CASE REPORT

NOT SO INNOCENT INDAPAMIDE

Shayan Aziz[1], Abdullah[2], Satyan Rajbhandari[1]

[1]Diabetes and endocrine department, Chorley and South Ribble District General Hospital, Lancashire Teaching Hospitals
[2]Lancashire Cardiac Centre, Blackpool Victoria Hospital, Blackpool Teaching Hospitals NHS Foundation Trust-United Kingdom

A 58-year-old asymptomatic man was referred by his general practitioner for abnormal blood results. Routine blood tests to monitor blood count and kidney functions showed neutropenia and hyponatremia. He was euvolemic on examination. A further detailed investigation did not reveal any cause of neutropenia and hyponatremia. After careful assessment of their drug history, it transpired he recently started Indapamide for uncontrolled hypertension. Hyponatraemia is a common side effect of Indapamide and in addition, it can rarely cause agranulocytosis and leukopenia. Indapamide was stopped and the blood counts started to improve and became normal after two weeks.

Keywords: Indapamide; Hyponatremia; Neutropenia

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INTRODUCTION

Neutropenia is a common haematological finding but a potentially life-threatening condition.[1] Neutropenia is defined as an absolute neutrophil count of less than 1.5×10^{9}/L and severe neutropenia is when the neutrophil count is less than $0.5\times10^{9/L}$.[2] The common causes of neutropenia are viral infections, use of chemotherapeutic agents, haematological diseases, malignancies, autoimmune conditions, vitamin deficiencies and drugs.[3] The prevalence of hypertension is high, and it affects about 1 in 3 adults in the UK.[4] Antihypertensives are among the top 6 medications prescribed in England.[5] Indapamide is a commonly prescribed drug for hypertension. It is an orally active sulphonamide thiazide like diuretic agent.[6] Antihypertensive action of Indapamide is primarily a result of its diuretic activity and also by decreasing vascular reactivity and peripheral vascular resistance.[6] It was approved by the United States Food and Drug Agency (FDA) in 1984 for the treatment of hypertension.[7] The most common side effects of indapamide are electrolyte imbalance, skin reactions, erectile dysfunction, fatigue, headache, hyperglycaemia, hyperuricemia, and postural hypotension.[8] Haematological side effects of Indapamide are uncommon.[8] We present a rare case of Indapamide-induced neutropenia.

CASE

A 58-year-old male patient was admitted to the hospital by his general practitioner (GP) following abnormal routine blood test results of hyponatraemia and neutropenia. On clinical review, he was asymptomatic with no history of fever, flu-like symptoms, night sweats, rash, or bleeding. No history of weight loss and his appetite was normal. He denied using over-the-counter medications or recreational drugs and he did not travel abroad recently.

Patient comorbidities included hypertension and anxiety. Blood pressure had been well controlled on ramipril 10mg and amlodipine 10 mg daily until recently. Due to persistently raised blood pressure for the last three months, GP added indapamide 2.5 mg once daily to his prescription a month before admission to the hospital.

His father had prostate cancer and his mother had myocardial Infarction. There was no family history of blood disorders. He did not smoke and drank alcohol less than 10 units per week. No history of exposure to any chemicals in the past.

On examination, the patient was afebrile, with normal heart rate and blood pressure. He was not pale or jaundiced, clinically euvolemic with a moist mucous membrane and normal skin turgor without any ankle oedema. There was no rash, bruises, petechia, lymphadenopathy or hepatosplenomegaly.

Investigations at admission are given in Table-1. Chest X-ray was normal with no signs of lymphadenopathy or consolidation.

The list of differential diagnoses for neutropenia is wide but in this case, clinical history, examination and baseline investigations narrowed it down to recent viral infections, adverse reactions to drugs or haematological malignancies. The differential diagnosis for hyponatraemia included the Syndrome of inappropriate antidiuretic hormone (SIADH) due to drugs or occult malignancies or due to the diuretic effects of Indapamide.

The patient received a single dose of intravenous antibiotic according to hospital policy for neutropenic sepsis pending investigation results. Indapamide was stopped as it is commonly associated

with hyponatraemia. Further investigations including blood film, haematinics, autoimmune screen, viral screening, blood, and urine cultures were also performed. He had routine screening testing for COVID infection as per local protocol for all hospital admissions. He was then transferred to a side room in line with neutropenic patient care. In view of hyponatremia, the patient was restricted to 1500 ml of fluid per day. Full blood count and serum electrolytes were daily monitored. An expert haematology opinion was requested due to neutropenia. Urine electrolytes and osmolality were initially not done as the cause of hyponatremia was deemed high likely due to Indapamide.

The antibiotic was stopped the next day due to the absence of symptoms and signs of infection. The second routine COVID-19 infection screening using nasal and throat Polymerase Chain Reaction (PCR) tests was negative. The haematology team advised vasculitis screening and planned to perform a bone marrow biopsy as the next step if neutropenia does not improve and remains unexplained following the negative results of other investigations.

The blood film report showed leukopenia, anisocytosis and poikilocytosis. Folic acid, vitamin B12 and Iron profile were all within normal limits. Viral screen, immunoglobulins and vasculitis screen were all negative. Repeat swabs for COVID performed after 48 hours as per hospital screening policy were again negative. Urine and blood cultures did not show any growth. The patient remained asymptomatic but remained isolated due to neutropenia. On day 3 of admission, CT Thorax, Abdomen and Pelvis (CT TAP) were performed to rule out underlying malignancy as the blood picture was not improving. CT TAP was normal. On day 5, neutrophil count, platelets count, and serum sodium started to improve but lymphocyte count further dropped to 0.2 (Ref: 1-4) x 10^9/L). He tested positive for COVID-19 on routine screening possibly due to nosocomial infection, but the patient remained asymptomatic. On Day 9, neutrophil count (Figure-1), platelet count (Figure-2) and serum sodium (Figure 3) returned to safe levels and therefore the patient was discharged from the hospital. Two weeks follow-up full blood count and serum electrolytes were almost normal (Table-2). All blood tests returned to normal after 2 months.

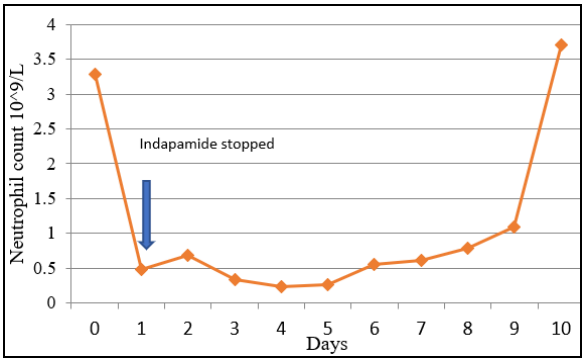

Figure-1: Improvement of neutrophil count after stopping indapamide

Table-2: Investigations 2 weeks after discharge

Investigations	Result (Reference range)	Investigations	Result (Reference range)
Haemoglobin	139 (Ref: 130-180) g/L	Platelets	5.4 (Ref: 2.5 – 7.8) mmol/L
White cell count	3.71 (Ref: 4-11) x 10^9/L	Urea	82 (Ref: 59-104) µmol/L
Neutrophils	2.51 (Ref:1.6-7.5) x 10^9/L	Creatinine	134 (Ref:133-146) mmol/L
Lymphocytes	0.72 (Ref: 1- 4) x 10^9/L	Sodium	4.2 (Ref: 3.5-5.3) mmol/L
Monocytes	0.41 (Ref: 0.2-1) x 10^9/L	Potassium	4.2 (Ref: 3.5-5.3) mmol/L
Eosinophils	0.00 (Ref: 0.04-0.44) x 10^9/L		

Table-1: Admission investigations; TSH: Thyroid stimulating hormone

Investigations	Result (Reference range)	Investigations	Result (Reference range)
Haemoglobin	128 (130-180) g/L	Platelets	132 (140-440) x 10^9/L
White cell count	1.62 (4-11) x 10^9/L	Urea	7.1 (2.5 – 7.8) mmol/L
Neutrophils	0.48 (1.6-7.5) x 10^9/L	Creatinine	77 (59-104) µmol/L
Lymphocytes	0.64 (1- 4) x 10^9/L	Sodium	128(133-146) mmol/L
Monocytes	0.46 (0.2-1) x 10^9/L	Potassium	3.9 (3.5-5.3) mmol/L
Eosinophils	0.46 (0.2-1) x 10^9/L	TSH[1]	2.05 (mIU/L)

The final diagnosis was Indapamide induced neutropenia, hyponatremia and hospital acquired COVID-19. The diagnosis was supported by negative results of all investigations and improvement of neutrophil count to normal following withdrawal of Indapamide. Patient was discharged back to his GP with the recommendation to monitor blood pressure and start an alternative drug in case of uncontrolled blood pressure. A yellow card was filled to report the adverse event to the local drug regulatory authority.

DISCUSSION

Neutropenia is a life-threatening condition. This case report describes a rare side effect of Indapamide induced severe neutropenia which improved gradually after withdrawing the drug.

NICE recommends thiazide diuretics first line agents as an alternative to calcium channel blockers in patients with hypertension without diabetes over the age of 55. Chaffman *et al*, have described Indapamide as a thiazide-like orally active sulphonamide diuretic agent.[6] The mechanism of action and side effect profile of Indapamide is similar to the thiazide diuretics.[5] Hyponatraemia due to Indapamide is well recognised.[9] British National Formulary describes agranulocytosis as a known but uncommon side effect of thiazides and related diuretics.[8] In a literature search, we did not find any published case report or review of Indapamide-induced blood dyscrasias. Chrein *et al* have reported a case of agranulocytosis secondary to hydrochlorothiazide.[10]

The patient described in this case report presented with severe neutropenia which improved significantly 9 days after stopping Indapamide. There were no other causes of reversible neutropenia identified on detail investigations. Although the patient acquired COVID-19 during the hospital stay, neutropenia was present when the PCR test was negative on admission.

This case report also raises the question of nosocomial COVID-19 infection in a vulnerable patient even when he was in an isolated room. The most likely exposure occurred during the early admission process before he was transferred to isolation. This gives serious thought to the route of admission of immunocompromised patients during the COVID pandemic time.

In conclusion, neutropenia is a rare side effect of indapamide that potentially can become serious, especially in the immunocompromised patient, therefore, full blood count should be monitored

LEARNING POINTS

- Indapamide can rarely cause blood dyscrasias therefore baseline full blood count should be performed before starting indapamide and then periodically monitored by the general physician in the community.
- Indapamide should be stopped in the event of new findings of neutropenia.
- During COVID pandemic, it is reasonable to monitor a patient with asymptomatic neutropenia at home to reduce the risk of nosocomial COVID infection.

REFERENCES

1. Kuderer N, Dale D, Crawford J, Cosler L, Lyman G. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006;106(10):2258–66.
2. Dale DC. How I diagnose and treat neutropenia. Curr Opin Hematol 2017;12(1)1–4.
3. Gibson C, Berliner N. How we evaluate and treat neutropenia in adults. Blood 2014;124(8):1251–8.
4. National Institute for Health and Care Excellence. Hypertension in adults: Diagnosis and management. NICE guideline No.136. [Internet]. [cited 2021 Nov 18]. Available from: https://www.nice.org.uk/guidance/ng136
5. Audi S, Burrage D, Lonsdale D, Pontefract S, Coleman J, Hitchings A, *et al*. The top100 drugs and classes in England: an updated starter formulary for trainee prescribers. Br J Clin Pharmacol 2018;84(11):2562–71.
6. Chaffman M, Heel RC, Brogden RN, Speight TM, Avery GS. Indapamide. A review of its pharmacodynamic properties and therapeutic efficacy in hypertension. Drugs 1984;28(3):189–235.
7. Vukovich RA, Zisblatt M, Caruso F, Losi M, Barton J, Schotz WE, *et al*. Multi-centre clinical investigation of indapamide in the United States: a review. Curr Med Res Opon 1983;8(suppl 3):109–22.
8. Joint Formulary Committee. British National formulary. 82. London. BMJ group and Pharmaceutical Press; 2021. [Internet]. [cited 2021 Nov 18]. Available form: https://bnf.nice.org.uk/drug/indapamide.html1
9. Liamis G, Filippatos TD, Elisaf MS. Thiazide-associated hyponatremia in the elderly: what the clinician needs to know. J Geriatr Cardiol 2016;13(2):175–82.
10. Chiren MB, Rubin IL. Agranulocytosis secondary to hydrochlorothiazide therapy. Report of a case. JAMA 1962;181:54–5.

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Address for Correspondence:

Dr Shayan Aziz, Department of Endocrine and Diabetes, Chorley and South Ribble District General Hospital Lancashire Teaching Hospitals NHS Foundation Trust, Preston Rd, Chorley, Lancashire, United Kingdom. PR7 1PP
Tel: +44(0)7474133250
Email: shayan.aziz@lthtr.nhs.uk