UNC MEDICAL CENTER GUIDELINE

High-Dose Ibuprofen Use in Cystic Fibrosis Patients

This guideline is intended to review high-dose ibuprofen's clinical use, dosing regimen, and monitoring parameters. This information is intended to help clinician's identify therapeutic considerations regarding the use of high-dose ibuprofen.

BACKGROUND

Inflammation is a key aspect of the lung disease of cystic fibrosis, leading to lung destruction. High-dose ibuprofen has been shown to be beneficial as an anti-inflammatory treatment option to prevent lung deterioration in CF patients with mild disease in two clinical studies.

The first clinical trial by Konstan et al. was conducted at a single-site in the US that included 84 patients between 5 to 39 years of age with an FEV_1 above 60% predicted who were randomized to receive either high-dose ibuprofen (20-30mg/kg, max 1600mg) or placebo for four years. Results found a significant 40% slower rate of FEV1 decline in patients treated with ibuprofen compared to placebo. A post-hoc analysis showed that this effect was concentrated in those 5 to 13 years, who had an 89% reduction in rate of decline.[1] Notable adverse effects related to ibuprofen included conjunctivitis and epistaxis.

The second trial by Lands et al. was conducted in 12 centers in Canada that included 142 patients 6 to 18 years of age with a FEV_1 above 60% predicted. The study found a statistically insignificant 45% reduction in mean annual rate of FEV_1 decline. There was a significant decrease in the annual rate of decline of FVC% predicted.[2]

Data from these two trials were pooled in a meta-analysis, which supported a beneficial effect on the annual rate of decline of FEV_1 predicted in children with mild lung disease. Additionally, an analysis of patients in the US CF Foundation patient data registry was conducted of children age 6 to 17 years with an $FEV_1 > 60\%$ predicted. Results also supported that high-dose ibuprofen slowed the rate of progression of lung disease.[3]

Goal ibuprofen plasma concentration is a range between 50-100 µg/mL to inhibit neutrophil migration. Levels less than 50 µg/mL increase neutrophil influx to mucosal surfaces, leading to higher neutrophil counts. Levels greater than 100 µg/mL are associated with increased adverse effects.[3]

Table 1. Key Pharmacokinetic & Pharmacodynamic Information[4]

High-Dose Ibuprofen	Comments
Mechanism of Action	Reversibly inhibits cyclooxygenase-1 and 2 enzymes, leading to decreased prostaglandin precursors
Onset	Peak reached within 3 hours of oral dosing
Metabolism	Hepatic via oxidation Substrate of CYP2C19 and CYP2C9 Inhibits OAT 1/3
Dosage Forms	Capsules, tablets, chewable tablets, oral solution
Administration	Administer with food or milk to decrease GI upset Shake oral suspension well before use
Adverse Effects	GI inflammation, ulceration, bleeding, and perforation

	Transaminase elevations Adverse renal effects

PATIENT CONSIDERATIONS

Consider avoiding use of high dose ibuprofen in the following clinical scenarios:

- Systemic corticosteroids or NSAIDs > 1 month in the past year
- Known hepatic, renal, or hematologic disorder
- Documented peptic ulcer disease or allergic bronchopulmonary aspergillosis

DOSING

Patients need to undergo a three-hour pharmacokinetic study prior to starting therapy to determine the appropriate dosage. It is recommended to conduct the study using the brand and dosage strength that the patient intends to use.

Initial Starting Dose: 20-30 mg/kg (maximum of 1600 mg) twice daily

Completing the PK Study:

1. Administer a dose of 20-30 mg/kg at least 2 hours after eating.
2. Hourly blood samples are drawn for a total of three consecutive ibuprofen levels (send out lab).
3. Goal is to have a peak of 50-100 µg/mL on at least one of the 3 hourly measurements. Ideally, want to have all three measurements within goal range.

Figure 2. Dose Adjustments with High-Dose Ibuprofen

Ibuprofen Level (µg/mL)			Ibuprofen Dose adjustment
1 hour level	2 hour level	3 hour level	
<50	<50	<50	Increase dose by 200mg*
50-100	50-100	50-100	No adjustment needed
50-100	50-100	<50	No adjustment needed
50-100	<50	<50	No adjustment needed
<50	50-100	50-100	No adjustment needed
<50	50-100	<50	No adjustment needed
<50	<50	50-100	No adjustment needed
Any level > 100 (regardless of timing)			Decrease dose by 200mg*

**Consider checking ibuprofen level ~3 months after dose adjustment. Adjustment based on tablet size.*
Ideally, by the third measurement, the level should start decreasing.

MONITORING

Table 3. Monitoring Recommendations for High-Dose Ibuprofen[1,2]

Laboratory Parameters	Frequency
Pharmacokinetic Study	Every 2 years, or sooner if a 25% weight change occurs
Blood chemistries	Annual
Urinalysis	Annual
CBC	Annual (or if concern for GI bleeding)

THERAPY CONSIDERATIONS

- Due to the risk of gastrointestinal irritation and bleeding, use of proton pump inhibitors or other acid-suppressing medications are recommended as concurrent therapy.
- Consider discontinuing high-dose ibuprofen 48-72 hours, or at a minimum 24 hours, before patients receive IV or PO nephrotoxic antibiotics to treat acute pulmonary exacerbations.
- Some patients may experience rebound headaches when discontinuing therapy. Consider titration of ibuprofen if therapy needs to be stopped or held.
- Although published literature included patients up to 39 years of age, clinical benefit was most significant in patients less than 18 years old. For this reason, consideration should be given for risk versus benefit of continuation of therapy after age 18, including:
    - Medication adherence
    - Need for treatment with nephrotoxic antimicrobials for pulmonary exacerbations
    - Overall medication burden

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