Regulatory Review of Acetaminophen Clinical Pharmacology in Young Pediatric Patients

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ABSTRACT: The acetaminophen dosage schedule in pediatric patients below 12 years of age for the over-the-counter (OTC) monograph is one of the many issues being evaluated and discussed in the development of the Proposed Rule for Internal Analgesic, Antipyretic, and Anti-rheumatic drug products. The dosage regimen based on age and weight, with instructions that weight-based dosage should be used if a child's weight is known, is currently being assessed by the agency. This review summarizes the available pharmacokinetic and pharmacodynamic (fever reduction) data of oral acetaminophen in pediatric patients of 6 months to 12 years of age. Acetaminophen is metabolized in the liver mainly through glucuronidation, sulfation, and to a lesser extent oxidation. Because of the difference in the ontogeny of various metabolizing pathways, the relative contribution of each pathway to the overall acetaminophen metabolism in children changes with age. The sulfation pathway plays a more important role in metabolizing acetaminophen than the glucuronidation pathway in younger children as compared with older children and adults. The pharmacokinetic exposure of acetaminophen in pediatric patients of 6 months to 12 years of age given oral administration of 10–15 mg/kg is within the adult exposure range given the OTC monograph dose. The antipyretic effect of acetaminophen is dose dependent and appears to be better than placebo at the dose range of 10–15 mg/kg in pediatric patients of 6 months to 12 years of age. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:4383–4389, 2012

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REGULATORY HISTORY OF ACETAMINOPHEN PEDIATRIC OVER-THE-COUNTER MONOGRAPH DOSAGE SCHEDULE

Oral acetaminophen was initially approved by the US Food and Drug Administration in 1951, and was first marketed in the United States in 1953. Tylenol Elixir was introduced in 1955 as the first aspirin-free antipyretic and pain reliever. In 1960, Tylenol® was approved for sale over-the-counter (OTC). Currently, acetaminophen is available in a variety of dosage forms and formulations, either as single-entity products or in combination with other drugs, and either as OTC or prescription products. Multiple strengths of rectal suppositories (80, 120, 325, and 650 mg) and an extended-release oral formulation (650 mg tablet, capsule, and geltab) are marketed as OTC products under the New Drug Application process. Intravenous acetaminophen is available by

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Table 1. Age-Based Pediatric Dosing Schedule for Acetaminophen.

	Pediatric (80 mg) Dose Units[a]		Adult (325 mg) Dose Units[a]	
Age (years)	Dose Units	Total Dose (mg)	Dose Units	Total Dose (mg)
Under 2	No recommended dose except under the advice and supervision of a physician.			
2–3	2	160	1/2	162.5
4–6	3	240	3/4	243.8
6–9	4	320	1	325.0
9–11	4–5	320–400	1–1 1/4	325.0–406.3
11–12	4–6	320–480	1–1 1/2	325.0–487.5

[a]Every 4 h and not exceed five single dosages in 24 h or to use more than 5 days except under the advice and supervision of a physician.

prescription only. Single-ingredient immediate-release oral acetaminophen products are marketed under the OTC monograph, which is the primary focus of this review. The acetaminophen OTC monograph pediatric dose was originally proposed as follows:

- from 6 to under 12 years—one-half adult dose
- from 3 to under 6 years—one-fifth adult dose
- under 3 years—labeled as "Do not use unless directed by a physician."

In the 1977 Advance Notice of Proposed Rule Rulemaking (ANPR) for Internal Analgesic, Antipyretic, and Anti-rheumatic drug products, acetaminophen was categorized as a category I analgesic antipyretic and a category II antirheumatic, and age-based pediatric dosing was proposed. This schedule was essentially based on the commonly used daily pediatric dose of 1.5 g/m^2, with a maximum of five doses daily for aspirin. The pediatric acetaminophen dosing schedule in the 1988 tentative final monograph is the same as proposed in the 1977 ANPR except that the lowest adult dose has been added to the dose ranges for pediatric patients of 9 years and over (Table 1).[1]

Weight-based dosing was also discussed in the 1977 ANPR. On the basis of the efficacy data for pain and fever relief in children at 10–15 mg of aspirin per kg of body weight, the daily pediatric dose of 65 mg/kg of body weight with a maximum of five doses daily was proposed and used to derive the weight-based dose for all OTC analgesics including acetaminophen. Temple[2] elaborated this weight-based dose in detail, and proposed a weight-based OTC monograph for acetaminophen. In the 2009 final rule addressing acetaminophen and nonsteroidal anti-inflammatory drug safety labeling changes [71 FR 77314],[3] age-based pediatric dosing for acetaminophen was listed as one of the many issues being further evaluated and discussed. On December 3, 2009, the Division of Anesthesia, Analgesia, and Rheumatology Products in the agency organized a Pediatric Analgesic Clinical Trials Workshop with a panel of external experts to discuss aspects related to extrapolation of efficacy of analgesic drugs from adults to children, design considerations for efficacy studies, strategies to overcome the barriers to enrollment, and approaches to dose finding and the metrics that can be used in the evaluation of efficacy in neonates and infants. At this meeting, it was agreed that (1) the efficacy of certain analgesics, including acetaminophen, in children of 2 years of age and above could be extrapolated from efficacy data in adults, (2) dosing for this age group would be confirmed based on pharmacokinetic data, and (3) the safety of these analgesics would be based on data from clinical trials.

For children under 2 years of age, in addition to the pharmacokinetic and safety data, efficacy data would also be required. As such, dosing of acetaminophen in pediatric patients for OTC monograph use for the pain and fever indications will be based on adequate pharmacokinetic and safety data in the age group of 2–12 years, and pharmacokinetic, safety, and efficacy data in the age group of 6 months to 2 years.

This manuscript reviews the development of acetaminophen-metabolizing pathways, and assesses the proposed weight-based dosing regimen of 10–15 mg/kg in young pediatric patients by examining the pharmacokinetic exposure and dose–response relationship. Well-controlled pain studies in pediatric patients of less than 2 years of age are scarce, but there are data from studies with fever. Therefore, the dose–response relationship discussion will be limited to fever in this review.

PHARMACOKINETICS OF ACETAMINOPHEN

Absorption

Acetaminophen is absorbed from the gastrointestinal tract primarily by passive nonionic diffusion.[4] It is considered a borderline compound between Biopharmaceutics Classification System class I and class III.[5] The absolute oral bioavailability of acetaminophen was reported to be an average value of 80%.[6] The apparent rate constant for acetaminophen

absorption following oral administration of different formulations in healthy subjects ranged from about 1 to 10 h^{-1}.[6] Dose proportionality has been demonstrated with oral acetaminophen for doses up to 8 g daily.[7] The effect of food on the pharmacokinetics (PK) of acetaminophen in solid tablet formulation is to delay the time to reach the maximum concentration (T_{max}) and reduce the peak plasma concentration (C_{max}), but there is no effect on the area under the plasma concentration time curve (AUC).[8,9] The gastric emptying in neonates and infants was reported as slow and erratic, and normal adult rates may not be reached until 6–8 months of age.[10–12]

Distribution

The binding of acetaminophen to plasma proteins is low (10%–25%).[13] It is widely distributed, with a volume of distribution of 0.8–1 L/kg as reported by most investigators.[6] Acetaminophen has been shown to be able to penetrate into the cerebrospinal fluid (CSF) and placenta, and is excreted in breast milk at low levels.[14–16] In pediatric patients, it was also shown to be well distributed in the CSF in a open-label, prospective study published by Kumpulainen et al.[17] In this study, 32 pediatric patients (aged 3 months to 12 years) undergoing surgery requiring spinal anesthesia were given a single intravenous injection of acetaminophen (15 mg/kg). The median acetaminophen concentrations in CSF and plasma were 7.2 and 14 mg/L, respectively. The highest CSF acetaminophen concentration was detected at 57 min.[17] Anderson et al.[18] evaluated the developmental PK of acetaminophen in premature neonates through infancy, and reported that the volume of distribution of acetaminophen decreased exponentially with a maturation half-life of 11.5 weeks from 109.7 l/70 kg at 28 weeks after conception to 72.9 l/70 kg by 60 weeks (adult level).[18]

Metabolism and Elimination

In adults, acetaminophen is metabolized mainly in the liver via glucuronidation (50%–60%), sulfation (25%–30%), and oxidation (<10%).[19,20] Additionally, hydroxylation to form 3-hydroxyacetaminophen and methoxylation to form 3-methoxyacetaminphen, along with excretion of free or unconjugated acetaminophen in the urine, typically represent minor clearance pathways.[21] None of the metabolites of acetaminophen have analgesic or antipyretic effects. All of the metabolites are excreted in the urine in a dose-dependent manner, with more than 90% of an administered dose excreted within 24 h. Enterohepatic circulation is negligible.

Glucuronidation and sulfation follow first-order kinetics. Glucuronidation is catalyzed primarily by UGT1A6 glucuronyltransferase, and to a lesser extent by UGT1A9, with uridine 5′-diphosphoglucuronic acid as an essential cofactor,[22–24] However, the sulfation pathway is capacity limited, primarily because of unavailability of inorganic sulfate and, to a lesser extent, of sulfotransferase activity.[7] Literature reports have shown that oxidation of acetaminophen occurs via a CYP450-dependent, mixed-function oxidase enzyme pathway, primarily by CYP2E1, to form N-acetyl-*p*-benzo-quinone imine (NAPQI). The contribution of other CYP isozymes is negligible.[25] NAPQI is not measurable because of its reactivity and near-instantaneous conjugation with intracellular glutathione to 3-glutathione-*S*-yl-acetaminophen by reacting with either intracellular glutathione directly or through a glutathione-transferase-catalyzed reaction.[26] The NAPQI–glutathione conjugate is further metabolized to form nontoxic glutathione adducts such as 3′-[*S*-cysteinyl] acetaminophen, acetaminophen mercapturate, and 3′-*S*-methylacetaminophen, which are excreted in urine and can provide an indirect estimate of the amount of NAPQI formed from a given dose of acetaminophen. NAPQI may cause hepatotoxicity after a massive acute overdose if glutathione stores are exhausted. However, with therapeutic doses of acetaminophen, sufficient glutathione stores are present to conjugate the small amount of NAPQI produced. Additionally, there is an active repletion process for glutathione.[27] A review of more than 100 literature publications on oral acetaminophen showed that the total clearance and plasma half-life at therapeutic doses in healthy subjects were usually about 12–33 L/h per 70 kg and 1–3 h, respectively.[6] In patients with a variety of conditions taking therapeutic doses, the half-life also usually fell between 1 and 3 h with an average of about 2 h.[6]

In children, although acetaminophen metabolism pathways are the same as in adults, the relative contribution of each pathway or enzyme to the overall acetaminophen metabolism changes with age. The sulfation pathway is mature at birth; however, the glucuronidation pathway takes about 2 years to mature, according to van der Marel et al.[28] As the glucuronidation activity in younger children is less than that seen in older children and adults, the sulfation pathway is a more important route of metabolism for acetaminophen in younger children. Miller et al.[29] evaluated the urinary excretion (0–36 h) of unchanged acetaminophen, acetaminophen-sulfate, and acetaminophen-glucuronide following administration of 10 mg/kg acetaminophen to neonates (1–2 days old), children (3–9 years), 12-year-old children, and adults. They found the ratio of acetaminophen-glucuronide to acetaminophen-sulfate excreted in the urine is 0.34, 0.75, 1.61, and 1.80 for neonates, children (3–9 years), children (12 years), and adults, respectively. In this study, renal excretion was completed within 30 h with 75% of the administered dose appearing

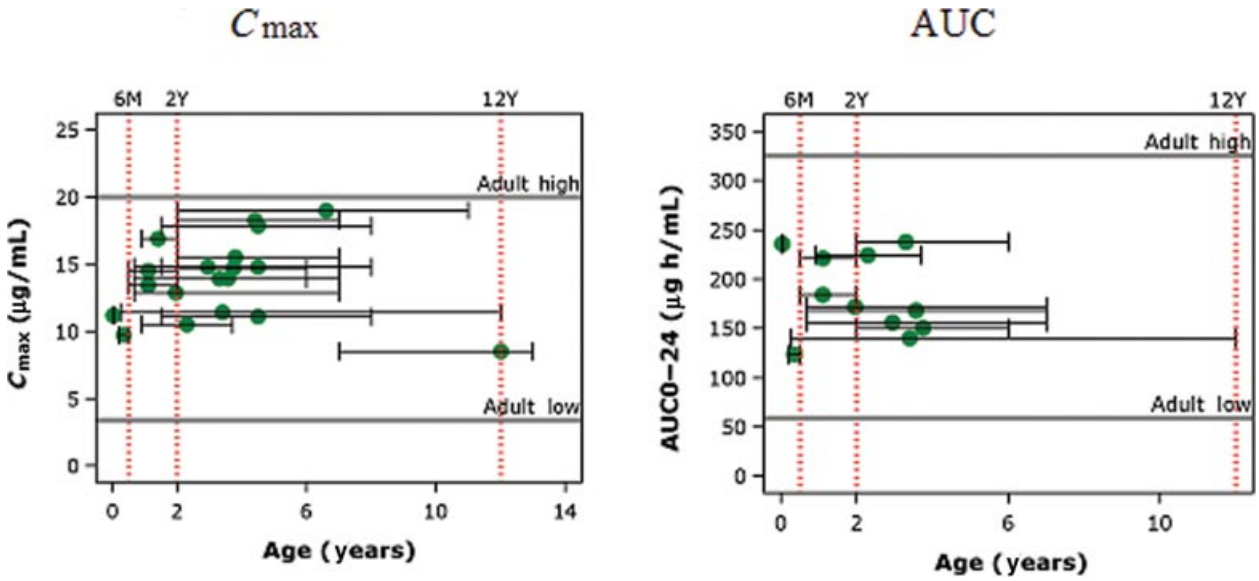

Figure 1. Acetaminophen C_{max} and AUC in pediatric patients after single dose administration (normalized to 15 mg/kg). Data are from the following references: Windorfer and Vogel,[33] Perterson and Rumack,[34] Wilson et al.,[35] Nahata et al.,[36] Brown et al.,[37] Kelly et al.,[38] Hopskins et al.,[39] Romsing et al.,[40] and McNeil in house data.

in the urine as acetaminophen and its sulfate and glucuronide conjugates. They also found that, although the rate of excretion of various acetaminophen metabolites changes with age, the plasma half-life of acetaminophen is similar across different age groups. CYP2E1 levels are low in neonates, and gradually increase during the first year to reach the adult value in children aged 1–10 years.[30] The development of hepatotoxicity caused by acetaminophen is dependent on the balance of the formation rate of NAPQI, the elimination rate from sulfate and glucuronide conjugation pathways, and the initial content and the repletion rate of hepatic glutathione.[31] Young children appear to be most resistant to acetaminophen-induced hepatotoxicity because of both reduced rates of oxidation by CYP2E1 and the neonate's increased ability to replete glutathione compared with adults.[32]

C_{max} and AUC Comparison between Young Pediatric Patients and Adults After the Proposed Monograph Dosing

To understand acetaminophen exposure for the proposed monograph dose(s), pediatric studies including PK exposure data and enrolling patients 12 years of age and below were reviewed.

A total of 10 studies enrolling 239 patients were reviewed.[33–40] The reported pharmacokinetic data were often combined across different pediatric age groups. The age range varied from neonates to 12 years. The number of subjects in each dose group varied from four to 47. Oral acetaminophen doses ranged from 5 to 30 mg/kg. The T_{max} of 0.5–1.8 h and the half-life of 1.4–2.9 h after oral administration of acetaminophen in pediatric patients were comparable to those in adults. The acetaminophen dose-normalized C_{max} and AUC0–24 (normalized to 15 mg/kg oral dose) are summarized and presented in Figure 1. The mean values of C_{max} and AUC in younger patients over various age ranges were generally within the adult exposure range following dosing consistent with the proposed OTC monograph dose.

As acetaminophen clearance is both age and body weight dependent in young pediatric patients, to further understand the exposure of acetaminophen at each age and body weight, simulations were conducted using parameters from a population pharmacokinetic model published in the literature.[28,41] The simulation takes into consideration the normal weight variability in children of 6 months to 12 years of age. The simulated C_{max} and AUC0–24 for the oral dosage regimen of 10–15 mg/kg are shown below in Figure 2. The simulation results show that acetaminophen AUC0–24 and C_{max} are also generally comparable to that in adults given OTC monograph dose at each age and weigh range.

DOSE–RESPONSE RELATIONSHIP FOR FEVER IN YOUNG PEDIATRIC PATIENTS

Adequate data investigating the antipyretic effect of acetaminophen and establishing a dose–response relationship in the age group of 6 months to less than 2 years were not available. However, available data that included pediatric patients below 2 years of age along

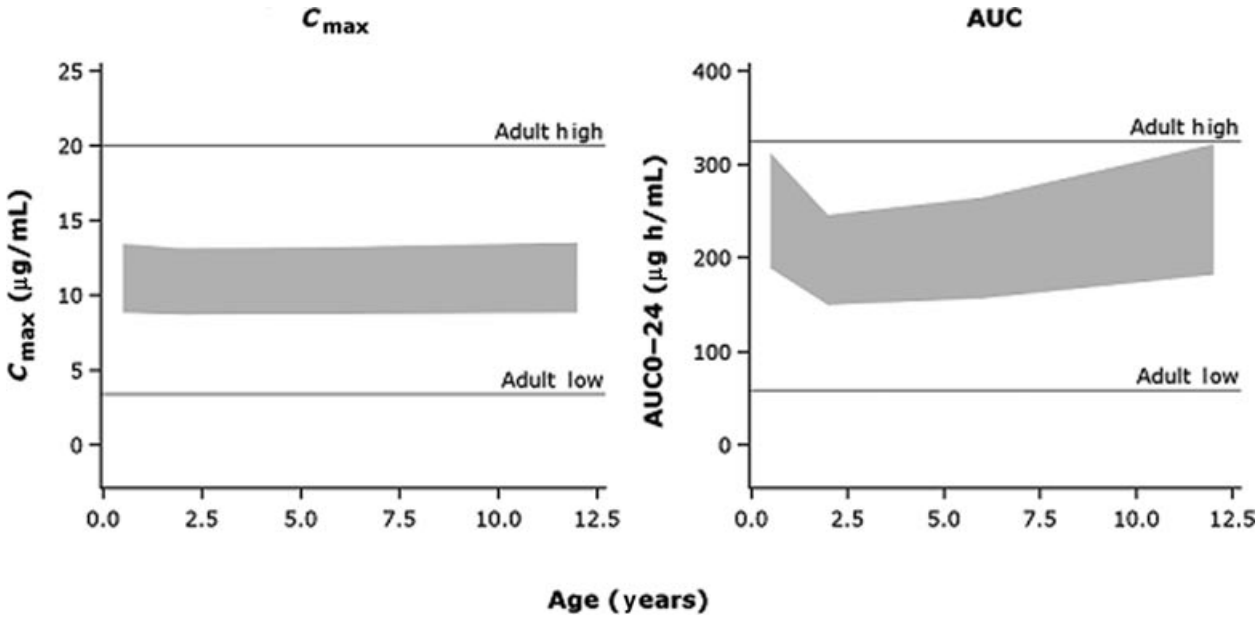

Figure 2. Simulated acetaminophen C_{max} and AUC in pediatric patients of 6 months to 12 years of age following oral 10–15 mg/kg dose.

with older pediatric patients were reviewed to assess whether there was a dose–response relationship. The temperature reduction in an acetaminophen-treated group administered with an oral dose of 10–15 mg/kg was significantly better than the placebo group in two placebo-controlled studies[42,43] and comparable to an ibuprofen-treated group in an active comparator study of pediatric patients of 6 months to 11 years of age.[44]

After oral dosing, there was a lag time between the maximum fall in temperature and the maximum plasma concentration. Kelley et al.[38] reported that, although the time to maximum plasma concentration was 24 min, the time to maximum temperature decrease was 133 min for acetaminophen. The delay in pharmacodynamic response to acetaminophen reflects the time taken to reduce heat production and increase heat loss after the change in the central set point for temperature regulation.

To understand the acetaminophen dose–fever reduction relationship, fever studies that included raw temperature reduction versus time data (up to 6 h) and enrolled pediatric patients of 2 years of age and below were reviewed. Studies with mean data only or with the lowest pediatric patient age of 2 years were not included. A total of 15 studies fit in this criteria and were included.[33,38,42,43,45–55] The weighted sum of temperature reduction for 6 h (WSTD6) was calculated as the fever reduction endpoint. If subjects were given multiple doses of acetaminophen, then only the first 6 h of temperature time data were used in the calculation of WSTD6. The formula for WSTD6 calculation is shown below:

Let Time(i) be the time of the ith assessment Fever(i), $i = 1,\ldots,N$

$$\begin{aligned}\text{TimeDiff}(i) &= \text{Time}(i) - \text{Time}(i-1), i = 1, \ldots\ldots N\\ \text{FeverDiff}(i) &= \text{Fever}(i) - \text{Fever}(0)\\ \text{WSTD6} &= \sum_{i=1}^{N} \text{TimeDiff}(i) \times \text{FeverDiff}(i)\end{aligned}$$

As shown in Figure 3, the temperature reduction for acetaminophen was dose dependent. At the proposed OTC monograph dose range of 10–15 mg/kg, the average temperature reduction in the first 6 h, calculated by dividing WSTD6 with 6, was 0.7–1.5°C. The average temperature reduction in the placebo group was less than 0.25°C in the first 6 h.

CONCLUSIONS

This brief review summarizes available acetaminophen PK and PK/PD data in pediatric patients of 6 months to 12 years of age. Although acetaminophen has been on the market for over half a century, a complete understanding of its efficacy in young pediatrics is still evolving and the monograph dose in pediatric patients has, therefore, yet to be finalized. Acetaminophen is metabolized in the liver mainly through glucuronidation, sulfation, and less through oxidation. The sulfation pathway plays a more important role in metabolizing acetaminophen than the glucuronidation pathway in younger children as compared with older children and adults. The

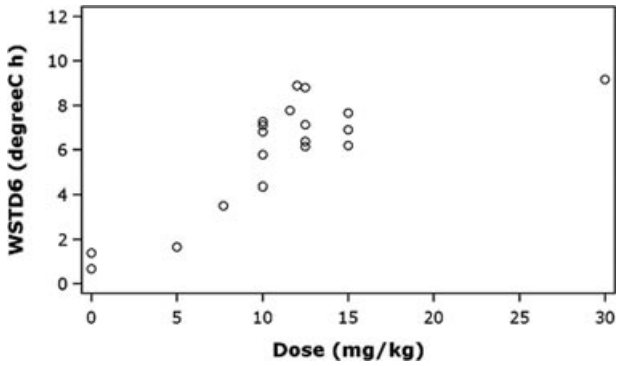

Figure 3. Dose response in fever reduction for acetaminophen in pediatric patients. Data obtained from the following references: Windorfer and Vogel,[33] Kelly et al.,[38] Wilson et al.,[42] Simila and Hull,[45] Keinanen et al.,[46] Simila and Kylmamaa,[47] Walson et al.,[48] Duhamel et al.,[49] Van Esch et al.,[50] Mclntyre et al.,[51] Autret et al.,[52] Treluyer et al.,[53] Autret-Leca et al.,[54] Gupta et al.,[43] Celebi et al.[55]

activity of CYP2E1, the major enzyme responsible for the oxidation pathway, is present, but at low levels, in neonates. The level of CYP2E1 gradually increases during the first year of life to reach the adult value in pediatric patients aged 1–10 years, indicating that younger children may not have the same degree of susceptibility to oxidative metabolites associated with liver toxicity as compared with older children and adults. The exposure of acetaminophen in pediatric patients of 6 months to 12 years of age given oral administration of 10–15 mg/kg is comparable to that in adults given the OTC monograph dose. The antipyretic effect for acetaminophen is dose dependent. On the basis of the literature data reviewed, at the proposed OTC monograph dose range of 10–15 mg/kg in pediatric patients between 0.2 and 12 years of age, the weighted average temperature reduction was 0.7–1.5°C, whereas in the placebo group, this value was less than 0.25°C in the first 6 h. Because these studies have an indeterminate number of patients of below 2 years of age, these results should be interpreted with caution with regard to the applicability of these conclusions to pediatric patients in the age group of 6 months to less than 2 years of age.

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