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Study Title: **Baclofen as a Perioperative Analgesic Adjuvant for Kidney Stone Surgery**

Principal Investigator: **Mark Mandabach MD**

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1.0 SUMMARY OF STUDY

The present study proposes to study the effect of a single preoperative dose of baclofen on pain treated in the first 24 hours after kidney stone-related surgeries using a placebo-controlled, double-blind methodology. Because this patient population often has a history of significant opioid use, which would be expected to alter postoperative pain medication requirements, patients will be stratified into those which would be expected to be opioid tolerant (use >30 OME daily) and those who are generally opioid naïve.

2.0 BACKGROUND & RATIONALE

Postoperative pain continues to be a significant clinical problem. Use of perioperative adjuvants has improved postoperative pain control. The GABA-B receptor agonist, baclofen, is an appropriate drug to trial as such an analgesic adjuvant. Support for this assertion is given below

Baclofen pharmacology. The drug baclofen (chemical name) is a GABA derivative. Its mechanisms of action is through the metabotropic GABA-B receptor and is G-protein linked to potassium channels leading to neuronal hyperpolarization. Baclofen is a white powder, practically odorless powder which is manufactured in 10 and 20 mg tablets with typical doses for spasticity of 10-20 TID. It is rapidly absorbed and has half-life of 2-4 hours. 85% of the compound is excreted unchanged in urine.

Sites of action are peripheral, spinal and supraspinal. Selective spinal infusion is utilized to control spasticity. Notable for this discussion, CASL imaging of the brain before and after 21 days of baclofen treatment (20 QID) demonstrated reduced rCBF in the ventral striatum and medial prefrontal cortex and increased rCBF in the lateral OFC, (a region involved in suppressing previously rewarded behavior) and cerebellum. rCBF was also blunted in the insula bilaterally [Franklin et al, 2011].

Baclofen produces analgesia. Baclofen produces analgesia by itself as measured in rats and mice in the hot plate, tail flick and acetic acid-induced writhing [Aley and Kulkarni, 1989, 1991; Balerio and Rubio; mult other] In rats with chronically inflamed paws baclofen increased Substance P release raising issues related to acute vs. chronic analgesic benefits of the GABA-B agonists [Malcangio and Bowery, 1994; Galeotti et al 1996]. Baclofen produced analgesia in primates in the formalin test [Sharma et al, 1993]. In chemotherapy-induced neuropathic pain models baclofen produced significant but erratic analgesia [Xiao et al, 2008]. Intrathecal nociceptin antagonized baclofen-induced analgesia in a mouse tail flick assay [Citterio et al, 2000] and baclofen-induced analgesia was absent in GIRK2 knockout mice [Blednov et al] Baclofen administered spinally (intrathecally) produces analgesia in rat thermal pain models that can be antagonized by GABA-B antagonists [Aran and Hammond]. Whitehead et al [2012] demonstrated peripheral analgesic effects of baclofen in a mouse arthritis model.

Baclofen's analgesic effects may be acting via the same mechanism by which heterosegmenal noxious stimuli produce inhibition (nocigenic inhibition) since such inhibition has been demonstrated to act via GABA-B and mu opioid mechanisms [Tambell et al, 2009]. Consistent with this, analgesia produced by 100 Hz electroacupuncture as involves GABA-B mechanisms [Silva et al]. GABA-B receptor blockade also blocks foot-shock induced "stress-induced" analgesia, but not forced swim stress or psychological stress [Tokuyama et al] although others have observed potentiation of forced swim stress-induced analgesia by baclofen [Houston et al, 1997]. In the spinal substantia gelatinosa activation of GABA-B receptors presynaptically block neurotransmitter release [Yang and Ma] and NK1 receptor expression [Enna et al]. Other sites of action related to pain include the rostral agranular insular cortex [Jasmin et al] and lateral preoptic area [Lim et al]. The supraspinal analgesic effects of baclofen appear to act via adrenergic and opioidergic spinal mechanisms [Jasmin et al; Ignatov and Andreev;] with potentially a cholinergic and GABA-A portion to contribution [Tamayo et al 1988; Zarridast MR and Djavdan M].

In humans, baclofen has had a particular role as an anesthetic for cranial nerve-related neuropathic pains such as trigeminal neuralgia [Knotkova and Pappagallo] . Early anecdotal reports (e.g. Harmer and Larson] suggested it worked for postherpetic neuralgia in facial distributions but not spinal distributions [Terrence et al, 1985]. In humans, the spinal administration of baclofen has also demonstrated short-term analgesic effects on spinal cored injury-related pain and post-stroke pain [Taira et al, 1995]. One presumed mechanism for the action of baclofen on facial pain is the presence of GABA-B receptors on

trigeminal primary afferent neurons whose activation leads to a potentiation of voltage-dependent potassium currents. Baclofen has demonstrated analgesic effects on surgical pain in females [Corli et al]

Baclofen interacts with opioids synergistically. Gordon et al (1995) observed potentiation of morphine analgesia on post-operative pain but not of pentazocine-induced (kappa) analgesia. Panerai et al [1985] had previously demonstrated baclofen prolonged the analgesic effect of fentanyl on post-operative pain. Notably, baclofen also potentiates the analgesia produced by clonidine in rat models [Przesmycki et al]

Baclofen reduces addictive behaviors. In a randomized, double-blind placebo-controlled clinical trial Assadi et al [2003] used baclofen for the maintenance treatment of opioid dependence. In a 12 week trial of 20 TID. Baclofen was superior over placebo in terms of opiate withdrawal syndrome and depressive symptoms. Trends towards reductions in opioid craving and self-reported opioid and alcohol use were noted but not proven.

Baclofen has also been noted to reduce cigarette consumption [Franklin et al, 2009]

Corwin et al [2012] in a double-blind, placebo-controlled, crossover study in 12 subjects demonstrated that baclofen (20 TID) reduced binge-eating. Slight but significant increases in depression symptomatology occurred. Tiredness, fatigue and upset stomach were the most commonly reported side effects.

Ling and Shoptaw [1998] in a clinical series of ten patients reported reduced cocaine-craving due to baclofen with good safety and tolerability. General reviewes posit its benefcial effects in multiple forms of addiction [Kumar et al, 2013]

The place in the treatment of addictive behaviors where baclofen treatment has found its greatest audience is in the realm of alcohol addiction [reviewe – Gorsane et al] but with mixed results for efficacy by placebo-controlled, double-blind randomized trials [e.g. Garbutt et al 2010] . Effects on alcohol craving, use and abuse have also been demonstrated with general acceptance of beneficial effects but varying levels of effect [Dore et al, 2011; Vuittonet et al 2014; Tyacke et al, 2010; Leggio et al, 2010; Johnson et al, 2005] – similar benefits have been noted for GABA-B positive allosteric modulators [Filip et al, 2014]

Baclofen reversed cognitive deficits induced by acute cocaine in rhesus monkeys and normalized activation of prefrontal cortex sites[Porrino et al, 2014]

In rat models, baclofen dose-dependently reduced heroin-seeking behavior [Spano et al, 2007], reversed behavioral sensitization to morphine [Bartoletti et al, 2007] and prevents heroin-induced reinstatement of heroin-seeking behaviors [Spano et al, 2007] and enhances extinction of opiate and methamphetamine-induced conditioned place preference [Heinrichs et al, 2010; Voigt et al, 2011] particularly stress-accenuated morphine-induced conditioned place preference [Meng et al, 2014]. In rodent models of cocaine- or heroin-seeking behaviors, baclofen was found to attenuate these behaviors [DiCiano and Everitt, 2003]. Similar results are noted for alcohol-seeking and drinking behavior [Maccioni and Colombo, 2009].

Baclofen reduced ethanol consumption in mice, but only in those which were phenotypically less prone to heavy drinking behaviors [Villas Boas et al, 2012]. Baclofen reduced nicotine- [Paterson et al, 2004] and morphine self-administration in rats and a GABA(B)-antagonist increased morphine administration [Ramishini et al, 2013]

Baclofen administered into the locus coeruleus attenuated morphine withdrawal signs [Riahi et al, 2009]

Presumed mechanisms for baclofen's actions on addictive behaviors is an interaction wth dopaminergic neurons of the ventral tegmental area where baclofen leads to Girk signaling [Arora et al, 2011] with a subsequent reduction in dopamine release in the nucleus accumbens.

Baclofen toxicology and drug/drug interactions. There have been limited toxicities or side effects of baclofen. Odd reactions include things such as the induction of hiccup-like respirations [Srivasta et al, 2014] or diabetes insipidus [Silversides and Scott] In rats, intraventricular baclofen impaired memory [Zarrindast et al, 2001] CB1 receptor antagonism decreases analgesia due to baclofen and GABA(B) antagonists reduce analgesia due to cannabinoids [Naderi et al, 2005].

Most toxicity reports relate to withdrawal [Ross et al, 2011] or excessive dosing [Roy and Wakefield, 1986; Leung et al2006] with CNS effects predominant (loss of consciousness, delirium, hypertension). Because it is kidney-cleared, toxicity is more common in patients with advanced nephropathy [El-Husseini et al, 2011]

Some increases in depression have been noted, but in the spinal cord injury patients, use of baclofen improved psychiatric symptoms [Margetis et al, 2014]

DeFeudis [1984] suggested that GABAergic drugs might have a role in both analgesia and drug addictions, particularly related to opioids but did not go so far as to suggest co-administration.

3.0 OBJECTIVE(S) & HYPOTHESIS

Purpose of study:

To determine whether a single, oral dose of baclofen alters postoperative opioid requirements

Study Hypothesis:

We hypothesized that a single, oral dose of baclofen given to patients undergoing kidney stone surgery will reduce postoperative opioid requirements measured in the PACU and in the first 24 hours following surgery.

4.0 INCLUSION & EXCLUSION CRITERIA

Inclusion criteria:

Adult patients (age >= 19 y.o.) scheduled for kidney stone-related surgery

Exclusion criteria:

[1] History of allergy to baclofen [2] Any condition which might limit appropriate report and treatment of postoperative pain (e.g., non-English speaking; severe psychiatric disease)

5.0 RANDOMIZATION/RECRUITMENT DETAILS (If applicable)

- Randomization groups, how will subjects be randomized:

  All subjects who are patients of Drs. Assimos and/or Wood and scheduled for kidney stone-related surgery will be potentially recruited.

  Part 1: In an initial open run-in period, six patients will be recruited and given a dose of 10 mg baclofen preoperatively so that potential side effects can be assessed in an unblinded fashion.

  Part 2: After that, patients will be identified and initially stratified into two groups based on preoperative opioid use. If daily using >30 Oral Morphine Equivalents (OMEs) for more than one month they will be designated as Opioid Tolerant. Otherwise, they will be included in the Opioid Naïve group. These two groups will then be each randomized (envelope assignment) into receiving either baclofen (10 mg, p.o. x 1) or placebo as a preoperative medication such that there will be 4 groups of 20 patients identified:
  Group 1: Opioid Tolerant – baclofen
  Group 2: Opioid Tolerant – placebo
  Group 3: Opioid Naïve – baclofen
  Group 4: Opioid Naïve - placebo

- Blinded ☒ Yes ☐ No (Single ☐ Double ☐ please check box).

6.0 STUDY INTERVENTIONS/PROCEDURES

- Study design: Placebo-controlled double-blind

- Comparison groups (for prospective and clinical trials only).

  Placebo treated individuals

- Timeline of interventions (for prospective and clinical trials only).

  Patients will be recruited preoperatively by Drs. Assimos and Wood, in addition to anesthesiology-related personnel in the KPAC. Informed consent will be obtained at that time. On the Day of Surgery, subjects will be contacted by study personnel in the Preoperative Holding area to confirm patient participation and then a randomization envelope containing a single dose of either baclofen or placebo will be opened (Groups 1&2 intermixed; Groups 3&4 intermixed; envelopes will be prepared ahead of time by a different investigator according to a randomization table). Subjects will then consume the pill in the envelope and this will be recorded. Patients will then be treated intraoperatively and postoperatively according to the standard of care associated with these surgeries but with an attempt to utilize consistent doses of intraoperative opioids other agents across groups and standardized PACU orders. After discharge from the

PACU patients' pain will be treated with PCA morphine. Notably, the treating anesthesiologist and all PACU personnel will be blinded to the drug that was administered preoperatively. The total use of analgesics, measures of any other side effects (nausea, excessive sedation) will be recorded for 24 hours.

- Measured Outcomes:
  a. Primary outcomes: Postoperative opioid consumption (measured as OMEs)
  b. Secondary outcomes: Incidence of nausea/vomiting; excessive sedation per patient self assessment; any other untoward events

7.0 **PLAN FOR STUDY:** Click here to enter text.

a. What is the potential impact of your study findings (e.g., how will findings impact clinical outcomes)? Baclofen may prove beneficial as a perioperative analgesic adjuvant – the long term goal would be to determine potential efficacy, safety and tolerability of baclofen use and to perform a follow-up study in which baclofen would be co-administered postoperatively for up to 2 weeks. The conversion from acute to chronic pain and the potential anti-reward effects produced by baclofen could impact subsequent opioid use and abuse.
b. Do you plan to submit an abstract based on this project? ☒ Yes ☐ No (If yes, to which meeting venue? Click here to enter text.
c. Do you intend to publish the finding from this research project: ☒ Yes ☐ No

8.0 **DRUG INFORMATION**

Drug Name:	baclofen hydrochloride
Classification:	Antispastic; GABA-B receptor agonist
Mode of Action:	GABA-B receptor agonist
Storage and Stability:	Pharmacologically stable
Metabolism:	Cleared unchanged through kidneys; half-life 2-4 hours
Preparation:	Pill
Administration:	Oral
Incompatibilities:	None

- *Contraindications: allergy to baclofen*
- *Precautions: very safe medication with long track record of clinical use*

Click here to enter text.

Side Effects: Adverse effects indicated in *italics* are the most frequent adverse effects. Adverse events in bold are severe/life-threatening, otherwise they are mild to moderate in reaction.

CNS: *sedation, mild*

CV: *no major*

EENT: *no major*

ENDO: *no major*

GI: *no major*

GU: *no major*

INTEG: *no major*

MS: *weakness at excessive doses*

Investigational New Drug (IND) Application required (check yes or no): ☐Yes ☒No

9.0 STATISTICAL CONSIDERATIONS

- Original Plan for Statistical Analysis : Data analysis will be by ANOVA analysis using Tukey's HSD for post-hoc analysis for primary outcome data and Fishers Exact test for categorical incidence data. A mid-point analysis was proposed after the study of 40 subjects.

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