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Syndrome of Severe Pain Associated with a Continuous Bumetanide Infusion

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Severe pain associated with high doses of bumetanide has been reported sporadically in the literature. We present a report of a patient who developed debilitating pain while receiving bumetanide for treatment of a heart failure exacerbation. We discuss possible etiologies of this effect based on the role of Na-K-2Cl cotransporters (NKCC) and K-Cl cotransporters (KCC) in pain regulation.

A 68 year old Caucasian female with chronic diastolic heart failure, aortic and tricuspid valve repair, atrial fibrillation, and stage IV chronic kidney disease (CKD) presented to the hospital with increased shortness of breath for one week. Exam on admission was notable for elevated jugular venous pressure, pulmonary rales, and lower extremity pitting edema. On admission, her brain natriuretic peptide was 1050 pg/mL, troponin-I 0.02 ng/mL, and creatinine 2.36 mg/dL. She was diagnosed with an acute heart failure exacerbation and treated with intravenous furosemide 80 mg every 8 hours. Her home medications including chlorthalidone, amiodarone, and spironolactone were continued. Due to a poor diuretic response after 48 hours her furosemide was converted to a continuous infusion of 10 mg/hour. After an additional 48 hours with poor diuresis, she was converted to IV bumetanide with a 2 mg bolus followed by a continuous infusion titrated up to 2 mg/hr.

Approximately 4 hours after starting bumetanide the patient began to experience diffuse pain that worsened over the next 48 hours. The pain was described as a severe, superficial tenderness of the skin. The pain was worsened by any pressure or light touch, including ambulation or even wearing clothing. The patient herself attributed the pain to the bumetanide bolus and infusion during our assessment.

During this episode of pain her potassium and magnesium were repleted regularly to maintain a level greater than 4 mmol/L and 2 mg/dL, respectively. Her serum creatinine remained near baseline, between 2.19 and 2.51 mg/dL, throughout this illness (creatinine clearance 33 to 27 mL/min) from a baseline of 2.7 mg/dL (27 mL/min). A CK on admission was 29 IU/L and a recheck after 72 hours on the bumetanide infusion was 95 IU/L. Her albumin was 4.3 g/dL. Her pain was treated with a combination of acetaminophen and narcotics with some relief. Approximately 72 hours after initiation of the bumetanide infusion her pain began to improve and later resolved. No change in the dose of her bumetanide infusion was made during this time.

Pain syndromes are a known adverse effect associated with bumetanide whose mechanism is not understood. In all reported cases, the episodes are characterized by generalized musculoskeletal pain, cramping, and/or weakness, sometimes severe enough to limit mobility [1-3]. In one series, nine patients with baseline CKD developed severe pain with oral and IV bolus doses of bumetanide starting 2-4 hours after dosing [2]. Eight patients also had hypoalbuminemia. Another report described similar symptoms in patients receiving continuous bumetanide infusions [1]. However, no laboratory abnormalities were noted to be associated with symptoms, including renal failure or hypoalbuminemia. In all cases the symptoms resolved with discontinuation of bumetanide, and in 2 cases the symptoms recurred during re-challenge with bumetanide. Changing to equivalent or higher doses of furosemide did not cause symptoms to recur.

Those prior cases are similar to the case presented above except for our patient's extreme sensitivity to touch. This presentation of allodynia suggests a possible neuropathic mechanism for bumetanide-induced pain. We speculate that this pain syndrome may be related to bumetanide's effects on KCC2 and NKCC1, two cation-chloride cotransporters that play important roles in regulating pain transmission (Figure 1).

Allodynia is thought to result from a disruption in the way nociceptive neurons respond to non-painful stimuli. Normally these non-painful signals inhibit the transmission of pain by stimulating GABAergic interneurons in the spinal cord. The interneurons alter the intracellular chloride concentration in nociceptive neurons by opening GABA-A ligand-gated chloride channels. NKCC1, a Na-K-2Cl cotransporter sensitive to bumetanide, promotes a high resting chloride concentration in peripheral afferent neurons. Therefore, non-painful stimuli open GABA-mediated chloride channels and the resulting chloride efflux partially depolarizes the cell. This so-called primary afferent depolarization reduces the magnitude of nociceptive action potentials and decreases transmission of pain signals [4-5]. NKCC1 is upregulated in chronic pain and inflammatory conditions resulting in elevated intracellular chloride levels. As a result, normally non-painful stimuli produce a larger chloride efflux and generate sufficient depolarization to induce full action potentials, leading to allodynia [6]. Using bumetanide to block NKCC1 can decrease allodynia in animal models of chronic pain [7].

However, blocking KCC2, a bumetanide-sensitive K-Cl cotransporter located on central ascending afferent neurons, seems to have the opposite effect of inducing allodynia. KCC2 maintains a low resting chloride concentration in ascending neurons such that GABAergic

interneurons stimulate chloride influx. This hyperpolarizes the neuron and blocks nociceptive action potentials [5, 8]. Blocking KCC2 reverses this effect by raising chloride concentrations and promoting GABA-induced depolarizations, resulting in hypersensitivity to pain.

While blockade of KCC2 provides a possible etiology of bumetanide-induced pain syndromes, bumetanide has an approximately 500 fold higher affinity for NKCC1 than KCC2 [9]. Thus, doses of bumetanide necessary to inhibit KCC2 would also be expected to cause NKCC1 inhibition resulting in ototoxicity, which was not reported by our patient. Yet loop diuretics may have different effects on pain depending on the baseline state of the subject. For example, one study found that intrathecal furosemide increased the pain threshold in rats that had been subjected to trauma but decreased the pain threshold in intact rats [10]. Thus, in the setting of inflammation and NKCC1 upregulation, there may be an increased NKCC1/KCC2 receptor expression and/or activity ratio that would result in a net effect of analgesia after bumetanide exposure. This ratio may be substantially lower under normal physiological conditions, leading to allodynia after administration of bumetanide. Alternatively, as bumetanide-associated pain syndromes are only seen in a subset of patients, these patients may have an isoform of KCC2 that is more sensitive to bumetanide. The mechanisms of bumetanide-associated pain syndromes will need to be more fully elucidated in order to devise strategies to counter-act this effect.

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Figure 1. Model of bumetanide interaction with nociception

A. NKCC1 in tactile induced pain perception: bumetanide as an analgesic. Under normal conditions, NKCC1 maintains a high intracellular chloride concentration within peripheral afferent neurons. Non-painful tactile stimulation leads to GABA release, opening GABA-activated chloride channels on the afferent neurons. The resulting efflux of chloride depolarizes the cell, reducing the magnitude of nociceptive action potentials and resulting in decreased transmission of pain signals. In the setting of chronic pain, NKCC1 expression increases, resulting in higher levels of intracellular chloride. As a result, non-painful stimuli generate a much larger GABA-mediated chloride efflux. This higher magnitude depolarization is thought to be powerful enough to generate nociceptive action potentials in the afferent neurons. Under these conditions, bumetanide blocks excess NKCC1 activity, ultimately inhibiting the nociceptive action potential and exerting an analgesic effect.

B. KCC2 in central ascending pain perception: bumetanide as an allodynic. KCC2 maintains a low intracellular chloride concentration within the ascending afferent neurons of the spinal cord. Here, GABA release from non-painful stimuli induces an influx of chloride, hyperpolarizing the neuron and preventing transmission of nociceptive action potentials. Bumetanide at sufficient concentrations will block KCC2, and raise the intracellular chloride concentration such that non-painful stimuli now induce a GABA-mediated chloride efflux. A sufficiently large depolarization will generate nociceptive action potentials under these conditions.