Pharmacology & Toxicology Research
https://acadpub.com/ptr

Beyond the Liver: Diuretic-Induced Hyperammonemia in Patients Without Cirrhosis: A Case Series

[1]Ashish D. Rajput, [1]Priyanka R. Diwan, [2]Sapna D. Gupta and [1]Supriya D. Malhotra

[1]Department of Pharmacology, Smt. N.H.L. Municipal Medical College, Ahmedabad, Gujarat, India
[2]Department of Emergency Medicine, SVP Hospital, Ahmedabad, Gujarat, India

About the Article

Open Access

Case Report

DOI: 10.68163/ptr.2026.73

How to Cite:
Rajput AD, Diwan PR, Gupta SD, Malhotra SD. Beyond the liver: Diuretic-induced hyperammonemia in patients without cirrhosis: A case series, *Pharmacol Toxicol Res.* 2026;2:71-75.

Keywords:
Diuretics, hepatic encephalopathy, Hyperammonemia, non-cirrhotic

Corresponding author:
Supriya D. Malhotra,
Department of Pharmacology, Smt. N.H.L. Municipal Medical College, Ahmedabad, Gujarat, India

© The Authors, 2026. Published by the Academia Publications. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (CC-BY) 4.0. (http://creativecommons.org/licenses/by/4.0)

ABSTRACT

Background and Objective: Hyperammonemic encephalopathy is conventionally attributed to hepatic failure, inherited urea-cycle defects, or portosystemic shunting. Diuretic therapy, widely used for hypertension, heart failure and fluid overload, is a less recognized trigger that can increase serum ammonia levels through mechanisms unrelated to the severity of underlying liver disease. We describe three such cases and examine their implications for clinical recognition.

Materials and Methods: We conducted a retrospective review of three patients who developed hyperammonemia temporally associated with diuretic therapy, identified through pharmacovigilance reporting and clinical evaluation.

Results: We report three elderly women, aged 68-72 years, with hypertension and cardiometabolic comorbidities but no documented chronic liver disease, who developed hyperammonemia temporally associated with diuretic use. The implicated regimens included a combination of hydrochlorothiazide, torsemide and spironolactone; spironolactone monotherapy and torsemide monotherapy. Clinical presentations varied widely, ranging from altered sensorium accompanied by diarrhea and generalized weakness, to progressive breathlessness with pedal edema, to sudden eyelid myoclonus with high-grade fever, none of which was initially suggestive of hyperammonemia. Serum ammonia concentrations ranged from 110 to 153 mcg/dL. Two patients recovered following diuretic withdrawal, whereas the third did not survive despite similar management.

Conclusion: Diuretic-induced hyperammonemia is not restricted to loop or thiazide diuretics and can occur with potassium-sparing therapy alone. A low threshold for ammonia testing may therefore be warranted in diuretic-treated patients presenting with unexplained neurological, respiratory, or systemic symptoms, irrespective of hepatic status.

INTRODUCTION

Ammonia is produced continuously throughout the body, primarily through amino acid deamination and intestinal bacterial urease activity and is cleared predominantly by hepatic conversion to urea, with lesser contributions from renal and skeletal muscle glutamine metabolism. When ammonia production exceeds its clearance, the resulting systemic hyperammonemia can manifest as impaired cognition, asterixis, altered consciousness, seizures, cerebral edema, or coma.

Causes of hyperammonemia are conventionally categorized as hepatic or non-hepatic. Hepatic causes include cirrhosis, acute liver failure and portosystemic shunting, whereas non-hepatic causes include inherited urea-cycle disorders, drug toxicity, with valproate being a classic example, infection with urease-producing organisms, gastrointestinal hemorrhage, total parenteral nutrition, multiple myeloma and certain post-transplant or post-bariatric surgery states. Isolated reports of severe hyperammonemic encephalopathy in adults without documented liver disease further illustrate that this syndrome can arise outside the classic hepatic and inherited metabolic categories[1,2]. Diuretic therapy fits uneasily into either category.

It is most familiar as a precipitant of hepatic encephalopathy in patients with cirrhosis, yet the pathways through which it may increase ammonia levels, including reduced effective circulating volume and hypokalemia-driven renal ammoniagenesis, can operate independently of cirrhosis and do not necessarily require advanced liver disease.

Among patients with cirrhosis, diuretic treatment is a well-recognized precipitant of hepatic encephalopathy. In patients with tense ascites treated with high-dose diuretics, encephalopathy occurs in approximately one-quarter, whereas renal impairment and hyponatremia each occur in approximately one-fifth[3]. This has traditionally been attributed to diuretic-induced circulatory dysfunction superimposed on impaired hepatic function. Physiological data, however, suggest that diuretics may also influence ammonia metabolism through other mechanisms, including alterations in renal hemodynamics, renal ammoniagenesis and potentially hepatic urea synthesis, which, at least theoretically, may not depend on the severity of underlying liver disease[4].

Two mechanisms appear particularly relevant: Contraction of effective circulating volume, which may increase renal ammonia production while reducing its clearance[3] and hypokalemia, which can independently stimulate renal ammoniagenesis, potentially even before serum potassium falls below the reference range[4]. Older comparative animal studies also indicate that individual diuretics differ in their effects on hepatic and renal ammonia handling and that carbonic anhydrase inhibitors may impair hepatic urea synthesis through a mechanism distinct from volume depletion[5,6].

Because ammonia is rarely measured in diuretic-treated patients unless liver disease is already under consideration, diuretic-associated hyperammonemia may be underrecognized, particularly among patients receiving diuretics for heart failure or hypertension rather than cirrhotic ascites. This case series presents three such patients, none of whom had documented liver disease, in whom hyperammonemia developed in temporal association with three different diuretic regimens: A triple-drug combination, loop diuretic monotherapy and , more notably, potassium-sparing diuretic monotherapy. We examine the potential mechanisms underlying these differing presentations and their implications for clinical recognition and management.

Case series

Case 1: A 72-year-old woman with a 15-year history of hypertension and a 7-year history of ischemic heart disease presented with a 2-day history of altered sensorium characterized by decreased responsiveness. She also reported increased stool frequency (5-6 episodes per day), nausea, generalized weakness and low-grade fever. She had no history of chronic liver disease.

Her regular medication regimen comprised aspirin, clopidogrel and rosuvastatin once daily for ischemic heart disease; metoprolol 50 mg once daily for hypertension; a fixed-dose combination of torsemide and spironolactone (20/50 mg) twice daily for fluid overload; and a fixed-dose combination of losartan and hydrochlorothiazide (20/12.5 mg) once daily, also for hypertension.

Serum ammonia was elevated at 141 mcg/dL and evaluation revealed no alternative hepatic or metabolic explanation. Hydrochlorothiazide, torsemide and spironolactone were each considered potentially contributory. Hydrochlorothiazide was withdrawn, whereas torsemide and spironolactone were continued to maintain control of her fluid overload. With supportive care alone, her sensorium progressively improved and her serum ammonia concentration subsequently normalized. She was discharged in stable condition.

Case 2: A 71-year-old woman with a 20-22-year history of hypertension and diabetes mellitus and a history of cerebrovascular accident 8-9 years earlier presented with breathlessness at rest, a 6-day history of productive cough and bilateral pedal edema that had recurred intermittently for approximately 2 years. She had no known history of chronic liver disease.

Her regular medications were aspirin, clopidogrel and atorvastatin 75/75/40 mg once daily for secondary stroke prevention; metoprolol 25 mg and amlodipine 5 mg once daily for hypertension; dapagliflozin 10 mg once daily for diabetes mellitus; and digoxin 0.125 mg once daily together with spironolactone 25 mg once daily for heart failure and fluid overload.

Serum ammonia was elevated at 110 mcg/dL. Spironolactone was identified as the most probable offending agent and was withdrawn. Despite withdrawal and supportive care, her clinical status failed to improve and she died during the admission.

Case 3: A 68-year-old woman with hypertension, diabetes mellitus and ischemic heart disease developed sudden-onset involuntary bilateral eyelid movements on the morning of admission, accompanied by high-grade fever. She had no history of chronic liver disease.

She was receiving torsemide 10 mg once daily for fluid overload, together with aspirin 75 mg once daily and atorvastatin 75 mg once daily for ischemic heart disease and metformin 500 mg once daily for diabetes mellitus.

Serum ammonia was elevated at 153 mcg/dL. Liver function tests were essentially unremarkable, with an albumin concentration of 3.5 g/dL, total bilirubin of 0.42 mg/dL and alkaline phosphatase of 105 U/L, arguing against overt hepatic dysfunction as an alternative explanation. Torsemide was identified as the suspected causative agent and discontinued. She was empirically treated with rifaximin

and lactulose in addition to supportive care. Her serum ammonia concentration subsequently decreased, her clinical condition improved and she was discharged in stable condition.

Across all three cases, diuretic-associated hyperammonemia was suspected based on documented exposure to the implicated agent(s), the absence of an alternative hepatic or metabolic explanation and a plausible temporal relationship between drug exposure and symptom onset. The suspected diuretic was withdrawn in each case, specifically hydrochlorothiazide in Case 1, spironolactone in Case 2 and torsemide in Case 3, followed by supportive management and close observation. All three suspected adverse drug reactions were reported to the Indian Pharmacopoeia Commission through the Pharmacovigilance Programme of India (PvPI) and were assigned the identification numbers IN-IPC-301305579 (Case 1), IN-IPC-301305578 (Case 2) and IN-IPC-301304962 (Case 3). Table 1 provides a comparative summary of the three cases.

DISCUSSION

Mechanistic basis: Two complementary pathways: At least two physiological pathways plausibly connect diuretic therapy to hyperammonemia and both are relevant to the interpretation of the present cases. In cirrhotic ascites, diuresis that outpaces the rate of ascitic fluid reabsorption can produce intravascular volume depletion and a further decline in effective arterial blood volume, thereby increasing renal ammonia generation while simultaneously reducing its clearance. This circulatory mechanism has been implicated in the approximately 25% incidence of hepatic encephalopathy reported among cirrhotic patients receiving high-dose diuretics for tense ascites[3]. Further support for a circulatory contribution comes from evidence that diuretic-associated hepatic encephalopathy improves following intravenous albumin but not after an equivalent volume of synthetic colloid, suggesting that the benefit is not attributable solely to volume expansion[7].

Separately, hypokalemia, a frequent consequence of loop and thiazide diuretic use, can independently stimulate renal ammonia production by increasing proximal tubular glutamine uptake and the activity of glutaminase, glutamate dehydrogenase and phosphoenolpyruvate carboxykinase, as well as by upregulating expression of the collecting-duct ammonia transporter Rhcg. These changes can occur within approximately 2 days of potassium deprivation, potentially before serum potassium itself falls below the laboratory reference range[4].

Diuretics in the broader landscape of drug-induced hyperammonemia: Diuretics rank well below the most frequently reported causes of drug-induced hyperammonemia. A review of the WHO pharmacovigilance database (VigiBase) covering 1967-2019 identified 73 drugs associated with hyperammonemia, with valproate, fluorouracil, topiramate, oxaliplatin and asparaginase among the most frequently reported agents (Table 2); corticosteroids have also been implicated through increased skeletal muscle ammonia production[8]. Diuretics are conspicuously absent from this list of commonly reported agents, even though the circulatory and hypokalemia-driven mechanisms described above have been recognized in the hepatology literature for more than two decades[3,4].

This discrepancy may reflect underrecognition rather than true rarity. Ammonia is not routinely measured in the evaluation of altered mental status outside settings in which hepatic or oncologic causes are already being considered and a diuretic may be an unexpected suspected contributor when liver function appears normal. The three cases described here, none of which had documented chronic liver disease, support consideration of diuretics in the differential diagnosis of unexplained hyperammonemia alongside more established drug-related causes.

A unified view of the three cases: These cases can be viewed as lying along a mechanistic spectrum rather than representing three unrelated categories. At one end, hypokalemia-driven and circulatory mechanisms may plausibly account for the patient receiving torsemide monotherapy. Torsemide and hydrochlorothiazide are both potassium-wasting agents used in this case for fluid and blood pressure management and may have contributed to the

Table 1: Summary of cases

Case	Age/sex/comorbidities	Suspected diuretic(s) and dose	Presenting features	Serum ammonia	Action taken
1	72/F: hypertension (15 y); ischemic heart disease (7 y)	Hydrochlorothiazide 12.5 mg OD; torsemide 20 mg BD; spironolactone 50 mg BD	Altered sensorium with reduced responsiveness; increased stool frequency (5-6/day); nausea; generalized weakness; low-grade fever	141 mcg/dL	Hydrochlorothiazide discontinued; torsemide and spironolactone continued
2	71/F: hypertension; diabetes mellitus (20-22 y); CVA (8-9 y prior)	Spironolactone 25 mg OD	Breathlessness at rest; cough with expectoration for 6 days; bilateral pedal edema, intermittent for 2 years	110 mcg/dL	Spironolactone discontinued; patient died during admission
3	68/F: hypertension; diabetes mellitus; ischemic heart disease	Torsemide 10 mg OD	Sudden-onset involuntary eyelid movements on day of admission; high-grade fever	153 mcg/dL	Torsemide discontinued; rifaximin and lactulose started

Table 2: Drugs associated with hyperammonemia

Drug/class	Reported cases	Serious (%)	Fatal (%)	Proposed mechanism
Valproate	1260	54	4	Valproyl-CoA inhibits N-acetylglutamate synthase and depletes carnitine, reducing carbamoyl phosphate synthetase-1 activity
Fluorouracil	221	96	9	Toxic catabolites impair the Krebs cycle and ATP-dependent urea-cycle steps
Topiramate	96	68	0	Carbonic anhydrase inhibition reduces bicarbonate and glutamine synthetase activity, limiting ammonia incorporation into glutamine
Oxaliplatin	74	92	12	Mechanism unclear; may potentiate hepatotoxic and urea-cycle effects of concurrent fluorouracil
Asparaginase	71	70	6	Ammonia is a direct byproduct of asparagine hydrolysis, the drug's intended therapeutic action
Corticosteroids	Not systematically quantified	N/A	N/A	Increased skeletal-muscle amino acid catabolism; possible suppression of urea-cycle enzyme expression
Diuretics (loop, thiazide, potassium-sparing)	Not among the most frequently reported agents	N/A	N/A	Circulatory dysfunction and hypokalemia-driven renal ammoniagenesis; aldosterone-antagonist-mediated impairment of renal ammonia excretion (present series)

Case counts and the proportions of serious and fatal events, are drawn from a VigiBase pharmacovigilance analysis summarized by Shakerdi and Ryan[9]

presentation of the patient receiving the triple-drug regimen. However, spironolactone was also part of her treatment and as a potassium-sparing agent, it would be expected to counteract some of the hypokalemic effects of the other two drugs. Consequently, her presentation cannot readily be attributed to hypokalemia alone and may instead reflect circulatory and volume-related effects associated with the combined diuretic regimen. The regimen included twice-daily dosing for fluid overload in addition to a separate antihypertensive combination, potentially increasing the risk of volume contraction.

At the other end of this spectrum is the patient receiving spironolactone monotherapy, whose presentation cannot readily be explained by hypokalemia. Spironolactone, if anything, predisposes to hyperkalemia rather than hypokalemia. Her case therefore raises the possibility of a mechanism distinct from those associated with potassium-wasting diuretics and related to aldosterone antagonism. Aldosterone normally upregulates Rhcg, the collecting-duct ammonia transporter involved in urinary ammonia excretion[10]. By antagonizing aldosterone action, spironolactone could plausibly reduce renal ammonia excretion independently of serum potassium. This mechanism could potentially coexist with, rather than replace, the volume- and potassium-related pathways implicated in the other two patients.

It is also notable that this patient was the only one of the three with clinical heart failure. Passive hepatic congestion associated with decompensated heart failure may contribute to impaired hepatic ammonia clearance and could have compounded a renal excretory defect. However, because the available clinical information does not establish the presence or severity of hepatic congestion, this possibility should be regarded as a potential contributing factor rather than a demonstrated mechanism. The combination of a possible drug-related impairment of ammonia excretion and hemodynamic or hepatic effects associated with heart failure may help explain why this patient did not improve despite withdrawal of the suspected diuretic and supportive care.

Taken together, the three cases may represent different manifestations of impaired ammonia handling rather than three identical drug reactions. The first and third cases are compatible with mechanisms involving volume status and potassium balance, whereas the spironolactone-associated case raises the possibility of an aldosterone-dependent effect on renal ammonia excretion that does not require hypokalemia. Furosemide, a related loop diuretic not used by any of the three patients, provides additional context for the potential class-level relevance of these mechanisms. It has long been associated with electrolyte disturbances and volume-depletion complications in patients with cirrhosis[11]. It has also been reported to blunt the therapeutic response to rifaximin, raising the possibility that continued loop-diuretic exposure could both contribute to hyperammonemia and reduce the effectiveness of a standard treatment for hepatic encephalopathy[12].

None of the three patients had documented chronic liver disease, none initially presented with a classical hepatic encephalopathy picture and clinical outcomes varied substantially. These observations underscore the clinical heterogeneity of diuretic-associated hyperammonemia and suggest that impaired ammonia handling may arise through multiple interacting pathways rather than a single uniform mechanism.

Clinical implications: Clinicians should maintain a low threshold for checking serum ammonia in diuretic-treated patients who develop unexplained altered mentation, asterixis, lethargy, a new movement disorder, or otherwise unexplained clinical deterioration, regardless of whether cirrhosis is present.

Serum potassium should be monitored and corrected when abnormal; however, a potassium concentration within the normal range does not necessarily exclude diuretic-associated hyperammonemia, particularly during the early period following a dose increase.

Potassium-sparing diuretics should not be assumed to be free of this potential adverse effect. As illustrated by the patient who received spironolactone alone, this drug may be associated with hyperammonemia, potentially through an aldosterone-antagonist-specific effect on renal ammonia excretion rather than through hypokalemia[10].

When multiple diuretics are used concurrently, as in the patient receiving combination therapy, attributing the reaction to a single agent is inherently difficult. Clinicians should therefore weigh the potential benefits of withdrawing suspected agents against the clinical urgency of the underlying indication, such as ongoing fluid overload.

Volume status should be reassessed whenever circulatory dysfunction is suspected and intravenous albumin should be considered in appropriate patients, given evidence that albumin, rather than volume replacement alone, may improve diuretic-associated encephalopathy[7].

Concomitant heart failure with possible hepatic congestion, as seen in the patient receiving spironolactone alone, may further impair ammonia clearance and warrants consideration when diuretic-associated hyperammonemia fails to improve after withdrawal of the suspected drug alone.

CONCLUSION

These three cases illustrate that diuretic-associated hyperammonemia may not represent a single, uniform clinical entity. It may occur during multidrug therapy combining thiazide, loop and potassium-sparing diuretics; during loop diuretic monotherapy, potentially involving hypokalemia and circulatory mechanisms; or, as illustrated by the patient receiving spironolactone monotherapy, during treatment with a potassium-sparing aldosterone antagonist, potentially through a mechanism that is largely independent of serum potassium. None of the three patients had documented chronic liver disease and none initially presented with clinical features that clearly suggested hyperammonemia. Taken together, these observations support a low threshold for ammonia testing in diuretic-treated patients with unexplained neurological, respiratory, or systemic deterioration.

The patient receiving spironolactone monotherapy did not recover despite prompt withdrawal of the suspected drug, indicating that clinical improvement may not necessarily follow drug withdrawal, particularly when other factors potentially affecting ammonia clearance are present. Clinicians prescribing diuretics for hypertension, heart failure, or fluid overload and not only for cirrhotic ascites, should consider diuretic-associated hyperammonemia in appropriate clinical settings, monitor potassium and volume status and report suspected cases to pharmacovigilance programs to improve recognition and help characterize its true frequency.

ACKNOWLEDGMENTS

The authors thank the Department of Pharmacology, Smt. N.H.L. Municipal Medical College, Ahmedabad and the Department of Emergency Medicine, SVP Hospital, Ahmedabad, for their support in identifying the cases.

REFERENCES

1. Barnhill M, Yaman R, Renszel K, Alzubaidi S, Vargas H, Chascsa D. Not your typical hyperammonemia: Non-hepatic severe hyperammonemia in an adult. *ACG Case Rep J*. [Internet]. 2023;10. Available from: https://doi.org/10.14309/crj.0000000000001225
2. Palleschi L, Paolantonio P, Galasso UG, Giudice ED, Iacomino M, Schipa C et al. Unusual case of hyperammonemic encephalopathy in elderly patient without liver disease. *Ann Case Rep*. [Internet]. 2024;9(3). Available from: https://doi.org/10.29011/2574-7754.101803
3. Arroyo V, Colmenero J. Ascites and hepatorenal syndrome in cirrhosis: Pathophysiological basis of therapy and current management. *J Hepatol*. 2003;38:69-89.
4. Han KH. Mechanisms of the effects of acidosis and hypokalemia on renal ammonia metabolism. *Electrolytes Blood Pressure*. 2011;9(2):45-49.
5. Häussinger D, Kaiser S, Stehle T, Gerok W. Liver carbonic anhydrase and urea synthesis the effect of diuretics. *Biochem Pharmacol*. 1986;35(19):3317-3322.
6. Yamada T, Yoshida T, Koshikawa S, Obuchi Y. The effects of diuretics on ammonia metabolism in normal and cirrhotic rats. *Gastroenterologia Japonica*. 1968;3:218-219.
7. Jalan R, Kapoor D. Reversal of diuretic-induced hepatic encephalopathy with infusion of albumin but not colloid. *Clin Sci*. 2004;106(5):467-474.
8. Pang J, Xia H, Mi S, Zhang W, Pendrick D, Freeman C et al. Benchmarking bioinformatics approaches for tumour mutational burden evaluation from a large cancer panel against whole-exome sequencing. *J Clin Pathol*. 2022;76(8):276-280.
9. Shakerdi, L. and A. Ryan, 2023. Drug-induced hyperammonaemia. J. Clin. Pathol., 76: 501-509.
10. Eguchi K, Izumi Y, Yasuoka Y, Nakagawa T, Ono M, Maruyama K et al. Regulation of rhcg, an ammonia transporter, by aldosterone in the kidney. *J Endocrinol*. 2021;249(2):95-112.
11. Naranjo CA, Pontigo E, Valdenegro C, González G, Ruiz I, Busto U. Furosemide induced adverse reactions in cirrhosis of the liver. *Clin Pharmacol Thers*. 1979;25(2):154-160.
12. Uchida Y, Tsuji S, Uemura H, Kouyama J, Naiki K, Sugawara K et al. Furosemide as a factor to deteriorate therapeutic efficacy of rifaximin in patients with decompensated cirrhosis. *Hepatol Res*. 2020;50(11):1264-1274.