**FAST FACTS AND CONCEPTS #302**

**ORAL VS INTRAVENOUS ACETAMINOPHEN**

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**Background** Acetaminophen (Tylenol) is one of the most commonly prescribed analgesics. Until recently, only oral and rectal formulations were available in the US. In 2010, the FDA approved intravenous (IV) acetaminophen (Ofirmev) for treatment of mild to moderate pain, fever, and as an opioid adjunct for moderate to severe pain. This *Fast Fact* will examine the clinical role of IV acetaminophen and compare its efficacy with oral acetaminophen.

**Mechanism of Action** Though the exact mechanism of action is unknown, acetaminophen’s analgesic effects are thought to occur via inhibition of prostaglandin synthesis in the CNS and blockage of peripheral pain receptors (1).

**Pharmacokinetics** There are several potential pharmacokinetic benefits of IV acetaminophen. The time to peak analgesic effect of IV acetaminophen is within 10 minutes after its administration compared with 1 hour for oral acetaminophen. It is also associated with significantly higher mean cerebrospinal fluid concentrations than oral or rectal formulations (2). This makes it well suited for settings where quick analgesia is required, such as the perioperative period, especially since the duration of action appears to be the same between both formulations (4 to 6 hours). IV acetaminophen has better bioavailability when gastric function is compromised (i.e. post-operative ileus) (3). Finally, due to differences in first pass metabolism, IV acetaminophen may expose the liver to 50% less initial acetaminophen (4).

**Efficacy in Perioperative Pain Management** IV acetaminophen has been well studied in perioperative settings. Despite the theoretical pharmacokinetic benefits of IV acetaminophen, research has shown that the number need to treat (NNT) for a 50% reduction in post-operative pain is 5.3 for IV acetaminophen compared with 3.8 for oral when both are dosed at 1000 mg every 6 hours (5,6). In a direct comparison trial, no significant differences in intraoperative or post-operative pain measures were identified between 1000 mg of oral versus IV acetaminophen (7). A separate head-to-head trial demonstrated a significant opioid sparing effect with IV acetaminophen compared with oral; however, the reduction in opioid dosing did not correlate with a decrease in nausea and vomiting and its comparative effects on delirium, inpatient length of stay, and constipation were not evaluated (8). Hence the clinical significance is still in question. When 1000 mg of IV acetaminophen was compared with 30 mg of IV ketorolac (a reasonable therapeutic alternative to IV acetaminophen) there was no significant difference in pain relief (9).

**Potential Uses of IV Acetaminophen** IV acetaminophen has not been well studied in patients with terminal illnesses. Empirically some experts hope that it may have an unique clinical role for fever and pain management in imminently dying patients who cannot swallow, especially in situations when rectal acetaminophen is not preferred or possible (e.g. neutropenic or post-colectomy patients) (10).

**Safety** IV acetaminophen can be safely administered at doses of 1000 mg in patients who weigh over 50 kg, with a maximum daily limit of 4000 mg. For patients and children over 2 years, who weigh less than 50 kg, the dose is weight based at 15 mg/kg. Given its favorable first pass effects, the theoretical risk of hepatotoxicity with IV acetaminophen is believed to be low. A review of the literature suggests that when hepatotoxicity occurs, it is mostly due to dosing errors and can be potentiated by malnutrition (11). Of note, IV acetaminophen overdose has no validated nomogram for treatment decision-making. The most common side effects are similar to oral acetaminophen and include nausea, vomiting, and insomnia (12).

**Cost** IV acetaminophen costs more than 20 times the equivalent dose of oral acetaminophen. Therefore, there is controversy whether IV acetaminophen is a cost-effective analgesic.

**Summary** IV acetaminophen has only been evaluated in a perioperative setting, which limits its extrapolation to other clinical settings. Even in the post-operative period, IV acetaminophen has not shown clinical superiority; hence, the increased cost of IV acetaminophen may outweigh any benefit it offers. Until further investigation shows otherwise, IV acetaminophen may be best reserved for clinical settings where GI absorption is compromised or the use or the use of reasonable therapeutic alternatives such as NSAIDS and opioids may be undesirable.

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