

Furosemide and pancreatitis

Importance of dose and latency period before reaction

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Acute pancreatitis is estimated to occur in more than 600 000 Canadians annually, accounting for 13 000 hospital admissions per year.¹ The severity can range from mild dysfunction to multiorgan dysfunction, with a mortality rate of up to 30%. Acute pancreatitis of drug origin is often overlooked if a thorough drug history is not obtained. We describe a case of a patient with long-standing hypertension who developed acute pancreatitis after furosemide use.

Case

A 60-year-old man presented to the emergency department with a 3-day history of abdominal pain. His medical history was relevant for membranous glomerulopathy for 2 years, dyslipidemia, and hypertension, for which he had been taking atenolol (50 mg per day), spironolactone (50 mg per day), valsartan (80 mg per day), atorvastatin (10 mg per day), clonidine (0.075 mg per day), and prednisolone (20 mg every other day) for years. He had been discharged 5 days previously with furosemide (40 mg per day) prescribed for leg edema. On examination, he appeared distressed, with a bent posture. His vital signs were as follows: blood pressure of 168/94 mm Hg, heart rate of 60 beats per minute, and respiratory rate of 16 breaths per minute. He was afebrile. He had abdominal pain that was dull and radiated to the back. Visual inspection of the abdominal wall showed no ecchymosis over the umbilicus or flank area. Bowel sounds were hypoactive. Abdominal palpation elicited epigastric tenderness. A complete blood count revealed leukocytosis (white blood cell count of $16.82 \times 10^9/L$). Serum biochemistry showed impaired renal function (serum creatinine level of 173 $\mu\text{mol/L}$) and normal sodium, potassium, calcium, and magnesium levels. Serum amylase (885 IU/L) and lipase levels (487 IU/L) were both elevated. Abdominal computed tomography showed prominent fat stranding over the pancreatic body and tail.

Acute pancreatitis was diagnosed. Workup for the origin of his pancreatitis was performed. Abdominal magnetic resonance imaging revealed no congenital pancreatic bile duct abnormalities or biliary stones. His serum triglyceride level was within the reference range. He was abstinent from alcohol, and denied any recent trauma or insect or spider bites. He had no symptoms of respiratory tract infection or recent viral infections. Although there are case reports in the literature of atorvastatin-related² and prednisolone-related³ pancreatitis, he had been taking both for 2 years without problems. After careful questioning, he recalled that abdominal fullness with polyuria occurred 1 day after he started furosemide, and his abdominal pain worsened later. According to the Naranjo adverse drug reaction probability scale,⁴ the event was probably related to furosemide. His symptoms subsided soon after discontinuation of furosemide and all other drugs, and he was discharged without further complications 1 week later. He resumed atorvastatin and prednisolone thereafter without pain recurrence.

Discussion

In this case, we used the Naranjo adverse drug reaction probability scale (Table 1) to rate the likelihood of medication side effects. The scale was introduced in 1981 by Naranjo et al,⁴ and has been validated in multiple cases of adverse drug reactions. The total event score of our patient was calculated to be 5 (answered yes on questions 1, 2, 3, and 10), rated as probably related to furosemide.

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Cet article a fait l'objet d'une révision par des pairs.

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EDITOR'S KEY POINTS

- Furosemide-related pancreatitis is rarely recognized. Low dose (40 mg per day) and time between drug exposure and reaction (latency period) are used to define new patterns of reactions to furosemide, and might suggest an important underlying mechanism that has yet to be identified.
- Accurate medication history is vital and might obviate the exhaustive search for the cause of pancreatitis.
- Discontinuing furosemide can be expected to lead to complete symptom reversal.

POINTS DE REPÈRE DU RÉDACTEUR

- Le furosémide comme cause de la pancréatite est rarement reconnu. De faibles doses (40 mg par jour) et l'intervalle de temps entre l'exposition au médicament et la réaction (période de latence) sont utilisés pour définir de nouveaux modes de réactions au furosémide et pourraient laisser présager un mécanisme sous-jacent important qu'il reste encore à identifier.
- Il est essentiel de faire un bilan exact de la médication et cela pourrait éviter une recherche exhaustive de la cause de la pancréatite.
- On peut s'attendre à ce que la cessation du furosémide entraîne la disparition complète des symptômes.

Table 1. The Naranjo adverse drug reaction probability scale

QUESTIONS	YES	NO	DO NOT KNOW	SCORE
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
Total score*				

*Total score is the sum of all subcategory scores. The relationship is categorized as *definite* if the score is greater than 8, *probable* if the score is 5 to 8, *possible* if the score is 1 to 4, and *doubtful* if the score is 0. Modified from Naranjo et al.⁴

Drug-related pancreatitis is a neglected entity, with an incidence of approximately 0.1% to 2% (but underestimation is likely). Many drugs have been reported in the literature to cause pancreatitis, including anti-hypertensive agents (enalapril, methyldopa, losartan), antibiotics (isoniazid, metronidazole, tetracycline), proton pump inhibitors (omeprazole), anticonvulsant agents (valproate), and chemotherapeutic agents (cytosine arabinoside, ifosfamide, azathioprine).³ In our patient, prednisolone and atorvastatin were also suspected to have contributed. However, reported cases of adverse atorvastatin reactions have an average latency period of several days,² while the latency periods for reported cases of adverse prednisolone reactions are obscured by comorbidities.³ From a chronologic view, we believe furosemide was more likely to have caused the reaction.

Reports of furosemide-related pancreatitis are sparse. We performed a retrospective literature search using the key words *furosemide*, *diuretics*, *pancreas*, and *pancreatitis* in MEDLINE and PubMed, and 7 reports were retrieved (Table 2).⁵⁻¹¹

Risk factors. Previously identified risk factors for drug-related pancreatitis (pediatric population, female sex, complex medication regimen, advanced immunodeficiency)¹² do not apply to the reported adverse furosemide reaction cases. The mean age is older (50 years, range 23 to 64 years), and vascular risk factors are present in nearly all cases. We believe a currently unidentified association between these factors and susceptibility to pancreatotoxic damage exists, likely from mesenteric vessel atherosclerosis. Furosemide might impair

pancreatic perfusion by diuresis and intravascular volume depletion. The exact mechanism is still unclear, and there are multiple hypotheses including pancreatic exocrine stimulation by furosemide, or hypersensitivity from an immunologic response against a drug-protein adduct.¹¹ As reported in Table 2,⁵⁻¹¹ many confounders exist, but they only increase pancreatic susceptibility. The precipitating event is still furosemide administration.

Latency and mechanism. A range of latency periods (several hours to 7 weeks) has been reported. A review of drug-related pancreatitis³ classified cases into 3 latency categories: short (<24 hours), intermediate (1 day to 1 month), and long (>1 month). The Jones and Oelbaum⁶ and Juang et al¹¹ reports of low dose and extended exposure fit into the long category. These cases are best explained by hypersensitivity reactions. However, we identify another 2 patterns within the short category. First, in the Buchanan and Cane⁸ and Stenvinkel and Alvestrand⁹ reports, high-dose (≥ 250 mg) and short-term (≤ 1 day) furosemide use led to immediate adverse reactions. The pathophysiology seems different from the long category. We propose that pancreatic microcirculatory hypoperfusion might contribute to or direct furosemide pancreatotoxicity.¹³ The second pattern is a short latency period (1 to 3 days) with low-dose (40 mg per day) furosemide, as seen in our patient and as reported by Call et al.¹⁰ The mechanism of this pattern has not yet been elucidated, but it is not likely to be an immunologic response owing to the rapidity of its onset. Further investigation of this pattern is warranted owing to the short latency period and the low dose needed to exert an undesirable effect.

Table 2. Published case reports of furosemide-related pancreatitis

STUDY	AGE, Y	SEX	COMORBIDITY	DOSAGE	LATENCY PERIOD	OUTCOME	RECHALLENGE	RECURRENCE	OUTPATIENT OR INPATIENT	CONFOUNDERS
Wilson et al ⁵	23	M	Malignant HTN, CHF, emphysema	40 mg/d	3 wk	Recovery	No	No	Inpatient	Tetracycline, methyldopa; alcoholism
Jones and Oelbaum ⁶	64	F	HTN, AMI, CHF	40 mg/d	7 wk	Recovery	Yes	Yes	Inpatient	Dyslipidemia
Strunge ⁷	53	F	CHF	1000 mg/d	NA	Death	No	No	Inpatient	Ventricular fibrillation
	72	F	AMI	240 mg/d	NA	Death	No	No	Inpatient	Cardiogenic shock
Buchanan and Cane ⁸	46	M	DM	500 mg, single dose	12 h	Death	No	No	Inpatient	Alcoholism
	56	M	CHF	250 mg, single dose	8 h	Recovery	No	No	Inpatient	Alcoholism
	49	M	Varices	250 mg, single dose	18 h	Recovery	No	No	Inpatient	Alcoholism
Stenvinkel and Alvestrand ⁹	34	M	CHF	750 mg/d	1 d	Recovery	Yes	Yes	Inpatient	Captopril
Call et al ¹⁰	41	F	HTN	40 mg/d	3 d	Recovery	Yes	Yes	Inpatient	Dyslipidemia
Juang et al ¹¹	57	F	DCM, SSS, HTN, Hashimoto thyroiditis	80 mg/d	5 wk	Recovery	Yes	Yes	Inpatient	Dyslipidemia, sulfonamide allergy
Current case	60	M	HTN, MG	40 mg/d	1 d	Recovery	No	No	Outpatient	Dyslipidemia

AMI—acute myocardial infarction, CHF—congestive heart failure, DCM—dilated cardiomyopathy, DM—diabetes mellitus, F—female, HTN—hypertension, M—male, MG—membranous glomerulopathy, NA—not applicable, SSS—sick sinus syndrome.

Disease course. Furosemide-related pancreatitis is usually self-limited, and symptoms improve promptly after drug withdrawal. However, mortality has been reported, and physicians prescribing furosemide should bear this in mind. We believe the high mortality rate (3 of 11 patients in **Table 2**) might come from publication bias. Our patient was advised to refrain from taking any loop diuretics in the future, owing to the high risk of symptom recurrence from re-exposure.

Conclusion

We should pay attention to rare pancreatitis from furosemide use. We urge every practitioner who prescribes furosemide to inquire about symptoms of pancreatitis, especially in patients with the risk factors of older age and cardiovascular comorbidities. Furosemide-related pancreatitis can be divided into 3 categories according to latency period and dosage, each with different mechanisms. The overall prognosis is good if furosemide is promptly withdrawn. Awareness of the detailed medication history of each patient is vital for a rapid diagnosis.

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Competing interests

None declared

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