Cook Children's

SAFE AND SOUND Pain Management PRESCRIBING

Ibuprofen and Acetaminophen Recommendations
Key Takeaways:

The opioid stewardship committee recommends dosing ibuprofen and acetaminophen at the top of the mg/kg dosing range with lower maximums than if these agents were used separately.

Medication	Dosing	Max dose
Ibuprofen	10mg/kg scheduled q6hrs	400mg
Acetaminophen	15mg/kg scheduled q6hrs	500mg

NOTE: These maximum recommendations only apply when ibuprofen and acetaminophen are scheduled to be given at the same time. The standard maximum recommendations apply for prn ibuprofen and acetaminophen, as well as, alternated dosing of ibuprofen and acetaminophen.

1. **Why these doses?**
   A Cochrane Review Meta-Analysis including 3 studies (a total of 1647 patients age ≥16 years of age), showed that there was no significant difference between dosing with ibuprofen 200mg + acetaminophen 500mg and ibuprofen 400mg + acetaminophen 1000mg compared to placebo. This shows that increased doses are not needed to maintain adequate pain scores in adult patients.

   The doses of ibuprofen 400mg + acetaminophen 500mg were selected because it combines the two dosing schemes seen in this article. Doses of ibuprofen 200mg + acetaminophen 500mg were shown to be effective in adult patients, so the committee feels confident that these max doses should help to maintain adequate pain control in our pediatric patients, but not put them at higher risk for adverse events with seemingly unneeded high doses of acetaminophen.

2. **Why together and not alternating?**
   A meta-analysis including six studies (a total of 915 patients) that compared combined and alternating paracetamol and ibuprofen for the treatment of fever showed that there was inconclusive evidence to decide that combined vs. alternating therapy was better at decreasing temperature. Both methods were effective and better than monotherapy.

   The opioid stewardship committee recommends dosing acetaminophen and ibuprofen together, because it has been shown to be as effective as alternating, but is less difficult for the family and poses less risk for doses being missed. Additionally, all recent studies have shifted to comparing combined acetaminophen and ibuprofen to opioids. These study have showed that combined therapy is as effective as opioid therapy.

Please review the following pages which include a more in-depth look at the studies that support the above recommendations.

Ibuprofen and Acetaminophen Concurrent Dosing Recommendations

Situation: When using ibuprofen and acetaminophen at the same time for pain control the normal max dose does not apply. Lower upper limits are recommended when these medications are used concomitantly.

Background: There have been questions about the max doses for ibuprofen and acetaminophen when used together. Due to the lack of a consistent recommendation, Dr. Gandhi and the opioid stewardship committee has reviewed the literature and come up with dosing recommendations for these medications.

Assessment: Based on a Cochrane Review Meta-Analysis including 3 studies and a total of 1647 patients age ≥16 years of age, the recommended dosing scheme at Cook Children's Medical Center is 10mg/kg of ibuprofen (max 400mg) and 15mg/kg of acetaminophen (max 500mg) when used together.

The studies looked at 200mg and 500mg compared to placebo and then 400mg and 1000mg compared to placebo. As you can see in the chart below, the difference between the dosing schemes is not significant. When reviewing this articles and others, increased doses were not needed to maintain adequate pain scores. The committee has decided on 400mg and 500mg max doses because this dosing range is between these two dosing schemes allowing for higher doses of ibuprofen than 200mg, but will not put the patients at seemingly unneeded high doses of acetaminophen.

Dosing Scheme	Total number of patients between all 3 trials	Proportion of patients achieving at least 50% pain relief over 6 hours	NNT (number needed to treat)	Time to remedication	Need for rescue pain medication	NNT to prevent the use of rescue medication	Percentage of patients who experienced ≥1 ADR
Ibuprofen **200mg** + acetaminophen **500mg** vs. placebo	508	69% vs. 7% for placebo	1.6 (1.5-1.8)	7.6 hours vs. 1.7 hrs for placebo	34% vs. 79% for placebo	2.2 (1.8-2.9)	30% vs. 48% for placebo
Ibuprofen **400mg** + acetaminophen **1000mg** vs. placebo	543	73% vs. 7% for placebo	1.5 (1.4-1.7)	8.3 hours vs. 1.7 hrs for placebo	25% vs. 79% for placebo	1.8 (1.6-2.2)	29% vs. 48% for placebo
Ibuprofen **400mg** + acetaminophen **1000mg** vs. Ibuprofen 400 alone	359	73% vs. 52% for ibuprofen alone	5.4 (3.5-12)		25% vs. 48% for placebo	4.3 (3.0-7.7)	

Recommendations: The opioid stewardship committee recommends dosing ibuprofen and acetaminophen at the top of the mg/kg dosing range with lower maximums than if these agents were used separately.

Medication	Dosing	Max dose
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NOTE: These maximum recommendations only apply when ibuprofen and acetaminophen are scheduled to be given at the same time. The standard maximum recommendations apply for prn ibuprofen and acetaminophen, as well as, alternated dosing of ibuprofen and acetaminophen.

Citation: Derry CJ, Derry S, Moore RA. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. *Cochrane Database of Systematic Reviews*. 2013;(6).

Included studies in this meta-analysis are as follows:

- Daniels SE, et al. *Pain* 2001;152(3):632-42.
- Mehlisch DR, et al. *Clinical Therapeutics* 2010;32(5):882-895.
- Mehlisch DR, et al. *Clinical Therapeutics* 2010;32(6):1033-49.

Other sources:

The following studies compare combined ibuprofen and acetaminophen to an opioid containing product post-surgical.

- Article #1: Mitchell A, et al. *Journal of the American College of Surgeons* 2008 March; 206(3):472-479.
- Article #2: Mitchell A, et al. *Annals of Surgical Oncology* 2012 Nov; 19(12): 3792-3800.
- Article #3: Kelly LE, et al. *Pediatrics* Feb 2015; 135(2):307-313.
- Article #4: Chang AK, et al. The Journal of the American Medical Association 2017;318(17):1661-1667.

Dosing Scheme	Patient Type	Total number of patients	Results	P value
Article #1 **Combined** ibuprofen 400mg /acetaminophen 325mg Vs. Tylenol #3 (canada acetaminophen 300mg, codeine 30mg, caffeine 15mg) (give 4x daily for 7 days or until pain-free)	Post inguinal/ umbilical/ ventral hernia repair or laparoscopic cholecystectomy	146 72 combination 74 Tylenol #3	No significant difference in mean or max daily pain scores, except on post-op day #2 On post-op day #2 there was better pain scores in the combined ibuprofen and acetaminophen group	**0.025**
			Mean pain scores were modestly lower with the ibuprofen and acetaminophen combination	**0.018**
			More patients in the ibuprofen and acetaminophen combined group were satisfied with their pain control (83% vs. 64%)	**0.02**
			There were more side effects with Tylenol #3 (11% vs. 3%)	**0.044**
Article #2 **Combined** ibuprofen 400mg /acetaminophen 650mg Vs. Tylenol #3 (canada acetaminophen 300mg, codeine 30mg, caffeine 15mg) (give 4x daily for 7 days or until pain-free)	Post breast surgery	141 71 combination 70 Tylenol #3	No significant difference in average pain intensity over 7 days	0.78 not significant
			No significant difference in pain relief	0.46 not significant
			No significant difference in the incidence of adverse effects	0.94 not significant
			Tylenol #3 had to be discontinued due to adverse effects more than the combination of ibuprofen and acetaminophen (19% T3 vs. 6%)	**0.018**
			No significant differences in days until freedom from pain or patient satisfaction (89% T3 vs. 92%)	0.55 not significant
Article #3 **Combined** acetaminophen with ibuprofen 10mg/kg Or morphine 0.2-0.5mg/kg	Post tonsillectomy +/- adenoid removal	91 CHILDREN Age 1-10 years	Ibuprofen group showed more improvement the first postop night compared with the morphine group Improvement with respect to oxygen desaturations (68% vs. 14%)	**<.01**
			The number of desaturations with the morphine group was significantly higher than the ibuprofen group (average increase of 11.17 ± 15.02 events per hour)	**<0.1**
			No significant different in analgesic effectiveness, tonsillar bleeding, or adverse effects	
Article #4 **Combined** acetaminophen 1000mg /ibuprofen 400mg Vs. Percocet 5-325mg, Norco 5-325mg, Tylenol with Codeine #3 (300mg acetaminophen, 30mg codeine)	ED patient with moderate/ severe acute extremity pain	416 104 per each analgesic group	No significant difference in change in pain scores between the four groups from baseline to 2 hours Acetaminophen/ibuprofen- pain scores decreased by 4.3 Acetaminophen/oxycodone- pain scores decreased by 4.4 Acetaminophen/hydrocodone- pain scores decreased by 3.5 Acetaminophen/codeine- pain scores decreased by 3.9	0.053 not significant
			No significant difference in change in pain scores between the four groups from baseline to 1 hour	0.13 not significant

The following study compares combined and alternating paracetamol and ibuprofen for the treatment of fever. In this review, randomized controlled trials that compared combined and alternating paracetamol and ibuprofen to monotherapy for fever and where published from 2009-2011 were included. Six trials were included in this meta-analysis (total of 915 patients). It showed that there was inconclusive evidence to decide that either combined or alternating therapy was better at decreasing temperature, although both were better than monotherapy.

- Wong T, et al. *Evidence-Based Child Health: A Cochrane Review Journal* 2014 Sept;9(3):730-732.
  Included studies in this meta-analysis are as follows:
  - Erlewyn-Lajeunesse MD, et al. *Archives of Disease in Childhood* 2006;91(5):414-416.
  - Hay AD, et al. *British Medical Journal* 2008;337:a1302.
  - Kramer LC, et al. *Clinical Pediatrics* 2008;47(9):907-911.
  - Nabulsi M, et al. *BMC Medicine* 2006:4(4):b3540
  - Paul IM, et al. *Clinical Therapeutics* 2010;32(14):2433-40.
  - Sarrell EM, et al. *Archives of Pediatrics & Adolescent Medicine* 2006:160(2):197-202.

Dosing Scheme	Total number of patients	Result	Mean difference	95% confidence interval	Quality of Evidence
Antipyretic monotherapy vs. **combined** paracetamol and ibuprofen	163 (between 2 trials)	Can result in lower mean temperature at 1 hour after treatment	-0.27 °C	-0.45 to -0.08	Moderate
Antipyretic monotherapy vs. **combined** paracetamol and ibuprofen	196 (between 2 trials)	May lower mean temperature at 4 hours after treatment Also showed that fewer children remained or become febrile for up to 4 hours after treatment	-0.70 °C	-1.05 to -0.35	Moderate
Monotherapy vs. **combined** therapy (measuring child discomfort)	156 (1 trial)	No statistical difference in child discomfort (associated symptoms with fever at 24 and 48 hours)			
Antipyretic monotherapy vs. **alternating** paracetamol 15mg/kg and ibuprofen 10mg/kg	78 (between 2 trials)	May lower mean temperature at 1 hour after the second dose Also showed that fewer children remained or became febrile for up to 3 hours after the **second** dose was given	-0.60 °C	-0.94 to -0.26	Low
Monotherapy vs. **alternating** paracetamol 12.5mg/kg and ibuprofen 5mg/kg therapy (measuring child discomfort) Patients were loaded with either 25mg/kg of paracetamol or 10mg/kg of ibuprofen	480 (1 trial) Age 6-36 months	Mean pain scores at 24, 48, and 72 hours were lower with alternating therapy vs. monotherapy			Low
Compared **combined vs. alternating** Ibuprofen 10mg/kg **and** acetaminophen 15mg/kg	40 (1 trial) Age 6 months to 8 years	No statistical differences between mean temperature or the number of febrile children at 1, 4, or 6 hours			Low