Cardiorenal Actions of the Designer Natriuretic Peptide, CD-NP, in a Severe Heart Failure Model Treated with Furosemide

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ESC Meeting, Paris, France
August 31, 2011
Disclosures

- Mayo Clinic has licensed cenderitide to Nile Therapeutics.
- John C. Burnett, Jr. is Chair of the Scientific Advisory Board of Nile Therapeutics.
Patients with congestive heart failure (HF) have symptomatic improvement with diuretic therapy; however, diuretic resistance and renal dysfunction are frequent complications.

Renal dysfunction is a major risk factor for adverse outcomes.

Therefore, there is a need for novel therapies that protect or enhance renal function.

Guanylyl cyclase A (GC-A) and GC-B, which generate cGMP, are attractive drug targets for enhancing renal function.
GC-A Agonists

ANP (carperitide)

Urodilatin (ularitide)

BNP (nesiritide)

CNP

DNP

GC-A Agonists

GC-B Agonist
CNP
- Targets GC-B rather than GC-A
- Venodilation >> arterial dilation
- Lacks natriuretic actions
- Lacks a C-terminal tail and so is rapidly degraded by neprilysin

Lisy O et al JACC 2008;52:60-8
Cenderitide (CD-NP)
• Mayo-designed chimeric peptide \(^1\)
• Consists of CNP and the 15 aa C-terminus of DNP; more resistant to enzymatic degradation \(^2\)
• Binds GC-B and GC-A, GC-B > GC-A \(^1\)
• Less hypotensive than BNP and enhanced renal actions \(^1\)
• Currently in Phase II trials in HF

CNP
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• Venodilation >> arterial dilation
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1Lisy O et al JACC 2008;52:60-8
2Dickey DM et al, J Mol Cell Cardiol 2011;51:67-71
Hypothesis

• We hypothesized that combining cenderitide with furosemide would increase diuresis and natriuresis compared to furosemide alone without causing excessive hypotension or renal dysfunction in experimental HF
Methods

• We assessed the acute cardiorenal and humoral actions of furosemide + cenderitide (n=4) vs. furosemide + saline (n=5) in a canine model of tachypacing-induced heart failure (240 beats/min for 10 days)

• An acute study under general anesthesia was done on day 11 of pacing

• Surgical preparation included a Swan-Ganz catheter, a catheter in the left ureter, and an electromagnetic flow probe on the left renal artery to measure renal blood flow
Acute Protocol

Inulin bolus

Base-line

Equilibration

C1

60’ 30’

Inulin 1 mL/min

Saline

Saline
Acute Protocol

Inulin bolus

Equilibration

Baseline

C1

60'

30'

15'

C2

30'

C3

30'

C4

30'

Inulin 1 mL/min

Saline

Furosemide 1 mg/kg/h

Saline

100 ng/kg/min Cenderitide
Acute Protocol

Inulin bolus

Equilibration

Baseline

C1

60'

30'

15'

C2

30'

C3

30'

C4

30'

Washout

C5

30'

30'

Inulin 1 mL/min

Saline

Furosemide 1 mg/kg/h

Saline

Saline

100 ng/kg/min Cenderitide

Saline
Acute Protocol

**Inulin bolus**

**Equilibration**

**Baseline**

**C1**

**C2**

**C3**

**C4**

**Washout**

**C5**

**Post infusion**

- **60’**
- **30’**
- **15’**
- **30’**
- **30’**
- **30’**

**Inulin 1 mL/min**

**Saline**

**Furosemide 1 mg/kg/h**

**Saline**

**Saline**

**Saline**
Methods

• Neurohormones were measured by radioimmunoassay, glomerular filtration rate by inulin clearance.
• Differences between groups were analyzed by comparing the changes from baseline with unpaired t-test (or Mann-Whitney U-test for data that is not normally distributed).
• Statistical significance was accepted at p<0.05.
Results
Δ Cenderitide and Δ Plasma cGMP

Δ cenderitide (pg/mL)

C1 C2 C3 C4 C5

* p<0.05 between groups

- Red: Furosemide + saline
- Yellow: Furosemide + cenderitide
\( \Delta \text{Cenderitide} \) and \( \Delta \text{Plasma cGMP} \)

**Graph 1:**
- **Y-axis:** \( \Delta \text{cenderitide (pg/mL)} \) from C1 to C5.
- **Graphs:** Yellow and red lines.
- **Legend:**
  - Red: Furosemide + saline
  - Yellow: Furosemide + cenderitide
- **Note:** *p<0.05 between groups

**Graph 2:**
- **Y-axis:** \( \Delta \text{cGMP (pmol/mL)} \) from C1 to C5.
- **Graphs:** Yellow line.
- **Legend:** *p<0.05 between groups
Δ Mean Arterial Pressure and Δ Right Atrial Pressure

All p>0.23

*p<0.05 between groups

Furosemide + saline
Furosemide + cenderitide
Δ Mean Arterial Pressure and Δ Right Atrial Pressure

All p > 0.23

* p < 0.05 between groups

Furosemide + saline
Furosemide + cenderitide
Δ Renal Vascular Resistance and Δ Renal Blood Flow

* p<0.05 between groups
Δ Renal Vascular Resistance and Δ Renal Blood Flow

* p<0.05 between groups

Furosemide + saline
Furosemide + cenderitide

* p=0.08
Δ Urine Flow and Δ Urinary Sodium Excretion

Δ UVolR (mL/min)

C1 C2 C3 C4 C5

* p<0.05 between groups

Furosemide + saline
Furosemide + cenderitide

* p<0.05 between groups
∆ Urine Flow and ∆ Urinary Sodium Excretion

* p<0.05 between groups

- Furosemide + saline
- Furosemide + cenderitide
△Urinary cGMP Excretion

- **Furosemide + saline**
- **Furosemide + cenderitide**

* p<0.05 between groups
Δ Angiotensin II and Δ Aldosterone

* p<0.05 between groups
Δ Angiotensin II and Δ Aldosterone

- **Δ Angiotensin II (pg/mL)**
  - C1
  - C2
  - C3
  - C4
  - C5

- **Δ Aldosterone (ng/dL)**
  - C1
  - C2
  - C3
  - C4
  - C5

* p<0.05 between groups

**Legend**
- Red: Furosemide + saline
- Yellow: Furosemide + cenderitide

p=0.08
Summary

Cenderitide when added to furosemide
• increased levels of the second messenger cGMP in plasma and urine
• reduced right atrial pressure, no hypotension
• increased urine flow and sodium excretion
• preserved GFR
• decreased renal vascular resistance
• reduced angiotensin II levels
Conclusions

• Cenderitide when added to furosemide reduces cardiac preload, enhances renal excretory function, and decreases activation of the renin-angiotensin-aldosterone system

• These beneficial findings support the further evaluation of cenderitide in heart failure and its interactions with diuretics
Thank you