Effects of Ibuprofen on COX-2 Activity Following Third Molar Extraction

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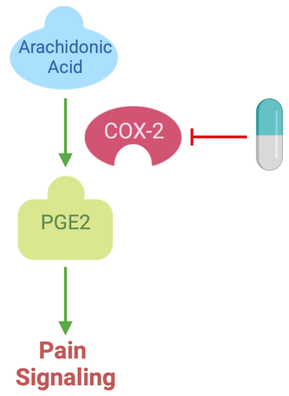
Background

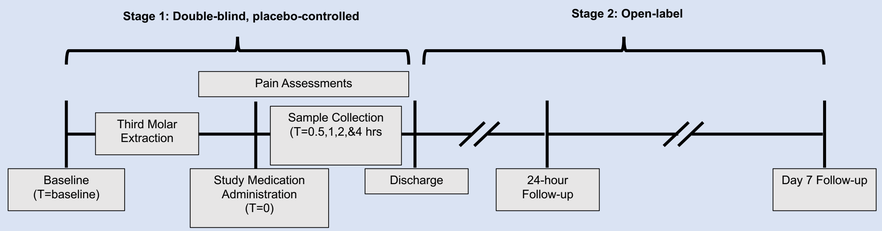
- Non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen are regularly used to treat pain following third molar extraction.
- Most patients have excellent pain relief with Ibuprofen, but a small minority requires a short course of opioids in addition.
- Ibuprofen inhibits cyclooxygenase (COX) enzymes, which produce prostaglandins that cause inflammation and sensitize nociceptors to pain stimulation.
- This study examines suppression of COX-2 *ex vivo* to investigate potential pharmacokinetic effects contributing to variability in response.
- We hypothesized that Ibuprofen would decrease COX-2 activity in patients to a similar degree, regardless of need for opioids.

Figure 1: Inhibition of COX-2 by Ibuprofen



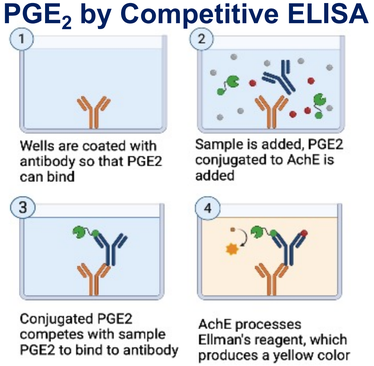
Study Design (NCT03893175)

- Eighty-five healthy subjects underwent removal of partial or full bony impacted third molars using a standardized local anesthetic and sedation protocol.
- Pharmacologic and pain intensity responses were evaluated according to the following study design:



- When pain intensity reached ≥4/10, subjects were administered rapid-acting ibuprofen (400 mg; N=59) or placebo (N=26) in a randomized, double-blind design.
- After discharge, all patients received ibuprofen 400 mg + acetaminophen 500 mg every 4h for 2 days, then as needed for pain.
- Rescue medication (oxycodone 5 mg) was available upon request.

Figure 2: Quantification of PGE_2 by Competitive ELISA



Methods

- COX-2 activity was assessed *ex vivo* by quantifying plasma prostaglandin (PG) E_2 levels following lipopolysaccharide (LPS) stimulation in whole blood.
- Heparinized whole blood was treated with aspirin (1mM) and incubated at room temperature for 15 minutes.
- LPS (E. coli, serotype O111:B4, 10 µg/ml whole blood) was added, and the sample was incubated at 37˚C for 24 hours.
- Plasma was separated by centrifugation.
- Cayman Chemicals PGE_2 ELISA kit was used to quantify PGE_2 in plasma.

Results

Table 1: Patient Characteristics

	Ibuprofen (n=59)	Placebo (n=26)
Men/Women	29/30	10/16
Age (years)	24.2 ± 3.7	24.1 ± 3.6
BMI	23.2 ± 2.9	22.9 ± 4.1
Length of Surgery (minutes)	30 ± 16	23 ± 15 *
Number of Teeth	4 (3,4)	4 (2,4)
Trauma Score	6 (4,8)	7 (3.75,8)
Time to study drug (minutes)	135 ± 33	144 ± 39
Inpatient rescue	3 (5%)	21 (81%)*
Second inpatient rescue	1 (1.7%)	13 (50%)*
Outpatient opioid use	12 (20%)	4 (15%)

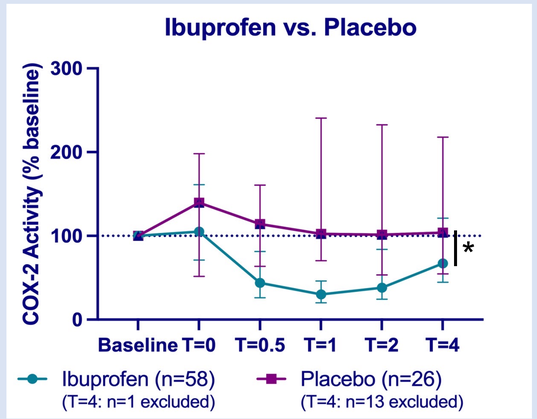


Figure 3: COX-2 Activity in Patients Treated with Ibuprofen vs. Placebo

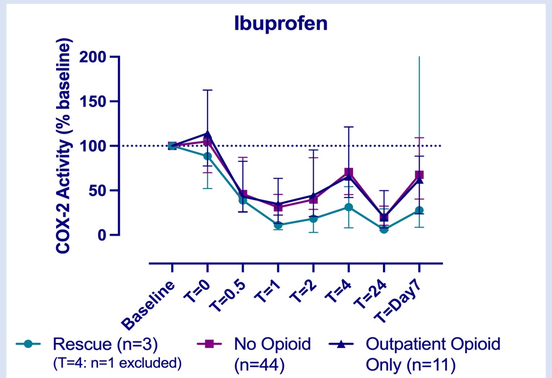


Figure 4: COX-2 Activity in Ibuprofen-Treated Patients by Opioid Use

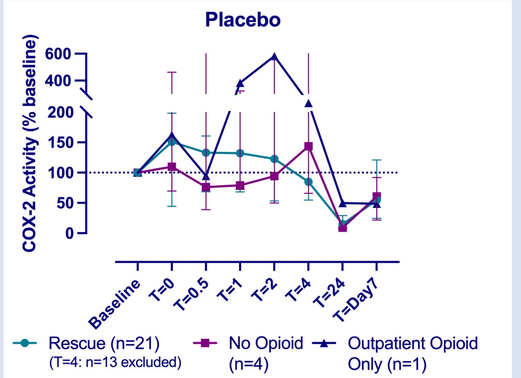


Figure 5: COX-2 Activity in Placebo-Treated Patients by Opioid Use

Conclusions

- Ibuprofen inhibited COX-2 activity to a greater extent than placebo.
- The degree of COX-2 inhibition was similar among all Ibuprofen-treated patients, regardless of the degree of pain relief patients experienced.
- This suggests that variability in relief is not a pharmacokinetic effect; thus, changing dosage will not improve efficacy for partial responders.
- Investigating other components of the COX-2 pathway, or studying PGE_2 concentrations *in vivo*, may provide further insight on variability and improve prediction of when additional medication such as opioids will be necessary to prescribe.

This work was supported by the Penn Center for Precision Medicine, an Oral and Maxillofacial Surgery Foundation Clinical Research Grant, and an Ernest M. Brown, Jr. College Alumni Society Undergraduate Research Grant.