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REVIEW

Beyond oral and intravenous diuretics: intranasal bumetanide for heart failure decongestion

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Abstract

Heart failure (HF) remains a major cause of morbidity, hospitalization, and healthcare expenditure, with acute decompensated HF accounting for more than 1.2 million hospital admissions annually in the United States. Intravenous loop diuretics remain the standard for acute decongestion; however, their reliance on venous access, monitoring, and hospital infrastructure limits outpatient use and contributes to recurrent healthcare utilization. These limitations have driven interest in alternative strategies capable of achieving effective decongestion in ambulatory settings. Intranasal bumetanide has emerged as a potential option by bypassing the gastrointestinal tract, where intestinal edema, impaired splanchnic perfusion, and gastrointestinal dysmotility during HF decompensation may lead to unreliable oral absorption. In a randomized three-way crossover trial involving 68 healthy participants, intranasal bumetanide demonstrated systemic exposure comparable to oral and intravenous administration, with similar peak concentrations and area under the curve. It also showed reduced pharmacokinetic variability compared with oral therapy (~27% *vs* >40% intrasubject variability) and more rapid absorption, with time to maximum concentration of approximately 1.0 hours (intranasal) *vs* 1.5 hours (oral), suggesting a more predictable onset of diuretic effect. Pharmacodynamic responses, including urine output and urinary sodium excretion at 2 and 24 hours, were comparable across all routes, with a favorable safety profile and minimal adverse effects. Despite these findings, important limitations remain, particularly the absence of data in patients with HF, uncertainty regarding absorption during acute congestion, and concerns related to unsupervised outpatient administration. Further clinical studies are required to define the efficacy, safety, and clinical role of intranasal bumetanide in HF management.

Key words: heart failure; acute decompensated heart failure; loop diuretics; intranasal delivery.

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Introduction

The lifetime risk of heart failure (HF) is now approximately 24%, with the number of affected individuals in the United States (US) projected to exceed 8 million by 2030.[1,2] Parallel to this rising prevalence, hospitalizations for acute decompensated heart failure (ADHF) continue to increase, with more than 1.2 million admissions occurring annually in the US alone.[1,3] These admissions account for nearly 40% of the estimated $32 billion annual expenditure associated with HF care, underscoring the substantial clinical and economic burden imposed by recurrent decompensation.[3]

ADHF is characterized by the rapid onset or worsening of HF signs and symptoms, frequently necessitating emergency department evaluation or hospitalization.[4] Central to its management is the prompt relief of congestion, most commonly achieved with intravenous (IV) loop diuretics, as oral therapies may become unreliable during acute decompensation because of unpredictable absorption and bioavailability.[4-8] Though effective, IV therapies require vascular access, trained personnel, and close monitoring, thereby increasing procedural complexity, resource utilization, and healthcare costs.[3] Importantly, although advances in guideline-directed medical therapy have improved the long-term management of HF, outcomes following episodes

of decompensation remain poor, with readmission rates approaching 25% within 30 days and nearly 50% within 6 months.[4] This persistent cycle of hospitalization, coupled with financial penalties for hospitals with higher HF readmission rates, has shifted attention toward strategies focused on earlier outpatient intervention and prevention of clinical deterioration.[9,10] Many centers across the US have now established specialized multidisciplinary outpatient clinics aimed at facilitating early treatment of congestion and reducing hospitalizations.[11] Although these approaches can successfully avert hospitalization in carefully selected patients, their broader implementation remains limited by substantial logistical and operational challenges.[2] In many institutions, outpatient IV diuretic therapy is restricted to single administrations or brief infusions, whereas serial dosing is often constrained by staffing requirements, transportation barriers, limited patient mobility, and insurance-related limitations.[2] Even when feasible, serial dosing of diuretic agents in the outpatient setting may be difficult to deliver safely and effectively in patients at high risk of electrolyte disturbances, worsening renal function, or hemodynamic instability.[2]

In light of these limitations, there is growing interest in alternative strategies capable of delivering effective decongestion while preserving the practicality required for ambulatory care.[12] One such approach is the intranasal delivery of bumetanide, which bypasses the gastrointestinal tract and may provide more reliable absorption without the need for IV access.[12] Therefore, in this review, we seek to examine the potential therapeutic role of intranasal bumetanide in HF, with particular emphasis on the clinical evidence, current limitations of the available data, and future directions that could help define its role in contemporary decongestive management for HF.

Intranasal bumetanide as a therapeutic strategy in heart failure

Among currently available loop diuretics, bumetanide exhibits unique pharmacokinetic properties that make it well-suited for intranasal delivery.[13] Its high potency enables therapeutic efficacy at very low administered volumes, while its lipophilic structure enhances transmucosal permeability across the nasal epithelium.[13,14] These attributes have facilitated the development of an intranasal formulation (RSQ-777), designed for short-term outpatient management of volume overload in patients with HF, hepatic dysfunction, renal impairment, and nephrotic syndrome.[15] Following intranasal administration, bumetanide is rapidly absorbed through the highly vascularized nasal mucosa, enabling prompt systemic entry while circumventing gastrointestinal absorption and first-pass hepatic metabolism.[12] This route of delivery may be particularly relevant in decompensated HF, where intestinal wall edema, impaired splanchnic perfusion, and gastrointestinal dysmotility collectively contribute to erratic and often unreliable oral drug absorption.[12] By bypassing these barriers, intranasal administration offers the potential for more consistent and predictable systemic drug exposure compared with conventional oral therapy (Table 1).[12] From a practical standpoint, intranasal delivery provides a non-invasive, easily administered route that obviates the need for venous access, sterile preparation, or supervised infusion.[3] This may reduce dependence on hospital-based IV diuretic regimens and diminish the frequency of acute healthcare encounters.[16] In turn, such a strategy could potentially alleviate hospitalization burden, mitigate readmission risk, reduce overall healthcare expenditure, and streamline congestion management in selected HF patients (Figure 1).

Early clinical evidence for intranasal bumetanide

Studies evaluating intranasal bumetanide are largely preclinical and primarily focused on pharmacokinetic assessment. Recently, a randomized, three-way crossover trial involving 68 healthy participants evaluated the pharmacokinetics and pharmacodynamics of intranasal bumetanide.[17] In this study, participants received a single 2 mg dose of bumetanide via intranasal spray, oral tablet, and IV administration, with 48-hour washout periods between treatments. The primary pharmacokinetic

Table 1. Comparative characteristics of oral, intravenous, and intranasal bumetanide.

Characteristic	Oral bumetanide	Intravenous bumetanide	Intranasal bumetanide
Primary absorption pathway	Gastrointestinal tract	Direct systemic delivery	Nasal mucosa (transmucosal)
Bioavailability	Variable during HF decompensation	Complete and predictable	Comparable to oral and IV administration in healthy volunteers
Influence of gastrointestinal edema/perfusion	May significantly impair absorption	Not affected	Avoids gastrointestinal absorption
First-pass hepatic metabolism	Present	Avoided	Avoided
Risk of erratic absorption in ADHF	High (gut edema, dysmotility)	Not applicable	Potentially lower than oral administration
Need for trained personnel	Minimal	High	Minimal
Feasibility for ambulatory/outpatient use	Moderate	Limited	Potentially favorable

HF, heart failure; ADHF, acute decompensated heart failure.

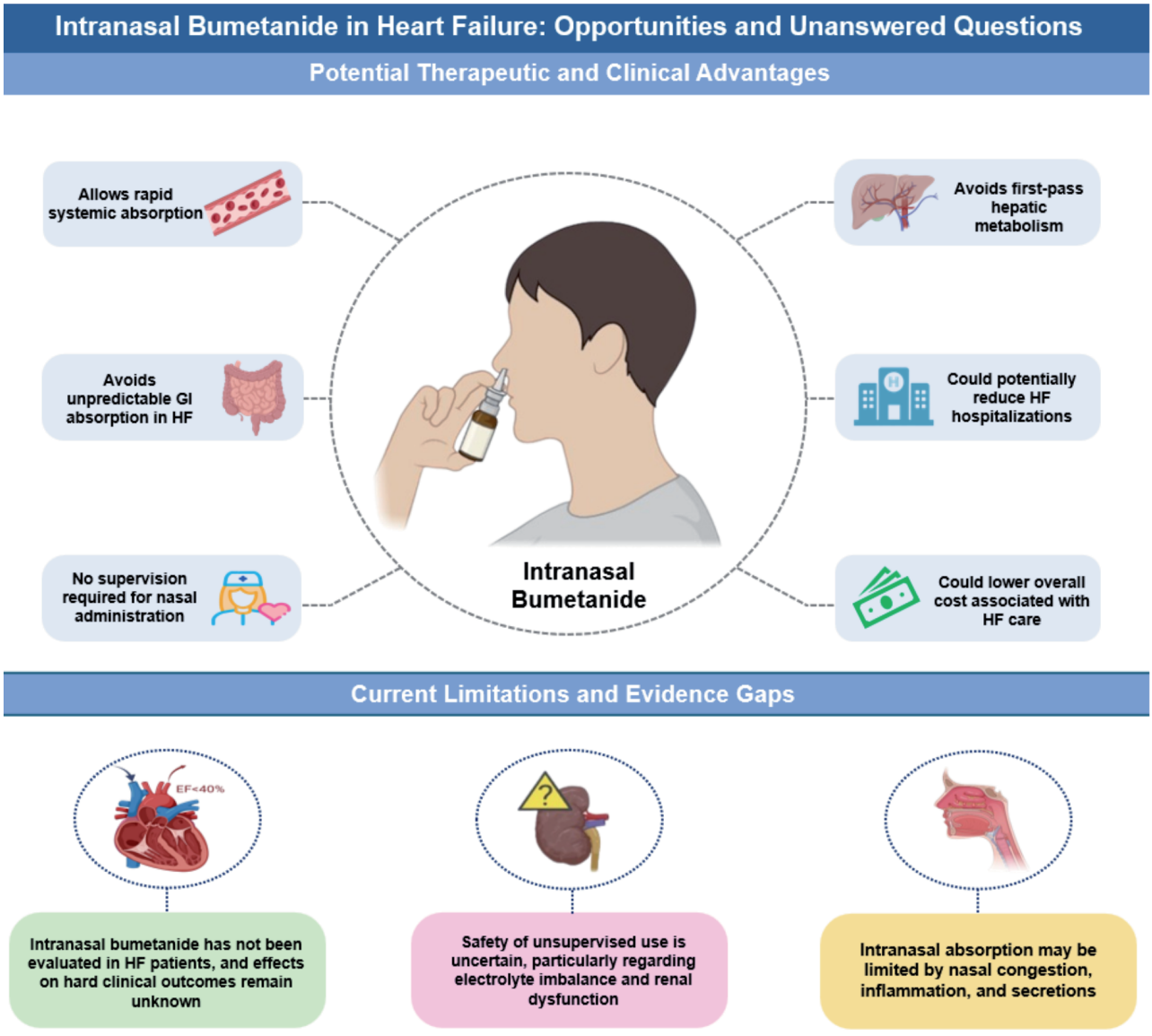

Figure 1. Intranasal bumetanide in heart failure: therapeutic advantages and evidence gaps. HF, heart failure; GI: gastrointestinal.

endpoints were maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC), while secondary endpoints included time to maximum concentration (Tmax), half-life, volume of distribution, plasma clearance, absolute bioavailability, safety outcomes, and pharmacodynamic measures such as urine output and urinary sodium excretion.

Results showed that intranasal bumetanide met its primary pharmacokinetic endpoints, demonstrating systemic exposure comparable to both oral and IV routes, with no meaningful differences in Cmax or AUC, indicating similar overall bioavailability across all administration routes. Importantly, both intranasal and IV administration were associated with lower intrasubject variability in systemic exposure (27%) compared with oral dosing (>40%), suggesting more consistent and reliable absorption with non-oral routes. Tmax was shorter with intranasal delivery compared with oral tablets (approximately 1.0 *vs*. 1.5 hours), indicating more rapid absorption and a potentially earlier onset of diuretic effect that may be relevant for outpatient decongestion strategies. Pharmacodynamically, intranasal bumetanide produced urine output and urinary sodium excretion at 2 and 24 hours that were comparable to both oral and IV administration, indicating preserved diuretic efficacy across routes. Safety outcomes were favorable, with only a single case of mild nasal dryness reported and no clinically significant differences in laboratory parameters, vital signs, or electrocardiographic findings between treatment arms.

Limitations of the current evidence base

Although intranasal bumetanide demonstrates comparable bioavailability to oral and IV administration, there are several limitations that should be considered when evaluating its potential role in HF management. First, current pharmacokinetic and pharmacodynamic data are derived exclusively from healthy participants, limiting applicability to patients with acute or advanced HF. This limitation is clinically relevant because HF is frequently associated with chronic kidney disease, reduced renal perfusion, heightened sodium avidity, and altered drug metabolism, all of which may influence loop diuretic pharmacokinetics and pharmacodynamic responsiveness.[12] Second, uncertainty exists regarding the reliability of intranasal delivery in patients with HF, as the extent to which nasal congestion, mucosal inflammation, and excessive secretions affect drug deposition and absorption remains poorly defined. This concern is amplified during acute decompensation, where reports of rhinorrhea and upper airway congestion suggest potential variability in intranasal drug delivery.[18,19] Third, although intranasal administration may offer practical advantages in outpatient settings, unsupervised use introduces additional concerns, including delayed recognition of electrolyte disturbances, worsening renal dysfunction, and inappropriate dose escalation in patients with persistent congestion.[20] As a result, the clinical role of intranasal bumetanide in HF remains incompletely defined, and extrapolation to patients with HF should be undertaken with caution.[20]

Future directions for the clinical evaluation of intranasal bumetanide in heart failure

With the growing burden of HF and the persistent challenges associated with outpatient decongestion, there is increasing interest in therapeutic strategies capable of bridging the gap between oral and IV loop diuretic therapy. Intranasal bumetanide represents a promising non-invasive approach; however, its clinical utility in patients with HF remains insufficiently defined.[3] Further studies are therefore needed to evaluate its efficacy, safety, and feasibility before its role in routine clinical practice can be established. Future investigations should assess not only the pharmacokinetic performance of intranasal bumetanide but also its ability to achieve effective and sustained decongestion in patients with HF, as reflected by natriuresis, urine output, short-term weight reduction, changes in renal sodium handling, and objective markers of congestion including cardiac filling pressures, pulmonary edema, BNP, and NT-proBNP levels.[21] Equally important are patient-centered and healthcare utilization outcomes, including improvements in dyspnea, peripheral edema, exercise tolerance, and functional status, as well as reductions in emergency department visits, HF hospitalizations, and readmissions.[22] In addition, patient-reported outcomes, including quality of life, treatment satisfaction, and ease of administration, will be important in determining the long-term feasibility, acceptability, and integration of intranasal bumetanide into outpatient HF management pathways.

Conclusions

Intranasal bumetanide offers a promising non-invasive approach to outpatient HF decongestion, with the potential to improve the reliability of diuretic delivery while reducing reliance on IV therapy. However, current evidence is limited to early pharmacokinetic data, and robust prospective HF trials are needed to establish its clinical efficacy, safety, and real-world utility.

Authors' contributions

All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval and consent to participate

Not required.

Availability of data and materials

The datasets used and/or analyzed during the current study are available upon reasonable request from the corresponding author.

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