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Genetic and Non-Genetic Factors Influencing Pharmacokinetics of B-type Natriuretic Peptide

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Abstract

Background—Natriuretic peptides (NP) represent a critical pathway in heart failure (HF). However, there is wide individual variability in NP system activity, which could be partially genetic in origin. We explored genetic and non-genetic contributions to BNP inactivation.

Methods—Chronic HF patients (n=95) received recombinant human BNP (nesiritide) at standard doses and BNP levels were measured at baseline, 2 hours of infusion, and 30 minutes after discontinuation. Genomic DNA was genotyped for 91 single nucleotide polymorphisms (SNP) in two candidate genes. We tested the association of patient characteristics and genotype with 5 pharmacokinetic (PK) parameters: elimination rate constant, BNP, BNP clearance, adjusted BNP clearance, and half-life. Linear regression with pleiotropic analysis was used to test genotype associations with PK.

Results—Participant mean age was 63 years, 44% were female, and 46% were African American. PK parameters varied widely, some >10-fold. HF type (preserved vs. reduced) was associated with PK ($p<0.01$), while renal function, demographics, and BMI were not. Two SNPs in *MME* (rs989692, rs6798179) and two in *NPR3* (rs6880564, rs2062708) also had associations with PK ($p<0.05$).

Conclusion—Pharmacokinetics of BNP varies greatly in HF patients, differs by HF type, and possibly *MME* or *NPR3* genotype. Additional study is warranted.

Keywords

Natriuretic peptide; heart failure; drug metabolism; pharmacogenetics; genetic polymorphisms

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DISCLOSURES

The authors have no disclosures.

INTRODUCTION

Heart failure (HF) continues to be an enormous public health problem despite the many advances in its pharmacotherapy over the past 25 years, with a prevalence of 5.7 million individuals affected and an incidence of over 500,000 new cases annually [1]. Thus better prognostics, improved targeting of current therapies, and novel therapies are still needed. The relevance of the natriuretic peptide (NP) system, particularly B-type NP (BNP), is well known in terms of HF pathophysiology [2,3], diagnosis [4], prognosis [5], and therapy [6,7]. Moreover, the response to extrinsic NP (e.g. nesiritide, carperitide) is also highly variable, with unclear therapeutic range and potential for adverse effects [8-10]. A portion of this variation in NP system functioning is likely to be genetic in origin,[11] evidenced by clear associations of genetic variants with cardiovascular disease states,[12,13] altered gene expression and protein abundance,[14,15] as well as native NP levels via either altered production or elimination [16-18]. NP system variability will continue to be a relevant clinical issue not only because our understanding of NP system biology is still incomplete, but also because BNP is being increasingly explored towards personalized care,[19] and because there are numerous investigational NP therapeutics currently under development. [20,21]

We sought to systematically assess the genetic and non-genetic associations of BNP clearance by infusing intravenous recombinant human BNP (nesiritide), quantifying key pharmacokinetic parameters, and focusing on common sequence variation in candidate genes relevant to BNP metabolism. The two primary molecular clearance mechanisms previously identified for NPs are Membrane Metallo-endopeptidase (aka NEP), encoded by the gene *MME*, and Natriuretic Peptide Receptor C [NPRc], encoded by the *NPR3* gene (Figure 1). MME enzymatically degrades natriuretic (and other) peptides to predominantly inactive forms. NPRC is a non-catalytic NP receptor which shares homology with the other NP receptors in the transmembrane portion, but lacks the intracellular guanylate cyclase domain. It is thought that its primary role is in peptide internalization and clearance, though effector roles have recently been proposed.

We prospectively enrolled patients with heart failure who were planned to receive nesiritide infusion in order to evaluate the overall variation in BNP kinetics in a typical HF population, examine the association with clinical and demographic characteristics, and test the association of genetic variation in the two candidate genes with pharmacokinetic parameters. We hypothesized that genetic variation in key genes may associate with differences in drug elimination. If true this could help improve patient selection and dosing of NP-based therapeutics, as well as possibly impact the interpretation of native BNP levels and prognostication.

METHODS

Patients and sample collection

The study was approved by the Henry Ford Hospital Institutional review board and all patients provided written informed consent. Patients with a history of heart failure who were receiving nesiritide either as part of clinical care (hospitalized HF patients) or only for the

purposes of the study (ambulatory chronic HF patients) were included. Subjects with baseline systolic blood pressure less than 110 mmHg or with end stage renal disease were excluded. Patients received intravenous nesiritide at standard doses; 2mcg/kg bolus followed by 0.01mcg/kg/min continuous infusion. Patients were monitored for 1 hour prior to bolus, then received drug and were monitored for additional 2 hours. Blood samples were drawn at baseline and at 2 hours of infusion. Blood pressure was monitored every 15 minutes throughout. For patients not receiving nesiritide as part of standard care during an episode of hospitalized HF nesiritide was discontinued after the 2 hour blood draw, and another level was checked after 30 minutes to assess drug half-life. All investigational patient samples were centrifuged, aliquoted, and frozen within 30 minutes. These were stored at -70°C until batch testing could be performed at the Henry Ford Hospital clinical chemistry lab.

Genotyping

DNA samples were genotyped using a custom Illumina Goldengate® array which contained candidate-gene coverage relevant to HF including focused attention on the genes of interest to the natriuretic peptide pathway. Single nucleotide polymorphisms (SNP) were chosen for the array by attempting to include all coding variants, and also utilizing HAPMAP to select optimal non-coding ('tag') variants to capture blocks with minor allele frequency >0.1 prevalence in whites or African Americans within the gene regions of interest. After processing requirements for the Goldengate technology and quality control of genotyping, 91 SNPs in the two candidate genes of interest, membrane metallo-endopeptidase (*MME*, 41 SNPs) and natriuretic peptide receptor 3 (*NPR3*, 50 SNPs), were thus available for analysis. Genotyping calls were made using GenomeStudio software automatic algorithms (Illumina, San Diego, CA), and then individual SNPs were reviewed manually. Sample call rates were $>90\%$ and none of the SNPs analyzed deviated significantly from Hardy-Weinberg Equilibrium.

B-type Natriuretic Peptide Levels and Pharmacokinetic Parameters

B-type natriuretic peptide levels were tested in plasma samples using the Henry Ford Hospital Clinical Chemistry lab and personnel. The lab utilizes the Centaur (ADVIA, Bayer Diagnostics), which has high precision (coefficient of variation $<5\%$) and is capable of directly measuring levels up to 5000 ng/L (higher levels measured with dilution). [22] The upper limit reported by our laboratory is 8000 ng/L after dilutions, which was assigned as the maximum possible BNP value. BNP levels were measured at two time-points in all patients, baseline (BNP_B) and at 2 hours of infusion. Two hours of infusion was chosen because it was felt to be representative of steady state BNP level (BNP_{SS}) since this is more than 6 times the previously reported average half-life of roughly 18 minutes.[23] A third time-point of 30 minutes after discontinuation of drug (BNP_D) was also tested in patients where the nesiritide could be stopped (i.e. those subjects who were *not* prescribed nesiritide for clinical purposes in the hospital). We then derived and tested 4 pharmacokinetic endpoints, calculated as follows:

1. Change in BNP level ($\text{BNP} = \text{BNP}_{SS} - \text{BNP}_B$)
2. Elimination rate constant ($K = (1,000,000 \times \text{infusion rate}) / (73 \times \text{BNP})$)

3. BNP clearance rate ($CL = 1000 \times \text{infusion rate} \times \text{weight} / \text{BNP}_{SS}$)
4. BNP adjusted clearance rate ($CL = 1000 \times \text{infusion rate} \times \text{weight} / \text{BNP}$)
5. Half-life ($HL = -30(\ln(0.5)) / \ln(\text{BNP}_{SS} / \text{BNP}_D)$).

Statistical Analysis

The cohort size was chosen based on previously published data regarding BNP level achieved during infusion and the standard error of measurement [24], with which we calculated that 95 subjects would provide 90% power to detect a 25% relative difference in

BNP between genotype groups for genotype frequencies as low as 10%. We investigated the association of clinical and demographic characteristics as well as the individual SNPs with the pharmacokinetic parameters above. Since the PK parameters had a skewed distribution we tested the association with clinical characteristics using the Wilcoxon test, for which the continuous variables (creatinine, age, BMI) were dichotomized at the median. Testing the association of genotype with PK was accomplished via linear regression and pleiotropic association analysis, using Fisher's statistic with permutation to estimate p-values. This strategy was chosen so that we could combine all PK endpoints and thus examine the association of each SNP with its overall pharmacokinetic impact. $P < 0.05$ was considered of interest for all tests. Multiple comparisons were assessed in the genetic analysis by the false discovery rate using the Benjamini and Hochberg approach.[25] All analyses were performed in SAS version 9.1.3 (SAS Institute, Cary, North Carolina) and R statistical software.

RESULTS

Study subjects and Pharmacokinetics

The primary study cohort included 95 subjects with a mean age of 63 years, 30% were female, and 50% non-white race (Table 1). All the subjects had established diagnosis of HF. Thirteen of the subjects were hospitalized for heart failure at the time of study entry and received nesiritide by clinical indication. The remaining 82 subjects were volunteer patients with a history of chronic HF that received nesiritide for study purposes only, in a controlled ambulatory setting. All patients received nesiritide at standard doses for at least two hours and had BNP levels collected at baseline and at two hours of treatment. For subjects receiving nesiritide for study purposes only, treatment was discontinued after the on-treatment sample was collected, and another sample was drawn after 30 minutes in order to calculate half-life.

The pharmacokinetic parameters of interest varied widely across the study cohort. Figure 2 displays histograms of the distribution of each PK parameter; the x axis shows seven equal sized bins dividing the range of PK values (units vary by measure) and the y axis shows the percentage of the cohort within each bin. The range of BNP (14 to 7900 pg/ml), Adjusted BNP Clearance (0.1 ml/min to 67 ml/min), BNP Clearance (0.027 ml/min to 7.25 ml/min), K (0.002 to 9.7) and Half-life (6.6 to 56.4) were roughly 10-fold or greater. The PK parameters stratified by patient characteristics are shown in Table 2. None of the PK parameters differed significantly across age, race, gender, creatinine, or body mass index.

However there was a difference in 4 of the 5 pharmacokinetic measures by HF type (preserved vs. reduced ejection fraction); these included BNP, Adjusted Clearance, Clearance, and K (all $p < 0.01$). There was one subject that was an extreme outlier who was excluded from genetic analyses.

Genetic Associations of Pharmacokinetic Parameters

We examined the association of all five pharmacokinetic parameters of interest simultaneously using a pleiotropic statistical analysis. Ninety one SNPs in the two genes of interest were tested. The linkage maps of *NPR3* and *MME* and primary association testing results are depicted in Figure 3. Within *MME* two SNPs were significant for association with PK parameters by pleiotropic testing (rs989692, $p = 0.034$; rs6798179 $p = 0.014$). Within *NPR3* an additional two SNPs were significant for association with PK parameters by pleiotropic testing (rs6880564, $p = 0.046$; rs2062708, $p = 0.049$). Given the number of SNPs examined and modest cohort size, the associations did not survive adjustment for multiple comparisons. However, among these, rs6798179 showed the strongest and most consistent relationship, with associations to individual parameters as follows; K ($p = 0.024$), change in BNP ($p = 0.019$), raw clearance ($p = 0.0068$), adjusted clearance ($p = 0.014$), but no association to half-life ($p = 0.88$). For the *NPR3* SNPs, rs6880564 was most consistent with individual parameter associations; K ($p = 0.047$), change in BNP ($p = 0.0497$), raw clearance ($p = 0.019$), adjusted clearance ($p = 0.037$), and no association to half-life ($p = 0.90$). In terms of magnitude of effect, on average the genotype at rs6798179 was associated with roughly 50% increase in K and Clearance, and a nearly 40% smaller change in BNP due to infusion.

DISCUSSION

This is the first pharmacogenetic observation of nesiritide, and the largest study of its PK characteristics in a real-world HF cohort to our knowledge. Our data yields several key observations; that BNP elimination varies dramatically across typical HF patients, that HF type (preserved vs. reduced EF) impacts this substantially, and finally our data suggest that genetic variation in molecular clearance mechanisms may affect BNP metabolism. Specifically, genetic variation at rs6798179 within the *MME* gene was associated with a 40-50% change in BNP pharmacokinetics. While our study is relatively small and should be viewed as hypothesis generating, it supports the need for additional investigation and has potential implications in terms of HF pathophysiology and treatment. The variants identified as potentially impacting clearance are relatively common, occurring in roughly 20% of healthy populations of European ancestry, 10% of those of African ancestry, and up to 50% in Asian populations. In addition the magnitude of pharmacokinetic effect that we observed could be expected to be clinically significant, relating a 1.5 fold difference in steady state BNP levels and 50% difference in clearance rates.

As indicated above, it's important to note that our data demonstrate that in a real-world HF population the increment in BNP achieved, the BNP clearance rate, and the elimination rate constant all vary substantially, and likely to a clinically relevant degree. Moreover this variability was not explained by factors typically considered such as renal function, body mass, or race. Interestingly, HF subtype (preserved EF vs. reduced EF) was most associated

with BNP clearance, with HFrEF showing about double the BNP bump (and a lower clearance rate) compared to HFpEF. This finding is consistent with the more attenuated BNP elevations seen in HFpEF, and could in theory contribute to potential differences of nesiritide effect of in this group. Subgroup analysis of the ASCEND HF study based on EF did not show any trend towards a difference in the primary outcome. However this was defined somewhat differently (dichotomized at 40%) and there was not data presented regarding blood pressure lowering. While preserved EF patients were included in both ASCEND and VMAC, our search of the literature did not identify published data addressing efficacy of nesiritide by EF subgroups; this may be an opportunity for further investigation utilizing existing studies.

The high degree of variability in drug elimination that we found (which seems to have both genetic and non-genetic contributors), could very reasonably be expected to result in sub or super-therapeutic BNP levels during nesiritide infusion, despite uniform dosing, and thus underlie part of the variable impact demonstrated in clinical trials. The largest study of nesiritide, the ASCEND HF trial, showed little or no benefit in terms of dyspnea improvement or clinical outcomes, but it also showed modest or no risk in terms of hypotension and renal insufficiency.[8] This is in contrast to previous studies that sometimes utilized higher doses,[26,7] were associated with more robust symptomatic and hemodynamic changes,[27] but also were associated with higher risks of hypotension and renal insufficiency.[9,10] Our data demonstrate substantial underlying variability in drug clearance and BNP level increment on therapy, and suggest that a portion of this variability is genetic in origin. Thus improved targeting or dosing of drug via genetics or using therapeutic drug monitoring could be theorized to improve the risk:benefit ratio of nesiritide treatment and thus potentially salvage clinical utility for this vasoactive peptide. This remains an important health issue despite the existence of a large negative clinical trial because there are still no effective therapies for acutely decompensated heart failure to date, and this remains an extremely common and high risk reason to be hospitalized. Furthermore, there are additional NP agents in use and under investigation so that genetic factors impacting their elimination or effect may be relevant for future drug development.

Moreover, the genetic-based differences in clearance would be expected to also affect the native NP pathway functioning, potentially making the naturally occurring peptides more or less abundant relative to the level of expression/release. Whether and how this may impact disease development, progression, or diagnosis/prognostic BNP test performance is not yet known. Additional studies are needed to examine the prevalence of the genotypes in HF cohorts and compare this to healthy populations, to test whether the alleles of interest correlate with disease incidence, progression among patients with established HF, or BNP test performance. Similarly the altered clearance in HFpEF (relative to HFrEF) may help explain the differences in BNP levels noted in the two conditions. On the other hand, the relevance of our findings to NTproBNP testing is less clear. Certainly the genetic factors are more established as being relevant to BNP itself, and thus would not obviously impact NTproBNP levels. In regards to whether the relatively enhanced BNP clearance in HFpEF could have any effect on NTproBNP, the mechanism of this effect is unknown and our data cannot shed any light. Additional study with NTproBNP testing would be needed to clarify this further.

The biologic mechanism of a potential pharmacogenetic effect for this intronic variant is unknown. It's possible that the relationship described in this study could be mediated via linkage disequilibrium with one or more functional variants, indeed rs6798179 appears in the linkage map to be part of a block of LD at that region. Additional investigation will be required to further test this. In terms of mechanism, we have previously evaluated RNA and protein expression of *MME* in relation to genotype but did not detect an alteration by rs6798179 genotype,[14] although that study was small (n= 103).

Limitations

Our study has several limitations that should be noted. Given our limited sample size, we did not adjust for multiple comparisons and therefore these findings should be interpreted as preliminary; they could have occurred by chance and replication and external validation is needed. On the other hand, the modest sample size could have also limited our power to detect true differences in pharmacokinetics by genotype, thus we may have missed potentially important associations. In addition, this study was focused on elimination of BNP, particularly exogenously administered BNP, so that we do not have information on genetic variants that might affect native production.

Conclusion

In a real-world cohort of HF patients, BNP PK parameters during nesiritide infusion varied greater than 10 fold. Variation in BNP elimination was associated with HF subtype (preserved vs. reduced EF) and possibly genetic variation in *MME* and *NPR3*, with rs6798179 in *MME* showing the most consistent and strong association. Additional study is warranted to validate and extend these observations, towards enhanced understanding of the NP system and increased utility (via improved targeting or dosing) of exogenously administered NP.

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- Study of 95 patients with heart failure receiving human recombinant BNP (nesiritide) infusion and measuring BNP elimination.
- BNP clearance varied greatly across the cohort.
- Heart failure type (i.e. preserved vs. reduced ejection fraction) correlated with BNP clearance rates.
- Genetic variation in *MME* and *NPR3* may affect BNP clearance rates; this needs replication.

Figure 1.
NPRC=Natriuretic Peptide Receptor C; MME= Membrane Metallo-endopeptidase; BNP= B-type natriuretic peptide

Figure 2.

Distribution of each PK parameter (BNP in ng/L; K, unitless; BNP clearance in mL/min; BNP adjusted clearance rate in mL/min; Half-life in minutes). The x axis shows seven equal sized bins dividing the range of PK values. The y axis shows the percentage of the cohort within each bin.

Figure 3.

The linkage maps of *NPR3* and *MME* by each SNP (red and white blocked triangle) and heatmap of association tests with overall PK (from pleiotropic testing, blue) and individual PK parameters (red-green). Dark shades indicate stronger association.

Table 1

Baseline Characteristics

Characteristic	N= 95
Age, years	62 (± 15.6)
Female gender	29 (31%)
Non-white race	47 (49%)
Ejection Fraction $\geq 50\%$	25 (26%)
Mean Ejection Fraction (among those $<50\%$)	25% (± 11)
Creatinine	1.38 (± 0.54)
Weight, kg	96.6 (± 24.5)
Body mass index	32.6 (± 7.9)
Inpatient status	25%

Table 2

Pharmacokinetic Parameters Compared to Baseline Characteristics in Primary Cohort

Characteristic	BNP, pg/ml	p	Clearance (adjusted), ml/min	p	Clearance, ml/min	p	Half-life, minutes	p	K	p
Overall (Q1, Median, Q3)	1034 1655 3120	NA	0.29 0.58 1.43	NA	0.23 0.51 0.76	NA	11.2 14.4 21.2	NA	0.0 0.081 0.13	NA
Female	2533	0.22	0.36	0.18	0.305	0.29	16.2	0.57	0.054	0.28
Male	1411		0.63		0.54		13.6		0.094	
Non-white	1889	0.14	0.52	0.53	0.41	0.80	13.3	0.49	0.073	0.21
white	1458		0.58		0.45		14.9		0.088	
EF < 50%	1967	0.001	0.44	0.002	0.3	< 0.001	12.9	0.064	0.067	<0.001
EF ≥ 50%	1102		0.84		0.72		16.8		0.12	
Age *, Low	1907	0.45	0.56	0.98	0.46	0.94	12.3	0.42	0.072	0.47
High	1507		0.58		0.39		15.8		0.086	
BMI *, Low	1643	0.65	0.49	0.08	0.37	0.08	14.9	0.67	0.083	0.79
High	1656		0.62		0.52		12.5		0.073	
Creatinine *, Low	1327	0.19	0.65	0.19	0.56	0.063	14.4	0.55	0.10	0.13
High	1870		0.48		0.35		14.4		0.073	

* Divided at the median