CASE REPORT

Hyperacute leucopenia associated with furosemide

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SUMMARY

A 72-year-old man presented to the hospital with exacerbation of congestive heart failure. He was given furosemide 40 mg intravenously twice at 4 hours apart. At 4 hours after the second dose of furosemide, his white blood cells (WBC) dropped acutely from 9.8 to $2.4 \times 10^9/L$ (reference range 4.1 to $9.3 \times 10^9/L$). With the discontinuation of furosemide, the WBC trended up to $7.1 \times 10^9/L$ about 13 hours after the second dose of intravenous furosemide and remained in normal range for the next 3 days. However, when the oral furosemide was started on hospital day 4, there was a mild drop in WBC count, which returned to and maintained at baseline since the next day. The dynamic changes in the patient's WBC were coincident with the use of furosemide. The possible mechanisms of furosemide-associated transient hyperacute leucopenia were discussed.

BACKGROUND

Furosemide is one of the core medications commonly used in the management of congestive heart failure (CHF).¹ It is a loop diuretics^{2,3} that belongs to a class of non-antibiotic sulfonamide.^{4,5} Furosemide is usually well tolerated.¹⁻³ The common adverse drug effects include electrolyte imbalance, ototoxicity or potential hypersensitivity.^{6,7} This paper presents a case of transient hyperacute leucopenia associated with intravenous furosemide use,

Figure 2 Differential cell counts in laboratory tests at different time points.

a phenomenon that has not been reported yet. It had a Naranjo Adverse Drug Reaction Probability Scale score of 7, which fell in the probable scale.⁸ The precise mechanism of the leucopenia associated with furosemide is unclear, but it deserves further investigation due to its great clinical importance as furosemide is one of the broadly used medications in various conditions.

CASE PRESENTATION

The patient was a 72-year-old man with a medical history significant for CHF, hypertension, hyperlipidaemia, coronary artery disease, diabetes mellitus and chronic obstructive pulmonary disease who presented to the hospital emergency room with a 2-day history of progressive dyspnoea. The patient took furosemide 20 mg daily at home. His other home medications include metoprolol tartrate 25 mg and metformin 500 mg (two times per day), and atorvastatin 20 mg, pioglitazone 15 mg, amlodipine 10 mg, lisinopril 10 mg, aspirin 81 mg and clopidogrel bisulfate 75 mg (one time per day). The patient had no known drug allergies. The physical examination revealed trace pitting oedema in the bilateral lower extremities. His vital signs were stable with 96% oxygen saturation on room air.

As detailed in table 1, the patient's first set of laboratory tests (lab-1) showed mild leucocytosis, moderate anaemia and elevated pro-B-type natriuretic peptide. The renal function was unremarkable. Chest X-ray revealed moderate pulmonary vascular congestion and tiny bilateral pleural effusions (figure 1). The patient's history, diagnostic data and physical examination were consistent with acute exacerbation of CHF.

The patient was given two doses of 40 mg furosemide intravenously at 3 hours and 7 hours after

Figure 1 Chest X-ray showing moderately diffuse pulmonary vascular congestion and trace bilateral pleural effusion consistent with decompensated congestive heart failure.

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Table 1 Patient's pertinent lab profiles

	Lab-1	Lab-2	Lab-3	Lab-4	Lab-5	Lab-6	Lab-7	Lab-8	Lab-9	Lab-10	Range	Unit
Hours since lab-1	0	11	13	18	22	26	41	75	95	119		
Haematogram												
WBC	9.8	2.4	2.4	2.8	3.8	7.1	7.2	7.2	5.7	7.0	4.1–9.3	10 ⁹ /L
RBC	4.13	4.55	4.06	3.83	4.11	4.13	3.66	3.64	3.72	3.59	3.66–5.56	10 ¹² /L
HGB	8.9	9.7	8.7	8.3	8.8	8.8	7.7	7.7	7.8	7.7	13.8–17.2	g/dL
HCT	28.6	31	27.7	25.9	28.3	28.7	25.1	25.1	25.7	25.4	40.6–51.8	%
PLT	294	348	325	344	370	350	358	369	403	424	150–450	10 ⁹ /L
Neutrophil	7.5	1.9								3.6	1.4–6.5	10 ⁹ /L
Lymphocyte	1.2	0.4								2.0	1.2–3.4	10 ⁹ /L
Monocyte	0.9	0.1								1.2	0.1–0.6	10 ⁹ /L
Eosinophil	0.2	0.0								0.1	0.0–0.7	10 ⁹ /L
Basophil	0.0	0.0								0.1	0.0–0.2	10 ⁹ /L
Chemistry												
BUN	6										7–18	mg/dL
Creatinine	0.7										0.6–1.3	mg/dL
Pro-BNP	4536										0–125	pg/mL

BUN, blood urea nitrogen; HCT, haematocrit; HGB, haemoglobin; PLT, platelet; pro-BNP, pro-B-type natriuretic peptide; RBC, red blood cell; WBC, white blood cell.

lab-1. At 11 hours post lab-1 (4 hours after the second dose of intravenous furosemide), the second lab showed markedly reduced WBC of $2.4 \times 10^9/\text{L}$, including decreased neutrophil, lymphocyte, and monocyte. Lymphocyte and monocyte counts were either below the normal limits or low normal (table 1 and figure 2). The repeated third laboratory tests 2 hours later (13 hours after lab-1) confirmed the same leucocyte profile (table 1 and figure 3).

INVESTIGATIONS

After thorough review of the patient's history and clinical data, it was felt that the intravenous furosemide was the only new medication that was added since admission.

This patient had been on chronic oral furosemide treatment (20 mg) for CHF, either one or two times per day. There was no evidence that the patient had been exposed to sulfonamide antibiotics in the past.

The patient had multiple times of ER visits and hospital admissions for worsening dyspnoea due to CHF (no clinical signs of infection). Each time, he was given intravenous

furosemide ranging from 40 to 80 mg. As detailed in table 2, the haematology laboratory tests in multiple hospitalizations showed consistent immediate reduction in the leucocyte count after the intravenous furosemide treatment. The reduction involved all major cell subtypes, including neutrophils, lymphocyte and monocytes. For neutrophils, there was occasional neutrophilia on initial presentation. Although significantly lower than that of pretreatment, the post intravenous furosemide neutrophils were still within normal limits. A similar profile was also observed in monocytes, of which the baseline monocytosis existed before the intravenous furosemide treatment, but it was significantly reduced after the treatment. In contrast, the baseline lymphocyte before the intravenous furosemide treatment was within normal limits. After the intravenous furosemide treatment, lymphocyte count was always below the normal limits (table 2 and figure 4).

TREATMENT

The furosemide was discontinued, and the CBC was monitored every 4 hours. The patient was initially placed on neutropenic precaution, and haematology consultation was also obtained.

OUTCOME AND FOLLOW-UP

With the discontinuation of intravenous furosemide, the WBC started trending up in lab-6, which was about 26 hours after the first lab and 13 hours after the second dose of intravenous furosemide, remained in normal range for the next 3 days (table 1 and figure 2). However, when oral furosemide was started on hospital day 4 (75 hours after lab-1), there was a mild drop in lab-9 (95 hours after lab-1), which returned to and maintained at baseline in lab-10 (119 hours after lab-1) until discharge (table 1 and figure 2).

Due to the rapid recovery of WBC count in 24 hours and lack of signs of infection, the patient was cleared from neutropenic precaution. His dyspnoeic symptoms improved on diuretic treatment and was ultimately discharged from the hospital.

DISCUSSION

In this case, the dynamic changes of patient's WBC were coincident with the use of furosemide, and the transient hyperacute

Figure 3 Hyperacute transient leucopenia associated with furosemide use. Arrows indicate the time points when either intravenous (solid arrows) or oral (dashed arrow) furosemide was given. HGB, haemoglobin; RBC, red blood cell; WBC, white blood cell.

Table 2 Comparison of cell counts of leucocyte, neutrophil, lymphocyte and monocyte pre-furosemide and post-furosemide treatment in multiple hospitalisations

Hospitalisation	Leucocyte		Neutrophil		Lymphocyte		Monocyte	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	9.2	4.0	7.7	3.4	1.0	0.6	0.4	0.1
2	11.2	4.7	7.4	4.3	2.7	0.3	0.9	0.1
3	12.2	9.2	9.0	7.9	1.9	0.9	1.2	0.3
4	11.9	5.7	5.4	5.0	5.0	0.5	1.2	0.1
5*	9.8	2.4	7.5	1.9	1.2	0.4	0.9	0.1
Mean	10.86	5.20	7.40	4.50	2.36	0.54	0.92	0.14
Reference range ($10^9/L$)	4.1–9.3		1.4–6.5		1.2–3.4		0.1–0.6	

*Hospitalisation with episode of leucopenia after intravenous furosemide treatment.

leucopenia was likely associated with the pulse doses of intravenous furosemide—a phenomenon that has not been reported in the literature. Although no definite causal effect relationship can be established in this single case, with Naranjo Adverse Drug Reaction Probability Scale score of 7 (table 3), this phenomenon had a probable causal effect.⁸ Analysis of the patient's laboratory data in the past demonstrated consistent reduction in total leucocytes and composite sub-cell types including neutrophils, lymphocytes and monocytes after the intravenous furosemide treatment. The precise mechanism of the leucocyte reduction and, in this particular admission, the flash leucopenia associated with furosemide is unclear, but it deserves further investigation due to its great clinical importance.

Furosemide is a potent loop diuretics that delivers its action in the ascending limb of the loop of Henle by inhibiting the Na-K-Cl co-transporter from reabsorbing these cations.^{2,3} It is one of the standard components for the treatment of acute decompensated heart failure and is usually well tolerated.^{1,3} Common side effects associated with furosemide include fluid and electrolyte imbalance (such as hyponatraemia as in this patient), ototoxicity and hypersensitivities, which were most frequently associated with intravenously administered furosemide.^{3,6,7}

Chemically, furosemide, like other thiazide diuretics and loop diuretics, is a non-antibiotic sulfonamide medication that shares a SO_2NH_2 moiety with the sulfonamide antibiotics.^{4,5} Sulfonamide antibiotics are one class of the widely used antibiotics for both inpatient and outpatient settings, and are also among the most common cause of drug allergies. Although most

allergic reactions are mild to moderate, with skin rashes being the most common, more severe reactions, such as anaphylaxis, myelosuppression, agranulocytosis or thrombocytopenia, may occur.^{5,9} However, well-conducted retrospective cohort study by Strom *et al*⁴ showed lack of cross-reactivity between the antibiotic sulfonamides and non-antibiotic sulfonamides, and the incidences had been limited to sporadic case reports.⁴ One of the mechanisms, as summarised by Brackett *et al*¹⁰ is that the immunogenic moiety of sulfonamide antibiotics to cause type 1 allergic reaction (anaphylaxis) is the N1 heterocyclic ring. This moiety is lacked in the non-antibiotic sulfonamide drugs. Another immunogenic functional group in sulfonamide antibiotics is the N4 amino nitrogen, which is also absent in any non-antibiotic sulfonamides. This N4 amino nitrogen structure can be metabolised to stereospecific cytotoxic or immunological active metabolites that may mediate non-type 1 hypersensitivity. It is believed that lack of N1 and N4 amino nitrogen functional groups in the non-antibiotic sulfonamides largely explained their lack of cross-reactivity between antibiotic and non-antibiotic sulfonamides.^{10,11}

For furosemide, the route of administration may play an important role for causing adverse reactions, including cross-reactions, if any, between the antibiotic and non-antibiotic sulfonamides. Ototoxicity was proposed to be related to the intravenous boluses of furosemide.⁶ Bretza *et al* reported a case of recurrent pancreatitis associated with intravenous, but not oral, furosemide in a patient who was allergic to trimethoprim/sulfamethoxazole. These authors proposed that the cross-reactivity between these two classes of sulfonamide medications was an immune-mediated reaction to furosemide.¹² Chao and Chao reported a case of recurrent pancreatitis associated with furosemide in a dose-dependent manner in a patient with no known allergy to sulfonamide antibiotics.⁸

A similar phenomenon was observed in our case. Analysis of the patient's laboratory data in multiple hospitalisations for CHF exacerbation showed that once the intravenous furosemide was given, it was always associated with acute reduction in the total WBC and the subtype cell counts of neutrophils, lymphocytes and monocytes (table 2 and figure 4). The adverse effect of furosemide on WBC count appears to be dose dependent with the intravenous dosing having the most pronounced effect, which, on rare occasion, may even result in leucopenia as in this particular hospitalisation.

The chronicity and low-dose oral furosemide (20 or 40 mg daily) may not be sufficient to cause significant adverse reactions. In addition, when given orally, the bioavailability of furosemide is highly variable ranging from 10% to 90%; in contrast, the bioavailability of other two commonly used loop diuretics,

Figure 4 Average white blood cell and differential counts before and after intravenous furosemide treatment in five hospitalisations.

Table 3 Naranjo Adverse Drug Reaction Probability Scoring System

Question	Yes	No	Do not know	Score
Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0	0
Did the adverse event appear after the suspected drug was administered?	+2	−1	0	2
Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	+1	0	0	1
Did the adverse event reappear when the drug was readministered?	+2	−1	0	1
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	2
Did the reaction reappear when a placebo was given?	−1	+1	0	0
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure?	+1	0	0	1
Was the adverse event confirmed by any objective evidence?	+1	0	0	0
TOTAL SCORE:				7

torsemide and bumetanide, is nearly 100%.² This makes the pharmacokinetics of furosemide less predictable than its siblings, torsemide and bumetanide.

Of particular note, the data in this report were selected from the hospitalisations for CHF exacerbation with no clinical signs of infection. In addition, for this patient, he had no known drug allergies; nor was he documented to use any sulfonamide antibiotics in the past.

In summary, this paper first reports a phenomenon of the intravenous furosemide-associated transient hyperacute leucopenia involving marked decrease of neutrophil, monocyte and lymphocyte counts. The laboratory data of this patient's previous hospitalisations for decompensated CHF showed a similar pattern of reduction in the leucocyte counts after each intravenous furosemide treatment in a degree of less severity. A probable causal effect of adverse drug reactions of furosemide can be established according to Naranjo scoring system.⁸ Although the precise mechanism of this adverse effect remains to be elucidated and this phenomenon can not be generalised,

the clinician should remain at high index of suspicion when the patient has unexplained acute disturbance of cytology and should implement appropriate interventions, such as discontinuation of the offending drug and exercising neutropenic precautions if indicated.

Contributors BJM is the corresponding author who contributed literature search, figures, data collection, data analysis, data interpretation and manuscript writing. BJM had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Learning points

- Furosemide is a widely used loop diuretic that belongs to a class of non-antibiotic sulfonamide medications and is usually well tolerated.
- Rare adverse drug reaction may occur with the intravenously administered furosemide. A probably causal effect of adverse drug reactions of furosemide-related leucopenia can be established according to Naranjo scoring system.
- Furosemide-associated leucopenia may be under-recognised. Clinicians shall remain at high index of suspicion when the patient has unexplained acute white blood cell reduction with the use of furosemide and implement appropriate interventions, such as discontinuation of the offending drug and exercising neutropenic precautions for the patient, if indicated.

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