

HYPERTENSION MANAGEMENT: TACKLING THE CLINICAL CHALLENGES OF OMAPATRILAT AND ITS ANALOGUES (SAMPATRILAT AND SAMASP) IN HYPERTENSION THERAPY

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ABSTRACT

Vasopeptidase inhibitors have shown great efficacy in treating hypertension patients over decades. VPIs like omapatrilat effectively target both neprilysin (NEP) and angiotensin-converting enzyme (ACE) for blood pressure control but suffer from severe side effects due to off-target activity. Omapatrilat inhibits NEP, nACE, and cACE, but it leads to excessive accumulation of bradykinin and substance P, which contribute to adverse effects such as angioedema. This review explores the dynamics of this drug and its analogue molecules, addressing the issues behind its stop in clinical usage and how adjusting the inhibitor design can reduce the off-target effects, mitigating bradykinin-related side effects.

Keywords: *Vasopeptidase, hypertension, Omapatrilat, Sampatrilat, off-target, angioedema.*

Introduction

Hypertension is the major chronic, non-communicable disease in the world, with high morbidity and mortality

related to it. The number of people aged 30 to 79 with hypertension in 2019 is approximately 1.28 billion, which is a surprising doubling of the 1990 number (Verdecchia et al., 2022). Although conventional antihypertensive drugs have significantly improved outcomes, there are still huge gaps in the majority of the patients who reach blood pressure control. Additionally, chronic HTN appears to greatly contribute to both cardiovascular and renal morbidity, highlighting the need for further exploration of alternative treatment strategies.

Human angiotensin-1-converting enzyme (ACE) is a zinc dipeptidyl carboxypeptidase that plays a pivotal role in vascular health by controlling blood pressure (Cozier et al., 2018). It is a component of the renin-angiotensin-aldosterone network that transforms angiotensin I to angiotensin II, which is a vasoactive peptide. ACE is made up of two domains- 612 amino acids in N-terminal domain and a C-domain of 650 amino acid residues. Although the substrate specificity of both domains is expansive, certain biochemical characteristics vary (Tzakos & Gerotheranassis, 2005).

Omapatrilat was the first-in-class dual inhibitor of both neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE) among vasopeptidase inhibitors (VPIs) (Packer et al., 2002; Campese et al., 2016). Vascular homeostasis is modulated and vasodilation is encouraged by the dual mechanism. But negative side effects including angioedema have raised questions about their clinical progress in the medical field (Sharma et al., 2020).

Current State of Omapatrilat and Its Analogues

Omapatrilat, although highly effective, was discontinued due to the high incidence of angioedema observed in trials. Researchers have since focused on analogues like sampatrilat and SamASP, which aim to retain its efficacy while minimizing adverse effects. Sampatrilat, in particular, has shown improved performance in selective inhibition, reducing the accumulation of bradykinin (Rajni et al., 2016). SamASP, while less potent, still provides insight into structural modifications that could improve drug design (Sharma et al., 2020).

The key challenge is to develop compounds that maintain antihypertensive benefits while mitigating angioedema risk (Maki et al., 2003). In addition, computational modeling has aided in the design of next-generation vasopeptidase inhibitors that refine molecular interactions and improve enzyme specificity.

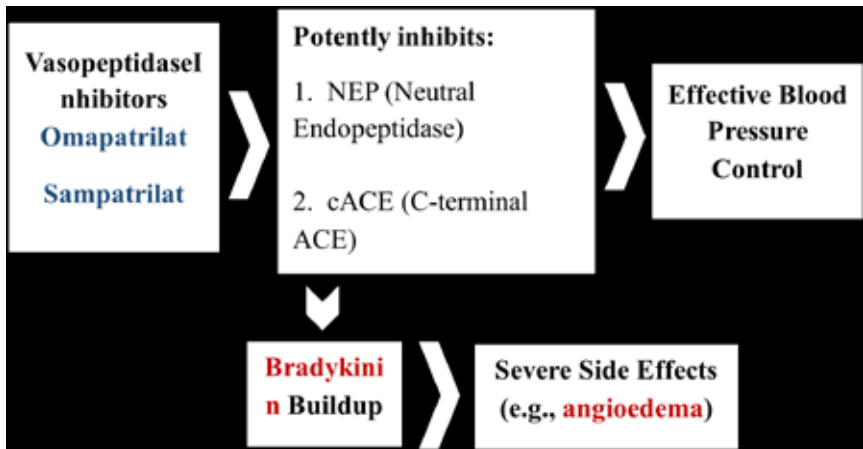


Fig 1: A schematic diagram of how these VPIs control blood pressure as well as increase side effects

Advantages Over Conventional Therapies

Compared to traditional antihypertensive drugs, vasopeptidase inhibitors present unique advantages. While ACE inhibitors or angiotensin receptor blockers (ARBs) primarily reduce angiotensin II levels, they fail to significantly influence natriuretic peptide activity i.e. vasodilation. By targeting NEP in addition to ACE, vasopeptidase inhibitors augment vasodilation and natriuresis while reducing systemic vascular resistance (Campese et al., 2001). This dual mechanism results in pronounced reductions in systolic and diastolic blood pressure.

Moreover, studies suggest that vasopeptidase inhibitors can attenuate arterial stiffness, enhance cardiac output, and reduce vascular remodeling (Mitchell et al., 2002). These properties are especially valuable for patients with comorbidities like

heart failure, where vascular and myocardial adaptations are critical. By contrast, dual inhibitors like omapatrilat enhance natriuretic peptide effects, improving vasodilation and sodium excretion (Campese et al., 2001)

Path of Action and Pharmacodynamics

Omapatrilat and its analogues exhibit a unique mechanism of action through the simultaneous inhibition of two pivotal enzymes: angiotensin-converting enzyme (ACE) and neprilysin (NEP). In a dose-based research, angiotensin converting enzyme function was suppressed by over 80%, 24 hours following the dosage of omapatrilat (Liao et al., 2003). Compared with placebo, omapatrilat increased 24-h urinary excretion of ANP at doses of 10 mg and higher on days 1, 3, and 10 in the multiple dose study and at doses of 7.5 mg and higher in a single-dose study. **Sampatrilat** increased plasma aldosterone levels, decreasing plasma ACE concentration at days 28 and 56 (Reza Tabrizchi, 2003). Urinary cGMP release was elevated by all three dosages of sampatrilat after 10 days ($P < .05$ compared to control for 100 mg and 200 mg sampatrilat; $P = \text{NS}$ for the 50 mg dosing). Administered in doses varying from 50 mg to 200 mg, it exhibited minimal antihypertensive efficacy following the initial dosage (Wallis et al., 1998).

Pharmacokinetics

In 3–4 days, steady-state plasma concentrations for omapatrilat were attained, indicating consistent existence (Liao et al., 2003). After oral administration, it is well-absorbed, reaching peak plasma concentrations approximately 2 to 4 hours post-dose. The drug exhibits high plasma protein binding (~95%) and is widely distributed throughout the body, including the central nervous system, though its concentration in the brain is lower compared to peripheral tissues. Omapatrilat is heavily metabolized in the liver, primarily by the cytochrome P450 pathway (particularly CYP2C9), which produces inactive metabolites. When treating cardiac failure and hypertension, its stimulation of ANP, a protein having vasodilatory effects, may be more advantageous than using an ACE inhibitor (Vesterqvist et al., 1999). Its elimination is primarily renal, with a half-life of around 11 hours, which can

be prolonged in patients with renal impairment, necessitating dosage adjustments.

Similar to Omapatrilat, Sampatrilat is a dual inhibitor of ACE and NEP, used to manage hypertension and heart failure. It is absorbed efficiently after oral administration, reaching peak plasma concentrations within approximately 2 hours. The drug is highly protein-bound (~95%) and distributed throughout the body, with limited penetration into the central nervous system. Sampatrilat undergoes extensive hepatic metabolism, primarily via the cytochrome P450 enzymes, and is metabolized into inactive compounds. The drug is eliminated primarily through the kidneys, with a half-life of around less than 24 hours.

SamASP (also known as **Samapril**) is an ACE inhibitor used in the treatment of hypertension. It is moderately absorbed after oral administration, with peak plasma levels occurring within 2 to 4 hours. The drug exhibits low bioavailability (~30%) and is widely distributed throughout the body, with high plasma protein binding (~80-90%). It undergoes hepatic metabolism, converting into active metabolites, although it experiences considerable first-pass metabolism. The elimination of **SamASP** occurs primarily through renal excretion, and both the parent compound and its metabolites are eliminated via urine. The half-life of **SamASP** is approximately 10 hours, and its clearance is slower in patients with renal impairment, requiring dose adjustments to prevent accumulation.

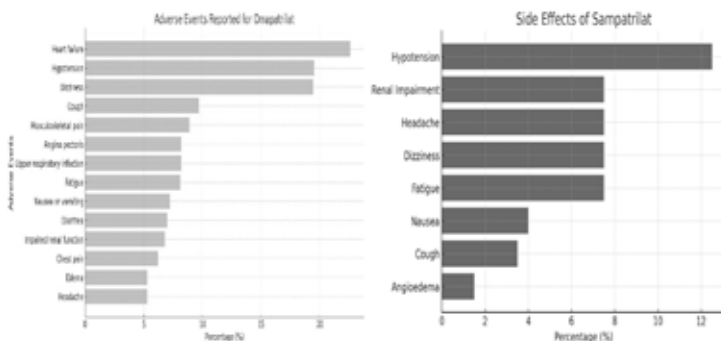


Fig 2: Adverse events reported in Omapatrilat and % of Side effects of in Sampatrilat.

Ligand Interactions

The efficacy of vasopeptidase inhibitors such as omapatrilat, sampatrilat, and SamASP is deeply rooted in their ligand interactions with the active sites of ACE and NEP.

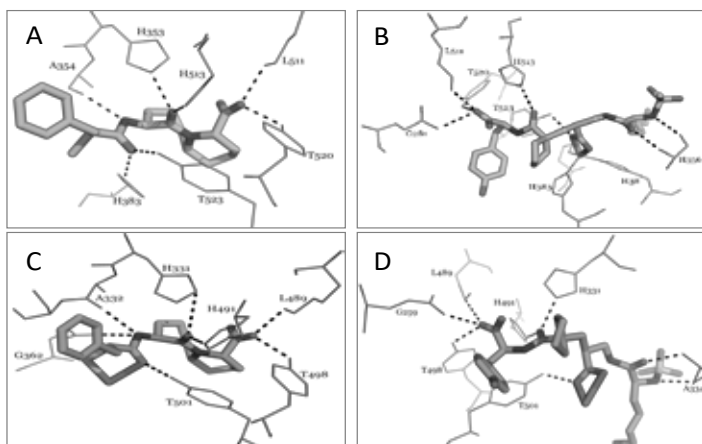


Fig 3: Omapatrilat in carbon domain of ACE enzyme (PDB ID: 6H5W). B.Sampatrilat in carbon domain of ACE enzyme (PDB ID: 6F9T).C. Omapatrilat in nitrogen domain of ACE enzyme (PDB ID:6H5X). D. Sampatrilat in nitrogen domain of ACE enzyme(6F9V).

Omapatrilat is designed as a tripeptide mimic, enabling its simultaneous binding to the catalytic sites of ACE and NEP. It establishes bidentate coordination with zinc ions present in both enzymes' active sites. In NEP, omapatrilat occupies the S1', S2', and partially the S3' subsites, with its bicyclic group extending towards non-prime regions. Its C-terminal carboxylate group interacts with residues like Glu584 in NEP and Glu411 in ACE, stabilizing the binding. These strong interactions contribute to high affinity and slow dissociation rates, which underlie omapatrilat's potency but exacerbate bradykinin accumulation.

Sampatrilat shows a unique binding pattern, demonstrating selectivity for ACE's C-domain over the N-domain. Its lysine side chain forms hydrogen bonds with Glu748 and Glu1008

in the S1 and S2 subsites of ACE's C-domain. This selectivity reduces bradykinin buildup, offering a safer profile compared to omapatrilat. In NEP, sampatrilat binds to S1' and S2' subsites with slightly weaker interactions than omapatrilat, balancing its potency across both enzymes.

SamASP binds to NEP and ACE similarly to sampatrilat but with reduced affinity due to weaker electrostatic interactions. Its C-terminal modifications increase steric hindrance, limiting its access to key residues like Lys461 and Asp422 in NEP. Additionally, its lack of domain selectivity for ACE reduces its therapeutic potential while increasing the likelihood of side effects such as angioedema (Sharma et al., 2020).

Key Ligand-Residue Interactions

Ligand	Enzyme	Key Binding Residues	Subsites Occupied	Zinc Interaction	Binding Affinity
Omapatrilat	ACE	Glu411, His383, His387	S1, S1', S2'	Bidentate	High
	NEP	Glu584, Lys421, Asp642	S1', S2', S3'	Bidentate	High
Sampatrilat	ACE	Glu748, Glu1008, Lys511	S1, S2	Monodentate	Moderate
	NEP	Lys461, Asp422, Glu460	S1', S2'	Monodentate	Moderate
SamASP	ACE	Glu748, Asp422	S1, S2	Weak	Low
	NEP	Asp422, Lys461	S1', S2'	Weak	Low

Comparison of Binding

Compound	Ki for NEP	Ki for ACE	Ki for nACE	Ki for cACE	Selectivity (cACE/nACE)
	(nM)	(nM)	(nM)	(nM)	
Sampatrilat	8	1.2	171.9	13.8	12.4
Omapatrilat	8.9	0.5	0.015	0.016	1.06
SamAsp	Not available	8.7	10.6	7.4	1.4

Omapatrilat binds extensively across the S1', S2', and S3' subsites of NEP, forming strong interactions with zinc ions and catalytic residues (Sharma et al., 2020). Sampatrilat inhibited both cACE and nACE in the low nanomolar range, but it was 12.4-fold more selective for cACE (Ki of 13.8 and 171.9 nM respectively) (Cozier et al., 2018). H-bond interaction between the lysine side chain of sampatrilat and nACE (due to Glu403 of cACE being replaced by Arg381 in nACE), and a less extensive hydrophobic network. The comparison of the N1/C1 and N2/C2 poses indicates that the lysine side chain of sampatrilat exhibits considerable flexibility within the S2 pocket of both nACE and cACE, while demonstrating more precise interactions in the S1 pocket (Rajni et al., 2016). On the other hand, in SamASP, the aspartate group replaces the lysine chain of sampatrilat, showing non-specific and low micromolar affinity (Cozier et al., 2018).

Lipinski's Rule of Five

Lipinski's Rule of Five (Ro5) serves as a fundamental guideline in drug discovery, helping researchers evaluate the potential of a compound for oral bioavailability. It provides insights into whether a molecule is likely to be well-absorbed and distributed in the human body, making it a valuable tool in pharmaceutical development. By applying

these criteria early in the drug design process, scientists can improve the chances of selecting compounds with favorable pharmacokinetic properties while minimizing failures due to poor absorption. According to the rule, an orally active drug should not exceed five hydrogen bond donors, ten hydrogen bond acceptors, a molecular weight of 500 Daltons, and a logP value greater than five, ensuring a balance between solubility and permeability. Although some drugs may deviate from these parameters, Ro5 remains an essential reference point in medicinal chemistry, guiding the development of effective and bioavailable therapeutic compounds (Karami et al., 2022).

Table: Lipinski's Rule of Five Analysis for Omapatrilat, Sampatrilat, and SamASP

Comparison Table of Lipinski's rules: Omapatrilat vs. Sampatrilat

<i>Parameters</i>	<i>Lipinski's Threshold</i>	<i>Omapatrilat</i>	<i>Sampatrilat</i>	<i>Compliance</i>
Molecular Weight	≤ 500 daltons	492.52 daltons ✓	563.63 daltons ✗	Omapatrilat complies; Sampatrilat exceeds the threshold, possibly reducing membrane permeability.
Hydrogen Bond Donors	≤ 5	2 ✓	7 ✗	Both compounds comply with the rule for hydrogen bond donors.
Hydrogen Bond Acceptors	≤ 10	6 ✓	13 ✗	Both compounds comply with the rule for hydrogen bond acceptors.
LogP (Lipophilicity)	≤ 5	2.47 ✓	2.90 ✓	Both compounds have favorable lipophilicity, supporting good absorption potential.

Discussion

Omapatrilat is consistent with many criteria for productive drug development, though its high polar surface area may adversely affect permeability and ultimately bioavailability. In contrast, Sampatrilat complies most with Lipinski's rules, generating better pharmacokinetic characteristics and higher clinical future potential. In opposing, SamASP is deficient for its high molecular weight and polar surface area, indicating

that structural modifications are required for SamASP to be used as a drug candidate. These findings underscore the need for iterative optimization to enhance the drug-like properties of next-generation vasopeptidase inhibitors.

Comparison of Binding

Omapatrilat binds extensively across the S1', S2', and S3' subsites of NEP, forming strong interactions with zinc ions and catalytic residues (Sharma et al., 2020). Sampatrilat inhibited both cACE and nACE in the low nanomolar range, but it was 12.4-fold more selective for cACE (K_i of 13.8 and 171.9 nM respectively) (Cozier et al., 2018). H-bond interaction between the lysine side chain of sampatrilat and nACE (due to Glu403 of cACE being replaced by Arg381 in nACE), and a less extensive hydrophobic network. The comparison of the N1/C1 and N2/C2 poses indicates that the lysine side chain of sampatrilat exhibits considerable flexibility within the S2 pocket of both nACE and cACE, while demonstrating more precise interactions in the S1 pocket (Rajni et al., 2016). On the other hand, in SamASP, the aspartate group replaces the lysine chain of sampatrilat, showing non-specific and low micromolar affinity (Cozier et al., 2018).

Challenges of Bradykinin Accumulation

Bradykinin, while essential for vasodilation, poses a dual-edged sword in the context of ACE and NEP inhibition. Excessive accumulation increases vascular permeability and risk of angioedema. Recombinant full-length ACE have shown that the K_m of ACE for bradykinin is substantially lower than for Ang I, reflecting a greater affinity for metabolism of bradykinin than for the production of Ang II (Corti et al., 2001).

Future Directions in Vasoepitidase Inhibitor Design

Emerging technologies, including AI-driven drug discovery and advanced docking simulations, are accelerating the design of next-generation inhibitors. Combining vasoepitidase inhibition with complementary pathways, such as endothelin receptor antagonism, is being explored to enhance efficacy further. Additionally, biomarker-guided approaches are

improving patient stratification, tailoring therapies to individual needs. C-domain-selective ACE inhibitors offer hope for a new generation of ACE inhibitors with improved safety but are unlikely to offer improved efficacy unless combined with other drugs (Arendse et al., 2019).

Conclusion

Vasopeptidase inhibitors, spearheaded by omapatrilat, represent a transformative approach to hypertension management. Despite challenges, advances in analogues like sampatrilat highlight their potential to overcome existing limitations. Through innovative design and rigorous clinical evaluation, these agents are poised to redefine hypertension treatment paradigms, offering hope for improved patient outcomes. The utilization of contemporary structure-based drug development techniques on established therapeutic regions will yield more selective molecules targeting ACE.

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