ONOMY Science

American Journal of Cardiology and Cardiovascular Diseases
ISSN 2641-2438

Case series Open Access

Incidence and characterization of gout attacks in patients hospitalized for acute heart failure receiving intensified diuresis: a case series of 27 patients

Anthony C.W. Lau, BSc Pharm, ACPR**, Mahsa Movahedan,** PharmD**, Vivian W.Y. Leung,**BSc(Pharm), ACPR**,** PharmD, PhD**, Herbert C. Wong,** BSc Pharm, ACPR

[1] Clinical Pharmacist, Surrey Memorial Hospital, Surrey, BC, 13750 96 Ave, Surrey, BC V3V 1Z2
[2] Entry-to-Practice (E2P) PharmD Graduate, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC
[3] Pharmacy Coordinator, Antimicrobial Stewardship, Fraser Health Authority & Lower Mainland Pharmacy Services
[4] Clinical Pharmacy Specialist (Cardiology), Surrey Memorial Hospital, Surrey, BC

***Corresponding Author: Anthony C.W. Lau,** BSc Pharm, ACPR, Clinical Pharmacist, Surrey Memorial Hospital, Surrey, BC 13750 96 Ave, Surrey, BC V3V 1Z2 Email: anthony.lau@fraserhealth.ca;
Tel. 604-760-8781

Citation: Incidence and characterization of gout attacks in patients hospitalized for acute heart failure receiving intensified diuresis: a case series of 27 patients. Am J of Card and Cardiovas Disc.2020; 3(1): 01-05.

Submitted: 29 April 2020; **Approved:** 01 May 2020; **Published:** 02 May 2020

Abstract

Diuretics are known to potentially trigger gout attacks, but the incidence in acute decompensated heart failure patients who receive intensified diuretic therapy is unknown. It has been speculated that diuretic-associated gout attacks negatively impact patients' quality of life and mobility, as well as unnecessarily prolong their length of hospital stay.

This case series which examines a community hospital cohort of acutely decompensated heart failure patients reports the incidence rate of gout attacks related to aggressive diuresis use and characterizes these patients who developed gout attacks. It also highlights the importance of identifying patients at risk of gout attacks when managing heart failure exacerbations with diuretics as it may improve patient-care and also reduce unnecessary use of healthcare resources. Further studies are needed to evaluate the role of early detection and intervention for heart failure patients at high risk for iatrogenic gout attacks.

Keywords: diuretic, furosemide, gout, heart failure, hyperuricemia

Introduction

Gout attacks are characterized by the acute clinical onset of painful and inflammatory arthritis, with monosodium urate monohydrate crystals depositing into the bony joints, and are often accompanied by the presence of hyperuricemia. Hyperuricemia, or elevated serum urate concentrations, occurs as a result of increased uric acid reabsorption or reduced uric acid excretion in the kidneys.[1] It has been observed that the use of diuretics has been associated with an increased risk of hyperuricemia. Loop diuretics and thiazide-like diuretics have been associated with a five to seven percent increased risk for gout attacks in hypertensive patients.[2,3]

Diuretics compete with uric acid for secretion in the proximal tubule of the kidneys, which increases urate reabsorption at this site.[4,5] In hypertensive patients, diuretics appear to increase serum uric acid concentrations in a dose-dependent manner.[8]

Patients who are hospitalized with decompensated heart failure often receive higher doses of diuretics acutely compared to their baseline diuretic regimen, and it has been speculated that the risk of gout attacks may be more profound in this patient population.

Cite this article: Incidence and characterization of gout attacks in patients hospitalized for acute heart failure receiving intensified diuresis: a case series of 27 patients. Am J of Card and Cardiovas Disc.2020; 3(1): 01-05.

New gout flares during heart failure hospitalizations anecdotally impair patients' quality of life and mobilization, which may unnecessarily prolong hospital length of stay. Thus, better characterization of these patients may help identify patients at high risk for gout attacks and potentially improve patient care and clinical outcomes.

Methods

The association between aggressive diuresis and acute gout flares was observed in a large cohort of patients who were admitted into a large-sized community hospital for decompensated heart failure and received aggressive diuretic treatment between July 2013 and July 2018. Computer-generated lists of patients with an admission diagnosis of "heart failure" and those who received furosemide, prednisone or colchicine within the same time frame were initially cross-referenced and screened to identify heart failure patients who developed acute gout attacks. The diagnoses of both heart failure and gout were subsequently confirmed by documentation in patients' charts.

The term "aggressive diuresis" was defined as intravenous diuretics or higher doses of diuretics compared to their baseline diuretic dose or its equivalent. The diuretic dosing equivalency between different agents and routes of administration are summarized in Table 1.

Table 1. Diuretic Dosing Equivalency

The following diuretic doses were considered less potent than oral furosemide 40 mg:

- Hydrochlorothiazide 25 mg
- Chlorthalidone 25 mg
- Indapamide 2.5 mg
- Amiloride 20 mg
- Spironolactone 25 mg
- Epleronone 25 mg
- Triamterene 100 mg
- Metolazone 2.5 mg

Loop Diuretic	Equivalent Dosing
PO Bumetanide	1 mg
PO Furosemide	40 mg
IV Furosemide	20 mg
PO Ethacrynate	50 mg

(Chart adapted from Pham D, Grodin JL. Dilemmas in the Dosing of Heart Failure Drugs: Titrating Diuretics in Chronic Heart Failure. Card Fail Rev. 2017 Nov;3(2):108-112.)

For the primary objective, we determined the incidence rate of gout attacks from this cohort. For the secondary objective, we further screened beyond this initial cohort of patients in reverse chronological order to identify more heart failure patients with gout attacks for characterization. Data were retrospectively collected from the patients' electronic health records; these data parameters for characterization included demographics (age and gender), incidence of gout attack, serum uric acid level, comorbidities that may increase the risk of gout attacks (hypertension, diabetes mellitus, dyslipidemia, atherosclerosis, chronic kidney disease, coronary artery disease, history of myocardial infarction, history of stroke or transient ischemic attack (TIA), history of gout and organ failure), concurrent medications (angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, beta-blocker, calcium channel blocker, nitrates, low dose acetylsalicylic acid (ASA), allopurinol or other gout prophylactic therapy (probenecid or febuxostat), chemotherapy, nicotinic acid, cyclosporine, levodopa, interferon, ribavirin and tacrolimus), diuretic use and type of diuretics prior to admission, inpatient diuretic use and type of diuretic, time to gout resolution, and length of hospital stay. Data was analyzed and presented using descriptive and summary statistics.

Results

Within a cohort of 271 patients admitted to the hospital for heart failure, gout attacks had occurred in nine (3.3%) patients. Altogether, the characteristics of all 27 gout attack cases are summarized in Table 2, describing their comorbidities, concurrent medications, diuretic therapy, and length of hospital stay. The 27 patients who experienced a gout attack were predominantly male (57%) with a mean age of 74 years, who shared similar comorbidities such as hypertension (93%), dyslipidemia (74%), chronic kidney disease (56%), history of coronary artery disease (52%), diabetes mellitus (52%), and history of gout (30%). These patients were documented to have received concomitant, beta-blockers (90%), angiotensin-converting enzyme inhibitors (48%), calcium channel blockers (44%), acetylsalicylic acid (44%), nitrates (41%), gout prophylaxis (22%),

Cite this article: Incidence and characterization of gout attacks in patients hospitalized for acute heart failure receiving intensified diuresis: a case series of 27 patients. Am J of Card and Cardiovas Disc.2020; 3(1): 01-05.

angiotensin receptor blockers (15%). These patients also received loop diuretics (100%), potassium-sparing diuretics (18.5%), thiazide diuretics (4%) and thiazide-like diuretics (4%) at the time of and leading up to the onset of gout attacks. The median oral furosemide dose equivalency was 160 mg/day for a median duration of four days. The median duration of hospitalization for these heart failure patients who developed gout attacks was 14 days.

Table 2. Case Series Characteristics

patiant Number	Sex	Age	Relevant comorbidities	Concurrent medications	Uric acid level	Diuretics prior to go out development	Oral furosemide equivalent dose*(mg/day)	Time to go out resolution (days)	Length of stay in the hospital (days)
1	F	78	HTN, dyslipidemia,CKD,CVA,history of gout	CCB, BB, ARB, allopurinol	478	Loop	320	7	14
2	F	74	HTN, DM, dyslipidemia,CKD,CVA,MI	CCB, nitrates	498	Loop	120	4	12
3	M	57	HTN, DM, dyslipidemia,MI	BB, nitrates, low dose, ASA	637	Loop, potassium sparing	480	13	20
4	M	80	HTN, DM, dyslipidemia,MI, CVA,history of gout	ARB, BB, low dose, ASA	485	Loop	160	7	8
5	M	78	HTN, DM, dyslipidemia,MI	BB, low dose ASA	615	Loop	160	4	5
6	M	62	HTN, DM, MI, CVA	ACEI, BB, nitrates, low dose ASA	607	Loop	120	5	9
7	F	78	HTN, DM	ACEI, BB	N/A	Loop	80	11	161
8	F	88	HTN, history of gout	ACEI, BB, nitrates, low dose ASA, chemotherapy	N/A	Loop	160	4	22
9	F	81	HTN, dyslipidemia, CKD	ACEI, BB	627	Loop, thiazide, potassium sparing	40	10	12
10	M	80	HTN, DM, dyslipidemia, CKD, history of gout	ACEI, BB, CCB, allopurinol	N/A	Loop	40	3	17
11	M	73	HTN, DM, dyslipidemia,MI	ACEI, BB, chemotherapy	597	Loop	120	4	9
12	M	83	HTN, CKD, MI, history of gout	ACEI, BB, allopurinol	635	Loop, potassium sparing	200	26	60
13	F	74	Dyslipidemia, CKD, MI	CCB	543	Loop	240	21	65
14	F	80	HTN, DM, dyslipidemia, CKD, CVA	BB, nitrates, levodopa	756	Loop	480	3	20
15	M	48	HTN, dyslipidemia, history of gout	ACEI, BB, allopurinol	641	Loop	160	6	21
16	F	58	HTN, DM, dyslipidemia, CKD, MI	ACEI, BB, CCB, nitrates, low dose ASA	570	Loop	160	4	8
17	F	95	HTN, DM, dyslipidemia, CKD, MI, history of gout	BB, nitrates, low dose ASA	594	Loop	160	6	11
18	F	87	HTN, DM, dyslipidemia, CKD, MI	ACEI, BB, CCB, nitrates	604	Loop	240	4	19
19	M	54	HTN, DM, dyslipidemia, CKD	BB, CCB, allopurinol	563	Loop	320	5	8
20	F	94	HTN	CCB	393	Loop	60	10	17
21	M	66	HTN, dyslipidemia, CKD, organ transplant	BB, low dose ASA, tacrolimus	685	Loop	240	8	19
22	M	86	HTN, DM, dyslipidemia, CKD, MI, CVA	ACEI, BB, CCB, nitrate, low dose ASA	894	Loop	160	5	12
23	M	50	HTN,DM, CKD, organ transplant	BB, CCB, nitrates, low dose ASA, tacrolimus	440	Loop, thiazide-like diuretic	640	7	66
24	M	54	None documented	ACEI, BB, low dose ASA	N/A	Loop, potassium sparing	200	5	6
25	M	83	HTN, dyslipidemia, CKD, MI	ARB, BB, CCB, nitrates, low dose ASA	863	Loop, potassium sparing	260	3	8
26	M	80	HTN, dyslipidemia, MI, history of gout	ACEI, BB, CCB, allopurinol	N/A	Loop	80	4	7
27	F	83	HTN, DM	ARB, BB	597	None	0	7	28

ACEI= Angiotensin Converting Enzyme Inhibitors; ARB= Angiotensin Receptor Blocker; ASA= Acetylsalicylic acid; BB= Beta Blocker; CCB= Calcium Channel Blockers; CKD= Chronic Kidney Disease; CVA= Cerebrovascular accident; DM = Diabetes Mellitus; HTN = Hypertension; loop diuretics = Lasix/furosemide; MI = Myocardial Infection; potassium sparing diuretics = Spironoiactone; thiazide = hydrochlorothiazide; Thiazide- like diuretic = metolazone

Discussion

To our knowledge, this is the first North American case series illustrating the potential increased risk of developing gout attacks from aggressively diuresing patients hospitalized for acute decompensated heart failure.

McAdams DeMarco, et al. reported incidence rates of gout attacks of between five to seven percent, but this study investigated only patients with hypertension rather than patients specifically with acutely decompensated heart failure.[2] They identified 22 gout cases among patients with chronic congestive heart failure, of whom only four cases had received diuretic therapy, which is vastly different from our cohort. We speculate the plausible reasons for this higher incidence

Cite this article: Incidence and characterization of gout attacks in patients hospitalized for acute heart failure receiving intensified diuresis: a case series of 27 patients. Am J of Card and Cardiovas Disc.2020; 3(1): 01-05.

rate compared to our findings are a result of differences in patient population, as well as diagnostic criteria for gout. This study was conducted in the United States where there are differences in diet, exercise, ethnicity (predominantly caucasian and African american), and age (younger age population) of the patients compared to our case series' patient population. Furthermore, gout was identified through self-reporting and diagnosed without uric acid levels by the physicians in the study by McAdams DeMarco et al. In our case series, the diagnosis of gout was confirmed by clinical symptoms of gout and initiation of drug treatment, and further supported by elevated serum uric acid concentrations when available.

A large percentage of the gout attack patients had concomitant hypertension and dyslipidemia, both of which are known and published risk factors for acute gout in hypertensive patients.[9] These risk factors can be explained by the following pathophysiological mechanisms. Hypertension decreases renal blood flow and increases uric acid reabsorption at the site of the proximal convoluted tubules.[10] Whereas, dyslipidemia promotes triglyceride lipolysis which causes an inflammatory response to soluble urate, resulting in increased risk of gout development.[11] Furthermore, the patients who experienced gout flares during their heart failure admission also received higher diuretic doses (median oral furosemide dose equivalency of 160 mg/day versus 80 mg/day for their baseline regimen) for a median duration of four days. Diuretics increase urate reabsorption and reduces urate excretion in a dose-dependent manner.[12]

In the study by McAdams DeMarco et al, the most common diuretic used was hydrochlorothiazide, a thiazide diuretic, while in our case series, all our patients received furosemide, a loop diuretic. We would expect to see a higher incidence of gout attacks in our cohort as the reported adjusted odds ratio for loop diuretics and thiazide diuretics were 2.64 and 1.70 respectively.[13] Unfortunately, several of our cases included combination diuretic therapy and the gout attack risk of using multiple diuretics is unknown based on our findings and the lack of available literature. Given that combination diuretic therapy is often utilized in treating heart failure patients, further investigation of gout risk in this specific patient population is warranted.

The median length of hospital stay for patients with New York Heart Association Class IV symptoms has been reported to be between six to eight days[14,15], while the median length of stay for our cohort of heart failure patients who experienced a new gout attack was 14 days. The findings from our case series suggests an association between diuretic use and observed gout attacks and increased length of hospital stay for heart failure patients, which is consistent with other studies showing that medication-related adverse events result in considerable excess length of hospital stay and costs.[16] Therefore, early identification of high risk patients may be an opportune pathway to mitigate this risk of potential iatrogenic gout attacks and unnecessarily prolonged hospitalization.[17] An example of this may be to measure serum urate concentrations in heart failure patients identified as high risk for developing gout upon that particular admission and initiating antihyperuricemic prophylaxis therapy as an adjunct to aggressive diuresis in select individuals to prevent gout flares. This may translate into improved quality of life and shorter hospitalizations, which is supported by literature suggesting the use of high dose allopurinol to reduce the risk of hyperuricemia in heart failure patients.[18]

Conclusion

This case series suggests that an important association between increasing diuretic intensity in acute heart failure patients and potentiating gout flares exists in clinical practice - that for every 30 patients receiving aggressive diuresis, one patient may experience a gout attack during hospitalization. It emphasizes the importance of understanding the mechanism of the various diuretics, including their potential risk of precipitating gout attacks at higher doses. By understanding this phenomenon, clinicians may be able to identify patients at risk of gout attacks when managing heart failure exacerbation and minimize harm to patients, which may further translate into reduced healthcare associated costs. Prospective studies are warranted to further explore the role of early detection and treatment of gout attacks in this clinical setting.

Cite this article: Incidence and characterization of gout attacks in patients hospitalized for acute heart failure receiving intensified diuresis: a case series of 27 patients. Am J of Card and Cardiovas Disc.2020; 3(1): 01-05.

Acknowledgements

The authors acknowledge the support from Dr. Doson Chua, Cardiology Clinical Pharmacy Specialist at St. Paul's Hospital in Vancouver, BC, Canada for providing advice and feedback on the manuscript and submission process.

The authors have no financial or industrial affiliations to declare.

References

1. Spieker LE, Ruschitzka FT, Luscher TF, Noll G. The management of hyperuricemia and gout in patients with heart failure. Eur J Heart Fail. 2002 Aug;4(4):403-10.
2. McAdams DeMarco MA, Maynard JW, Baer AN, Gelber AC, Young JH, Alonso A et al. Diuretic use, increased serum urate levels, and risk of incident gout in a population-based study of adults with hypertension: the Atherosclerosis Risk in Communities cohort study. Arthritis Rheum. 2012 Jan;64(1):121-9.
3. Hueskes BA, Roovers EA, Mantel-Teeuwisse AK, Janssens HJ, van de Lisdonk EH, Janssen M. Use of diuretics and the risk of gouty arthritis: a systematic review. Semin Arthritis Rheum. 2012 Jun;41(6):879-89.
4. Nijenhuis T, Vallon V, van der Kemp AW, Loffing J, Hoenderop JG, Bindels RJ. Enhanced passive Ca2+ reabsorption and reduced Mg2+ channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. J Clin Invest. 2005;115(6):1651.
5. El-Sheikh AA, van den Heuvel JJ, Koenderink JB, Russel FG. Effect of hypouricaemic and hyperuricaemic drugs on the renal urate efflux transporter, multidrug resistance protein 4. Br J Pharmacol. 2008 Dec;155(7):1066-75.
6. Bagatin J, Sardelic S, Pivac N, et al. Comparison of chlorthalidone, propranolol and bopindolol in six-month treatment of arterial hypertension. Int J Clin Pharmacol Res 1998;18:73 –8.
7. Dunn CJ, Fitton A, Brogden RN. Torasemide. An update of its pharmacological properties and therapeutic efficacy. Drugs 1995;49:121 –42.
8. Kahn AM. Effect of diuretics on the renal handling of urate. Semin Nephrol. 1988 Sep;8(3):305-14.
9. Singh JA, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. Curr Opin Rheumatol. 2011 Mar;23(2):192-202.
10. Messerli FH, Frohlich ED, Dreslinski GR, Suarez DH, Aristimuno GG. Serum uric acid in essential hypertension: an indicator of renal vascular involvement. Ann Intern Med. 1980 Dec;93(6):817-21.
11. Chawla A, Nguyen KD, Goh YP. Macrophage-mediated inflammation in metabolic disease. Nat Rev Immunol. 2011 Oct 10;11(11):738-49.
12. Kahn AM. Effect of diuretics on the renal handling of urate. Semin Nephrol. 1988 Sep;8(3):305-14.
13. Bruderer S, Bodmer M, Jick SS, Meier CR. Use of diuretics and risk of incident gout: a population-based case-control study. Arthritis Rheumatol. 2014 Jan;66(1):185-96.
14. Wright SP, Verouhis D, Gamble G, Swedberg K, Sharpe N, Doughty RN. Factors influencing the length of hospital stay of patients with heart failure. Eur J Heart Fail. 2003 Mar;5(2):201-9.
15. Jaagosild P, Dawson NV, Thomas C, Wenger NS, Tsevat J, Knaus WA et al. Outcomes of acute exacerbation of severe congestive heart failure: quality of life, resource use, and survival. Arch Intern Med. 1998 May 25;158(10):1081-9.
16. Hoonhout LH, de Bruijne MC, Wagner C, Asscheman H, van de wal G, van Tulder MW. Nature, occurrence and consequences of medication-related adverse events during hospitalization: a retrospective chart review in the Netherlands. Drug Saf. 2010 Oct 1;33(10):853-64.
17. Sharim R, Musselman M, Blum M. Factors associated with a prolonged hospital length of stay for patients with acute gout. 2012 ACR/ARHP Annual Meeting.
18. Struthers AD, Donnan PT, Lindsay P, McNaughton D, Broomhall J, MacDonald TM. Effect of allopurinol on mortality and hospitalisations in chronic heart failure: a retrospective cohort study. Heart. 2002 Mar;87(3):229-34.

Cite this article: Incidence and characterization of gout attacks in patients hospitalized for acute heart failure receiving intensified diuresis: a case series of 27 patients. Am J of Card and Cardiovas Disc.2020; 3(1): 01-05.