglycaemia was seldom seen in these patients before while on their concomitant medications. Acetaminophen-related hypoglycaemia usually occurs after liver failure, but the Food and Drug Administration (FDA) reported Acetaminophen and Humalog insulin interaction.[4] Other frequently prescribed analgesics were Tramadol-Acetaminophen and Pregabalin which can cause hypoglycaemia.[1,2] Hypoglycaemia is rarely caused by Diclofenac, Celecoxib, Etoricoxib, and Ketorolac Tromethamine.[5,6] Case 5 was symptomatic for hypoglycaemia at 90mg/dL glucose level and this might be considered as relative hypoglycaemia.

Concomitant drugs Ondansetron, Atorvastatin, Apixaban, Nebivolol, Metoclopramide, and Omeprazole, Atenolol, Amantadine, and Valsartan rarely cause hypoglycaemia.[7-10] Furthermore, Piperacillin-Tazobactam

and Ciprofloxacin might cause hypoglycaemia.[11] The current report provides valuable insight regarding potential hypoglycaemia risk in elderly diabetic and hypertensive patients after administration of certain analgesics concomitantly with anti-diabetic and anti-hypertensive agents. This event might be due to a combinatory effect of these drugs. Future studies with sufficient similar cases are needed to draw a firm conclusion. Cautiously managing at-risk patient populations to prevent hypoglycaemia and mortality could be suggested. Serum cortisol and C-peptide levels were not measured in this research for further patient workup which is the limitation of the study.

Conclusion

The preliminary data suggest that elderly diabetic and hypertensive fracture patients on anti-diabetic and anti-hypertensive agents were likely at risk of hypoglycaemia after administration of certain analgesics which seemed to be a combinatory effect. The use of a combination of multiple analgesics with different mechanisms made it difficult to predict the specific analgesic that is likely related to hypoglycaemia. Future studies with enough at-risk patients are needed to further explore this finding and to draw a firm conclusion. Based on the current research findings, careful analgesic selection, anti-diabetic and analgesic dosage adjustment, and close blood glucose monitoring could be suggested to minimise hypoglycaemia risk.

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