# Painstaking Diuresis:

## Hyperalgesia from bumetanide

Oregon Health and Science University
Portland VA Medical Center
Erik Wells MD, Joseph Chiovaro MD

U.S. Department of Veterans Affairs
Veterans Health Administration
VA Portland Health Care System

## Introduction

- Bumetanide is a commonly used diuretic that is known to cause musculoskeletal pain syndromes by an unknown mechanism, especially during continuous infusion. Here we review a different pain syndrome, one mediated by a neuropathic mechanism.

## Case Presentation

- **Patient**: A 57-year-old man with chronic diastolic heart failure presented with acute heart failure exacerbation
- **Exam**: 30 pounds above dry weight, JVP elevated, pulmonary rales, lower extremity edema
- **Studies**: NT-proBNP elevated, creatinine slightly above baseline, chest x-ray with pulmonary edema
- **Home medications include**: torsemide 100 mg twice daily, spironolactone 50 mg daily

## Clinical Course

- After failing IV Lasix infusion, the patient was started on bumetanide continuous infusion with metolazone augmentation.
- Shortly after initiation the patient developed diffuse burning pain and hypersensitivity to light touch
- The drip was stopped, and the pain resolved. When re-challenged with bumetanide the same pain returned.
- Gabapentin was added yielding partial relief

## Allodynia

- The abrupt onset + offset with infusion pointed to bumetanide as the cause of the syndrome
- The pain to light touch and response to gabapentin suggested a neuropathic cause of pain

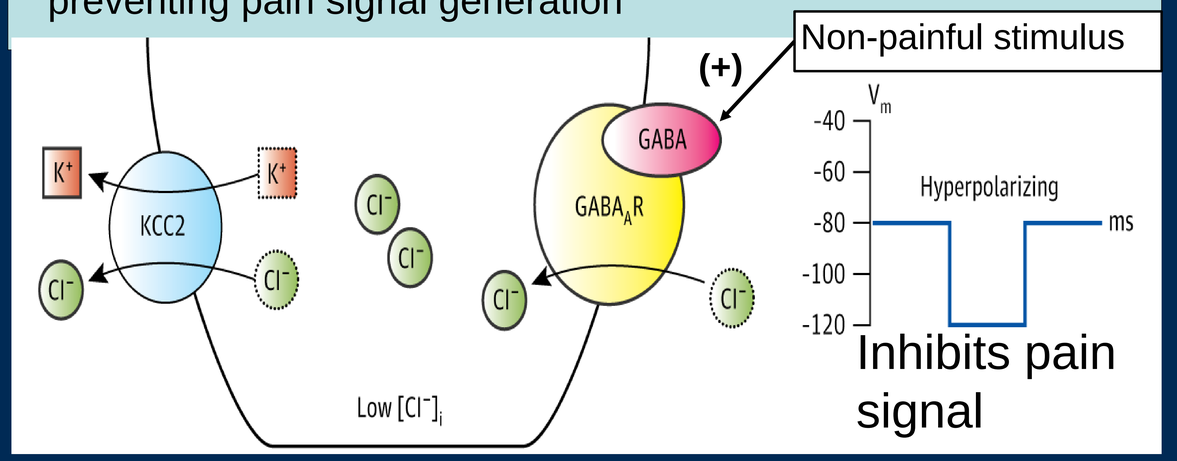
## Nervous System Effects

- A prior case report with nearly identical medications and symptoms suggested a mechanism
- Bumetanide at high doses has effects on the nervous system via the following two mechanisms:
  - inhibits NKCC1 receptors in afferent peripheral nerves (analgesic effect)
  - inhibits KCC2 receptors in the afferent spinal cord (hyperalgesic effect)

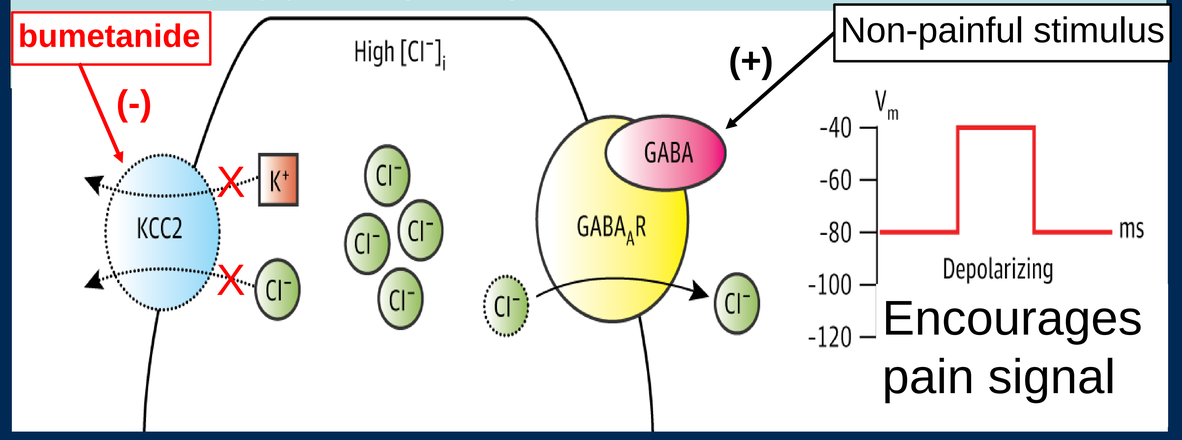
## A Proposed Mechanism

- Normally KCC2 maintains a low intracellular chloride ion concentration
- This chloride ion gradient is important for inhibitory interneurons to distinguish painful from non-painful stimuli

- **Normal - Low intracellular chloride state**: Non-painful stimuli cause GABA-A mediated chloride ion channels to open and chloride rushes into the cell, causing hyperpolarization preventing pain signal generation




- **Abnormal - High intracellular chloride state:** However, when KCC2 is inhibited intracellular chloride remains high, and non-painful stimuli can cause chloride ion *efflux*, paradoxically encouraging pain signaling




## Take home points

- Continuous infusions of bumetanide can cause diffuse pain syndromes
- Neuropathic pain, evidenced by allodynia and burning pain, is a rare side but possible effect
- Gabapentin, and possibly other medications for nerve pain, can be helpful for symptom control

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