### Acetaminophen Toxicity: A Potential Consequence of Lengthy Operating Room Wait Times

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#### Source of the Problem

Inaccessibility of the operating room (OR) for dental treatment in the pediatric population could easily lead to inappropriate use of oral analgesics. Acetaminophen toxicity (AT) is a real concern for patients in moderate to severe pain and experiencing extended wait times for treatment in the OR. Although access to these settings was not limitless pre-COVID, access to general anesthesia has dramatically dropped or been non-existent since COVID.<sup>1,2</sup> Hospital networks posted large financial losses, and to financially get back on track, began to reevaluate what OR procedures were producing the most revenue. Although a review of several state Medicaid programs revealed no isolated reason for the decrease in access,<sup>3</sup> many anecdotally agree it is financially driven. In general, medical procedures are reimbursed at higher rates than dental; therefore, access of pediatric dentists and their patients into these facilities has dramatically decreased. Other minor contributing factors – such as preauthorization requirements, justification of medical necessity, and variable insurance coverage - have compounded issues with accessing these treatment settings.4

Inevitably, there are repercussions for this change in accessibility and most are felt by the patient and patient's caregivers. With limited access to surgical space, either lines for what little appointment time does exist become longer or patients are turned away.<sup>5</sup> With little doubt, the number of children with untreated early childhood caries (ECC) will continue to grow. ECC, in combination with less definitive treatment for the disease, can be expected to cause a further decrease in oral health, overuse of antibiotics, and more emergency department (ED) visits.<sup>4</sup> As non-traumatic dental complications are already a common reported reason for pediatric ED visits, less access to definitive care with the assistance of general anesthesia can be expected to correspond to an increased number of children dealing with intermittent or chronic dental pain and therefore more visits to the ED.

## Consequences Leading to Potential Toxicity

Pain is a real complication of ECC. Often, caregivers do not seek treatment for their children until there is an initial complaint of pain. In addition, children go an average of almost 18 days with tooth-based pain before caregivers decide to pursue treatment.<sup>6</sup> In a study by Thikkurissy et al, nearly 80% of patients who reported pain before their initial dental visit experienced moderate to severe pain at some point.

Even though accurate identification of pain in pediatric patients has historically been difficult,<sup>4,6-9</sup> the consequenc-



es have been measurable. Increased ED visits, missed school, poor academic performance, blunted social interactions, poor nutrition, sleep disturbances, and future orthodontic complications have all been correlated with dentally related pain.<sup>1</sup>

#### Acetaminophen Use For Pain

To treat the caries-related pain, parents and providers usually turn to over-the-counter **(OTC)** medications. In fact, use of OTC medications to treat ECC is a possible measure of ECC disease morbidity.<sup>10</sup> Ibuprofen and acetaminophen **(APAP)** are the two most used medications to treat pediatric dental pain. Of the two, APAP is by far more utilized.<sup>11</sup>

APAP has been on the market for decades, so APAP and the brand name, Tylenol<sup>™</sup>, are well known. Far less known is that APAP is also an active ingredient found in many cold and flu products (about 300) because of its antipyretic and analgesic properties. When surveyed, thirty-six percent of Americans admitted they would likely use multiple OTC products if they had more than one symptom, such as sore throat, cold, a toothache, or headache.<sup>12</sup> Previous research has also shown that less than fifty percent of people regularly read the OTC label, and only 26% of people read to find out what active ingredient the product contains.13

The combination of products containing APAP, the lack of attention given to OTC product labeling, and children requiring OTC pain medications for longer periods of time due to inadequate hospital and surgery center access all could increase the possibility of APAP toxicity and hepatocellular damage. This damage can progress to acute liver failure (ALF).<sup>14</sup> Between 1983 and 2003, Larson et al. found a profound increase (30%) in unintentional cases of APAP overdose leading to ALF.<sup>15</sup> As an example of potential APAP-related overdosage, in 2021, the US poison control centers received over 80,000 different reports involving APAP or APAP-containing products.<sup>16</sup>

APAP is extensively metabolized in the liver with the major pathway of metabolism being APAP conjugation to sulfated and glucuronidated metabolites excreted renally. About 8% of the drug undergoes Cytochrome P-450 oxidation to form a reactive metabolite called N-acetyl-p-benzoquinone imine (NAPQI). Normally, NAPQI reacts with sulfhydryl groups in glutathione and is harmlessly excreted. However, with large single doses or chronic elevated consumption (over 8 hours) the major metabolic pathway is saturated, and more is shunted toward the NAPQI pathway. The metabolite accumulates in the hepatocytes and can cause damage.

Within 12-24 hours after supratherapeutic ingestion, initial toxicity symptoms may begin. The non-specific nature of these symptoms, such as nausea, vomiting, diaphoresis, anorexia, and lethargy may be easily misinterpreted as other ailments and thus not addressed quickly. The next phase of toxicity usually becomes evident 24-48 hours after ingestion. Symptoms are more representative of hepatocellular injury and include right upper quadrant or abdominal pain. Abnormal liver enzymes can also be seen during this phase. The last phase includes signs of serious hepatic injury, as well as CNS depression (somnolence, confusion, and coma) and occurs approximately 3-5 days after ingestion.<sup>17</sup> A glutathione-mimicking antidote for APAP toxicity, N-acetylcysteine, does exist and is effective when administered in a timely fashion. Despite antidote therapy, irreversible damage may exist after treatment.

The APAP dosage for children is weight-based, which is more complex to understand, dose, and administer than the adult dosage of 500-650 mg every 4 to 6 hours. The normal pediatric dose is 10 to 15 mg/kg every 4 to 6 hours (not to exceed adult dosage). The maximum dosage for children less than 12 years old is 5 doses (2.6 grams) in a 24-hour period. Unfortunately, according to different surveys, only 18-21% of people correctly identified weight as the appropriate way to dose medication for children. This could potentially result in supratherapeutic dosages for pediatric patients.<sup>6,12</sup>

Historically, caregivers have undertreated the pain of pediatric patients, but an increased use of OTC products for children lingering in chronic dental pain can be expected.<sup>6,18-20</sup> Treating pediatric dental pain adequately and safely should be of utmost importance for every pediatric dentist.

### What Pediatric Dentists Can Do to Prevent APAP Toxicity

Being on the frontline of treatment delivery, pediatric dentists can and should take steps to help prevent their patients from experiencing APAP toxicity. The first and easiest step a pediatric dentist can take is to make sure caregivers are familiar with dosing and maximum daily limits of APAP.

Since about 80% of caregivers are unaware weight is the ideal dosing mechanism for APAP, pediatric dentists should provide the necessary education and assist with determining the appropriate dosage for the patient.<sup>13</sup> Most liquid APAP products contain 160 mg/5 ml. Being able to calculate the weightbased dosage and converting it into how many milliliters are to be administered, may be challenging for many caregivers, and *dentists* should be able to adequately explain how to determine the exact amount of the medication to be administered using patient-friendly terminology.

The dentist should avoid generic information, and provide exact instructions for the specific patient using a measuring tool provided in the product packaging, how often it is to be given, for how long the medication should be taken, what caregivers should be taken, what caregivers should do if the child is still experiencing pain, and what toxicity symptoms they should look for as a result of taking the medication.

Counseling should also address that APAP is found in many other OTC products used to treat conditions, such as cold and flu. Caregivers should be instructed to check with their pharmacist before starting a new OTC product while the patient is being treated for dental pain to avoid unintended overdose.

Educating and in some cases physically showing patients how to check labels on OTC medications may be advisable, especially when the patient's caregiver may have a lower health literacy.

#### Pediatric dentists should also be able to discuss different treatment options for patients experiencing dental pain.

OTC nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, may also be used to treat dental pain. Dentists should be familiar with the appropriate Ibuprofen dosing of 5-10 mg/kg/dose (not to exceed adult dosing) every 4 to 8 hours with a maximum of 40 mg/kg/day (1200mg/day for OTC use). Liquid-ibuprofen containing products usually come as a 100 mg/5 ml oral suspension. Dentists should help parents/caregivers select the most appropriate product and corresponding weight-based regimen.

For patients experiencing moderate dental pain, the combination of APAP and ibuprofen is an effective treatment and may be advisable in lieu of caregivers trying to administer larger amounts of APAP. If the dentist determines it is necessary to use multiple products to achieve pain control, specific instructions should be given to patients.

Caregivers should be provided with information regarding when and how much of each medication should be administered. It may be advisable to provide parents with an exact schedule, including times and dosages of each medication and advise them to carefully record this information as a reminder. Concomitant use of multiple products is not recommended for prolonged periods of time and should only be used when necessary.

# Supportive Co-Therapies to Reduce APAP Toxicity

Pediatric dentists should triage their patients. Rather than leave a patient experiencing dental pain at the bottom of the waitlist, it may be advisable to move them to the front of the line. Utilization of other treatment modalities may be indicated to help decrease treatment wait times. Attempting to first treat the patient with excellent behavior management techniques and nitrous oxide or using oral sedation, which has become less utilized in recent years, may be viable treatment options for eligible patients. *The use of nondefinitive treatment can* be employed when definitive treatment cannot be provided in a timely fashion. Silver diamine fluoride application, Hall crown placement, and glass ionomer interim restorations using atraumatic restorative techniques are treatments that can be expected to increase as the lack of accessibility grows more pronounced. Some practices, which had moved away from traditional treatment modalities in lieu of treatment with general anesthesia, may need to reinstitute those techniques.

Combining dental treatment with already scheduled medical general anesthesia appointments, the use of traveling anesthesia groups, and the development of dentist-owned surgery centers may also help reduce the access to care burden many pediatric practices and patients are now experiencing. Hospitals and payers should also work together to allow adequate use of hospital surgery areas with appropriate payor reimbursement. All these options are necessary to decrease the number of patients left in chronic dental pain. The longer patients go without receiving definitive care, the longer they will be on medications like APAP. The inappropriate or unintentional misuse of APAP can easily have toxic effects. With limited options for addressing major dental pain in the OR setting, pediatric dentists must strengthen their medication education, apply ingenuity with treatment options available, and advocate for the expansion of care for their patients at every level.

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