Hypertension

NOVEL THERAPEUTIC

First-in-Human Study of MANP: A Novel ANP (Atrial Natriuretic Peptide) Analog in Human Hypertension

Horng H. Chen, Siu-Hin Wan, Seethalakshmi R. Iyer, Valentina Cannone, S. Jeson Sangaralingham, Joel Nuetel, John C. Burnett Jr

ABSTRACT: M-atrial natriuretic peptide (MANP) is a novel ANP (atrial natriuretic peptide) analog engineered to be an innovative particulate GC-A (guanylyl cyclase A) receptor activator. The rationale for its design was to develop a best-in-class GC-A activator with enhanced cGMP activating, natriuretic, aldosterone-suppressing, and blood pressure–lowering actions, compared with endogenous ANP, for the treatment of hypertension. Here, we report the first-in-human study on the safety, tolerability, neurohumoral, renal, and blood pressure–lowering properties of MANP in hypertension subjects. This was an open-label sequential single ascending dose design in which all subjects stopped all antihypertensive agents for 14 days before receiving a single subcutaneous injection of MANP. MANP was safe, well tolerated, activated cGMP, induced natriuresis, reduced aldosterone, and decreased blood pressure at or below the maximal tolerated dose. Thus, MANP has a favorable safety profile and produced expected pharmacological effects in human hypertension. Our results support further investigations of MANP as a potential future blood pressure–lowering, natriuretic and aldosterone-suppressing drug for hypertension especially resistant hypertension. (***Hypertension*.2021;78:1859–1867. DOI:10.1161/HYPERTENSIONAHA.121.17159.)**

Supplemental Material

Key Words: aldosterone ■ blood pressure ■ cardiovascular disease ■ guanylyl cyclase ■ natriuresis

Hypertension is the leading cause of worldwide death and morbidity for cardiovascular disease. Despite the knowledge that controlling blood pressure (BP) reduces the risk for cardiovascular disease, Muntner et al[1] recently reported that the prevalence of controlled BP has decreased. Indeed, Oparil and Schmieder[2] recently stated that despite a plethora of antihypertensive drugs, there is an unmet need of controlling BP in high-risk patients by the development of new drugs and devices that are designed to treat hypertension. Furthermore, with the ever-growing burden of hypertension, a recommendation from the Report of the National Heart, Lung and Blood Institute Working Group on Hypertension was to "develop new drugs and treatments to target diverse hypertensive patient populations, such as patients with resistant hypertension.[3]"

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In 1981, de Bold et al[4] established the concept of the heart as an endocrine organ with his discovery that the heart synthesizes and releases the hormone ANP (atrial natriuretic peptide). Studies reported that ANP is the endogenous ligand for the particulate GC-A (guanylyl cyclase A) receptor which functions via the second messenger cGMP.[5,6] This ANP/GC-A/cGMP signaling cascade regulates BP homeostasis through natriuresis, vasodilatation, and suppression of the renin-angiotensin-aldosterone system.[7,8] Furthermore, studies have also reported that ANP exerts favorable metabolic actions as well as sympathoinhibitory and antihypertrophic properties.[9–12] The importance of ANP/GC-A in BP regulation has been demonstrated in murine studies in which the ANP or GC-A genes have been genetically deleted resulting in a hypertensive mouse phenotype.[13,14] Moreover, investigations have also revealed that the ANP gene variant, rs5068, is associated with higher ANP circulating levels, lower systolic BP, lower risk for hypertension,

Correspondence to: Horng H Chen, MB, BCh, Cardiorenal Research Laboratory, Guggenheim 915, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. Email chen.horng@mayo.edu

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Novelty And Significance

What Is New?

- M-atrial natriuretic peptide is a novel ANP (atrial natriuretic peptide) analog engineered to be an innovative particulate (GC-A [guanylyl cyclase A]) activator. Here, we report the first-in-human clinical study on the safety, tolerability, neurohumoral, renal, and blood pressure–lowering properties of M-atrial natriuretic peptide in hypertension subjects.

What Is Relevant?

- Hypertension is the leading cause of worldwide death and morbidity for cardiovascular disease. Indeed, the ever-growing burden of hypertension resulted in a recommendation from the Report of the National Heart, Lung and Blood Institute Working Group on Hypertension to "develop new drugs and treatments to target diverse hypertensive patient populations, such as patients with resistant hypertension."

Summary

Thus, M-atrial natriuretic peptide has a favorable safety profile and produced expected pharmacological effects in human hypertensive subjects off antihypertensive medications. Our results support further investigations of M-atrial natriuretic peptide as a potential future blood pressure–lowering, natriuretic and aldosterone-suppressing drug for hypertension especially resistant hypertension.

Nonstandard Abbreviations and Acronyms

ANP	atrial natriuretic peptide
BP	blood pressure (BP
DBP	diastolic BP
GC-A	guanylyl cyclase A
IDE	insulin-degrading enzyme
MANP	M-atrial natriuretic peptide
NEP	neprilysin
SBP	systolic BP

and protection from obesity and metabolic syndrome.[15,16] Most recently, Vandenwijngaert et al[17] have reported that a low frequency and rare genetic gain of function variant of the GC-A gene (NPR1 [natriuretic peptide receptor 1]) is associated with reduced BP. Indeed, cells expressing this gene variant (rs61757359) displayed greater ANP-mediated cGMP production than wild-type GC-A cells. Moreover, recent studies demonstrate an ANP deficiency state in hypertension which further underscores the physiological importance of ANP in BP regulation.[18] Both the favorable BP regulating properties of the ANP/GC-A/cGMP pathway, as well as an ANP deficiency in hypertension, support the rationale for ANP-based therapy. Despite this scientific rationale, a challenge is the rapid degradation of ANP by peptidases, such as NEP (neprilysin) and IDE (insulin-degrading enzyme) necessitating intravenous infusion, thus limiting the ability for chronic administration.[19,20] Nonetheless, intravenous infusion of ANP as well as B-type natriuretic peptide in hypertensive and normotensive subjects reduced BP and enhanced natriuresis.[21,22]

M-atrial natriuretic peptide (MANP) is a novel ANP analog that was engineered at the Mayo Clinic to be more potent and long-lasting than native ANP and whose molecular target is GC-A resulting in enhanced production of its effector molecule cGMP.[23] MANP is a 40 amino acid peptide consisting of the 28 amino acids of native ANP with a unique 12 amino acid C terminus extension. Importantly, MANP (also called fsANP [frameshift atrial natriuretic peptide]), unlike ANP, has been shown to be highly resistant to enzymatic degradation by NEP and IDE.[20,24] Moreover, intravenous administration of MANP exhibited markedly greater and more sustained BP-lowering ($P<0.05$ greater reduction sustained over 150 minutes postinfusion), natriuretic ($P<0.001$ greater doubling of natriuresis during infusions), glomerular filtration enhancing ($P<0.05$ more sustained increase in glomerular filtration rate postinfusions), and aldosterone-suppressing actions ($P<0.01$ for 150 minutes postinfusion) compared with native ANP in normal canines.[23] In a large animal model of hypertension produced by acute angiotensin II infusion, intravenous MANP administration potently reduced BP and had favorable renal and aldosterone inhibiting actions.[25] In addition, MANP was administered daily for 7 days by subcutaneous injection in hypertensive rodents resulting in cGMP activation and sustained BP lowering.[26] Taken together, these findings support the significant therapeutic potential of ANP for the treatment of hypertension, including the challenging syndrome of resistant hypertension for which there is no Food and Drug Administration–approved drug. Indeed, MANP possesses as a single peptide entity the pleiotropic properties of cGMP activation, natriuresis, aldosterone suppression, and BP-lowering properties in preclinical studies which do not exist in any single current antihypertensives drug.

The current study was designed as a first-in-human study of MANP, and it was performed in subjects with hypertension bypassing normal volunteers based upon its efficacy and safety in multiple studies, including in normal, hypertensive, and heart failure canine and rodent models.[23,25,27] Our goal was to determine MANP's overall safety, tolerability, and plasma cGMP activating properties via subcutaneous injection in hypertensive subjects who were off

standard-of-care antihypertensive medications. Our study was an open-label sequential single ascending dose design in 3 cohorts of 4 hypertensive subjects each, in which all antihypertensive agents were stopped for 14 days before MANP administration so as to assess the specific actions of a single subcutaneous injection of MANP at 3 doses. In addition to the safety, tolerability, and cGMP activation to MANP, we assessed its natriuretic, aldosterone-suppressing, and BP-lowering actions, including pharmacokinetics.

METHODS

Authors declare that all supporting data are available within the article and its Supplemental Material.

Study Design

This first-in-human study of MANP was designed as an open-label sequential single ascending dose study in 3 cohorts of 4 essential hypertensive subjects withdrawn from antihypertensive medications for 2 weeks. The 3 cohorts were represented by 3 doses (cohort 1: 1 µg/kg SC; cohort 2: 2.5 µg/kg SC; and cohort 3: 5 µg/kg SC).

The study was performed at Integrium Research Facility (Tustin, CA) under the IND 114829. As this was a first-in-human clinical study, no clinical trial registration number was required. All subjects provided written, informed consent before enrollment. Study documentation was reviewed and approved by the Ethics Committee Integrium. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its amendments, the US Food and Drug Administration Principles of Good Clinical Practice, and International Conference on Harmonization Guidelines, where applicable. There was no control of dietary sodium in the current first-in-human study as approved by the Food and Drug Administration.

The primary objectives of the study were to establish the safety, tolerability of single MANP dose and to determine the maximum tolerated dose as defined by a systolic BP (SBP) reduction ≥30 mm Hg. Inclusion and exclusion criteria are listed in Table S1 in the Supplemental Material.

After the screening visit, subjects underwent a 2-week wash-out of antihypertensive medications. If the BP during the wash-out period was >180/95 mm Hg, patients were excluded and restarted on their antihypertensive medications.

After the 2-week wash-out period, subjects were admitted at 5 AM and observed in an in-house study unit for dosing of MANP. A 2-hour baseline timed urine collection was performed, followed by measurements of baseline BP, heart rate, orthostatic BP, and blood draw for pharmacokinetic and neurohumoral assessment. Subcutaneous injection of MANP was administered at time zero (at ≈8 AM), followed by the start of the 24-hour postdose observation period, during which the following procedures occurred at the designated hours following dosing:

- Clinic BPs at 0.5, 1, 2, 4, 6, 12, and 24 hours.
- Orthostatic BPs at 1, 2, 4, 6, 12, and 24 hours.
- Blood samples collected at 0.25,0.5, 1, 1.5, 3, 6, 12, and 24 hours.
- Timed urinary volume collection from baseline (2 hours before MANP dose to 0 hour), 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, and 12 to 24 hours.

Note that there were no cardiovascular measurements between 12 and 24 hours. Subjects were discharged from the study unit after at least 24 hours of postdose observation.

Subjects

Twelve subjects were recruited and completed the study (3 cohorts of 4 hypertensive subjects each). We started dosing at 1 µg/kg, followed by 5 µg/kg. It was prespecified in the protocol that during the ascending dose phase of the trial, dose escalation will be stopped if 2 subjects in the cohort had SBP reduction of >30 mm Hg. Two subjects in the 5 µg/kg did have a reduction of SBP ≥30 mm Hg. Hence, we dosed the third cohort at 2.5 µg/kg.

Monitoring of Safety and Tolerability

All subjects who have taken a single dose of the study drug and provided follow-up information were included in the safety analysis population. All safety variables (including adverse experiences, vital signs measurements, clinical laboratory results, ECG results, and other safety variables) were listed by subject and domain. The incidence of all adverse events, treatment-emergent adverse experiences, and treatment-related adverse experiences were tabulated by Medical Dictionary for Regulatory Activities preferred term, system organ class, dose, and treatment group. The incidence of treatment-emergent abnormalities was summarized by dose.

Assessment of Plasma MANP and cGMP

Plasma MANP was determined by employing ANP radioimmunoassay as previously reported with 70% cross-reactivity to MANP.[28] Plasma cyclic GMP and aldosterone were also measured by methods previously reported.[29,30]

Assessment of Urinary Sodium Excretion and Aldosterone

As stated above, urine was collected in 4-hour intervals up to 12 h and one collection from 12 to 24 hours during the study protocol. Urinary sodium excretion was calculated for each for our clearance. Urinary sodium concentration was determined by flame photometry (IL943; Instrumentation Laboratory, London, United Kingdom).

Assessment of BP and Heart Rate

Sitting SBP and diastolic BP (DBP) were measured at time points stated above. Three measurements were averaged for a given value. ECG monitored heart rate continuously.

Pharmacokinetic Variables

The pharmacokinetic analysis was conducted using model-independent methods as implemented in WinNonlin (version 4.0 or later) and was based on plasma concentrations of MANP and cGMP from those subjects who received subcutaneous MANP and have evaluable plasma concentration-time profiles. The following pharmacokinetic parameters were determined for MANP: C_{max}—maximum plasma concentration; AUC_{last}—area under the plasma concentration-time curve from time zero to 24-hour postdosing.

Statistical Methods

This human study was not powered for statistical significance. Descriptive statistics are presented for the study variables within the study portion. For continuous variables, these descriptive statistics include number and mean. For categorical variables, counts and percentages are presented.

RESULTS

Demographics and Baseline Data

Table 1 summarizes the clinical characteristics of the study population.

Safety

The first cohort (n=4) received 1 µg/kg and the second cohort (n=4) received 5 µg/kg. In the current study, the maximum tolerated dose was defined as SBP reduction ≥30 mm Hg. Furthermore, the protocol stated that during the ascending dose phase of the trial, dose escalation would be stopped if 2 subjects met the SBP reduction of ≥30 mm Hg. In the 5 µg/kg cohort, 2 subjects had an SBP reduction ≥30 mm Hg despite tolerating the dose. Hence, dose escalation was stopped, and the next cohort was dosed at 2.5 µg/kg (n=4).

There were no serious adverse events. Table 2 reports adverse events, including mild headache (n=3), transient lightheadedness lasting for 10 seconds (n=1), and transient orthostatic vasovagal syncope lasting for 7 s (n=1). No significant changes in laboratory values or ECG from baseline were observed.

Plasma MANP and cGMP

Figure 1 reports neurohumoral responses in the 3 treatment groups. Plasma MANP increased in all groups with the highest concentration occurring at 30 minutes after subcutaneous injection. Plasma cGMP paralleled changes in MANP.

Urinary Sodium Excretion and Plasma Aldosterone

There was a dose-dependent increase in urinary sodium excretion during the first 4 hours after subcutaneous administration of MANP (Figure 2). At 24 hours after dosing, plasma creatinine trended to be lower as compared to predose in the 5 µg/kg (data not shown).

Plasma aldosterone decreased in all 3 groups with subcutaneous injection of MANP (Table 3).

BP and Heart Rate

Figure 3 illustrates the changes in SBP, DBP, and heart rate from baseline in response to MANP. In cohort 1, baseline SBP and DBP were 166±10 and 106±8 mm Hg; in cohort 2, they were 156±11 and 101±9

Table 1. Baseline Characteristics

Variable	1 µg/kg (n=4)		2.5 µg/kg (n=4)		5 µg/kg (n=4)	
Age, y (SD)	58	(14)	59	(8)	58	(8)
Sex male, n (%)	2	(50)	3	(75)	2	(50)
Race White, n (%)	3	(75)	3	(75)	2	(50)
Race Black, n (%)	0	(0)	1	(25)	2	(50)
Body mass index, kg/m^2 (SD)	38	(13)	30	(3)	27	(2)
Tobacco history, n (%)	2	(50)	0	(0)	2	(50)
Beta blockers, n (%)	0	(0)	0	(0)	0	(0)
ACE inhibiton, n (%)	1	(25)	3	(75)	1	(25)
ARB, n (%)	2	(50)	1	(25)	0	(0)
CCB, n (%)	2	(50)	2	(50)	0	(0)
Thiazide diuretics, n (%)	1	(25)	4	(100)	4	(100)
Potassium sparing diuretics, n (%)	0	(0)	0	(0)	2	(50)
Aldosterone antagonists, n (%)	0	(0)	0	(0)	0	(0)
Systolic BP, mm Hg (SD)	148	(4)	145	(2)	150	(6)
Diastolic BP, mm Hg (SD)	96	(5)	94	(3)	93	(3)
Heart rate, bpm (SD)	75	(6)	68	(5)	72.4	(7)
eGFR, mL/(min·1.73 m^2) (SD)	85	(17)	83	(12)	83	(17)
ANP, pg/mL (SEM)	4.5	(4.5)	31.4	(27.1)	32.3	(13.1)
Plasma cGMP, pmol/mL (SEM)	2.4	(0.2)	1.9	(0.17)	3.0	(0.42)
Aldosterone, ng/dL (SEM)	7.2	(1.9)	8.7	(3.8)	7.2	(2.7)

ACE indicates angiotensin-converting enzyme; ANP, atrial natriuretic peptide; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; and eGFR, estimated glomerular filtration rate.

Table 2. Adverse Events

Adverse events	MANP (N=12)
Mild headache, n (%)	3 (25%)
Lightheadedness, n (%)	1 (8%)
Orthostatic vasovagal syncope, n (%)	1 (8%)
Arrhythmia, n (%)	0 (0%)
Second- or third-degree atrioventricular block, n (%)	0 (0%)
Ventricular tachycardia >5 beats, n (%)	0 (0%)
Ventricular fibrillation or asystole, n (%)	0 (0%)
Tachycardia, n (%)	0 (0%)
Paresthesia, n (%)	0 (0%)
Dyspnea, n (%)	0 (0%)
Gastrointestinal symptoms, n (%)	0 (0%)

mm Hg; and in cohort 3, they were 157±10 and 98±8 mm Hg, respectively. Both SBP and DBP were reduced compared with baseline with the greatest reductions in all 3 groups occurring between 2 and 12 hours. At 24 hours after dosing, SBP remained lower than baseline in the 2.5 and 5 µg/kg cohorts, whereas DBP was lower in the 5 µg/kg cohort. It should be noted there were no cardiovascular measurements between 12 and 24 hours. Heart rate trended to increase as compared to baseline in a dose-dependent manner, which was most prominent from 4 to 24 hours postsubcutaneous injection in the 5 µg/kg cohort.

Pharmacokinetics

Table S2 reports pharmacokinetics. For MANP in plasma, the highest C_{Max} and AUC_{last} occurred with the highest dose of 5 µg/kg. Half-life (T 1/2) was 54, 75, and 55 minutes, respectively, for increasing doses. For plasma cGMP, there was a clear dose-response with increasing C_{Max} and AUC_{last}. Half-life was similar for each dose. The pharmacokinetic for cGMP (done on all subjects and at all time points) and MANP (done on only those with measurable levels of MANP) demonstrated a dose-response pattern.

DISCUSSION

This human study investigated for the first time the safety, tolerability, cGMP activating, natriuretic, aldosterone-suppressing, and BP-lowering actions of subcutaneous administered MANP in subjects with essential hypertension withdrawn from antihypertensive medications. The study showed that the subcutaneous administration of 3 single ascending doses of MANP was safe and well tolerated with increases in plasma cGMP and urinary sodium excretion, and aldosterone along with BP. Thus, the favorable in vivo actions observed in preclinical studies with MANP were successfully translated to human hypertensive subjects.

With the discovery of ANP, its molecular target the GC-A receptor, and its second messenger cGMP, the importance of the heart in BP regulation was realized.[4] Specifically, the main biological actions of ANP/GC-A/cGMP signaling are to lower BP through natriuresis, vasodilation, and aldosterone inhibition. The therapeutic rationale of targeting GC-A also is supported by the report that hypertension may, in part, be characterized by a relative ANP deficiency due to inadequate production, release, or excessive degradation of ANP.[18] The current study testing the GC-A targeted ANP analog, MANP, confirms the findings obtained in preclinical investigation and importantly, further supports the potential therapeutic role of GC-A/cGMP activation in hypertensive subjects through BP-lowering, natriuresis, and aldosterone-suppressing effects in hypertensive subjects. Notably, to date, no approved GC-A/cGMP activating drug exists for hypertension, thus underscoring the potential for MANP as a novel therapy whose molecular target is GC-A, with plasma cGMP serving as a readout for target engagement.

Natriuresis is a hallmark of MANP biological actions via GC-A/cGMP.[23,25,27] In the current study, we observed a clear dose-response to MANP in urinary sodium excretion during the 4 hours after injection. Thus, dose-dependent increases in natriuresis observed in previous animal studies with MANP are now validated in humans. In addition to renal actions of GC-A activation is the reported aldosterone inhibition in adrenal cell, animal, and human studies.[31–33] Although the duration of aldosterone reduction was variable among the treatment cohorts, a signal for a reduction and off-response by 24 hours was observed. Thus, MANP induces unique reno-adrenal responses in hypertensive subjects which combines natriuretic actions, similar to a diuretic, with the favorable action of aldosterone suppression. These promising findings should be confirmed with chronic studies to demonstrate sustained actions.

Subcutaneous administration of MANP at 3 different doses reduced BP over the 24-hour period of observation. This BP effect peaked between 2 and 12 hours, and we did not observe a clear dose-response. Indeed, all doses similarly reduced SBP by ≈15 mm Hg in our cohorts. This similar effect at all doses was unexpected based upon experimental studies in normal and in hypertensive canines. Our findings indicate that subcutaneous doses from 1 to 5 µg/kg may have already achieved a maximal effect. We now plan a clinical study in a similar cohort of subjects but exploring lower doses than those used in the current study. Although not a clear dose-response with the small number of subjects, the 5 µg/kg dose was the maximal tolerated dose as 2 of the 4 subjects experienced reductions in SBP >30 mm Hg. Thus, the high dose which was associated with the greatest natriuretic and cGMP action was the most hypotensive. Importantly, our studies establish that we can overcome the need for continuous

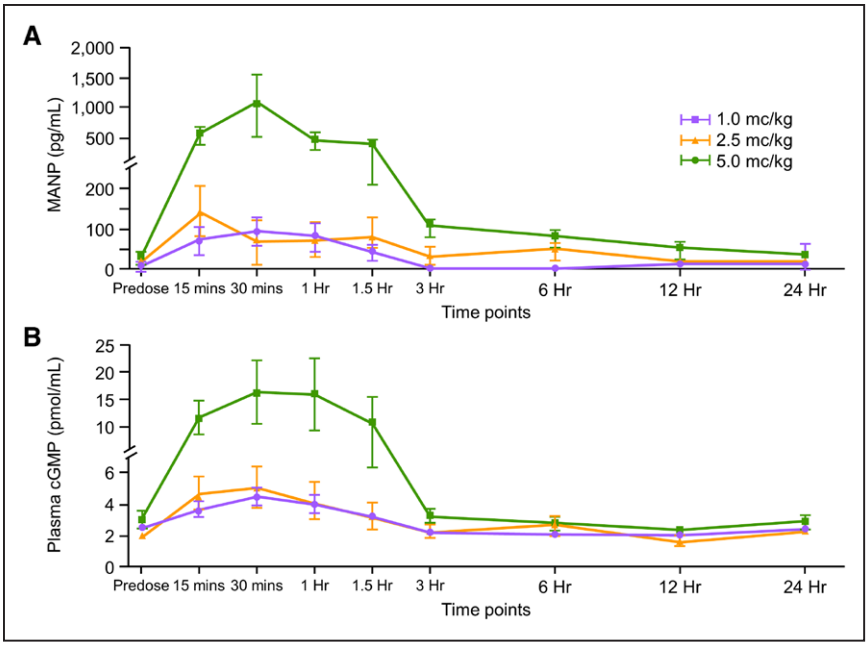

Figure 1. Effect of MANP on plasma MANP (A) and plasma cGMP (B).
Values are mean±SEM.

intravenous infusion of a natriuretic peptide with the efficacy of subcutaneous administration as is widely used for insulin and GLP-1 [glucagon-like peptide-1] analogs. Such a strategy supports our goal of chronic MANP therapy which will be investigated in future studies. Importantly, our study was performed after a 2-week wash-out of antihypertensive medications. Thus, our findings reveal the specific actions of MANP without the cofounding effects or interactions with other BP-lowering drugs.

We utilized well-characterized ANP and cGMP assays, which determined circulating MANP and cGMP concentrations to assess pharmacokinetics. We observed that indeed the highest level of MANP concentration in plasma was achieved with the highest dose which was paralleled by plasma cGMP. Future studies should also assess the presence of any post-translational modification of MANP in which could affect bioactivity. Indeed, this is important based on the report by Hansen et al[34] of presence of glycosylation of ANP which results in reduced activation of GC-A. As required by the Food and Drug Administration, surveillance studies to anti-MANP will be assessed in future chronic studies of MANP.

Furthermore, no major adverse events were observed in the current study. Of the 12 subjects, 3 developed mild headaches (1 in 5 µg/kg and 2 in 2.5 µg/kg), 1 developed lightheadedness (1 µg/kg), and there was 1 subject with orthostatic vasovagal syncope (5 µg/kg) all of which resolved without intervention or clinical consequence. We also observed no ECG changes in any of the subjects during the 24 hours of observation and there were no local reactions at the injection sites.

Our study has limitations, which will require further investigations. Our study included a small cohort and in a larger study in hypertensive subjects will be required to

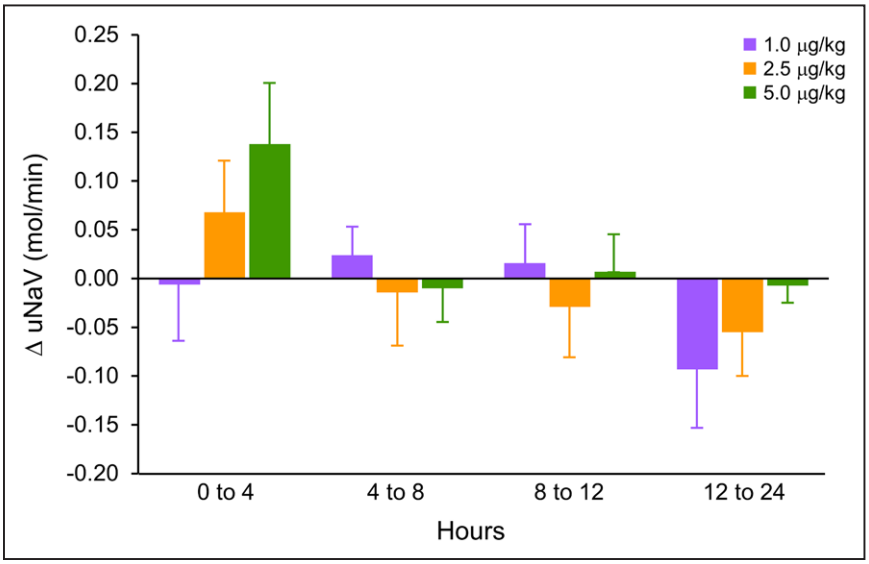

Figure 2. Effect of MANP on urinary sodium excretion (UNaV).
Values are mean±SEM.

Table 3. Plasma Aldosterone Levels Following Subcutaneous MANP Administration

Aldosterone, ng/dL	MANP, 1 µg/kg		MANP, 2.5 µg/kg		MANP, 5 µg/kg	
Predose	7.18	(1.90)	8.70	(3.83)	7.23	(2.74)
15 min	2.19	(0.58)	2.45	(2.13)	1.61	(1.06)
30 min	1.23	(0.46)	3.01	(2.19)	1.98	(1.02)
1 h	5.80	(0.54)	4.85	(0.48)	4.30	(0.81)
3 h	7.98	(1.69)	4.00	(0.40)	8.35	(3.32)
12 h	5.55	(1.22)	3.63	(0.39)	4.40	(1.36)
24 h	7.40	(1.59)	5.48	(0.39)	6.85	(1.84)

confirm the current findings. Future studies should also include a wider dose-ranging design to determine optimal dosing strategies including on top of current antihypertensive medications as well as including a placebo to assure that MANP BP reductions are truly related to MANP and not time. By design, our investigation was of short duration employing a single dose of MANP with an observation of 24 hours; therefore, longer duration studies will be required. No assessment of hypertensive damage by echocardiography or previous cardiovascular events other than HF were carried out in this study, these should be included in future studies. Our subjects were largely White patients (75%), and future studies need to include expanded numbers of racially mixed populations especially in African Americans in whom ANP levels are lower than White patients.[35] In addition, our hypertensive subjects were free of any signs of hypertensive damage and previous cardiovascular events. Therefore, the effect of MANP in complicated hypertension remains to be tested. Additionally, it will be important in future studies to determine the action of MANP on endogenous ANP as well as to define if baseline ANP influences responses to MANP. Finally, future studies need to also assess if BP-lowering actions of MANP can be sustained without excessive rebound in the sympathetic nervous system and renin-angiotensin system which could offset the actions of MANP.

MANP has a well-defined molecular target GC-A, which is expressed widely in multiple cells, and organs that have important roles in BP regulation and hypertension. Our approach builds on advances in peptide therapeutics in more commonly used in diseases like diabetes, cancer, and HIV therapeutics. Although biologics in hypertension are currently being pioneered to target angiotensinogen with gene silencing,[36] there are no peptide therapeutics for hypertension, which makes our approach highly innovative. Importantly, peptide therapeutics permit highly selective targeting of well-characterized receptors that avoid off-target actions associated with small molecules. A limitation however to peptide therapeutics is rapid degradation by proteases, which reduce bioavailability compared to small molecules. MANP is a product of advances in peptide engineering resulting in greater resistance to enzymatic degradation as previously reported.[20,24] In addition, subcutaneous administration of peptides has been highly safe and efficacious such as with insulin and GLP-1 analogs in diabetes.

Although regulatory requirements necessitated this first-in-human study to be performed in essential

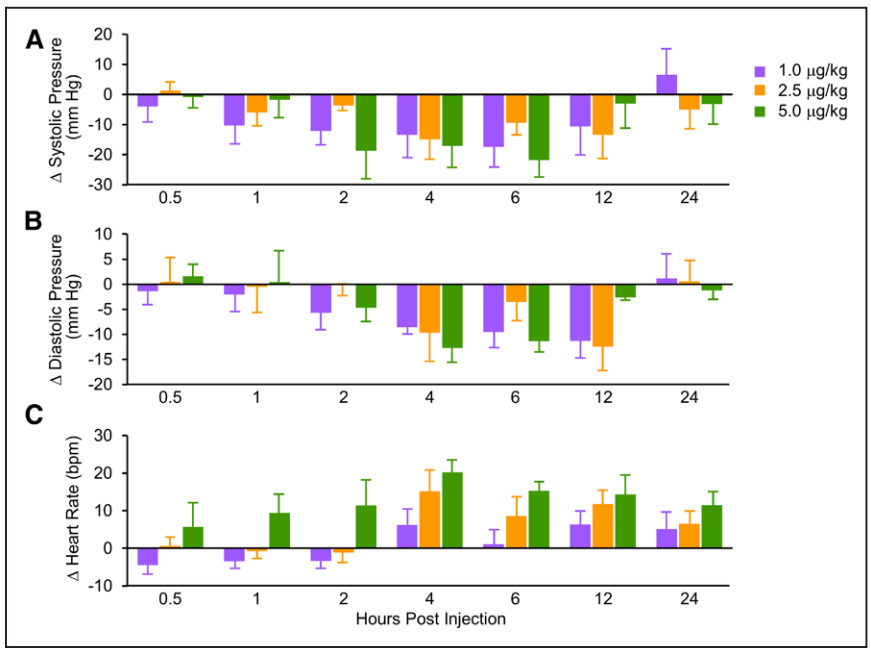

Figure 3. Absolute changes in systolic blood pressure; diastolic blood pressure and heart rate.
Values are mean±SEM.

hypertensive subjects off medications, our goal is to ultimate investigate the safety and efficacy of MANP in resistant hypertension. This is a high unmet need for which there are no approved drugs with protean complications, such as increased risk for heart failure, stroke, and chronic kidney disease.

In conclusion, this first-in-human study of MANP in essential hypertension establishes that the treatment with this designer ANP analog engages the GC-A receptor with cGMP activation and reduces BP, enhances sodium excretion, and suppresses aldosterone (See Graphic Abstract). Importantly, MANP was well tolerated, had a favorable safety profile without adverse effects, and can be effectively administered subcutaneously, all of these characteristics support a strategy for chronic delivery in hypertensive patients in future studies. Moreover, our findings lay the foundation for a clinical development program to investigate MANP as a therapeutic for resistant hypertension for which there is no approved drug. Overall, the current results encourage further investigations of MANP as an innovative new antihypertensive therapy, acting through multiple mechanisms via the GC-A/cGMP pathway.

PERSPECTIVES

In this first-in-human study, we demonstrate that the designer peptide MANP which is a novel ANP analog which was engineered to active the GC-A receptor is safe and well tolerated. In this single ascending dose study with 3 doses, MANP activated cGMP, induced natriuresis, decreased aldosterone, and reduced BP in hypertensive subjects.

ARTICLE INFORMATION

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Affiliations

Cardiorenal Research Laboratory, Department of Cardiovascular Medicine, Mayo Clinic, Rochester MN (H.H.C., S.R.I., J.S., J.C.B.). Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas (S.-H.W.). Department of Internal Medicine, University of Parma, Parma, Italy (V.C.). Integrium, Tustin, CA (J.N.).

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Disclosures

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